

# Brazilian Journal of ANESTHESIOLOGY

Revista Brasileira de Anestesiologia

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Two years of  
COVID-19



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## EDITORIAL

### Two years of the COVID-19 pandemic: an anesthesiology perspective



In a previous editorial approximately two years ago, we wrote about how the COVID-19 pandemic was unfolding worldwide and significantly impacting the routine of anesthesiologists around the world.<sup>1</sup> In the beginning of 2020, little was known about the potential consequences of the widespread dissemination of the SARS-CoV-2 virus in the population and how far this pandemic could reach. Today, approximately two years after the pandemic commencement, and following plenty of contamination waves, according to the Johns Hopkins Coronavirus Resource Center,<sup>2</sup> almost 6 million lives were lost worldwide, more than 600,000 souls only in Brazil. At the time we are writing this editorial, more than 400 million people have been officially infected around the world, a number that is vastly underestimated. Unfortunately, these records continue to rise and it is quite difficult to predict what is going to happen next in this pandemic.

The impact of COVID-19 pandemic has been unique, stressing our healthcare system far beyond its limits. During this pandemic, we have received unprecedent large amounts of data regarding the strengths and weaknesses of the healthcare system worldwide, highlighting the outstanding relevance of the scientific research, the application of protective measures, the benefits of extensive vaccination, and investigation of potential new anti-viral drugs. In spite of all scientific advances, mortality rates have been quite high and, for many patients, there has been a notable limitation of resources, especially in the developing world. Nevertheless, from our perspective, it is noteworthy to ask: how has the daily practice of anesthesiologists been affected, and which lessons have been learned in two years of pandemic?

Anesthesiologists have displayed a pivotal role in the COVID-19 pandemic. Considering that we are experts in airway and hemodynamic management, it is not surprising that anesthesiologists have been on the frontline of the treatment of patients with COVID-19. Additionally, in many countries, there is a significant educational crossover in the fields of anesthesiology, emergency medicine, intensive care, and

perioperative medicine. Particularly during the most critical phases of the pandemic, anesthesiologists have contributed considerably to the management of COVID-19 cases in both clinical and surgical intensive care units (ICU), actively participating in airway management teams, developing sedation and mechanical ventilation protocols, performing ultrasound-guided procedures, providing regional or systemic analgesia, and joining fast response resuscitations teams.<sup>3</sup> Particularly during the periods of medication and equipment shortage, anesthesiologists offered significant support to develop alternatives of sedation and mechanical ventilation in critically ill patients.

Thus, particularly in the initial response to the pandemic, there was a rapid proliferation of guidelines, recommendations, and checklists for the airway management and perioperative care of patients with COVID-19. Considering the lack of solid scientific evidence, anesthesiologists have been recommended to change their routine practices according to pragmatic recommendations. Most of those suggestions have not been developed based on a scientifically rigorous methodology. Although this was an appropriate reaction in response to an urgent public health concern, the publication of a large number of recommendations may be somewhat confusing to healthcare professionals, and potentially make it more difficult to adopt specific protocols. More recently, systematic identification of the beneficial and detrimental strategies to manage COVID-19 patients will ultimately lead to some standardization of care as we prepare for the endemic phase of the disease.<sup>4</sup>

Although some heterogeneity remains, there is still substantial agreement between professionals and societies on numerous aspects of COVID-19 perioperative and clinical care, especially in terms of anesthetic and airway management.<sup>4-6</sup> The choice of anesthetic technique should be based on patient factors and the planned procedure.<sup>6</sup> Regional anesthesia is not contraindicated by COVID-19, although the coagulation status may affect the timing or decision to use regional techniques.<sup>7</sup> Most guidelines and protocols provide similar personal protective equipment recommendations

and approaches to airway management, including reduced personnel exposure and suggesting the most experienced airway specialist to perform tracheal intubation.<sup>8</sup> There is also substantial agreement regarding specific tracheal intubation techniques, with most publications recommending a rapid sequence induction with the use of videolaryngoscopy.<sup>8</sup> Goals for tracheal intubation are to secure the airway rapidly, on the first attempt, providing immediate oxygenation. Although there are still some uncertainties and knowledge gaps, according to the present evidence, a protective mechanical ventilation strategy based on low tidal volume and low plateau pressures has been indicated in the management of COVID-19 patients displaying Acute Respiratory Distress Syndrome (ARDS).<sup>9,10</sup> Notably, consistent and congruent recommendations provided to anesthesiologists are essential to ease clinical decision-making and increase adherence to the best safety practices in the COVID-19 pandemic and afterwards.

Nonetheless, there is some concern regarding the lack of updates on the majority of recommendations on the anesthetic care of patients with COVID-19. As new SARS-CoV-2 variants emerge, and understanding about COVID-19 continues to grow rapidly, it is necessary to keep in touch with the pandemic evolution. For instance, in the beginning of the pandemic, concerns were raised about the risk of SARS-CoV-2 aerosolization during tracheal intubation. However, recent evidence has suggested that tracheal intubation in paralyzed patients may not be a highly aerosol-generating procedure.<sup>11</sup> Additionally, the usage of negative pressure rooms has been debated, with significant concerns regarding the risk of developing secondary infectious diseases.<sup>12</sup> Considering the endless growing evidence on the disease, it is not surprising that outdated recommendations remain easily accessible to the public and healthcare providers. This definitely contributes to ongoing misunderstanding and lack of adherence to the most up-to-date practices. In this context, medical societies and organizations might play a key role in the process of summarizing the plethora of accessible information about the paramount care of our patients, constantly updating their recommendations and achieving consensus on the light of the best evidence available.

In fact, the dissemination of knowledge was extraordinary during this rapidly evolving pandemic, especially considering factors such as rapid scientific publishing and the impact of social media in our lives. Recent advances in technology have enabled stable and wide-ranging global connectivity, allowing almost instantaneous access to COVID-19-related topics, fueling the dissemination of information and protocols. An enormous diffusion of preprints and open-access articles addressing COVID-19 topics have been witnessed, easing the access to information on the disease, even for ordinary citizens. Clearly, this movement should be celebrated and hopefully will continue to thrive.

Conversely, the dissemination of flawed information and poor quality of data is also present and may be related to deleterious consequences, including wrong clinical decisions and worse outcomes. A systematic review comparing COVID-19 versus non-COVID-19 studies published in the three highest ranked medical journals has demonstrated that COVID-19 articles were 18-fold more likely to be of lower evidence than the non-COVID-19 articles.<sup>13</sup> Interestingly, despite the lower quality, COVID-19 manuscripts were more likely to be

cited earlier. Although the quality of anesthesia papers during the pandemic has not been formally assessed, the bias may be similar. Therefore, it is of extreme importance that anesthesiologists and healthcare providers carefully analyze the most accurate data, always aiming to achieve the best evidence available in a specific topic. Since the knowledge is so dynamic in recent times, it is essential that professionals seek for constant updating on their fields of study.

For all the reasons above, in this issue of the *Brazilian Journal of Anesthesiology*, we invite readers to access several interesting studies providing new insights into the role of the anesthesiologist in the COVID-19 pandemic.<sup>14-20</sup> These studies have addressed a myriad of COVID-19-related topics, including the risk for environmental exposure to the SARS-CoV-2, potential protective measures to reduce contamination during airway management, mental health of healthcare providers and education concerns during the pandemic, a new technique for percutaneous tracheostomy in COVID-19 patients, and potential benefits of early awake prone positioning in patients displaying COVID-19-related ARDS.

Among these studies, it is tempting to highlight the alarming infection rates of anesthesiologists in Brazil.<sup>14</sup> Similarly to other countries, Brazilian anesthesiologists were often elected to perform orotracheal intubation in COVID-19 patients due to their airway management skills. In this study, Costa et al. have demonstrated that the prevalence of coronavirus infection among anesthesiologists was 5.57 times higher as compared with the overall infection rate of the Brazilian population, reflecting the high occupational exposure and risk of infection. These findings offer a relevant contribution to understanding the actual environmental risks during the assistance of our patients and establish strategies to estimate and reduce contamination rates among our workers.

Importantly, an issue that demands our attention is related to the potential consequences of the COVID-19 pandemic to the management of other diseases, as the pandemic has placed a significant strain on the worldwide healthcare system since the first wave of cases in 2020. The initial spread of COVID-19 and mortality rates were mostly affected by patterns of socioeconomic vulnerability, especially in low- and middle-income countries. In Brazil, the unequal distribution of economic resources and deep social gaps customarily affect the population access to the healthcare system. Unfortunately, the COVID-19 pandemic wreaked havoc on national medical institutions, turning a bad situation even worse. For instance, there is a pronounced uneven distribution of intensive care physicians and ICU beds among wealthier and poorer states in Brazil. These inequalities led to higher COVID-19 death rates in the most socioeconomically vulnerable regions.<sup>21</sup>

The disruption of equipment and pharmacological supply chain, interruption of routine therapies, shortage and rearrangement of staff have also produced an excess in morbidity and mortality related to other diseases. Although consequences of COVID-19 have been devastating also in high-income countries, with a huge impact on hospitals and ICUs, this situation is of substantial concern in places with limited resources. Initial recommendations included postponing elective surgeries as a way of increasing total hospital capacity, in addition of preserving the workforce of

healthcare providers.<sup>1</sup> However, the abrupt cessation of surgeries may have short- and long-term consequences that can be catastrophic, especially for cancer patients. Although most procedures are described as “elective”, these interventions are frequently time-sensitive. With much attention being diverted to COVID-19 management, it is important to be aware of the urgency of treating cancer patients, maintaining oncological and time-sensitive surgery and avoiding treatment delay during the pandemic.

The appropriate time to schedule elective surgery after COVID-19 is unclear. In a multicenter database study, major surgery in the first four weeks after COVID-19 diagnosis was associated with higher risks of postoperative pulmonary complications and sepsis.<sup>22</sup> These findings are consistent with a prior international study that found an increased 30-day mortality rate after surgery performed within seven weeks of COVID-19 diagnosis.<sup>23</sup> Therefore, the decision to schedule elective surgery should consider the severity of COVID-19, the risks of complications, and the risks of delaying surgery.

Of note, the COVID-19 pandemic has exacerbated healthcare disparities and will leave a significant residual impact on the surgical services, highlighting the need to adopt strategies that support the surgical caseload reopening to save lives. In the COVID-19 era, rapid and accurate presurgical testing for SARS-CoV-2 will probably continue to be critical to ensure quality and safety, along with sufficient availability of protective measures for staff and patients.<sup>24</sup>

The ICU mortality during the first pandemic wave ranged from 40% to 85% around the peak of the surge.<sup>25</sup> Nevertheless, those ICU survivors are frequently faced with persisting physical, cognitive and mental impairments, a type of post-intensive care syndrome that may vary in severity and duration. In general, long-COVID-19 is defined as four weeks of persisting symptoms after the acute illness, being estimated to occur in approximately 10% of infected patients.<sup>26</sup> Post-COVID-19 syndrome and chronic COVID-19 are the proposed terms to describe continued symptomatology for more than 12 weeks and its prevalence is still unknown.<sup>26</sup> The symptoms and the clinical manifestations are heterogeneous and suggest multi-organ involvement, including the cardiovascular and respiratory systems. Patients exhibiting COVID-19 sequelae or long-COVID-19 symptoms may require surgical and anesthetic care. The open question for anesthesiologists is what kind of perioperative care is going to be offered, protecting those patients at risk of unexpected events and worse outcomes.

Finally, we may reiterate some of our previous words, stated two years ago:<sup>1</sup> adequate communication and quality of information are still essential throughout the pandemic. COVID-19 will have both short- and long-term consequences on societies, healthcare systems, professionals, and individuals. In this scenario, inaccurate information is quite dangerous and must be fought intensively with solid scientific data, which is constantly changing and advancing. The COVID-19 pandemic should lead to transformative changes in how we provide critical and anesthetic care to our patients. Accordingly, anesthesiologists still display a crucial role to guide the correct management of COVID-19 patients and are challenged to build a better place to live by the end of this pandemic.

## Conflicts of interest

The authors declare no conflicts of interest.

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**ORIGINAL INVESTIGATION**

**Anxiety and burnout in anesthetists and intensive care unit nurses during the COVID-19 pandemic: a cross-sectional study**



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Intensive care unit

**Abstract**

**Background:** This study aimed to measure the levels of anxiety and burnout among healthcare workers, including attending physicians, residents, and nurses in intensive care units during the coronavirus disease 2019 (COVID-19) pandemic.

**Methods:** This is a cross-sectional survey analysis of healthcare workers in our institution. Data were collected on demographic variables, COVID-19 symptoms and test, disease status, anxiety level (assessed by the Beck Anxiety Inventory), and burnout level (measured by the Maslach Burnout Inventory). Subscales of the burnout inventory were evaluated separately.

**Results:** A total of 104 participants completed the survey. Attending physicians, residents, and nurses constituted 25%, 33.7%, and 41.3% of the cohort, respectively. In comparison to untested participants, those tested for COVID-19 had a lower mean age ( $p = 0.02$ ), higher emotional exhaustion and depersonalization scores ( $p = 0.001, 0.004$ , respectively), and lower personal accomplishment scores ( $p = 0.004$ ). Furthermore, moderate to severe anxiety was observed more frequently in tested participants than untested ones ( $p = 0.022$ ). Moderate or severe anxiety was seen in 23.1% of the attending physicians, 54.3% of the residents, and 48.8% of the nurses ( $p = 0.038$ ). Emotional exhaustion, personal accomplishment, and depersonalization scores differed depending on the position of the healthcare workers ( $p = 0.034, 0.001, 0.004$ , respectively).

**Conclusion:** This study revealed higher levels of anxiety and burnout in younger healthcare workers and those tested for COVID-19, which mainly included residents and nurses. The reasons for these observations should be further investigated to protect their mental health.

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## Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first detected in Wuhan, China, in December 2019 and was declared a pandemic by the World Health Organization in March 2020.<sup>1</sup> In Turkey, the first case of COVID-19 was diagnosed on March 10, 2020, and the first case of death due to this disease was reported on March 15, 2020.<sup>2</sup>

The rapidly growing numbers of cases, hospitalizations, and deaths have led to increased anxiety in people during the pandemic. Healthcare workers (HCWs) are one of the most affected groups as they give care to infected people directly.<sup>2</sup> Stress and anxiety disorders in the general population and HCWs were expected to increase during the COVID-19 pandemic,<sup>3-5</sup> as seen before during both the severe acute respiratory syndrome<sup>6,7</sup> and Middle East respiratory syndrome<sup>8</sup> epidemics.

Stress disorders and burnout syndrome (BOS) have been more prevalent among anesthetists<sup>9,10</sup> and intensive care unit (ICU) nurses.<sup>11,12</sup> The huge number of critically ill patients admitted to ICUs during the pandemic has placed a substantial burden on HCWs, the consequences of which have not been studied extensively.

During the pandemic, the ICU of our institution has been operating with 31 beds for patients with COVID-19 and 21 beds for other patients as well as 35 attending physicians (each working 3 night shifts per month) and 35 residents (each doing 8 night shifts per month). The present study aimed to evaluate the levels of anxiety and burnout among attending physicians, residents, and nurses in the ICU of our institution.

## Methods

This is a cross-sectional survey analysis of HCWs – consisting of attending physicians, residents, and nurses – in the tertiary ICUs of our institution. The study was approved by the local ethics committee on July 30, 2020 (No. 1577) and was performed between May 15, 2020, and May 25, 2020 (NCT04604119). All participants gave informed consent to take part in the survey, which was administered electronically.

The survey consisted of 3 distinct sections. In the first section, we asked for demographic information including age, sex, marital status (married vs. others), current position (attending, resident, or nurse), past medical history, and place of residence during the pandemic. Participants were also asked a multiple-choice question about what made them "feel well during the pandemic", with the possible answers being "staying at home", "cooking", "caring for family and children", "working", "caring for patients", "performing routine work", "learning new things", or "searching for information about COVID-19."

There was no systematic screening policy for COVID-19 in HCWs across our country during the pandemic, even if they were in charge of giving care to patients with COVID-19. The test was performed only in case of having symptoms related to COVID-19 or unprotected close contact with a patient with COVID-19. Hence, participants were also required to provide

personal details on the symptoms, test, and status of COVID-19.

The second section of the survey comprised of the validated Turkish version of the Beck Anxiety Inventory (BAI),<sup>13,14</sup> which included 21 questions about the somatic symptoms of anxiety. Participants indicated to what extent they had been bothered by each symptom in the past week by selecting 0 (not at all), 1 (mildly), 2 (moderately), or 3 (severely); thus, the total anxiety score could range between 0 and 63. Participants were categorized as having no or mild anxiety if the total BAI score was 0–16, and moderate to severe anxiety if it was over 16.<sup>15</sup>

In the last section, we used the validated Turkish version of the Maslach Burnout Inventory (MBI) to evaluate BOS components.<sup>16,17</sup> The MBI contains 9 items about emotional exhaustion (EE), 5 items about depersonalization (DP), and 8 items about personal accomplishment (PA), each of which is rated on a 7-point Likert-type scale. Higher scores on the EE and DP subscales and lower scores on the PA subscale imply higher levels of burnout.<sup>18</sup> Unlike the original MBI, the Turkish version has 5-point questions that are scored from 0 to 4. Cronbach's alpha coefficients for EE, PA, and DP were found to be 0.83, 0.67, and 0.72, respectively, in the validation study of the Turkish version of the MBI<sup>19</sup> and 0.904, 0.819, and 0.805, respectively, in our study.

BAI and MBI scores were compared in relation to age, gender, marital status, presence of chronic illness, HCW position, and history of experiencing COVID-19 symptoms, testing for COVID-19, and contracting the disease.

All statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean  $\pm$  standard deviation if distributed normally and as median (interquartile range) if distributed abnormally. Qualitative variables were presented as percentages. Comparison of normally distributed data was performed by the independent samples *t*-test or analysis of variance. Abnormally distributed data were compared with the Mann-Whitney U test or Kruskal-Wallis test, as appropriate. The chi-square test was employed to compare categorical variables. Pearson's correlation coefficient was used for correlation assessment when groups were distributed normally; otherwise, Spearman's correlation analysis was conducted. Differences were considered statistically significant for *p*-values less than 0.05.

## Results

A total of 104 participants completed the survey, of whom 25% (*n* = 26) were attending physicians, 33.7% (*n* = 35) residents, and 41.3% (*n* = 43) nurses (Table 1). The most common activity that made HCWs feel well during the pandemic was staying at home (75.2%), whereas the least common ones were working (8.9%) and searching for information about COVID-19 (8.9%). The total BAI score for the entire cohort was 17.5 (8–25). Moderate to severe anxiety was noticed in 44.2% of all participants. EE, PA, and DP scores were 22 (15–28.7), 23 (17–26), and 6 (3–9), respectively (Table 1).

Parameters in the first section of the survey were compared with the BAI and MBI. History of COVID-19 symptoms was found to be significantly associated with BAI categories (*p* = 0.018), and age was correlated with the EE score (*r* = -

**Table 1** Demographic details and details for COVID-19 related parameters, Beck anxiety inventory, and Maslach burnout inventory for all participants.

Parameter	All cohort
Age (years), median (IQR)	29 (27–36)
Female (%)	70.2
Married (%)	46.2
Chronic disease, positive (%)	11.5
Accommodation during pandemic	
Self-home (%)	90.4
Another home (%)	3.8
The others, e.g., hotel, dormitory (%)	5.8
Position (%)	
Attending physician	25
Resident doctor	33.7
Nurse	41.3
History of COVID-19 symptom, positive (%)	50.0
History of COVID-19 test, positive (%)	71.2
History of COVID-19 disease, positive (%)	7.7
Which activity makes you feel well? (%)	
Staying at home	75.2
Cooking	29.7
Caring for family and children	25.7
Working	8.9
Having attention to inpatients	11.9
Performing routine work	21.8
Learning new things	28.7
Searching for COVID-19	8.9
Beck anxiety inventory (%)	
No or mild anxiety	55.8
Moderate to severe anxiety	44.2
Maslach burnout inventory	
Emotional exhaustion, median (IQR)	22 (15–28.7)
Personal accomplishment, median (IQR)	23 (17–26)
Depersonalization, median (IQR)	6 (3–9)

COVID-19: Coronavirus disease 2019, IQR: interquartile range.

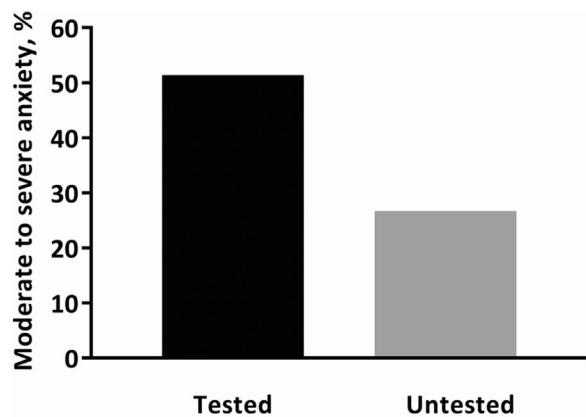
0.197,  $p = 0.045$ ). The DP score was 5 (2–8) in married HCWs and 7 (4.2–10) in others ( $p = 0.021$ ). HCWs with a COVID-19 history had a DP score of 9 (8.2–10.7), whereas it was 6 (3–9) in those without a COVID-19 history ( $p = 0.037$ ).

COVID-19 test status and position of the HCWs were caused significant differences in Beck anxiety categories and all subscales of MBI. They are separately given below.

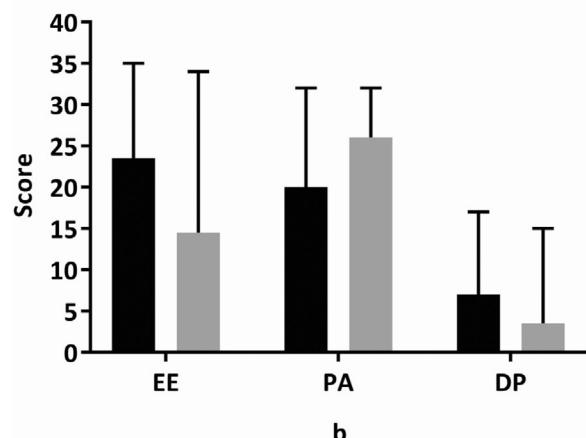
Overall, 71.2% of the cohort reported having tested for COVID-19. Demographic variables were compared between tested and untested HCWs (Table 2). The median age of tested HCWs was 28 (27–31) years, while untested HCWs had a median age of 35 (27–43) ( $p = 0.02$ ). COVID-19 symptoms were observed in 58.1% and 30% of the tested and untested participants, respectively ( $p = 0.009$ ).

Moderate to severe anxiety was present in 51.4% of the tested participants and 26.7% of untested ones ( $p = 0.022$ ; Fig. 1a).

Tested HCWs had an EE score of 23.5 (17–29), while this score was 14.5 (11–26.7) in untested ones ( $p = 0.001$ ; Fig. 1b). The PA score was 20 (17–26) in the tested group and 26 (22.5–28) in the untested group ( $p = 0.004$ ). DP scores



a



b

**Figure 1** Comparison of healthcare workers' COVID-19 test history with moderate to severe anxiety frequency ( $p = 0.022$ ) (Fig. 1a) and emotional exhaustion ( $p = 0.001$ ), personal accomplishment ( $p = 0.004$ ), depersonalization ( $p = 0.004$ ) scores (Fig. 1b). DP, depersonalization; EE, emotional exhaustion; PA, personal accomplishment. The black bar represents for healthcare workers with COVID-19 test history and gray bar represents for healthcare workers without it.

in the tested and untested groups were 7 (3–10) and 3.5 (0.75–7), respectively ( $p = 0.004$ ).

Attending physicians had a median age of 43 (39–49) years; residents, 29 (28–31) years; and nurses, 27 (25–28) years ( $p = 0.000$ ; Table 3). When binary comparisons were performed, the median ages were statistically different between attending physicians and nurses, attending physicians and residents, and residents and nurses ( $p = 0.000$  for all; Table 4). Attending physicians had a higher marriage rate (84.6%) than residents (37.1%,  $p = 0.000$ ) and nurses (30.2%,  $p = 0.000$ ).

Among residents, 97.1% reported having undergone a COVID-19 test, which was significantly greater than the test exposure rate among attending physicians (42.3%,  $p = 0.004$ ) and nurses (67.4%,  $p = 0.001$ ). Although reported in none of the attending physicians, COVID-19 was diagnosed in 20% of the residents and 2.3% of the nurses

**Table 2** Comparison of various parameters with status of COVID-19 test history.

Parameter	Status of COVID-19 test history		
	Yes	No	P
Age (years), median (IQR)	28 (27-31)	35 (27-43)	0.02
Female (%)	73	63.3	0.330
Married (%)	41.9	56.7	0.171
Chronic disease, positive (%)	10.8	13.3	0.715
Accommodation during pandemic (%)			0.432
Self-home	89.2	93.3	
Another home	5.4	-	
The others, e.g., hotel, dormitory	5.4	6.7	
History of COVID-19 symptom, positive (%)	58.1	30	0.009
Position (%)			0.000
Attending physician	14.9	50	
Resident doctor	45.9	3.3	
Nurse	39.2	46.7	

COVID-19, Coronavirus disease 2019; IQR, interquartile range.

**Table 3** Comparison of various parameters with position of the healthcare worker.

Parameter	Position			
	Attending physician	Resident	Nurse	P
Age (years), median (IQR)	43 (39-49)	29 (28-31)	27 (25-28)	0.000
Female (%)	73.1	65.7	72.1	0.774
Married (%)	84.6	37.1	30.2	0.000
Chronic disease, positive (%)	3.8	11.4	16.3	0.293
Accommodation during pandemic (%)				0.029
Self-home	100	82.9	90.7	
Another home	-	11.4	-	
The others, e.g. hotel, dormitory	-	5.4	9.3	
History of COVID-19 symptom, positive (%)	42.3	54.3	51.2	0.639
History of COVID-19 test, positive (%)	42.3	97.1	67.4	0.000
History of COVID-19 disease, positive (%)	-	20	2.3	0.003

COVID-19, Coronavirus disease 2019; IQR, interquartile range.

**Table 4** Binary comparison of healthcare worker's position with age, marital status, accommodation, COVID-19 test and disease history.

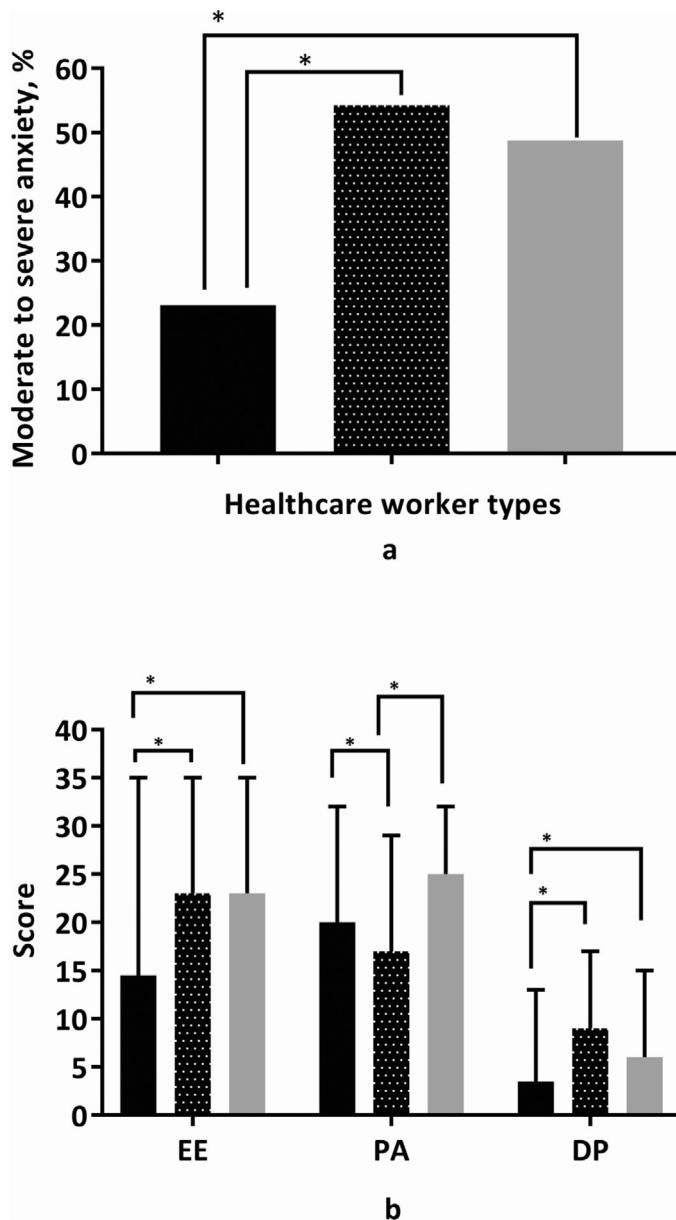
Parameter	Attending physician-resident	Attending physician-nurse	Resident-Nurse
Age (p)	0.000	0.000	0.000
Marital status (p)	0.000	0.000	0.520
Accommodation during pandemic (p)	0.084	0.109	0.068
History of COVID-19 test (p)	0.000	0.04	0.001
History of COVID-19 disease (p)	0.015	0.433	0.01

COVID-19, Coronavirus disease 2019.

( $p = 0.003$ ). The disease was more prevalent in residents than attending physicians and nurses ( $p = 0.015$  and 0.01, respectively).

Moderate or severe anxiety was seen in 23.1% of the attending physicians, 54.3% of the residents, and 48.8% of the nurses ( $p = 0.038$ ; Fig. 2a). A smaller proportion of attending physicians had moderate or severe anxiety compared to residents ( $p = 0.014$ ) and nurses ( $p = 0.034$ ).

The distributions of EE, PA, DP scores were significantly different among HCWs ( $p = 0.023$ , 0.000, and 0.000, respectively; Fig. 2b). Residents and nurses had almost the same EE scores ( $p = 0.872$ ), both of which turned out to be higher than that for attending physicians ( $p = 0.007$  and 0.003, respectively; Fig. 2b). The PA score for residents was lower than that for attending physicians ( $p = 0.039$ ) and nurses ( $p = 0.000$ ). Attending physicians and nurses had a signifi-



**Figure 2** Comparison of healthcare workers' position with moderate to severe anxiety frequency ( $p = 0.038$ ) (Fig. 2a) and emotional exhaustion ( $p = 0.023$ ), personal accomplishment ( $p = 0.000$ ), depersonalization ( $p = 0.000$ ) scores (Fig. 2b). DP, depersonalization; EE, emotional exhaustion; PA, personal accomplishment.

The black bar represents for attending physicians, dotted bar represents for resident doctors and gray bar represents for nurses.

\* $p$ -value is less than 0.05.

cantly lower DP score compared to residents ( $p = 0.000$  and  $0.006$ , respectively).

## Discussion

This study evaluated anxiety and burnout among HCWs working in the ICU during the COVID-19 pandemic. COVID-19 test status and HCW position were identified as factors affecting both of the aforementioned parameters.

Tested HCWs were younger than untested ones. This can be attributed to the low test exposure rate among attending physicians, who were older than residents and nurses.

The position of tested HCWs was different from that of untested ones. While residents were the most frequently tested HCWs, attending physicians represented the least frequently tested ones.

This study was conducted in the tertiary ICU of a teaching hospital, where services such as invasive procedures, daily physical examinations, and patient care were mostly offered by residents under the supervision of attending physicians. Nurses performed their routine nursing tasks and helped residents when necessary. Therefore, residents and nurses inevitably had more contact with patients with COVID-19 than did attending physicians, thus needing to undergo

more frequent COVID-19 tests. The majority of the residents tested for COVID-19 even though only approximately half of them reported COVID-19 symptoms, which suggests that residents had more unprotected close contact with patients with COVID-19. This probably explains why COVID-19 was most frequently observed in residents. Another reason for this finding might be the fact that procedures with a high risk of SARS-CoV-2 transmission (e.g., endotracheal intubation) were more often performed by residents, as shown by El-Boghdadly et al.<sup>20</sup>

Lee et al., who used the Hospital Anxiety and Depression Scale, found that 30.7% of HCWs (including anesthetists and ICU nurses) experienced at least moderate anxiety during the COVID-19 pandemic.<sup>21</sup> Que et al. measured anxiety level during this pandemic by the Generalized Anxiety Disorder Scale and found moderate to severe anxiety in 11.98% of physicians, 8.98% of residents, and 14.9% of nurses.<sup>22</sup> These proportions are lower than those observed in our study, which might be due to the scale used, differences in the target population, and national and local precautions taken to control the pandemic and improve mental health of HCWs. Our findings showed that tested HCWs were more anxious, probably due to the fear of becoming infected. Residents and nurses had the same level of anxiety and were more anxious than attending physicians, which is attributable to increased close contact with patients with COVID-19.

There are multiple ways to define BOS. Despite various definitions,<sup>18</sup> the use of cut-off values for subscales has not been advised since 2016.<sup>23</sup> Moreover, the Turkish MBI has not been evaluated in terms of cut-off values, and due to the difference in the number of possible responses to each question (i.e., 5 instead of 7), it would not be right to use categorization methods practiced for 7-point questions. These reasons prevented us from comparing our results head-to-head with those of similar studies from other countries. Notwithstanding this limitation, we acquired valuable information regarding BOS.

Anesthesia department and ICUs were places known with high BOS frequency both for anesthetists<sup>9</sup> and nurses.<sup>11</sup> In our study, attending physicians were found to be the least affected group with regard to the DP subscale, and residents were the worst group in the EE, PA, and DP subscales. The reason for this finding could be related to factors already known before the pandemic. Chiron et al. investigated BOS in 193 anesthetists in France and reported that the incidence of high EE decreased with age.<sup>24</sup> Vargas et al. demonstrated that working in the ICU and being younger than 40 years old were independent risk factors for BOS in an Italian cohort.<sup>25</sup> Additionally, Nysse et al. showed that BOS was more prevalent among younger doctors.<sup>9</sup> In our study, residents were the youngest group of HCWs, which may be one of the underlying causes of poor MBI scores in this group. With the increase of age, attending physicians may have learned to cope well with stress. Residents might have been unsupervised or empowered inadequately by their seniors, therefore failing to develop the ability to cope with stressful conditions. Besides, the inequality in the number of night shifts per month between residents and attending physicians might have contributed to this finding. The pandemic itself might also have given rise to some concerns such as fear of getting infected and dying, undefined quarantine length, excessive workload, inadequate protective personal equipment, and

fear of exclusion.<sup>3,26</sup> Residents had longer close contact with patients with COVID-19, performed most of the invasive procedures themselves, were more frequently affected by the disease, and underwent more COVID-19 tests. It could be speculated that these factors, too, accounted for the poor MBI scores in residents.

COVID-19 has affected people all over the world, so many countries have taken national and local actions to protect mental health of HCWs.<sup>26-28</sup> The Turkish Ministry of Health has developed a mobile application for HCWs to use during the pandemic.<sup>29</sup> However, it was downloaded only more than a thousand times until October 17, which seems quite infrequently given the number of HCWs in Turkey (over 1 million). Reduced workload has been shown to serve as the most important factor in reducing BOS,<sup>10</sup> so additional measures should be taken to lighten the workload for HCWs, especially residents. There are many other possible steps to improve their mental health without interrupting their education process.<sup>30,31</sup>

There are some limitations to the current study. Demographics and other variables were not detailed to limit the time required to fill the survey for a better participation rate. Furthermore, total weekly working hours were not separately calculated for different HCW groups, which might be less in attending physicians and more in the other groups due to the presence of more attending physicians and fewer residents in our institution.

## Conclusion

The present study indicated that younger HCWs, especially residents and nurses, who work in ICUs during the COVID-19 pandemic should be further supported and encouraged physically and mentally. Moreover, working conditions of residents – including the number of night shifts and scope of their responsibilities – should be revised. This could diminish the incidence of post-traumatic stress disorder likely to occur as a result of the pandemic.

## Conflict of interest

The authors declare no conflicts of interest.

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**ORIGINAL INVESTIGATION**

**Risk factors for SARS-CoV-2 infection and epidemiological profile of Brazilian anesthesiologists during the COVID-19 pandemic: cross-sectional study**



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**Abstract**

**Introduction:** The devastating effects of COVID-19 have caused economic and health impacts worldwide. Anesthesiologists were one of the key professionals fighting the pandemic and have been highly exposed at their multiple sites of clinical practice. Thus, the importance of determining the nature of the infection in this population that provides care to SARS-CoV-2 patients.

**Method:** We conducted a cross-sectional study administering an online questionnaire to examine the demographic and epidemiological profile of these professionals in Brazil, and to describe the risk factors for viral infection during the pandemic.

**Results:** A total of 1,127 anesthesiologists answered the questionnaire, 55.2% were men, more than 90% with age below 60 years, with infection and reinfection rates of 14.7% and 0.5%, respectively, and 47.2% reported a significant income reduction. The predictors of COVID-19 contamination were practicing in operating rooms ( $OR = 0.42$ ; 95% CI 0.23–0.78), direct contact with infected patients ( $OR = 5.74$ ; 95% CI 3.05–11.57), indirect contact with infected patients ( $OR = 2.43$ ; 95% CI 1.13–5.33), working in a pre-hospital setting ( $OR = 2.36$ ; 95% CI 1.04–5.03), and presence of immunosuppression, except for cancer ( $OR = 4.89$ ; 95% CI 1.16–19.01).

**Conclusion:** COVID-19 had enormous consequences on Brazilian anesthesiologists regarding sociodemographic aspects and contamination rates (5.57 times higher than in the general population). These are alarming and unprecedented findings for this professional group, as they reveal the considerable risk of infection and its independent predictor variables.

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## Introduction

In December 2019, COVID-19, a flu-like illness caused by the SARS-CoV-2 virus, emerged in Wuhan (China) and rapidly circulated worldwide, causing a massive number of infected people and deaths.<sup>1,2</sup>

COVID-19 is highly contagious and predominantly transmitted by droplets. It causes variable degrees of inflammatory response in the respiratory tract of the host, that can be associated with severe morbidity and death in patients with underlying diseases such as Hypertension, Diabetes Mellitus (DM), respiratory disorders, immunosuppression, and age over 60 years.<sup>3</sup>

Since the WHO acknowledged the pandemic on March 11, 2020, several health measures have been adopted by governments, mainly aimed to reduce the transmissibility and the stress on health systems caused by the high number of patients requiring hospital admission, frequently in Intensive Care Units (ICU) for invasive ventilatory support. Brazil was one of the countries most affected by the pandemic, with more than 5 million cases and 155,000 deaths as of October 2020.<sup>4,5</sup>

Anesthesiologists have played a key role in COVID-19 patient care, given their skills in airway management and role in intensive care units.<sup>6</sup> In Brazil, there is a wide-range spectrum of performance of anesthesiologists, from the site where they practice (region of the country, type of sector [operating suite, pre-hospital, intensive care, etc.]), resource availability logistics, public and/or private facility, among others. Anesthesiologists also exhibit great variability in epidemiological profiles (gender, color/ethnicity, age, time since graduation, underlying diseases, etc.). Such features can be related to differences in susceptibility to COVID-19, and the epidemiological mapping and identification of infection risk factors (modifiable or not) are essential components for designing protection strategies for these health professionals, who are highly exposed during a pandemic. It is also worth underlining the extent of the financial, welfare, professional, occupational, and physical and mental health impacts to anesthesiologists, which helped develop action strategies by regional and federal societies of Anesthesiology.<sup>7</sup>

In face of this disturbing scenario, the present study aimed to assess the sociodemographic profile, and determine the prevalence of infection and the risk factors for infection by COVID-19 in the population of anesthesiologists practicing in Brazil.

## Methods

The study was submitted to the Research Ethics Committee of Hospital Israelita Albert Einstein (São Paulo) and after its approval (4.017.866), a cross-sectional observational study was performed following the principles of the Declaration of Helsinki (2013). Between June and July 2020, an electronic questionnaire was sent by e-mail and social media, targeting to reach the population of Brazilian anesthesiologists as widely as possible (absolute number of 25,484 professionals, according to demographic data from the Federal Council of Medicine and University of São Paulo).<sup>8</sup> The analysis included all anesthesiologists who answered the questionnaire and

who consented to the Informed Consent Form and the Confidentiality Term provided digitally.

The questionnaire comprised 23 questions (structured data). Data were collected by non-probabilistic sampling (convenience sampling) during the months of June and July 2020, the most critical moment of the pandemic in Brazil. After this period, collection was discontinued, and we started data analysis. A priori calculation of sampling power was not performed, given the lack of knowledge and inaccuracy of information in the literature on COVID-19 and potential risk factors for infection by SARS-CoV-2.

The identity of study participants was protected, and participants were identified in the database only by sequential numbers for answers in the questionnaire. All data were collected and stored on Google Forms®, protected by password. All questions were compulsory, and participants were not able to complete the questionnaire if there were incomplete answers. All study variables were categorical in order to prevent completion errors due to mistyping or inadvertent insertion of outliers. To deter duplication of participants, the electronic mail (e-mail) was registered at the time the questionnaire was joined, ensuring that each participant answered questions only once, since the software recognized the email registered during access.

The strategy to increase the number of respondents consisted of weekly launching of the survey questionnaire via social media (Facebook®, Instagram®, Whatsapp®, Telegram®) in groups of anesthesiologists and sending it to the email of all anesthesiologists listed in their medical societies, during the study collecting period.

Access to the database was granted only to the statistician and administrative assistant not linked to the study.

The variables studied were: age, sex, ethnicity, time practicing anesthesiology, Brazilian region of practice, type of facility in which the anesthesiologist practiced (public and/or private), percentage of income reduction, infected or not by COVID-19 (we considered infected only participants who reported positive laboratory tests, serological tests or PCR test), symptoms presented, time started treatment after onset of symptoms, requirement of hospital admission and care unit, need and length of leave of absence, criteria used for resuming medical activities, PPE worn (personal protective equipment), PPE type worn, frequency PPE worn, report of care for patients with infection, care site, use of video laryngoscope, presence of difficult tracheal intubation, tracheal intubation failure requiring positive pressure ventilation, presence of reinfection of the anesthesiologist, type of therapeutic drugs received by infected anesthesiologist, occurrence of comorbidities, presence of pregnancy and use of anticoagulant medications.

Given the categorical nature of the study variables, data were described as frequencies and analyzed using the Fisher's exact test. Afterwards, a logistic regression model was performed (logit binding factor, binomial distribution), with the fact of having had or not COVID-19 diagnosed in laboratory (PCR and/or serology) as the dependent variable.

Variables showing  $p < 0.1$  for the association tests were candidates for entry into the regression model. Next, predictors were selected using the forced entry method, based on the likelihood ratio. Variables that caused a decrease in the Akaike Information Criterion (AIC) in their models were progressively separated. Next, the variables selected were time

practicing anesthesiology, region of predominant practice, type of facility where practice was developed, contact with SARS-CoV-2, pre-hospital setting practice, operating suite practice and presence of immunosuppression (except cancer), for building seven more logistic models, based on their individual and sequential addition, in the order mentioned. It became evident in the process that the model that best explained the variance of our data was the one that included all the variables highlighted above, having the lowest possible values of AIC and residual Deviance as criteria.

The Wald test was implemented for coefficients, as well as the respective degrees of freedom. Multicollinearities were verified and discarded (VIF [variance inflation factor], 1/VIF). The statistical significance level adopted was an  $\alpha$  value of 0.05.

For statistics analysis, R, version 4.0.2 was the software used (<https://www.r-project.org>).

## Results

The total number of participants was 1,127 anesthesiologists. The population was predominantly comprised by men (55.2%) and participants under the age of 60 years (90.51%). Monthly income reduction above 40% was reported by 47.2% of participants, a fact that reflects the large reduction in surgical/diagnostic volume during the pandemic, as well as loss of income due to leave of absence for health reasons. In the study population, the prevalence of infection by COVID-19 was 14.7%, from the beginning of the pandemic to the end of data collection. Among the 166 COVID-infected participants, the rate of laboratory-confirmed reinfection was 3.6%, that is, 6 participants.

The main symptoms among infected participants were asthenia (9.3%), dry cough (8.6%), hypo/anosmia (8.4%), myalgia/arthralgia (8.3%), odynophagia (7.4%), rhinorrhea (6.5%), nasal obstruction (6.2%), fever (6%), diarrhea (5.7%), and neurological symptoms such as dizziness, headache, and paresthesia (4.9%).

The medications most used by anesthesiologists during the period of the study were Vitamin D (31.3%), Vitamin C (27.7%), Zinc (22.4%) and Dipyrone (20.5%). The rate of using the drugs widely discussed in the media such as Ivermectin, Azithromycin and Hydroxychloroquine were 13%, 7.5% and 5.8% respectively. Corticosteroids and anticoagulants were used by 4.7% and 2.8%, respectively.

Regarding the criteria used for resuming clinical practice after laboratory-confirmed infection, 69.8% of participants adopted only improvement of symptoms as a parameter, and 30.2% based the decision on laboratory criteria (CRP and/or serology).

**Tables 1 to 5** describe association tests for each variable analyzed regarding SARS-CoV-2 infection with their respective *p*-values.

**Table 1** depicts demographic and clinical data.

**Table 2** describes PPE worn by anesthesiologists. Overall, 28.57% of participants had partial or inadequate availability of PPE, but this did not result in a statistically significant association with COVID-19 infection, or when PPE was assessed separately.

**Table 3** shows the different sites where anesthesiologists practiced during the study period and data related to airway

management. It is noteworthy that 29.1% of the participants had to manage at least one case of difficult airway.

**Table 4** shows which drugs were used by anesthesiologists for the treatment and/or prevention of COVID-19 and whether there was an association with SARS-CoV-2 infection.

**Table 5** reveals the prevalence of comorbidity among participants and the association with COVID-19 infection.

Independent predictors of SARS-CoV-2 infection were obtained by a logistic regression model and listed in **Table 6**.

## Discussion

To our knowledge, this is the first study designed to detect risk factors for SARS-CoV-2 infection specifically in a population of anesthesiologists nationwide.<sup>8</sup> The prospecting and analysis of these data offer a relevant contribution to the understanding of this serious health issue in this specialty, particularly exposed to infection and with a highly active role in the pandemic nationwide.

Anesthesiologists were often the specialists chosen to perform Orotracheal Intubation (OTI) in patients with COVID-19 due to their airway management skills, thus explaining the high viral contamination observed. Despite the overall infection rate of 2.64%<sup>4</sup> in the Brazilian population, the prevalence of coronavirus infection in the participants of the present study was 5.57 times higher, that is 14.7%, and it reflects the high exposure and risk of infection among anesthesiologists.<sup>4</sup>

El-Boghdady et al. reported similar results and reported a 10.7% infection rate when they assessed the risk of infection among healthcare professionals after participating in OTI of patients infected with the virus.<sup>9</sup> In the United States, Morcuende et al. performed an analogous study administering a questionnaire via e-mail. They reported an incidence of symptoms of 26.2% in anesthesiologists and intensivists after occupational exposure to the virus. The high incidence reported can be explained by the design of their study, which assessed the presence of symptoms and not only cases confirmed by serology and/or PCR.<sup>10</sup> A Canadian study published in April 2020 identified anesthesiology as one of the specialties in which most doctors died from COVID-19.<sup>11</sup> However, to date, mortality data for anesthesiologists are still scarce.<sup>1,10,12-14</sup>

Among our study participants who had SARS-CoV-2 infection, we reported the rate of reinfection confirmed by laboratory tests of 3.6% (6 participants), an observation that has already been reported in the literature and that has raised concerns of health authorities worldwide.<sup>15</sup>

No sociodemographic variables analyzed in our regression model proved to be independent predictors for risk of infection by COVID-19. Similarly, Leeds et al. were not able to associate parameters such as gender, age, and ethnicity with an increased risk of developing COVID-19.<sup>16</sup>

The fact that more than 25% of respondents did not have access to full PPE reflects heterogeneity of protocols and budgets among different services and geographic regions, or even individual/institutional negligence during the pandemic. Paradoxically, there was no association between low adherence to full PPE and contamination by SARS-CoV-2. This can be explained perhaps by the lower incidence of contact with infected patients in the group of anesthesiologists with

**Table 1** Demographic and clinical characteristics.

	SARS-CoV-2 infected subjects, n (%)	SARS-CoV-2 not-infected subjects, n (%)	p <sup>a</sup>
<b>Age in years</b>	166 (14.7)	961 (85.3)	
20 to 29	16 (9.6)	80 (8.3)	0.55
30 to 39	70 (42.1)	344 (35.8)	0.12
40 to 49	41 (24.7)	243 (25.3)	0.92
50 to 59	26 (15.8)	200 (20.8)	0.14
60 to 69	13 (7.8)	80 (8.3)	1
70 and +	0 (0)	14 (1.5)	0.24
<b>Sex</b>			
Female <sup>b</sup>	79 (47.6)	426 (44.3)	0.45
Male	87 (52.4)	535 (55.7)	
<b>Color/Ethnicity</b>			
Yellow	5 (3.0)	52 (5.5)	0.25
White	131 (78.9)	731 (76.0)	0.49
Black	2 (1.2)	20 (2.1)	0.76
Brown	28 (16.9)	158 (16.4)	0.91
<b>Time practicing anesthesiology</b>			
M.E.	12 (7.2)	60 (6.2)	0.6
≤5 years	51 (30.7)	192 (20.0)	0.003
6 to 10 years	22 (13.3)	156 (16.2)	0.36
11 to 15 years	11 (6.6)	140 (14.6)	0.004
16 to 20 years	25 (15.1)	95 (9.9)	0.06
≥21 years	45 (27.1)	318 (33.1)	0.12
<b>Predominant region of practice</b>			
North	5 (3.0)	26 (2.7)	0.8
Northeast	40 (24.1)	156 (16.3)	<0.01
Center-West	11 (6.6)	79 (8.2)	0.8
South	9 (5.5)	143 (14.9)	<0.001
Southeast	101 (60.8)	557 (57.9)	0.49
<b>Type of facility</b>			
Public	26 (15.7)	92 (9.6)	0.02
Private	28 (16.8)	277 (28.8)	0.001
Public & private	112 (67.5)	592 (61.6)	0.01
<b>Income reduction</b>			
No reduction	31 (18.7)	122 (12.7)	0.01
≤20%	19 (11.4)	98 (10.2)	0.48
21% to 30%	29 (17.5)	123 (12.8)	0.11
31% to 40%	20 (12.0)	153 (15.9)	0.24
41% to 50%	36 (21.7)	176 (18.4)	0.33
≥50%	31 (18.7)	289 (30.0)	0.002
<b>Level of care</b>			
Home	160 (96.4)	957 (99.5)	0.001
Ward	1 (0.6)	3 (0.3)	0.47
High-dependence unit	1 (0.6)	1 (0.2)	0.27
ICU	4 (2.4)	0 (0)	<0.001
<b>Oxygen therapy</b>			
Not required	162 (97.6)	961 (100)	< 0.001
Nasal cannula	1 (0.6)	0 (0)	0.15
TI/CMV	3 (1.8)	0 (0)	0.003
<b>Leave from work</b>			
No	23 (13.9)	883 (91.9)	<0.001
≤7 days	11 (6.6)	21 (2.2)	0.004
8 to 14 days	80 (48.2)	18 (1.9)	<0.001
15 to 21 days	40 (24.1)	4 (0.4)	<0.001

Table 1 (Continued)

	SARS-CoV-2 infected subjects, n (%)	SARS-CoV-2 not-infected subjects, n (%)	p <sup>a</sup>
≥21 days	12 (7.2)	35 (3.6)	<0.001
<b>SARS-CoV-2 contact</b>			
None	18 (10.8)	262 (27.3)	<0.001
Indirect	20 (12.0)	163 (17.0)	0.1318
Direct	128 (77.2)	536 (55.7)	<0.001
Red blood cell concentrate	6 (3.6)	7 (0.7)	0.006
Pregnancy	2 ((10)	77 (18.8)	0.75

M.E., Physicians under specialization; PPE, Personal Protection Equipment; TI/VMV, Tracheal Intubation/controlled Mechanical Ventilation; ICU, Intensive Care Unit.

<sup>a</sup> Fisher's exact test.

<sup>b</sup> Reference category.

Table 2 PPE.

	SARS-CoV-2 infected subjects n (%)	SARS-CoV-2 not-infected subjects n (%)	p <sup>a</sup>
<b>PPE Availability</b>	166 (14.7)	961 (85.3)	
Yes	123 (74.0)	682 (70.9)	0.75
No	5 (3.0)	20 (2.1)	0.39
Partially	38 (22.3)	259 (26.7)	0.29
<b>Protection offered by PPE (perception)</b>			
Very little	14 (8.4)	35 (3.6)	0.01
Little	17 (10.2)	114 (11.8)	0.6
Satisfactory	106 (63.8)	619 (64.4)	0.9
Very satisfactory	29 (17.4)	193 (20.1)	0.08
<b>Protection offered by PPE (quantity)</b>			
Very few	15 (9.0)	43 (4.5)	0.02
Few	27 (16.3)	150 (15.6)	0.73
Satisfactory	92 (55.4)	573 (59.6)	0.34
Very satisfactory	32 (19.3)	195 (20.3)	0.03
<b>PPE frequency</b>			
Did not wear	2 (1.2)	19 (1.9)	0.75
SARS-CoV-2 positive	8 (4.8)	28 (2.9)	0.22
SARS-CoV-2 positive and suspected cases	69 (41.5)	312 (32.4)	0.02
All cases	87 (52.4)	602 (62.6)	0.01
<b>Reasons for not wearing PPE</b>			
Unavailable	18 (10.8)	95 (9.9)	0.67
Negligence	10 (6.0)	53 (5.5)	0.71
Negligence and unavailable	118 (71.0)	671 (69.8)	0.78
PPE always worn	20 (12.0)	142 (14.8)	0.4
Acrylic tent	94 (56.6)	588 (61.2)	0.3
Gloves	165 (99.4)	950 (98.8)	1
<b>Waterproof apron</b>	164 (98.8)	931 (96.8)	0.21
<b>Acrylic protection goggles</b>	162 (97.6)	939 (97.7)	0.78
<b>N95/PFF2/PFF3 Masks</b>	165 (99.4)	949 (98.7)	0.7
<b>Surgical mask</b>	157 (94.6)	924 (96.1)	0.39
<b>Cap</b>	164 (98.8)	942 (98.0)	0.75
<b>Face Shield</b>	165 (99.4)	942 (98.0)	0.34

PPE, Personal Protection Equipment.

<sup>a</sup> Fisher's exact test.

less availability of protection resources. However, such a hypothetical explanation and cannot be verified by our data. Also, the absence of association between different types of PPE and COVID-19 can be understood by the complex and multifactorial nature of viral transmission. Thus, we could

have variables not evaluated by our study design that would explain this finding.

Practicing in the operating room seems to be a protective activity regarding the risk of acquiring the disease. This finding can be explained by the adoption of protocols of

**Table 3** Anesthesiologists' sites of practice and airway management.

	SARS-CoV-2 infected subjects, n (%)	SARS-CoV-2 not-infected subjects, n (%)	p <sup>a</sup>
Outpatient clinic	166 (14.7)	961 (85.3)	
Field hospital	5 (3.0)	28 (2.9)	1
PHC	15 (9.0)	28 (2.9)	0.001
Endoscopy	10 (6.0)	9 (0.9)	< 0.001
Other imaging sectors	45 (27.1)	166 (17.3)	0.003
ER	71 (42.7)	262 (27.3)	< 0.001
ICU	25 (15.0)	111 (11.5)	0.19
Surgical Suite	78 (46.9)	291 (30.3)	< 0.001
Video laryngoscope	129 (77.7)	619 (64.4)	< 0.001
All cases	38 (22.9)	248 (25.8)	0.49
Only for SARS-CoV-2	17 (10.2)	128 (13.3)	0.31
Not used	111 (66.8)	585 (60.8)	0.16
Difficult airways	66 (39.7)	262 (27.2)	0.001
TI failure + manual ventilation	19 (11.4)	80 (8.3)	0.18

ICU, Intensive Care Unit; PHC, Prehospital Care; TI, Tracheal Intubation.

<sup>a</sup> Fisher's exact test.**Table 4** Drugs administered (most common used drugs for SARS-CoV-2 treatment).

	SARS-CoV-2 infected subjects, n (%)	SARS-CoV-2 not-infected subjects, n (%)	p <sup>a</sup>
	<b>166 (14.7)</b>	<b>961 (85.3)</b>	
<b>Anticoagulants</b>			
Prophylactic <sup>b</sup>	7 (4.2)	10 (1.0)	0.01
Therapeutic	6 (3.6)	8 (0.8)	
BCG	4 (2.4)	3 (0.3)	0.01
Sarilumab	3 (1.8)	0 (0)	0.003
Tocilizumab	6 (3.6)	0 (0)	0.001
Favipiravir	3 (1.8)	0 (0)	0.003
Interferon- $\alpha$ -2B	5 (3.0)	0 (0)	0.001
Remdesivir	5 (3.0)	0 (0)	0.001
Convalescence plasma therapy	6 (3.6)	0 (0)	0.001
Lopinavir/Ritonavir	4 (2.4)	1 (0.1)	0.002
Vitamin C	62 (37.3)	249 (25.9)	0.003
Vitamin D	6 (3.6)	86 (8.9)	0.02
Zinc	51 (30.7)	201 (20.9)	0.006
Azithromycin	60 (36.1)	37 (3.8)	0.001
Other antibiotics	14 (8.4)	16 (1.6)	0.001
Ivermectin	33 (19.8)	112 (11.6)	0.005
Hydroxychloroquine	32 (19.3)	27 (2.8)	0.001
Chloroquine	2 (1.2)	1 (0.1)	0.058
Corticoids	27 (16.3)	26 (2.7)	0.001
Oseltamivir	10 (6.0)	6 (0.6)	0.001
Non-steroid anti-inflammatory drugs	21 (12.7)	63 (6.5)	0.009
Dipyrrone	101 (43.9)	129 (56.1)	0.001
Paracetamol	37 (60.8)	46 (4.8)	0.001

BCG, Calmette-Guérin vaccine.

<sup>a</sup> Fisher's exact test.<sup>b</sup> Reference category.

temporary deferment of elective surgeries and testing of patients who had to undergo subsequent elective surgeries,<sup>7</sup> and due to the segregated flow of care for SARS-CoV2 infected patients. Such measures may have ensured a safer environment in relation to virus transmission in the operating room.

Conversely, our study shows that working in Prehospital Care (PHC) was associated with a greater chance of infection among professionals, with OR = 2.36. The prehospital setting is a challenging place for the health professional. Equipment is generally less available, and patients often present in severe clinical status, either due to clinical or trauma condi-

**Table 5** Comorbidities.

	SARS-CoV-2 infected subjects, n (%)	SARS-CoV-2 not-infected subjects, n (%)	p <sup>a</sup>
Hypertension	166 (14.7)	961 (85.3)	
Diabetes mellitus	25 (15.0)	146 (15.2)	1
Cardiopathies	12 (7.2)	39 (4.0)	0.1
Dyslipidemia	11 (6.6)	34 (3.5)	0.08
Obesity (BMI > 30)	22 (13.2)	88 (9.2)	0.11
Asthma	21 (12.6)	87 (9.1)	0.15
COPD	5 (3.0)	98 (10.2)	0.33
CRF	6 (3.6)	4 (0.4)	0.004
Cancer	0 (0)	2 (0.2)	< 0.001
Immunosuppression (except for cancer)	9 (0.9)	3 (0.3)	< 0.001
Chronic alcohol consumption	6 (3.6)	7 (0.7)	0.006
Smoking	7 (4.2)	32 (3.3)	0.49
No comorbidity	103 (62.0)	579 (60.2)	0.73

BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CRF, Chronic Renal Failure.

<sup>a</sup> Fisher's exact test.

**Table 6** Predictors of SARS-CoV-2 infection, according to the logistic regression model.

	B (SE)	OR	95% CI	p
Intercept	-2.4 (0.58)	0.1	(0.02–0.27)	< 0.001
Surgical suite practice	-0.86 (0.31)	0.4	(0.23–0.78)	< 0.01
Direct contact with infected patients	1.74 (0.34)	5.74	(3.05–11.57)	< 0.001
Indirect contact with infected patients	0.88 (0.39)	2.43	(1.13–5.33)	< 0.05
Practicing with APH	0.86 (0.39)	2.36	(1.04–5.03)	< 0.05
Immunosuppressed (except for cancer)	1.58 (0.69)	4.89	(1.16–19.01)	< 0.05

Observations: R<sup>2</sup> 0.095 (Hosmer-Lemeshow), 0.075 (Cox-Snell), 0.133 (Nagelkerke);  $\chi^2(16) = 87.38$ .

B, Regression Coefficient; SE, Standard Error; OR, Odds Ratio; 95% CI, 95% Confidence Interval (lower limit – upper limit).

tions, requiring vital-sign stabilization with few resources, and under time pressure for definitive treatment.<sup>17,18</sup> We assume that anesthesiologists submitted to this clinical setting may have been highly exposed to the virus, and were wearing less protection. Another possible factor associated with this finding would be the scarce availability of COVID-19 tests and absence of precaution/knowledge of participants regarding the disease at the time data were collected, compared to later in the pandemic.

Both direct and indirect contact with patients known to be infected increased the chance of anesthesiologists acquiring the disease by nearly 5.7 and 2.4 times, respectively. Our findings are supported by a cohort study carried out in the United States and United Kingdom that revealed that health professionals working on the front line reported higher rates of infection when compared to the general population.<sup>12</sup> An interesting finding was the high risk of infection observed in professionals that reported only indirect contact. This fact reveals that the presence of the virus in theoretically safe environments can represent an important infection factor.

Immunosuppression (apart from cancer) was the only comorbidity reported as risk predictor for virus infection. Although several comorbidities such as diabetes, hypertension and obesity are mentioned in the literature as risk

factors for worse outcome in patients who develop the disease,<sup>3,19,20</sup> there are scarce data about which characteristics make patients more susceptible to the virus infection. Therefore, further prospective studies are required to address this issue.

Due to the inaccuracy of information on the purpose of prophylactic and/or therapeutic use of drugs (Table 5), their time of use, dosage, and the empiricism of their use, we considered it prudent to exclude these variables from the regression model, even with a  $p < 0.1$ . Thus, disclosing biased and inaccurate results was avoided, limiting ourselves exclusively to report descriptive data and the association with COVID-19 infection.

Further examination of our study enabled us to perceive the reduced use of corticosteroids (4.7%), that is one of the few classes of drugs with recently proven efficacy in the treatment of COVID-19.<sup>21,22</sup> Anticoagulants, also widely used to support infected patients,<sup>23</sup> had only a 2.75% use.

Studies show that the prevalence of difficult airway in emergency patients ranges from 9% to 12%.<sup>24–27</sup> Considering that anesthesiologists are professionals trained in airway management, it is surprising that 29.1% of participants reported at least one case of difficult airway. Some hypotheses can be pondered to justify this finding: OTI

performed outside the operating room (an environment where anesthesiologists feel less at ease); stress imposed by the pandemic; fear of contamination; urgency and patient severity. These factors would create a more adverse and stressful scenario for airway management, which could lead even the most trained professionals to neglect basic steps of OTI optimization, increasing the challenge of the procedure.

Concerning the limitations of the study, one can name the observational cross-sectional design, which would prevent the control of many variables, including the unobservable ones. Another issue related to the timing of our study is the possibility of contamination by SARS-CoV-2 after answering the questionnaire. Also on this topic, there is a limitation in the diagnosis of new cases of COVID-19, a fact that may have underestimated the incidence of the condition in our sample, as well as the rates of reinfection.

We also underscore that our results are exploratory in nature, devoid of sufficiently robust inference for causality, when compared to controlled and randomized clinical trials.

Another limiting issue was classifying data into categories. This fact can lead to loss of information in the collection and analysis process, despite increasing respondent participation by simplifying the questionnaire and avoiding outliers or typing errors while filling out answers.

## Conclusion

Our findings demonstrate a particular epidemiological profile in the population of anesthesiologists during the COVID-19 pandemic. They also reveal several points of potential care and occupational improvement, in addition to generating future hypotheses, especially in terms of exposure and protection of these professionals, considering the potential risk factors for SARS-CoV-2 infection.

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## Conflicts of interest

The authors declare no conflicts of interest.

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**ORIGINAL INVESTIGATION**

**Use of simulation to teach in the operating room – Don't let the COVID-19 pandemic interrupt education: an observational clinical trial**



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**KEYWORDS**

COVID-19 pandemic;  
Simulation training;  
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**Abstract**

**Background:** Simulation-based education has become the most important part of resident training in anesthesiology, especially during the pandemic. It allows learning the skills and the management of different situations without putting residents in risk of contamination, considering COVID-19 is highly contagious. The hypothesis was that simulation is still associated with improvement of knowledge acquisitions despite the context of the COVID-19 pandemic.

**Methods:** Residents of anesthesiology and intensive care subjected to an anaphylaxis simulation scenario. Their knowledge levels were assessed by true/false questions before and one month after the simulation session. The STAI test was used to measure anxiety levels before and after the scenario. Data were analyzed statistically using Wilcoxon and McNemar tests.

**Results:** Junior residents (< 2 years) received significantly higher scores in post-training theoretical tests compared to their pre-training scores ( $79.2 \pm 9.6$ ,  $84.5 \pm 8.2$ ,  $p = 0.002$ ,  $n = 21$ ). There was no difference between pre- and post-test scores of seniors ( $80.2 \pm 9$ ,  $81.8 \pm 10.4$ ,  $p = 0.3$ ). Pre- and post-anxiety inventory scores were nearly the same and both were in the moderate group ( $39.8 \pm 10.1$ ,  $39.3 \pm 12.1$ ,  $p = 0.8$ ).

**Conclusion:** Simulation-based education improved the knowledge levels of the residents without raising anxiety levels. Thus, simulation-based training showed its value as an important tool of education during the pandemic, which needs to be further popularized for training at all institutions. Enlightening medical educators about this accomplished teaching method may lead to improved quality of medical education in developing countries and reshape how tomorrow's doctors are trained during pandemics.

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## Introduction

During the COVID-19 pandemic, continuation of medical education programs has been interrupted because of restrictions, thus simulation training method was introduced for education and Anesthesiologists must manage different types of emergencies. In an emergency, it is essential to make a quick decision and to perform interventions at a proper time. Using all the knowledge and skills which were gained during the residency, requires practice. Through technological development and high-fidelity mannequins, residents have the opportunity to learn the skills and the management of different kinds of emergencies before facing them in real patients.<sup>1,2</sup>

Anaphylaxis is one of the rare but fatal emergencies. However, it is documented that after life-threatening allergic reactions morbidity is common and management of this emergency needs to be improved.<sup>3</sup>

University of Lyon is a highly experienced center for simulation training, it held master-class courses for instructors. As Ankara University educators, we attended one of these courses. We used an anaphylaxis scenario for in-situ simulation training in the operating room. The primary goal of this study was to evaluate the difference between the pre- and post-simulation knowledge test scores to evaluate the effectiveness of simulation training. The secondary goal was to examine whether it creates any anxiety on participants.

## Methods

### Subjects

This prospective, observational, single-center study was approved by the Ethics Committee of the Ankara University School of Medicine (Serial number: I4-166-19). After informed consent, 42 residents of the Department of Anesthesiology and Intensive Care were included in the study, without taking into consideration their training levels. Two of them did not want to participate in the study. Forty residents were randomly divided into seven groups of 5 or 6 residents in each group. The information on the seniority of residents, pre-test and post-test scores, and anxiety levels by the state-trait anxiety inventory before the session were collected.

### Study design

Before the simulation session, all subjects undertook a pre-test, including 20 theoretical true/false questions, assessing their basic knowledge about anaphylaxis mechanism and treatment strategies. The total score was 100, with 5 points for each question. Besides, subjects' anxiety levels were assessed by the State-Trait Anxiety Inventory (STAI).<sup>4</sup> STAI consists of two 20-item scales for measuring the intensity of anxiety as an emotional state (S-Anxiety) and individual differences in anxiety proneness as a personality trait (T-Anxiety). STAI scores are classified as "no or low anxiety" (20–37), "moderate anxiety" (38–44), and "high anxiety" (45–80).<sup>5</sup>

Following this, based on their randomization, all subjects received a short scenario about anaphylaxis in the operating room (Supplemental file-1) using the Resusci Anne mannequin

(Laerdal Medical, Stavanger, Norway). In-situ simulations were limited to 15-min duration, followed by a 30-min standardized debriefing to review technical skills, non-technical skills, and knowledge gaps. After the simulation training, residents were requested to complete STAI again.

Finally, they were requested to stop reading about anaphylaxis until they were assessed with a post-test, one month after the session with the same questions.

## Statistics

Descriptive statistics for the categorical and continuous data were given as frequency (percentage) and median (minimum-maximum), respectively. Changes in the correct answer percentage regarding each question were evaluated using the McNemar test, and pre-post differences in the total score were compared with the Wilcoxon Signed Rank Test. All statistical analyses were performed with Statistical Package for Social Sciences (SPSS Version 15.0, Chicago, IL), and the level of statistical significance was set to 0.05.

## Results

Forty residents were divided into two groups as seniors and juniors regarding their year of training 2 years of training accepted as a cut-off value for being senior. Out of 40 subjects, 21 had a working experience of less than 2 years (Fig. 1).

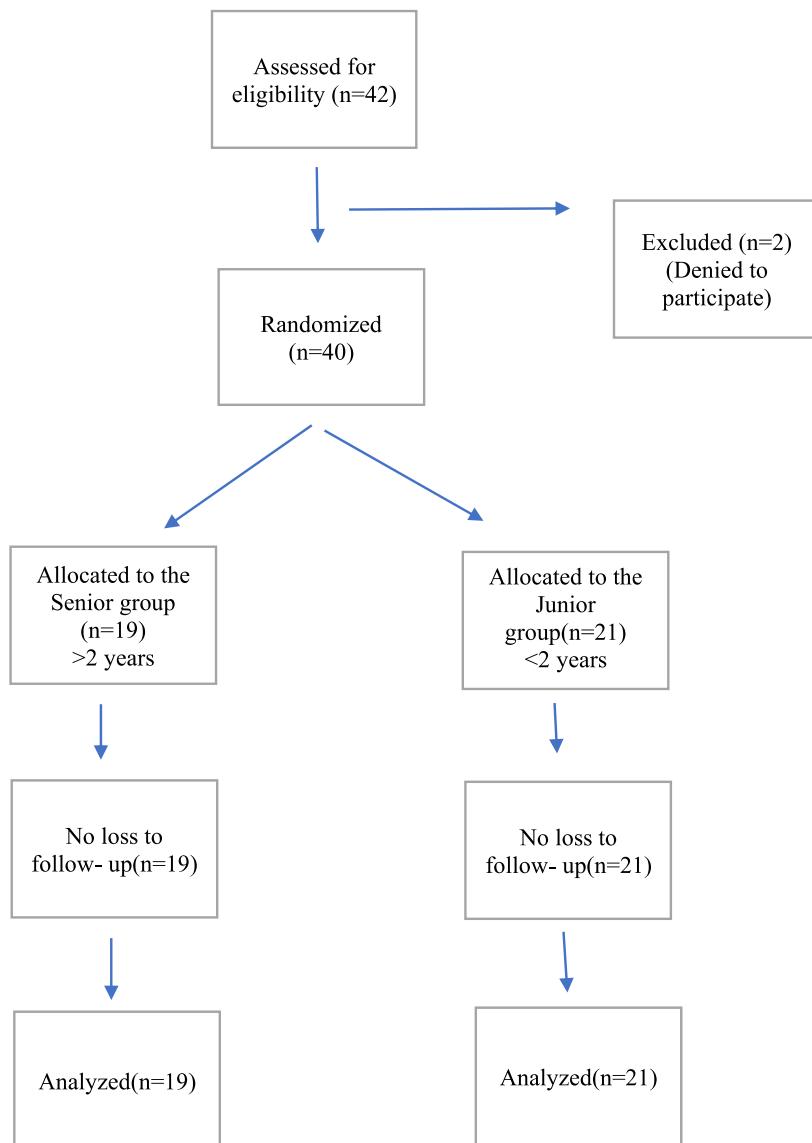
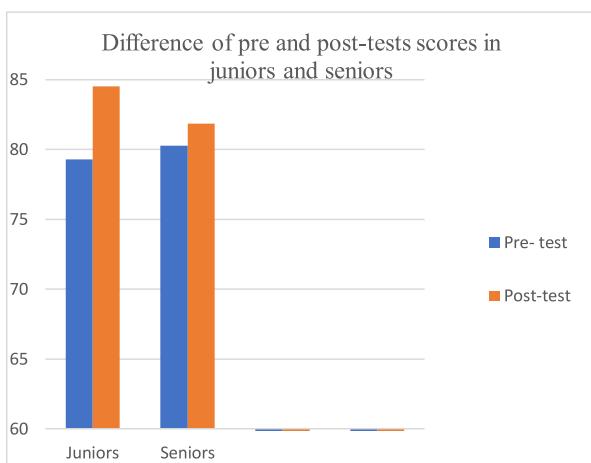
The theoretical score improved from  $79.7 \pm 9.2$  to  $83.2 \pm 9.3$  ( $p = 0.04$ ) in pretest and posttest results. Junior residents (< 2 years) received significantly higher scores in post-tests compared to their pre-test scores ( $79.2 \pm 9.6$ ,  $84.5 \pm 8.2$ ,  $p = 0.002$ ). However, there was no significant difference between pre- and post-test scores of seniors ( $80.2 \pm 9$ ,  $81.8 \pm 10.4$ ,  $p = 0.3$ ) (Fig. 2). Juniors scored higher than seniors in the post-test ( $84.5 \pm 8.2$ ,  $81.8 \pm 10.4$ ,  $p = 0.236$ ).

Both state and trait STAI scores were calculated, however only the state component is reported here as a reflection of anxiety experienced at the day of the simulation training. The pre-STAI-S score was  $39.8 \pm 10.1$  while the post STAI-S score was  $39.3 \pm 12.1$ . There was no difference between the pre- and post-state-trait anxiety inventory scores ( $p = 0.8$ ) (Table 1).

## Discussion

While there was an improvement in posttest scores compared to pretest, this increase was more significant for the junior residents. Even the posttest scores of the juniors were higher than the seniors, while there was no significant difference between pretest and posttest scores of seniors. Besides, the simulation training did not make any difference in anxiety scores.

Since March 2020, face to face medical education lectures, bedside visits, hands on practices in clinics had to discontinue for a while due to the pandemic restrictions. Training programs had to be restructured according to the new normal and simulation-based learning became much more important.<sup>6</sup> Faculties needed to determine a new road map for residents.<sup>7,8</sup> While the academic community is worrying about how to educate particularly the ones who have no experience in the operating room, this study may paint a promising picture.

**Figure 1** Flow chart depicting the study process.**Figure 2** Pre- and post-test scores of juniors and seniors.

Simulation-based training gives health care providers the opportunity to develop their skills to manage real-life cases in the hospital.<sup>9</sup> In this study, true/false questions were used to assess the efficacy of the simulation session which was supposed to improve the knowledge scores of participants. In a recent study by Shailaja et al from India,<sup>10</sup> 22 anesthesia residents had six scenarios. After that, they took pre and post simulation multiple choice question tests and the mean knowledge score was improved by 51%, whereas the mean knowledge score from pretest to posttest improved by 4.3% in our study. Furthermore, in another study by Etanaa et al. from Ethiopia,<sup>11</sup> non-physician anesthetists attended a 3-day course and they had nine simulation scenarios, and eventually, the posttest scores improved by 16%. This difference in results may be related to the timing of the post-tests. While Shailaja et al. applied the test right after the simulation session, Etanaa et al. applied the test after the end of all 3-day sessions. In our study, we aimed to evaluate the impact of the simulation training

**Table 1** Knowledge test and anxiety scores.

	Pre-test score	Post-test score	<i>p</i>	Pre-STAI	Post-STAI	<i>p</i>
Juniors	79.2 ± 9.6	84.5 ± 8.2	0.002	38.9 ± 8.4	38.7 ± 10.4	0.8
Seniors	80.2 ± 9	81.8 ± 10.4	0.3	40.7 ± 11.8	40.1 ± 10.4	0.8

method on long-term knowledge retention, so the questions were given one month after the simulation session. The increase in the scores of junior residents demonstrated the success of this education modality in long-term learning.

Anxiety can be seen in those who did not participate in any simulation training. Stein, C found that, post-simulation STAI scores of emergency medical care students were significantly higher than pre-simulation scores in scheduled simulation assessments.<sup>12</sup> In our study, moderate anxiety was detected in the participants. The fact that none of them had participated in any simulation training before may have caused moderate anxiety scores. In addition, the fact that this session was reported as training rather than evaluation may have caused this score not to increase.

During the pandemic, healthcare workers have a lot to bother about. Residents feel uneasy about patient safety, personal safety, and their education.<sup>13</sup> As educationists, one of our duties should be to protect our residents from burnout during a pandemic and keep them enthusiastic about learning. It will be wise if we use the simulation method to teach them without loading another stress factor during these difficult times.

As an outcome of our perfect collaboration with the simulation team of Claude Bernard University, this scenario represents the first successfully performed simulation-based training at our institution. Furthermore, our experience with the University of Claude Bernard indicates the importance of collaborative workshops and master classes as good tools for the dissemination of this educational modality.

## Limitations

Pre- and post-knowledge test questions that we used were chosen from our department's exam questions. Although these questions have not been validated, we have been using these questions to evaluate our residents' theoretical knowledge. Our results may be more impactful if our questions are validated.

We highlight the importance of simulation training, but our study comprised one emergency scenario although similar studies contain more scenarios. We indicate no difference between pre- and post-STAI scores. We held the simulation session with our residents in our operating room so, not only the environment but also trainers and the other participants were familiar to subjects and maybe anxiety scores could be different if this was a multicenter simulation with residents from different clinics. Future research with a larger number of scenarios and subjects from several clinics is required to demonstrate anxiety levels.

## Conclusion

As the response to the COVID-19 pandemic restricted in-person activity, medical schools had to invent new ways to

educate. Arrangements had to be made for students to retain clinical skills and knowledge to prepare them for real-life crises. Simulation is an effective training modality, which can be used to improve knowledge levels without any serious change in the state of anxiety of participants.

## Conflicts of interest

The authors declare no conflicts of interest.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.bjane.2021.11.010](https://doi.org/10.1016/j.bjane.2021.11.010).

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**ORIGINAL INVESTIGATION**

## Percutaneous tracheostomy in COVID-19 patients: a new apneic approach



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### KEYWORDS

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Apnea;  
Intensive care;  
Critical care

### Abstract

**Background:** Percutaneous dilation tracheostomy is an aerosol-generating procedure carrying a documented infectious risk during respiratory virus pandemics. For this reason, during the COVID-19 outbreak, surgical tracheostomy was preferred to the percutaneous one, despite the technique related complications increased risk.

**Methods:** We describe a new sequence for percutaneous dilation tracheostomy procedure that could be considered safe both for patients and healthcare personnel. A fiberscope was connected to a video unit to allow bronchoscopy. Guidewire positioning was performed as usual. While the established standard procedure continues with the creation of the stoma without any change in mechanical ventilation, we retracted the bronchoscope until immediately after the access valve in the mount tube, allowing normal ventilation. After 3 minutes of ventilation with 100% oxygen, mechanical ventilation was stopped without disconnecting the circuit. During apnea, the stoma was created by dilating the trachea and the tracheostomy cannula was inserted. Ventilation was then resumed. We evaluated the safeness of the procedure by recording any severe desaturation and by performing serological tests to all personnel.

**Results:** Thirty-six patients (38%) of 96 underwent tracheostomy; 22 (23%) percutaneous dilation tracheostomies with the new approach were performed without any desaturation. All personnel (150 operators) were evaluated for serological testing: 9 (6%) had positive serology but none of them had participated in tracheostomy procedures.

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**Conclusion:** This newly described percutaneous dilation tracheostomy technique was not related to severe desaturation events and we did not observe any positive serological test in health workers who performed the tracheostomies.  
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## Introduction

Acute respiratory distress syndrome (ARDS) is the most serious complication of the new coronavirus disease 2019 (COVID-19) which has led to a high and unexpected number of patients admitted to intensive care units (ICU) who required mechanical ventilation worldwide. Many COVID-19 patients require tracheostomy due to prolonged mechanical ventilation. Tracheostomy has the advantage to reduce the risk of laryngeal damage and the need for sedation, which facilitates the process of weaning from mechanical ventilation and the patient's discharge from the ICU.

The most widespread techniques of percutaneous dilation tracheostomy (PDT) in ICU patients are performed with a single dilator (e.g., Ciaglia or Percutwist techniques) or with special curved forceps (Griggs technique). All PDT techniques appear to be equally feasible at bedside in ICU, although the Griggs technique is associated with a higher incidence of intraprocedural bleeding and technical difficulties to complete the procedure (i.e., difficult cannula insertion, difficult dilation, or failure) than the single dilator technique.<sup>1</sup>

PDT is an aerosol-generating procedure that carried a documented infectious risk during the last Severe Acute Respiratory Syndrome (SARS) pandemic.<sup>2,3</sup> In most SARS-CoV-2 patients, low respiratory tract specimens could remain positive for longer periods than upper respiratory ones.<sup>4</sup> Therefore, postponing tracheostomy as much as possible could reduce the infectious risk for healthcare professionals. Stoma dilation is probably the most hazardous phase because air leaks are common at this point of the maneuver.

In the hypothesis that the PDT, as an aerosol generating procedure, could be dangerous for healthcare personnel, in this study we described a new technique which possibly reduces viral spreading. Then we evaluated the SARS-CoV-2 serological status of healthcare personnel.

## Methods

This study is part of the COVID-BioB study, an observational investigation performed at Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Raffaele Scientific Institute (NCT 04318366), and it received approval by the Ethical Committee. From February 25 to April 22, 2020 we admitted patients with ARDS requiring invasive mechanical ventilation in the seven COVID-19 ICUs activated in the hospital, which was re-shaped for the emergency.<sup>5</sup>

PDT (Ciaglia, Percutwist and Griggs technique) was performed in adult patients who had prolonged mechanical ventilation (> 8 days), favorable anatomy (i.e., BMI less than 35, absence of evident deformities, etc.) and no

severe hypercapnia (more than 60 mmHg). The specific technique was chosen according to operators' preference and availability of the devices (the pandemic rapidly depleted tracheostomy set stocks and we were not able to use the same technique on all patients).

### Modified PDT technique

Five out of seven COVID-19 ICUs performed PDT with the new approach described in this manuscript. The team was composed of two intensivists (one acted as bronchoscopist and the other was the operator), and two nurses. All the operators involved in the procedure wore a single-use cap, water-repellent coat or overalls, N100/FFP3 mask, goggles, protective visor, and gloves before entering the patient room. Before the procedure, a second sterile gown and a second pair of gloves were worn.

Before fiberscope insertion, the patient was deeply sedated with both propofol and remifentanil. Rocuronium or cisatracurium were administered to prevent cough and to obtain deep neuromuscular blocking. The patient was ventilated with 100% oxygen through the orotracheal tube. A fiberscope was connected to an external video unit so that the bronchoscopist could stay as far as possible from the patient's mouth. The fiberscope was inserted in the tracheal tube through a catheter mount with a flip-top cap to guarantee the sealing of the circuit. The tracheal tube was then retracted until the first tracheal ring was visualized. This phase needed the cuff of the tracheal tube to be deflated; ventilation was temporarily suspended. A guidewire was inserted by puncturing between the second and the third tracheal ring as in the usual practice. While the established standard procedure continues with the creation of the stoma by dilation without any change in mechanical ventilation setting parameters, we retracted the bronchoscope until immediately after the flip top cap in the catheter mount, allowing normal ventilation because the internal caliber of the airway was not reduced by the fiberscope (Fig. 1). After 3 minutes of ventilation with 100% oxygen, with the same positive end expiratory pressure by which the patient was ventilated, mechanical ventilation was stopped without disconnecting the circuit. During apnea, we performed the first dilation with 14Fr dilator then we created the stoma by dilating the trachea according to the chosen technique (Ciaglia, Griggs or Percutwist), and the tracheostomy cannula was placed. Correct positioning was confirmed by fiberoptic control. Ventilation was resumed immediately after confirmation of correct cannula positioning.

We collected data concerning the rate of severe hypoxic events during the PDT procedure (defined as any peripheral oxygen saturation (SpO<sub>2</sub>) less than 90%), timing of tracheostomy from tracheal intubation, length of ICU and



**Figure 1** Position of fiberscope (a) during modified percutaneous tracheostomy procedure, and (b) during ventilation before apneic stoma formation.

hospital stay, need for admission in rehab wards, and respective length of stay, deaths, and time to tracheostomy tube removal.

After the rapid reduction of COVID-19 ARDS prevalence in Italy<sup>7</sup> and the closure of all our COVID-19 dedicated ICUs, all personnel was evaluated by serological testing (Immunoglobulin G for Sars-CoV 2, Liason XL instrument, DiaSorin, Varese, Italy). The number of positive serology tests among healthcare providers was collected. Data were electronically collected and analyzed by Microsoft Excel®. Results are shown as n(%) for proportions, and median (interquartile) for continuous variable.

## Results

We admitted 96 COVID-19 patients with ARDS requiring mechanical ventilation in the ICUs and 36/96 (37%) tracheostomies were performed (first tracheostomy on March 1<sup>st</sup> and the last one on May 4<sup>th</sup>, 2020). A surgical technique was used in 14/36 (39%) patients; the modified PDT technique first described in this manuscript was used in 22/36 (61%) patients, and these were included in the analysis. Most patients received the Ciaglia's PDT (15/22, 68%), while Griggs's PDT was used in 6/22 patients (27%) and Percutwist in 1 patient (5%).

Amongst PDT patients, mean age was 67 (59–71) and 17/22 (77%) patients were male. PDT was performed after a median (interquartile) of 14 (10–17) days from tracheal intubation (Table 1). No severe hypoxic events were observed.

Concerning the duration of acute hospital admission, the length of ICU stay was 26.5 (20–43) days; the length of hospital stay was 52 (35–73) days. Hospital mortality was 10/22 (46%). Nine patients died in ICU and one in the ward.

From the 12 survivors, tracheostomy tubes were removed 41 (27–46) days after PDT. One patient was directly discharged at home after the acute hospital stay. Eleven

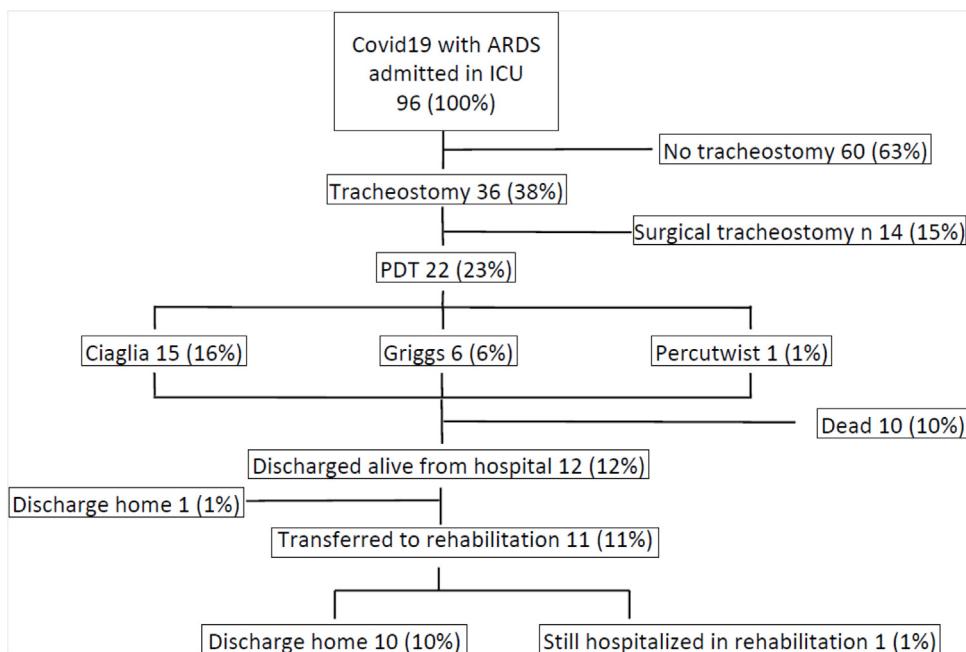
**Table 1** Demographics, complications, survival, and length of stay of 22 mechanically-ventilated patients for COVID-19 ARDS.

Parameter	Values
Age, years	67 (59–71)
Male sex	17 (77%)
Hospital mortality	10 (46%)
Days from tracheal intubation to PDT	14 (10–17)
Severe desaturation event	0 (0%)
LOS in ICU, days	27 (20–43)
LOS in hospital, days	52 (35–73)
LOS in rehabilitation, days	18 (11–30)
Tracheostomy tube removal time, days	41 (27–46)

ARDS, acute respiratory distress syndrome; PDT, Percutaneous dilation tracheostomy; LOS, Length of Stay; ICU, Intensive Care Unit.

patients were transferred to the rehabilitation ward and ten of them were discharged after 18 (11–30) days of rehabilitation. The flow chart with patients' flow and outcome is shown in Figure 2.

After the closure of all the COVID-19 intensive care units, 150 healthcare providers underwent serological testing and 9 (6%) were found positive. All the 23 resident doctors were negative, while 7/98 (7%) nurses and 2/29 (7%) physicians were positive. Thereafter, we retrospectively investigated if positive-tested healthcare providers had been involved in PDTs and found that no positive nurses or physicians had participated to PDT. Notably, one of the physicians had a positive swab in the early phase of epidemic, and the other one had the partner as a probable source of contagion. Among the nurses: one lived in the area of Bergamo (where an extremely high number of cases was registered), one had a relative as probable source of contagion, three had posi-



**Figure 2** Flow chart and outcome of included patients. ARDS, acute respiratory distress syndrome; ICU, intensive care unit; PDT, percutaneous dilation tracheostomy. Sum of percentages may not be 100% because of rounding.

tive swabs several weeks before starting to work in the ICUs and two were fully asymptomatic.

## Discussion

We described a modified technique for PDT which can be used in patients with Sars-Cov-2 or in other future respiratory pandemics. The technique was feasible, easy to perform, and we observed no severe hypoxia events among 22 consecutive patients. Briefly, after 3 minutes of pure oxygen ventilation and with the same positive end expiratory pressure already in use, stoma creation was performed during apnea, without disconnecting the patient from the ventilator. We also observed that none of the healthcare providers involved in the procedure developed a positive serology testing and we were able to identify a different and plausible chain of contagion in most of the positive healthcare providers working in the ICU during the pandemic event.

Despite the lack of data about superiority of surgical tracheotomies in terms of complications or safety for healthcare providers, this technique was generally favored over PDT during the SARS outbreaks,<sup>8–10</sup> since PDT was considered at risk of aerosolization.

Recent guidelines for tracheotomy in COVID-19 pandemic refer mainly to surgical procedures<sup>11,12</sup> and the Canadian society of otolaryngology, head & neck surgery even recommended to avoid tracheostomy in COVID-19 patient.<sup>12</sup>

Surgical tracheostomy is normally performed with initial advancement of the endotracheal tube, ensuring that the cuff is distal to the tracheostomy incision to prevent air flow through the stoma. Tracheal incision is performed, and ventilation is interrupted only before insertion of the tracheostomy tube. Early inflation of the cuff is advised to

ensure seal against the tracheal wall and, after confirmation of positioning, the orotracheal tube is removed. According to recommendations,<sup>11,12</sup> this technique has the advantage of minimizing the possibility of air leak and therefore the risk of aerosolization. However, it also has disadvantages: first of all, it requires transporting the patient to the operating theatre; sometimes a larger stoma is created, with the risk of air leakage (if the cuff of the tracheostomy tube is not sealing) also after tracheostomy; and it has a higher incidence of bleeding and stoma infections when compared to the percutaneous technique.<sup>1,10</sup>

Brendan et al., on the other hand, suggested a multidisciplinary approach in Sars-Cov-2-positive patients<sup>13</sup> and the execution of the procedure where the team has more experience and confidence.

In addition, the optimal timing of tracheostomy is not well-defined yet.<sup>14</sup> In Sars-Cov-2 positive patients, the same uncertainty exists, but an early tracheostomy could add an even higher infectious risk for healthcare providers. Considering the viral load, it seems that mouth and nose swabs become negative before the virus disappears in the lower respiratory secretions,<sup>15</sup> putting the healthcare professionals at risk during tracheostomy procedures even if the swab is negative.

Moreover, the development of specific antibodies is usually detectable 12 days after symptoms onset.<sup>16</sup> For this reason, tracheostomy should be performed  $\geq 14$  days after intubation according to Takhar et al.,<sup>12</sup> or  $\geq 10$  days following the suggestions of Brendan et al.<sup>13</sup>

The second issue against early tracheostomy is futility. The average time to death in ICU mechanically-ventilated COVID-19 patients was around 5 days in Wuhan,<sup>17</sup> 7 days in Lombardy-Italy<sup>18</sup> and 6 days in the UK.<sup>19</sup> Therefore, performing tracheostomy too early could be a futile maneuver.

Our study has limitations and, as all observational studies, causality cannot be inferred. We evaluated the safety of the described sequence only in relation to severe desaturation, which is the most expected event associated with apnea, while we did not record mean arterial saturation during the procedure. We also did not collect other complications rate (i.e., infections, bleeding, and hypotension). We assessed the serology of healthcare professionals only after the ICUs closure. However, positive swab results can occur despite subsequently negative serology and therefore, we cannot exclude that asymptomatic healthcare professionals could have had a positive swab without developing antibodies.

We performed tracheostomy after 14 days of mechanical ventilation and did not control swab results in patients at the time of tracheostomy, so we cannot exclude that, at the moment of PDT, the patient was already negative. Moreover, operators of PDT adopted maximal barrier precautions, so we cannot evaluate if absence of transmission of COVID-19 is related to barrier precautions or to the described new sequence. We did not collect rate of infections in surgical tracheostomy operators, so we cannot compare result to percutaneous tracheostomy. Overall, the sample size is small, and our results come from a single center, thereafter generalizability is overall low.

## Conclusions

We described a modified and safe sequence of percutaneous tracheostomy that, together with the correct use of PPEs, was associated with no virus transmission to any of the involved healthcare workers. Further studies are warranted, but we provide data that could be useful in current or future viral respiratory pandemics.

## Conflict of interest

The authors declare no conflicts of interests.

## Acknowledgements

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**ORIGINAL INVESTIGATION**

**Effect of early awake prone positioning application on prognosis in patients with acute respiratory failure due to COVID-19 pneumonia: a retrospective observational study**

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**KEYWORDS**

COVID-19;  
Respiratory failure;  
Prone position;  
Intensive Care Unit

**Abstract**

**Background:** We evaluated the effect of early awake prone position administration on oxygenation and intubation requirements and short-term mortality in patients with acute respiratory failure due to coronavirus disease 2019 (COVID-19) pneumonia.

**Methods:** This is an observational-cohort study. Patients receiving mask oxygen therapy in our intensive care units because of acute respiratory failure due to COVID-19 pneumonia were included. The Awake Prone Position (APP) group consisted of patients who were applied awake prone position, whereas non-APP group consisted of patients who were not applied awake prone position.  $\text{PaCO}_2$ ,  $\text{PaO}_2$ , pH,  $\text{SpO}_2$  values and  $\text{PaO}_2/\text{FiO}_2$  ratios were recorded at the beginning and 24th hour. Demographic data, comorbidities, intubation requirements, ventilator-free days, length of intensive care unit stay and short-term mortality of the patients were recorded.

**Results:** The data of total 225 patients were examined, and 48 patients who met our study criteria were included. At the 24th hour, the median  $\text{SpO}_2$  value of the APP group was 95%, the median  $\text{PaO}_2$  value was 82 mmHg, whereas the  $\text{SpO}_2$  value of the non-APP group was 90% and the  $\text{PaO}_2$  value was 66 mmHg. ( $p = 0.001$ ,  $p = 0.002$ ). There was no statistically significant difference between the groups in length of intensive care unit stay and ventilator-free days, but short-term mortality and intubation requirements was lower in the APP group ( $p = 0.020$ ,  $p = 0.001$ ).

**Conclusion:** Awake prone position application in patients receiving non-rebreather mask oxygen therapy for respiratory failure due to COVID-19 pneumonia improves oxygenation and decreases the intubation requirements and mortality.

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## Introduction

Severe acute respiratory syndrome coronavirus 2, which has led to the pandemic since the end of 2019, can cause acute respiratory failure due to coronavirus disease (COVID-19) pneumonia. Patients with acute respiratory failure must be monitored in the intensive care unit (ICU), largely under the support of mechanical ventilation. Despite close follow-up and treatment in this group of patients, the mortality rate is quite high.<sup>1</sup> In previous studies of acute respiratory distress syndrome (ARDS), early prone position (PP) application with neuromuscular blockers and low tidal volume administration improved the  $\text{PaO}_2/\text{FiO}_2$  ratio and decreased mortality at a moderate level. The PP is known to show a recruitment effect on the dorsal lung, increase lung volume at the end of expiration, increase chest wall elasticity, and reduce alveolar.<sup>2–4</sup> To avoid intubation in moderate-level ARDS cases, awake PP combined with noninvasive mechanical ventilation or nasal high-flow applications can correct ventilation/perfusion incompatibility and provide lung drainage.<sup>5</sup> Awake PP is prevalently used by clinicians during mask oxygen or nasal high-flow application in patients with mild to moderate acute respiratory failure after COVID-19. The fact that pulmonary compliance was largely preserved suggests that the benefit from PP may be more than expected. A paucity of literature is available that reports improved oxygenation and reduced intubation requirements when PP was applied during mask oxygenation or nasal high flow in patients with acute respiratory failure due to COVID-19 pneumonia.<sup>6–8</sup> None of the previous studies were randomized controlled studies, and their conclusions were largely suggestive not conclusive.

In our study, we evaluated the effect of early awake PP administration on oxygenation and intubation requirements and short-term mortality in patients with acute respiratory failure due to COVID-19 pneumonia.

## Methods

The study was retrospectively conducted in five COVID-cohort intensive care units in our hospital, including patients from March 15 to June 15, 2020. The study was started after approval from the local ethics committees of our hospital (2807) and the Ministry of Health (2020-04-30T19\_46\_45), and after registering in the Clinical Trials (NCT04427969). Informed consent form was obtained from the patient or patient relatives. The data of patients >18 years of age who were monitored and treated in the ICU for acute respiratory failure due to COVID-19 pneumonia were retrospectively identified. Patients who developed acute respiratory failure due to COVID-19 pneumonia and received conventional oxygen therapy with nonrebreather mask oxygen upon admission to the ICU were included in the study. Patients who were supported with noninvasive or invasive mechanical ventilation due to respiratory acidosis ( $\text{pH} < 7.30$  and  $\text{PaCO}_2 > 50 \text{ mmHg}$ ),  $\text{PaO}_2/\text{FiO}_2$  ratio <150, Glasgow Coma Scale score <12 points, or hemodynamic instability from the moment of admission to the ICU were excluded from the study. In addition, patients with primary pulmonary pathologies (lung cancer, cardiopulmonary edema, and Kartagener's syndrome) other than pneumonia, patients who underwent

nasal high-flow therapy, and those who applied awake PP < 12 hours in 1 day were excluded from the study.

COVID-19 was diagnosed using a polymerase chain reaction test. The diagnosis of pneumonia was made on the basis of clinical results and the appearance of multifocal frosted glass opacities forming consolidation on computed tomography. Acute respiratory failure was defined as a  $\text{PaO}_2/\text{FiO}_2$  ratio <300 despite conventional oxygen therapy using a non-rebreather mask at 6  $\text{L}\cdot\text{min}^{-1}$ . The  $\text{FiO}_2 (\%) = 21 + 4 \times \text{flow rate} (\text{L}\cdot\text{min}^{-1})$  formula was used for the calculation in the patients who received oxygen support through a nonrebreather mask.

The first group (APP) consisted of patients who applied 12–18 hours of awake PP with nonrebreather mask oxygen support, and the second group (non-APP) consisted of patients who had only nonrebreather oxygen support and did not receive awake PP. No patient selection criteria were applied for indicating awake PP. Awake PP was targeted for all patients admitted to the ICU with a diagnosis of acute respiratory failure due to COVID-19. However, awake PP could not be applied to all patients because of patient refusal or noncompliance.

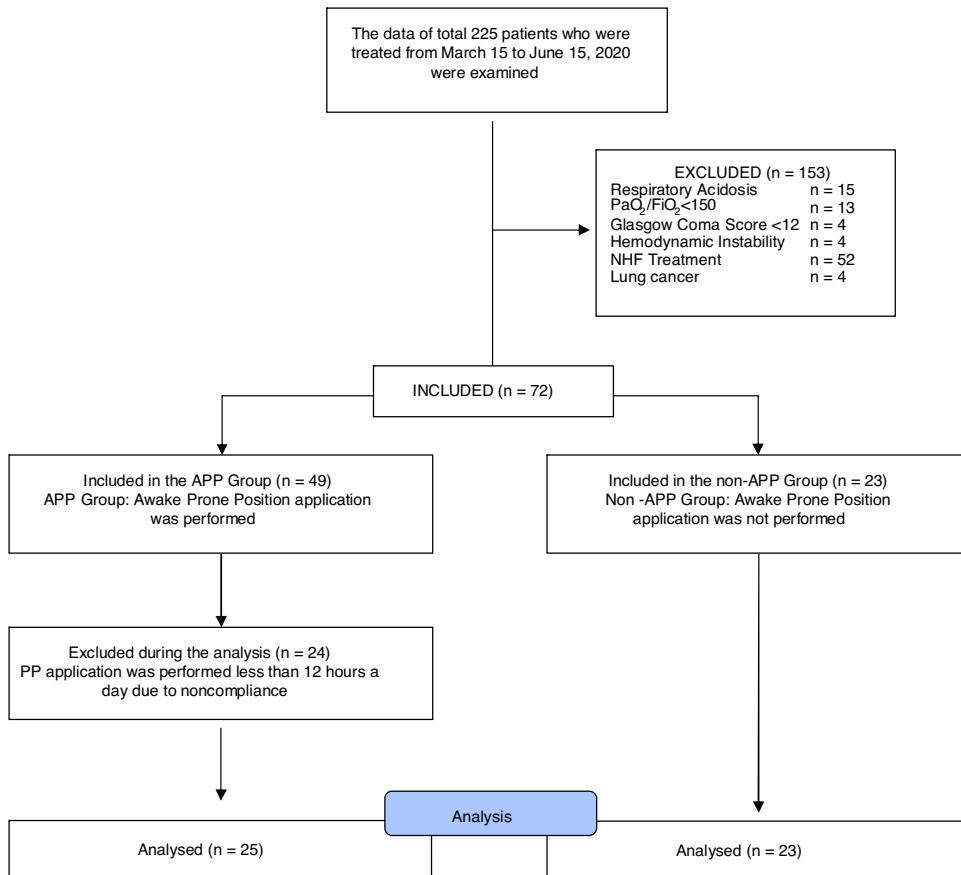
Age, sex, body mass index, and demographic data of all the patients and comorbidities (diabetes mellitus, hypertension, coronary artery disease, chronic obstructive pulmonary disease, congestive heart disease insufficiency, and chronic renal failure) were recorded. In both groups, the  $\text{SpO}_2$ ,  $\text{PaO}_2/\text{FiO}_2$ , pH,  $\text{PaCO}_2$ , and  $\text{PaO}_2$  values measured in arterial blood gas at the beginning and 24th hour (after awake PP application for at least 12 hours in the APP group) were recorded.

Conventional oxygen therapy was administered to all patients by using a nonrebreather mask, targeting  $\text{SpO}_2 > 93\%$  at a flow rate of 6–15  $\text{L}\cdot\text{min}^{-1}$ . It was aimed at applying awake PP for 18 hours intermittently in a day for all patients. However, the period varied between 12 and 18 hours owing to the uncomfortable position caused by the therapy. Unless treatment failure occurred, awake PP was applied to our patients at least 12  $\text{h}\cdot\text{day}^{-1}$ . Treatment failure was defined as a  $\text{PaO}_2/\text{FiO}_2$  ratio <150,  $\text{SpO}_2 < 93\%$ , Glasgow Coma Scale score <12, and respiratory acidosis ( $\text{pH} < 7.40$  and  $\text{PaCO}_2 > 50 \text{ mmHg}$ ). In case of treatment failure, the patients were intubated and received invasive mechanical ventilation.

The patients' intubation need, ventilator-free days, length of ICU stay, and short-term mortality were recorded. Short-term mortality was defined as death within 28 days of ICU stay, post intensive care hospitalization or home discharge.

## Statistical analysis

The data were evaluated using Windows SPSS 15. Descriptive results were obtained as number and percentage distributions for categorical variables and mean and standard deviations and median – interquartile range for numerical variables. For statistical analysis, normal distribution status of numerical values were evaluated according to Shapiro-Wilk test, histogram and Q-Q plots graph and Student's *t*-test. Mann-Whitney U test was used for comparisons. For categorical variables statistical analysis, Fisher's exact chi-square test was used when there is a value between 5–25 in any of the cells and Continuity Correction is less than 5.

**Figure 1** Flow diagram.

Results are interpreted practically/clinically with significant effect size values. An acceptable level of significance was  $p < 0.05$ .

## Results

The data of 225 patients who were treated between March 15 and June 15, 2020 were examined. Of the patients, 61 who were admitted to the ICU had already been intubated. Fifteen patients had respiratory acidosis, 13 had  $\text{PaO}_2/\text{FiO}_2$  ratios  $< 150$ , 4 had Glasgow Coma Scale scores  $< 12$ , and 4 had hemodynamic instability. These 36 patients were supported with noninvasive or invasive mechanical ventilation. Nasal high-flow treatment was applied in 52 patients. PP application was performed in 24 patients less than 12 hours a day due to patient incompatibility, and four had lung cancer among the comorbidities. For this reason, the data of 177 patients were excluded from the study. The data of 48 patients who met our study criteria were included in the study. The APP group consisted of 25 patients, whereas the non-APP group consisted of 23 patients (Fig. 1).

Table 1 lists the demographic data and comorbidity states. The median age of the patients in the APP group was lower than that of the patients in the non-APP group ( $p = 0.002$ ). We found no statistically significant differences between the groups in terms of sex, body mass index, and comorbidity states.

Moreover, no statistically significant differences were found between the groups in terms of initial  $\text{SpO}_2$ , pH,  $\text{PaO}_2$ , and  $\text{PaO}_2/\text{FiO}_2$  values. The initial  $\text{PaCO}_2$  values in the APP group were higher than those in the non-APP group ( $p < 0.001$ ; Table 2). No statistically significant differences in pH,  $\text{PaCO}_2$ , and  $\text{PaO}_2/\text{FiO}_2$  values were found between the groups at the 24th hour. The APP group had higher 24th-hour  $\text{SpO}_2$  and  $\text{PaO}_2$  values than the non-APP group ( $p = 0.001$  and  $p = 0.002$ , respectively; Table 3). When the changes in the initial values within the 24th hour were compared between the APP and non-APP groups, the decrease in pH value was significantly higher in the non-APP group than in the APP group ( $p = 0.002$ ). The  $\text{PaO}_2$  values increased in the APP group, whereas they decreased in the non-APP group, and the difference between the two groups was statistically significant ( $p < 0.001$ ). The  $\text{PaCO}_2$  values decreased in the APP group but increased in the non-APP group, and the difference between the two groups was statistically significant ( $p = 0.007$ ). The increase in  $\text{SpO}_2$  value was significantly higher in the APP group ( $p = 0.016$ ). The  $\text{PaO}_2/\text{FiO}_2$  ratios increased in the APP group and decreased in the non-APP group, but the difference between the two groups was not statistically significant (Table 4).

We found no statistically significant difference between the groups in length of ICU stay and ventilator-free days, but the short-term mortality and intubation requirements were

**Table 1** Characteristics of the participants at inclusion in the study.

	APP (n = 25)	non-APP (n = 23)	p	Cohen's d
				Median (IQR)
Age (years)	62.4 ± 10.9 (43–83)	72.6 ± 10.1 (51–89)	0.002 <sup>a</sup>	0.99
Body Mass Index (kg.m <sup>-2</sup> )	25.1 ± 2.5 (20.2–30.1)	26.6 ± 3.1 (21.6–36.7)	0.079 <sup>b</sup>	0.55
n (%)	n (%)	n (%)		Phi
Sex				
Female	14 (56.0)	14 (60.9)	0.732	0.05
Male	11 (44.0)	9 (39.1)		
Comorbidity	17 (68.0)	20 (87.0)	0.223	0.23
DM	10 (40.0)	6 (26.1)	0.475	0.15
HT	10 (40.0)	15 (65.2)	0.145	0.25
CAD	2 (8.0)	4 (17.4)	0.407	0.14
COPD	2 (8.0)	0	0.490	0.20
CHF	1 (4.0)	1 (4.3)	1.000	0.01
KBY	0	1 (4.3)	0.479	0.15
Cancer	0	2 (8.7)	0.224	0.22
Other	6 (24.0)	9 (39.1)	0.413	0.16

p, Chi-Square Test; BMI, Body Mass Index; DM, Diabetus Mellitus; HT, Hypertension; CAD, Coronary Artery Disease; COPD, Chronic obstructive pulmonary disease; CHF, Congestive Heart Failure; CRF, chronic renal failure.

\*Plus-minus values are median (IQR) Cohen's d ≥ 0.50 and Phi value ≥ 0.30 practically/clinically significant.

<sup>a</sup> Student t and Test.

<sup>b</sup> Mann Whitney U Test.

**Table 2** Initial SpO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub> and arterial blood gas values.

	APP (n = 25) Median (IQR)	non-APP (n = 23) Median (IQR)	p	Cohen's d
SpO <sub>2</sub> (%)	89 (85.5–93)	90 (82–96)	0.860	0.01
pH	7.45 (7.37–7.49)	7.48 (7.4–7.51)	0.100	0.58
PaCO <sub>2</sub>	36 (33–46)	30 (25–34)	<0.001	1.02
PaO <sub>2</sub>	65 (58–71.5)	63 (59–79)	0.368	0.37
PaO <sub>2</sub> /FiO <sub>2</sub>	175.7 (156.8–193.2)	167.6 (159.5–213.5)	0.649	0.28

SpO<sub>2</sub>, Saturation Pulse Oxygen; P/F:PaO<sub>2</sub>/FiO<sub>2</sub>, Partial Oxygen Pressure/Fraction of Inspired Oxygen; PaO<sub>2</sub>, Partial Oxygen Pressure; PaCO<sub>2</sub>, Partial Carbon Dioxide Pressure.

\*Plus-minus values are median (IQR). Cohen's d ≥ 0.50 practically/clinically significant p: Mann Whitney U Test #Student t test.

**Table 3** 24th hour SpO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub> and arterial blood gas values.

	APP (n = 25) Median (IQR)	non-APP (n = 23) Median (IQR)	p	Cohen's d
SpO <sub>2</sub> (%)	95 (92.5–96)	90 (89–94)	0.001	1.06
pH	7.46 (7.33–7.485)	7.40 (7.23–7.48)	0.268	0.38
PaCO <sub>2</sub>	37 (33.5–43.5)	35 (29–40)	0.243	0.17
PaO <sub>2</sub>	82 (74–92)	66 (60–70)	0.002	0.80
PaO <sub>2</sub> /FiO <sub>2</sub>	190.2 (166.7–214)	164.9 (154.1–186.5)	0.124	0.20

SpO<sub>2</sub>, Saturation Pulse Oxygen; PaO<sub>2</sub>/FiO<sub>2</sub>, Partial Oxygen Pressure/Fraction of Inspired Oxygen; PaO<sub>2</sub>, Partial Oxygen Pressure; PaCO<sub>2</sub>, Partial Carbon Dioxide Pressure.

\*Plus-minus values are median (IQR). Cohen's d ≥ 0.50 practically/clinically significant p: Mann Whitney U Test.

lower in the APP group than the non-APP group ( $p = 0.020$  and  $p = 0.001$ , respectively; Table 5).

## Discussion

The prevalence of acute respiratory failure in patients with COVID-19 pneumonia is approximately 19%. Based on the

preliminary data, the oxygen treatment requirement is 14% and the ICU admission and mechanical ventilation requirement is 5%.<sup>9</sup>

The initial data demonstrated that the risk factors associated with ICU admission are as follows: age >60 years, male sex, diabetes, and immunodeficiency, while cardiovascular disease, chronic respiratory disease, and diabetes were

**Table 4** Changes in SpO<sub>2</sub> and arterial blood gas values at the initial and 24th hour.

	APP (n = 25) Median (IQR)	non-APP (n = 23) Median (IQR)	p	Cohen's d
SpO <sub>2</sub> (%)	5 (0.5/10)	-1 (-54/5)	0.016	0.74
pH	0 (-0.025/0.045)	-0.05 (0/-0.19)	0.002	0.051
PaCO <sub>2</sub>	-1 (-4.5/4)	4 (-1/14)	0.007	0.086
PaO <sub>2</sub>	16 (5.5/31.5)	-1 (-14/7)	<0.001	1.14

SpO<sub>2</sub>, Saturation Pulse Oxygen; P/F:PaO<sub>2</sub>/FiO<sub>2</sub>, Partial Oxygen Pressure/Fraction of Inspired Oxygen; PaO<sub>2</sub>, Partial Oxygen Pressure; PaCO<sub>2</sub>, Partial Carbon Dioxide Pressure.

\*Plus-minus values are median (IQR). Cohen's d ≥ 0.50 practically/clinically significant p: Mann Whitney U Test.

**Table 5** ICU stay period, ventilator-free period, mortality rate, and intubation need.

	APP (n = 25) Median (IQR)	Non-APP (n = 23) Median (IQR)	p	Cohen's d
Ventilator free period (day)	3,5 (3–6,5)	2 (2–3)	0,004	1,64
ICU stay period (day)	5 (4–11)	8 (4–12)	0,258	0,30
n (%)	n (%)	n (%)		Phi value
Intubation requirements	8 (32)	19 (82,6)	0,001	0,51
Mortality rate	9 (36,0)	16 (69,6)	0,020	0,37

ICU, Intensive Care Unit.

\*Plus-minus values are median (IQR). Cohen's d ≥ 0.50 and Phi value ≥ 0.30 practically/clinically significant.  
p: Mann Whitney U Test and -Chi-Square Test.

associated with high mortality.<sup>9,10</sup> In our study, the median age of the patients in both groups was >60 years and most patients were male. The lower median age of the PP group might be associated with older patients being less compatible with PP application. A high proportion of patients in both groups had a history of comorbidities, and no significant difference was found between the groups in terms of the presence of comorbidities. Among the comorbidities, diabetes and hypertension had high prevalence rates.

Acute respiratory failure due to COVID-19 pneumonia was assessed as ARDS because it largely met the Berlin criteria at the initial stage.<sup>11</sup> With the acquired experience, two different phenotypes were identified (L and H phenotypes). In the prevalently-observed L phenotype, respiratory mechanics were well preserved in spite of severe hypoxia, lung weight did not increase, and the ventilation/perfusion ratio decreased. Moreover, the H phenotype was considered the conventional ARDS.<sup>12</sup>

The treatment recommendations for respiratory failure due to COVID-19 pneumonia are largely based on ARDS data, which show that early PP application >12 hours in a day reduces mortality and improves oxygenation. Moreover, PP shows a recruitment effect on the dorsal lung, reduces alveolar shunt, and increases end of expiration lung volume and chest wall elasticity.<sup>2–4</sup>

The Surviving Sepsis Campaign guidelines recommend PP application for 12–16 hours as a weak recommendation with a low evidence level for patients with COVID-19.<sup>13</sup> Studies on the clinical outcomes of PP application are unavailable in this group of patients, which are known to have different respiratory mechanics from ARDS.

Difficulties exist, such as extracting the intubation tube used during PP application in an intubated patient, preventing pressure wounds, reducing the need for deep sedation

and neuromuscular blockers, and meeting the large number of personnel required for application.<sup>14,15</sup> Therefore, the PP application rate was reported to be 32.9% in conventional ARDS and 11.5% in respiratory failure due to COVID-19 pneumonia because of excess contact.<sup>10,14</sup> However, the fact that additional staff and sedative agents are not required for awake PP leads to ease of application.

Based on the preliminary data from China and Italy, noninvasive mechanical ventilation or nasal high-flow applications were not preferred in patients with inadequate response to mask oxygenation because of high aerosolization, and early intubation was recommended.<sup>16,17</sup> However, the high postintubation mortality rate and severe ICU resource constraints led to the search for a new treatment strategy.<sup>18</sup> As a result, awake PP applied along with mask oxygenation or nasal high flow was introduced.<sup>6,7</sup>

Ding et al.<sup>5</sup> reported the positive effects of PP administration on oxygenation in patients with ARDS who underwent noninvasive mechanical ventilation and nasal high-flow therapy. They demonstrated that PP application in awake patients minimizes complications and the application difficulties observed in intubated PP. Moreover, awake PP is prevalently preferred for patients with COVID-19 in clinical practice; however, limited literature is available on this topic.<sup>6,7,19</sup>

In the study by Caputo et al.<sup>7</sup> in 50 patients admitted to the emergency service who had a COVID-19 preliminary diagnosis and required oxygen mask support, the effect of awake PP application for 5 minutes on SpO<sub>2</sub> changes was evaluated. The average SpO<sub>2</sub> was initially 80% in room air, 84% after oxygen support, and 94% after 5 minutes of awake PP. Moreover, the intubation requirement was 24% within 24 hours. In this study, which did not perform arterial blood gas and mortality evaluations, short-term PP application under oxygen sup-

port was demonstrated to improve oxygenation in patients with COVID-19 pneumonia. In our study, the average initial  $\text{SpO}_2$  value was 89% in both groups. After PP, these values increased, and the intubation requirement was reported to be 32% in the PP group and 82.6% in the non-PP group. In our study, the follow-up was not limited to 24 hours, and the median number of ventilator-free days was 3.5 days in the PP group and 2 days in the non-PP group.

In a case report, a 68-year-old patient with acute respiratory failure due to COVID-19 received awake PP application with nasal high flow for 16–18 hours daily. The  $\text{PaO}_2/\text{FiO}_2$  ratio increased from 100 to 150 to 250, and no intubation was required for 4 days. Moreover, the patient's abilities to participate in physiotherapy, conduct phone calls with family, and receive oral nutrition were highlighted as significant advantages.<sup>19</sup> In a Letter to the Editor, the success of COVID-19 treatments in the Jiangsu Province of China was reported to be higher and the need for invasive mechanical ventilation was lower than that in other provinces; moreover, self-PP was demonstrated as a reason for the treatment success.<sup>6</sup>

In our study, we found no significant difference in the initial  $\text{PaO}_2/\text{FiO}_2$  ratio between the two groups. The median  $\text{PaO}_2/\text{FiO}_2$  ratio was 175.7 in the PP group and 167.6 in the non-PP groups. At the 24th hour, the median  $\text{PaO}_2/\text{FiO}_2$  ratio was 190.2 after PP application and 164.9 in the non-APP group. Although the difference in the change in  $\text{PaO}_2/\text{FiO}_2$  ratio between the groups was not statistically significant, the increase in  $\text{PaO}_2/\text{FiO}_2$  ratio with PP application was remarkable. The  $\text{PaO}_2$  and  $\text{SpO}_2$  values increased significantly with awake PP application. A remarkable point was that although the initial  $\text{PaCO}_2$  value was higher in the PP group, it decreased at the end of 24 hours in the PP group but increased in the non-APP group.

Although the figures reported from different countries and centers vary, the mortality from COVID-19 due to respiratory failure in the ICU ranged from 30% to 40%; however, this rate reached 90% in patients with an invasive mechanical ventilation need.<sup>18,20,21</sup> In our study, the mortality rate was as low as 36% in the patients who received awake PP application and both the intubation requirement and mortality rates were as high as 69.6% in the non-APP group.

Our study is limited in that it was not a prospective randomized controlled study.

In conclusion, awake PP applied in patients receiving nonrebreather mask oxygen treatment for respiratory failure due to COVID-19 pneumonia improved oxygenation and decreased the intubation requirement and short-term mortality rate.

## Conflicts of interest

The authors declare no conflicts of interest.

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**ORIGINAL INVESTIGATION**

**Development of a recovery-room discharge checklist  
(SAMPE checklist) for safe handover and its comparison  
with Aldrete and White scoring systems**



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Anesthesia recovery period;  
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Models;  
Statistical

**Abstract**

**Background:** The postoperative care transition from the postanesthetic recovery room (PACU) to the common ward or even home discharge represents a critical step of the surgical patients' handover. Although some systems have been proposed to measure the ability to discharge after an anesthetic-surgical procedure effectively, there is no consensus defining which variables should necessarily be evaluated by these instruments. The instruments routinely used do not evaluate important domains for discharge and are laborious to fill, which compromises the professionals' adhesion. The objectives are to describe the creation of a new recovery room discharge tool (SAMPE checklist) and determine the degree of agreement of the new tool with two classical scales.

**Methods:** In a cross-sectional observational study, 997 patients were selected from the general population undergoing a wide range of surgical procedures in a quaternary care hospital. At 90 minutes after leaving the operating room (OR), patients were evaluated and information was collected to fill out the new SAMPE checklist and two other scores (Aldrete and White) to examine the degree of agreement between them.

**Results:** SAMPE checklist has presented a satisfactory agreement with the White score and lower agreement with Aldrete modified score.

**Conclusion:** This new instrument, as demonstrated in this study with nearly 1000 patients from different contexts, is easy to apply, has high adhesion potential, and can be considered a new option to formalize the discharge from the recovery room.

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## Introduction

Safety surgical handovers are essential to maintain continuity, to avoid adverse events and preventable errors.<sup>1</sup> The postoperative care transition from the postanesthetic recovery room (PACU) to the common care ward or even to home discharge represents a critical step of the surgical patients' handover. However, handing over information on many patients, with particular clinical scenarios, submitted to different severity of procedures can be complex, challenging, and staff demanding. Recovery is an ongoing process that lasts from the end of the intraoperative care until the patient returns to his/her preoperative physiological state.<sup>2</sup> The lack of standard strategies in moving patients from one care setting to another can result in patient harm, increased costs, and patient dissatisfaction.

The implementation of policies and procedures to ensure the safe recovery of patients after procedures is demanded by regulatory societies and accreditation committees around the world.<sup>3,4</sup> Although some systems have been proposed to measure the ability to discharge after an anesthetic-surgical procedure effectively, there is no consensus defining which variables should necessarily be evaluated by these instruments. Besides, to be useful, any instrument must be practical, simple, easy to apply by different caregivers, and applicable to any postanesthesia setting.<sup>5</sup>

Some discharge scores that have been used in the formal postoperative evaluation include domains related to hemodynamic stability, consciousness, airways, ventilation, and recovery from regional anesthesia. Meantime, some of these scales are compound with inessential unfoldings in each domain, which clouds the picture and avoids the caregiver's adhesion. Also, some scales do not include other fundamental domains for safety discharge, such as the presence of pain, bleeding, nausea, or vomiting. These fragilities can sometimes lead to a false readiness, which could result in an unsafe handover.

With the idea of helping caregivers and providing a safe assessment of the general conditions of patients in PACU, Aldrete and Kroulik proposed, in 1970, an index based on the assessment of the physiological conditions of the newborns (APGAR).<sup>6</sup> Thus, the authors scored from zero to two the evaluation of pulse rate, respiratory rate, blood pressure, state of consciousness, motor activity, and, recently, oxygen saturation, considering these clinical parameters as markers of the physiological systems compromised by the anesthetic procedure. The maximum score is ten and the patient needs a score of at least nine points to be discharged. This scale was not designed to be used for outpatient procedures, although it is also used for this purpose and has its limitations because it does not take into account frequent complications in post-surgical patients that make it impossible to discharge, such as nausea and vomiting, pain, and bleeding in the surgical site.

The White and Song scale<sup>7</sup> incorporated the evaluation of emetic symptoms and pain in Aldrete's, especially intending to evaluate outpatient discharge. This scale also adopts scores of zero to two for each evaluated item, being fourteen the maximum score. The patient is considered fit for discharge when it reaches at least twelve points, in which no

item can score less than one. The Aldrete and White scores are widely used as parameters for discharge in different PACUs.

We have two main goals with this study. First, we intend to describe the creation of a new recovery room discharge tool (SAMPE-Recovery Checklist) which provides a practical assessment of the recovery dimensions, being brief enough and easy to administer. Second, we look to determine the degree of agreement of the new Checklist SAMPE with two classical scales, the Aldrete and White scales. Our hypothesis is that the SAMPE checklist has a reasonable degree of agreement with the traditionally used scores, with the advantage of being more easily applicable and with a high potential of adherence by caregivers.

## Methods

### Conceptual development

#### First version of checklist SAMPE

In the quaternary hospital where this study was carried out, about 15,000 surgeries are performed each year. The SAMPE checklist construction was driven by the hospital demand for an instrument to guide efficiently patient's discharge from four different PACUs. An extensive review of the literature and consensus of senior anesthesiologists and nurses from the recovery room staff supported the instrument's first version, which contemplated eight domains considered utmost important for safe discharge. The domains were categorized, and the final sum configured a score, where 13 was the minimum score for discharge and 16 was the maximum. In addition, some conditions signalized in bold were contraindication for discharge. This instrument's first version (**Table 1**) was routinely used in our institution from 2013 to 2015. However, frequent audits had revealed checklist completeness and items' sum in less than 30% of the cases.

#### Second version of SAMPE checklist discharge: focusing on a lean process

To improve adhesion to the checklist documentation we applied some principles of Quality Improvement.<sup>8</sup> First, we verified the checklist content and semantic in regular discussions with professionals who work in the area: anesthesiologists, nurses, anesthesia residents, and technicians. Second, we looked for the reasons for the low adhesion to form filling, in spite of the adequate patients' evaluation at the bedside. The main reason was the difficulty in dealing with alternatives in each domain and to sum the final score. Then, we decided to simplify the instrument, since all of the items should be checked to consider patient readiness for discharge. The suppression of the final sum and the binary transformation of all items were carried out to improve the adhesion to the instrument. The same domains were maintained since all of them were considered determinants of recovery room stay if not solved.

Patients might have these following eight domains present to be considered for discharge: (1) Stability of vital signs, (2) Awake and oriented or with the prior sensory pattern, (3) Spontaneous ventilation, (4)  $\text{SpO}_2 > 90\%$ , (5) Controlled pain, (6) Absence of nausea and vomiting, (7)

**Table 1** The first version of the Recovery Room Discharge SAMPE Checklist.

Parameters	Score
Stable vital signs	2
<b>Significant change in blood pressure</b>	1
<b>Need for hemodynamic support</b>	0
Fully awake and oriented	2
Awake when called	1
<b>No responding</b>	0
Breathes deeply	2
<b>Needs ventilatory assistance</b>	1
$\text{SpO}_2 > 90\%$ on room air	2
<b><math>\text{SpO}_2 &lt; 90\%</math> with oxygen</b>	1
Controlled pain	2
<b>Moderate to severe pain</b>	1
Absence of nausea and vomiting	2
<b>Presence of nausea or vomiting</b>	1
No bleeding	2
<b>Presence of bleeding</b>	1
Move all extremities	2
Residual paresthesia after blockade <sup>a</sup>	1
<b>Unable to move extremities</b>	0
Total score: 16 Discharge with score $\geq 13$	

PACU, postanesthetic recovery room.

Items in bold/italic counter-indicate discharge.

<sup>a</sup> Patients who will be referred to the common ward with paresthesia in regression may be discharged from the PACU and followed by the Anesthesia Postoperative Team.

Absence of bleeding, (8) Absence of motor block. The SAMPE checklist definitions are shown in [Table 2](#).

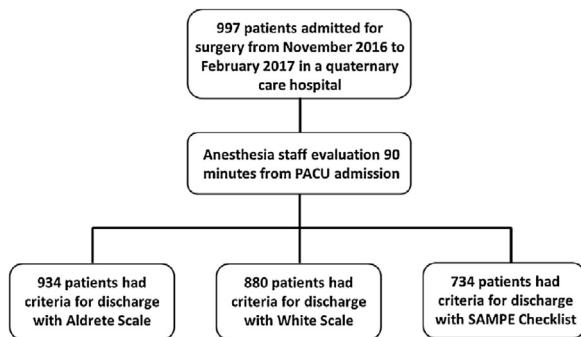
Third, the new checklist was inserted in the program of communication team training of the Anesthesia and Perioperative Service Residence Program. All residents and anesthesia PACU staff participated in sessions of simulation of communication handover training and postoperative patient's safety, where the checklist items importance was reinforced.

Lastly, the new checklist was compared to classical instruments of PACU discharge described in the following section.

#### Comparison of SAMPE checklist recovery room discharge with Aldrete and White scores

We chose a cross-sectional study to compare the new checklist with the other two scores. In- and outpatients were selected from the general population undergoing a wide range of surgical procedures from November 2016 to February 2017 at HCPA by two anesthesia residents from the Anesthesia and Perioperative Service (SAMPE). Only patients who went to the Critical Care Unit or those who remained overnight in the recovery room were excluded, all other patients admitted to the PACU were included.

To compare the agreement between the instruments, we chose to evaluate all patients in a fixed moment, at 90 minutes after leaving the operating room (OR), independently of the surgical procedure or the patient's readiness for discharge. Information was collected to fill out the new SAMPE checklist and the modified Aldrete<sup>6</sup> and White Fast-Track scores<sup>9</sup> at the same time. The complete instrument formu-

**Figure 1** Comparison of discharge readiness in 90 minutes after PACU admission. PACU, postanesthetic recovery room.

lary is in supplementary data. Demographic data, American Society of Anesthesiologists (ASA) physical status, surgical and anesthesia details, and final time to reach the discharge criteria according to the SAMPE checklist were also evaluated.

#### Statistical analysis

The sample size was calculated to evaluate the degree of agreement between the three discharge tools two by two by estimating the Kappa coefficient. For the calculation, an expected Kappa index equal to 0.4 (representing a reasonable agreement) with an accuracy of 0.1 (generating a lower limit equal to 0.3 and an upper limit equal to 0.5 for the confidence interval), a discharge prevalence of equal to 80% and a 95% confidence interval were considered. The calculated sample size was 490 subjects. The KappaSize, version 1.2, of R. was used.

This study aimed to examine the degree of agreement among the three instruments of recovery room discharge. We used the Bennett's Kappa measure<sup>10,11</sup> to verify the agreement between the scales. The Kappa coefficient is used to describe the agreement between two or more judges when performing a nominal or ordinal evaluation of the same sample. The value of the Kappa coefficient of agreement can vary from zero to one. The closer to one, the greater is the indication that there is a concordance between the judges and the closer to zero, the greater the indicative that the agreement is purely random.

In a second analysis, we focused exclusively on the cases of discordance between the instruments, specifically those that obtained criteria for discharge with Aldrete modified and/or with White but did not meet all the requirements for discharge with the SAMPE checklist. All the analyses were done with SPSS 22.0.

#### Results

A total of 997 patients admitted to the PACUs of the HCPA were evaluated over four months. Demographic and surgical characteristics are detailed in [Table 3](#).

[Figure 1](#) shows the number of patients ready to discharge according to each scale in 90 minutes. It was observed that 88% of the cases were discharged with the White scale, 92.7% with the Aldrete scale, and 73.6% with the checklist

**Table 2** The SAMPE checklist criteria.

Check	Condition	Parameters definition
(Y)	<b>Stable vital signs</b>	There should be stability of the cardiovascular system. The values of heart rate and blood pressure should approach the preoperative levels, or systolic blood pressure should be above 90 mmHg and below 180 mmHg.
(N) (Y)	<b>Awake and oriented or with prior sensory pattern</b>	Patient should be alert and oriented in time and space, recovered from the effect of anesthetic drugs or with their usual level of sensory.
(N) (Y)	<b>Spontaneous ventilation</b>	Spontaneous and deep breath and reflexes of coughing and swallowing should be present. The ventilatory pattern should be the usual.
(N) (Y)	<b>SpO<sub>2</sub> &gt; 90%</b>	The saturation should be satisfactory, above 90%. If necessary, oxygen therapy should be prescribed for discharge to hospitalization unit.
(N) (Y)	<b>Controlled pain</b>	Pain should be controlled (Verbal Pain Scale $\leq 3$ ) and adequate analgesic regimen should be prescribed. Postanesthetic Care team visit is required if neuroaxial anesthesia with opioids, epidural catheter or another advanced analgesia technique was applied.
(N)	<b>Absence of nausea and vomiting</b>	Nausea and vomiting should be controlled, and multimodal regimen should be prescribed.
(N) (Y)	<b>Absence of bleeding</b>	Any bleeding at the surgical site other than usual patterns contraindicates discharge and must be reported to the surgical team.
(N) (Y)	<b>Absence of motor block</b>	Patients who underwent anesthesia in the neuraxis who remained hospitalized should have sensory and motor block in visible regression. Ambulatory patients submitted to neuroaxial anesthesia should be able to deambulate and urinate before discharge.
(N)		

under study. The median time of conditions for discharge was 90 minutes (p25 – 90 min, and p75 – 120 min).

The agreement indexes of Bennett's Kappa are shown in Table 4, and the strength of agreement is classified as follows: slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80) and almost perfect (0.81–1.00).

Comparing the three instruments at 90 minutes, the SAMPE checklist had the most conservative approach, avoiding the discharge of 263 patients. From these, 146 could be discharged according to the White score, and 200 would be discharged according to the modified Aldrete score.

Domains and frequency that had avoided the patients' discharge from PACU, despite reaching readiness conditions according to White and Aldrete modified scores are summarized in Table 5.

## Discussion

In our study, we presented a new recovery room discharge checklist from its conception to its prospective comparison

with other instruments. Our main finding is the conceptualization of a feasible instrument with a good index of correspondence with the White scale and moderate agreement with Aldrete. It also demonstrated a conservative approach, since with SAMPE checklist criteria 26% of patients did not achieve conditions for discharge, in spite of being ready with White or Aldrete scales.

The substantial but not perfect agreement of the new checklist with White scale were expected results since our proposed checklist was a conservative instrument. The absence of alternatives or items in each dominium is the main difference between our instrument and the others. This approach prevented the discharge until complete recovery from each dominium, turning the process of discharge and handover more understandable and more precise by the different caregivers.

There is no uniform definition of which variables should be evaluated to determine if a patient is eligible for discharge from PACU. The domains most commonly evaluated are vital signs, pain, level of consciousness, and nausea

**Table 3** Demographic and surgical characteristics.

Item	Description	Number (%)
Gender	Male	468 (46.94%)
	Female	529 (53.05%)
Age	< 1 year	9 (0.9%)
	1–12 years	131 (13.14%)
	12–18 years	51 (5.11%)
	18–65 years	621 (62.29%)
ASA	> 65 years	185 (18.56%)
	I	225 (22.57%)
	II	540 (54.16%)
	III	224 (22.47%)
Procedure	IV	8 (8.02%)
	Elective	973 (97.59%)
Anesthesia	Urgency / Emergency	24 (2.41%)
	Sedation	93 (9.33%)
	General	637 (63.89%)
Surgical	Regional	193 (19.36%)
	Combined	74 (7.42%)
	Minor / Intermediate	647 (64.89%)
Surgical specialty	Major	50 (35.11%)
	Urology	149 (14.94%)
	General	111 (11.13%)
	Gynecological	102 (10.23%)
	Ophthalmology	101 (10.13%)
	Otolaryngology	81 (8.12%)
	Digestive	73 (7.32%)
	Orthopedics	69 (6.92%)
	Pediatric	60 (6.02%)
	Mastology	46 (4.61%)
	Thoracic	36 (3.61%)
	Vascular	35 (3.51%)
	Coloproctology	35 (3.51%)
	Head and neck	23 (2.31%)
	Plastic	20 (2.01%)
	Cardiac	12 (1.20%)
	Neurosurgery	7 (0.70%)
	Others	29 (2.91%)

**Table 4** Agreement on discharge from Recovery Room Scales.

KAPPA STATISTIC (PABAK)			
	Kappa	Confidence interval	
SAMPE vs White	0.69	0.65	0.74
SAMPE vs Aldrete	0.58	0.53	0.63
Aldrete vs White	0.48	0.39	0.57

Bennett's formula produces a result also known as the Prevalence-adjusted Bias-adjusted Kappa (PABAK).

and vomiting, with variations in the way of assessing them between the instruments.

Our instrument encompasses eight significant parameters, including nausea and vomiting, pain and surgical bleeding, that were not evaluated in Aldrete criteria. These differences are crucial to increase the quality of care. These parameters, even not life threatening, must be routinely evaluated and fully controlled before ward or home dis-

charge, especially considering the great hiatus at about 4–6 hours between vital signs evaluation in the common ward. Furthermore, uncontrolled pain, unavoidable nausea and vomiting or surgical bleeding are associated to readmission in ambulatory patients.<sup>12</sup> The main parameters associated to the PACU stay after 90 minutes in our study were uncontrolled pain (45%), sensory pattern not recovered (36%), residual block (15%), and nausea or vomiting (13%).

Circulatory and respiratory systems are also compromised by most anesthetic procedures and their instability brings life-threatening complications. Most instruments use blood pressure and oxygen saturation as objective markers of these systems. However, different parameters and combinations can be used. Gartner et al.<sup>13</sup> proposed the inclusion of respiratory rate, systolic blood pressure and heart rate, all with predetermined objective values, without considering previous patient measures. Song et al.<sup>14</sup> considered necessary to have no blood pressure difference greater than 30% in relation to preoperative levels and respiratory stability was evaluated by frequency and presence of cough reflex. Most of the studies consider oxygen saturation greater than 94% in room air suitable for discharge, being a parameter of easy evaluation and standardization, which provides essential information about the cardiopulmonary system. There is no evidence suggesting which combinations of vital signs would be superior to assess safe discharge conditions for PACU patients, but it seems reasonable that similar preoperative values will be reached in the postoperative period before discharge. There are also recent studies showing the deleterious effect of intraoperative<sup>15</sup> and postoperative hypotension,<sup>16</sup> and its association with renal and cardiac injury. For example, the POISE 2 substudy<sup>17</sup> demonstrated that clinically important postoperative hypotension (defined as systolic blood pressure less than 90 mmHg requiring intervention) was significantly associated with a composite of myocardial infarction and death even after adjustment for previous hypotension.

Also, a consensus published by the Perioperative Quality Initiative (POQI)<sup>18</sup> reviewed the relationships between postoperative arterial pressure and postoperative outcomes, and stated that there is evidence of harm associated with postoperative systolic arterial blood (SBP) pressure less than 90 mmHg and higher with preoperative hypertension.

This recommendation is based on studies which concluded that high postoperative MEWS scores (modified early warning systems) are strongly associated with postoperative outcomes. Systolic blood pressure below 90 mmHg, respiratory rate below 8 and saturation below 91% are the levels considered to segregate normal physiologic changes from pathologic vital variation. Patients presenting high MEWS scores had an increased risk of complications.<sup>19</sup> Furthermore, Roshanov et al.<sup>20</sup> showed that levels of systolic blood pressure below 90 mmHg of any duration until the end of postoperative day 3 were associated with cardiovascular events regardless presence or of the degree of coronary artery disease. These findings corroborate the recommendation of our checklist that established systolic blood pressure above 90 mmHg for all patients to be discharged. In an observational study, Stephenson<sup>21</sup> evaluated postoperative pain, and this experience was reported by patients as the most stressful factor associated with the surgical procedure. Pain is usually assessed with questionnaires that take into

**Table 5** Agreement on which domains patients were ready for discharge as a function of White and Aldrete scores, but not ready by SAMPE Checklist.

Checklist SAMPE item that prevented discharge in 90 minutes	Cases disagree with White criteria for discharge in 90 minutes (n = 146)	Cases disagree with Aldrete criteria for discharge in 90 minutes (n = 200)
(1) Stable vital signs	7 (4.8%)	7 (3.5%)
(2) Wake and oriented or sensory pattern as usual	53 (36.3%)	83 (41.5%)
(3) Spontaneous ventilation	0	0
(4) Saturation above 90%	2 (1.4%)	1 (0.5%)
(5) Controlled pain (verbal pain scale < 3)	66 (45%)	96 (48%)
(6) Absence of motor block, or residual block in regression	23 (15.8%)	27 (13.5%)
(7) Absence of nausea or vomiting	19 (13%)	31 (15.5%)
(8) Absence of bleeding in operative field	6 (4.1%)	5 (2.5%)
Total	146	200

account symptom intensity through scales with definitions of "mild", "moderate" and "severe", or with scores ranging from zero to ten. Some instruments allow only mild pain and others allow even moderate pain at the time of PACU discharge. Aggressive and satisfactory pain control in the PACU setting is one of the ways to provide good care and reduce patient suffering in any anesthetic-surgical setting, with a great repercussion on the unpleasant sensation experienced by the patients. It is desirable that a complaint so valued and feared by the majority of patients should be well controlled in the PACU, with the professionals used to this care, with resources for effective and aggressive management of pain.

Nausea and vomiting are highly unpleasant postoperative symptom, and most authors agree that these symptoms, when present, should be controlled prior to discharge from PACU. The most frequently used forms for assessing this dyad are to classify it as "light", "moderate" or "severe",<sup>12,13</sup> or as "absent", "transitory" or "persistent".<sup>14</sup> It is imperative to monitor and control these symptoms in the PACU, given the high frequency and discomfort caused, especially in the postoperative context.

Some psychomotor tests are available for assessment of postanesthetic recovery.<sup>22</sup> These tests are adapted from other areas, such as tests that evaluate time for reaction and attention. Unfortunately, most of these tests are very complex and impractical in the context of a PACU. In addition, discrete impairment of psychomotoricity does not appear to compromise the safety of discharge.

The assessment of the level of consciousness was responsible for a large number of disagreements between the instruments tested. This is because the SAMPE checklist allows discharge only for awake and oriented patients, or with their previous baseline pattern. Opting for safety and to be used in different settings, such as outpatient procedures, and in patients with different comorbidities, the SAMPE checklist does not tolerate any change in the state of consciousness at discharge.

Patients submitted to neuroaxial anesthesia are also submitted to the same criteria for discharge, along with the regression evaluation of the sensory, motor, and sympathetic

blocks.<sup>23</sup> It seems reasonable to grant discharge for patients with peripheral nerve block prior to complete regression of motor and sensory block, requiring that they receive verbal and written guidance of care to be taken with the limb blocked, including use of types, crutches, and the need for early use of analgesics.<sup>5</sup>

In 2017, Resolution 2174 was published in Brazil by the Federal Medical Council.<sup>24</sup> One of its articles attribute responsibility for discharge to anesthesiologists on duty at the unit and provide that during the stay in the recovery room up to the time of discharge, patients should be monitored and clinically evaluated for: circulation (including blood pressure and heart rate measurement, and continuous monitoring by cardioscopy), breathing (including determination continuous monitoring of hemoglobin peripheral saturation), state of consciousness, pain monitoring, movement of lower and upper limbs after regional anesthesia, control of body temperature, and nausea and vomiting. The SAMPE checklist includes all these safety proposal parameters, except for temperature.

Our study has some limitations. First, the evaluation was limited to one admeasurement at 90 minutes. We did not look to the postoperative outcomes, rates of complications or staff interventions, but it is not probable to have increased rates of complication with our simplified checklist because of its conservative approach.

Nevertheless, our objective was to develop a friendly and consistent instrument to overcome what would otherwise be a considerable challenge: the universal adoption of a handover instrument to improve surgical patient's safety during their in-hospital journey.

Second, our population consisted basically of low-risk patients from one single institution. It is utmost important to consider the lack of specificity of any instrument to the patient's risk. To overcome this issue, we are implementing strategies targeting better care to high-risk surgical patient, and some new items such as conference of fluid balance, urine debt and laboratories will be added to the recovery room checklist discharge of this vulnerable group (<https://clinicaltrials.gov/ct2/show/NCT0418764>).

## Conclusion

We presented a simplified and feasible checklist that contains all domains considered necessary for safety ward or home discharge. The SAMPE discharge checklist encompasses satisfactory agreement with the White score, though with few and assertive items, which seems to offer advantages over the current instruments adopted.

## Conflicts of interest

The authors declare no conflicts of interest.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.bjane.2021.07.004>.

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## ORIGINAL INVESTIGATION

### Emergence delirium in children: a Brazilian survey<sup>☆</sup>



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#### KEYWORDS

Emergence delirium;  
Child;  
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Survey

#### Abstract

**Background:** Pediatric emergence delirium is characterized by a disturbance of a child's awareness during the early postoperative period that manifests as disorientation, altered attention and perception. The incidence of emergence delirium varies between 18% and 80% depending on risk factors and how it is measured. Reports from Canada, Germany, Italy, United Kingdom, and France demonstrated a wide range of preventive measures and definitions, indicating that there is a lack of clarity regarding emergence delirium. We aimed to assess the practices and beliefs among Brazilian anesthesiologists regarding emergence delirium.

**Methods:** A web-based survey was developed using REDCap®. A link and QR Code were sent by email to all Brazilian anesthesiologists associated with the Brazilian Society of Anesthesiology (SBA).

**Results:** We collected 671 completed questionnaires. The majority of respondents (97%) considered emergence delirium a relevant adverse event. Thirty-two percent of respondents reported routinely administrating medication to prevent emergence delirium, with clonidine (16%) and propofol (15%) being the most commonly prescribed medications. More than 70% of respondents reported a high level of patient and parent anxiety, a previous history of emergence delirium, and untreated pain as risk factors for emergence delirium. Regarding treatment, thirty-five percent of respondents reported using propofol, followed by midazolam (26%).

<sup>☆</sup> This study was presented as e-poster during the Euroanaesthesia 2020, and it is published in the European Journal of Anaesthesiology Abstracts Programme.

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**Conclusion:** Although most respondents considered emergence delirium a relevant adverse event, only one-third of them routinely applied preventive measures. Clonidine and propofol were the first choices for pharmacological prevention. For treatment, propofol and midazolam were the most commonly prescribed medications.

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## Introduction

Emergence delirium (ED) is characterized by a disturbance of a child's awareness during the early postoperative period. Children with ED are disoriented and present with alterations in consciousness, attention and perception, including hypersensitivity to stimuli and hyperactive motor behaviors.<sup>1</sup> This postoperative phenomenon is self-limited and generally lasts 15 to 30 minutes, however long-lasting postoperative cognitive changes after ED is not well defined in children.<sup>2</sup> Children with ED can harm themselves and their caregivers, leading to an increased likelihood of accidentally removing catheters, drains, or dressings as well as an increased workload for nurses and anesthesiologists in the postanesthesia care unit (PACU).<sup>1,3</sup> The incidence of ED varies between 18% and 80% depending on how ED is defined and depending on which scale is used for diagnosis.<sup>4</sup> Several scales were developed but not validated.<sup>5,6</sup> To date, the only validated scale is the Pediatric Anesthesia Emergence Delirium (PAED).<sup>3</sup>

Risk factors for ED include the type of surgical procedures (ear, nose, and throat surgery, and ophthalmology), clinical characteristics (preschool age), and anesthesia technique (inhalation anesthesia with sevoflurane and desflurane).<sup>7</sup> The ideal approach to ED is prevention; various medications have been shown to be effective, especially propofol and alfa-2 agonists.<sup>8</sup>

The definition, diagnosis, and management of ED varies in the literature. Reports from Canada,<sup>9</sup> Germany,<sup>4</sup> the UK,<sup>10</sup> Italy,<sup>10</sup> and France<sup>11</sup> describe various methods for ED risk stratification, diagnosis, prevention, and treatment among pediatric anesthesiologists. However, little is known about Brazilian anesthesiologists' experience with ED management. Therefore, we aimed to assess the practices and knowledge among Brazilian anesthesiologists regarding the diagnosis, prevention, and treatment of ED in children.

## Methods

This study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)<sup>12</sup> and the Checklist for Reporting Results of Internet E-surveys (CHERRIES)<sup>13</sup> guidelines.

After obtaining approval from the local IRB (Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo. Research approval number: 3.158.799), a 37-item questionnaire was developed based on the publications of Rosen HD et al.<sup>9</sup> and Huett C et al.<sup>4</sup> The need for an informed consent form was waived by the IRB, as volunteering to respond to the survey was considered as consent.

The questionnaire was managed using the REDCap® electronic data capture tool hosted at Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo.<sup>14,15</sup> A pilot study was performed with ten anesthesiologists to test the usability, content, and ease of completion. After the correction of technical functionalities, the questionnaire was transferred onto the software, and the final version was protected and could not be changed. A link and a QR Code were created to distribute the survey.

A cover letter explaining the objectives of the study along and the link or QR Code for the study were emailed to a list of all anesthesiologists associated with the Brazilian Society of Anesthesiology (SBA). Two reminders were sent, including one in the beginning of April 2019 and one in May 2019. Data were automatically stored and protected in REDCap®.

Considering that there are 24,000 anesthesiologists in Brazil, a sample size of 648 anesthesiologists was required to obtain a 99% confidence interval and 5% margin of error for this study.<sup>16</sup> Data stored in the REDCap® were downloaded to a .csv (comma-separated values) file, and only completed questionnaires were analyzed. Statistical analysis was performed using STATA® 15.1. Data are presented as frequencies.

## Results

The link and QR Code for the questionnaire was available from April to June 2019 and was opened 863 times. We collected 671 completed questionnaires.

### Characteristics of participants and hospitals

The data in Table 1 demonstrates that the majority of respondents (53%) worked in tertiary hospitals, and only 11% worked in pediatric hospitals. Regarding experience in anesthesia practice, 36 respondents were practicing anesthesia for more than 15 years and 35% were practicing for less than five years.

### Incidence of emergence delirium

The majority of respondents (97%) considered ED a relevant adverse event in their clinical practice. When asked about how much ED affects the quality of anesthesia, 29% and 39% answered "a lot" and "too much", respectively. Thirty-five percent of respondents reported an increase in the work of nurses in the PACU to treat ED at least once a week, and 24% of respondents were called to the PACU to treat ED at least once a week. On the other hand, the majority of respondents (45%) were never called to the PACU to treat ED.

**Table 1** Characteristics of participants, hospital structures, and clinical practice.

Characteristic	N (%)
Type of hospital	
Tertiary	353 (53)
Secondary	101 (15)
University	121 (18)
Outpatient clinic	18 (3)
Pediatric	76 (11)
Years practicing anesthesia since end of residency program	
Less than 5	235 (35)
6-10	130 (20)
11-15	60 (9)
More than 15	243 (36)
Pediatric cases per day	
Less than 5	324 (48)
5-10	199 (29)
11-15	51 (8)
16-20	24 (4)
More than 20	70 (11)
Pediatric cases per week	
Less than 5	433 (65)
5-10	176 (26)
11-15	38 (6)
16-20	4 (1)
More than 20	17 (2)
Pediatric surgical and diagnostic specialties anesthesiologists mostly work with	
Pediatric general surgery	525 (78)
ENT	488 (73)
Radiology	363 (54)
Orthopedic	351 (52)
Endoscopic	299 (45)
Trauma and emergency	242 (36)
Urology	217 (32)
Neurosurgery	216 (32)
Ophthalmology	180 (27)
Dentist	157 (23)
Plastic surgery	108 (16)
Cardiac surgery	89 (13)

ENT, ear, nose, and throat.

### Characteristics of practice regarding premedication, induction, maintenance, and recovery of general anesthesia

Forty-eight percent of respondents reported using premedication routinely. Midazolam was the most commonly used medication (95%), and it was mostly administered orally (88%). A few respondents reported using another class of premedication, such as clonidine (2%) or dexmedetomidine (1%). Few respondents reported using intramuscular administration for premedication (1%).

When asked about anesthesia induction, the majority of respondents (86%) preferred inhalation induction. Regarding anesthesia maintenance, 59% reported a preference for inhalation with sevoflurane or balanced anesthesia (35%).

**Table 2** Potential risk factors for emergence delirium.

Risk factor	Yes (%)
Untreated postoperative pain	93
High level of patient anxiety	80
High level of parental anxiety	78
Previous history of ED	72
Preschool age	57
Use of sevoflurane	57
ENT or ophthalmology surgery	49
Rapid emergence	42
Developmental delay	37
Short duration of anesthesia	12

ED, emergence delirium; ENT, ear, nose, and throat.

Only a few respondents (4%) reported using intravenous anesthesia for maintenance in pediatric anesthesia.

Regarding anesthesia recovery, the majority of respondents (84%) reported that children recovered in a general PACU, and only 11% reported that children recovered in a "quiet and nice pediatric PACU". Eighty-three percent and 61% of respondents reported that nurse technicians and registered nurses worked in the PACU, respectively. Thirty-seven percent and 2% reported that general physician anesthesiologists and pediatric anesthesiologists worked in the PACU, respectively.

Parental presence was allowed in the PACU for the majority of respondents (77%), and only 9% reported that parents could wait for their children to awaken in the operating room.

### Risk factors

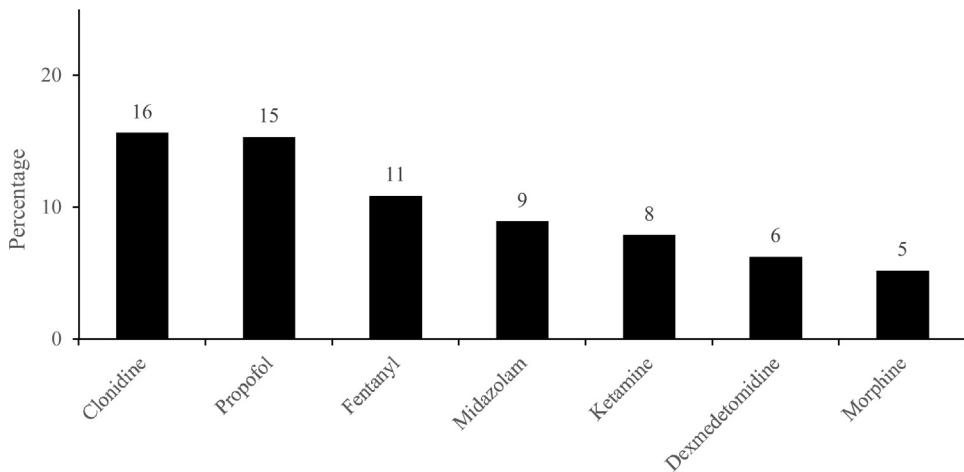
More than 70% of respondents reported that a high level of patient anxiety, a high level of parental anxiety, a previous history of ED, and untreated pain were risk factors for ED. The other potential risk factors for ED are listed in **Table 2**. When asked if they discussed the potential risk factors with parents during the preanesthetic visit, the majority of respondents (54%) answered "no". Forty-four percent of respondents reported that a PACU with considerable noise could influence the occurrence of ED.

Isoflurane and desflurane were considered risk factors by 55% and 52% of respondents, respectively. Midazolam was either considered to be a risk factor for ED (36%) or a protective factor against ED (34%). The majority of respondents (62%) reported that the presence of parents during induction protects against ED.

Sixty-five percent of respondents reported that when a child is agitated in the induction, she/he will awake agitated, and 47% reported that if a child is calm during induction, she/he will awaken calm.

### Evaluation and diagnosis

Sixty-one percent of respondents reported that they routinely evaluated their patients regarding ED. However, only a few (5%, 20 respondents) routinely assessed patients with a specific scale; most of them (14 respondents) reported using the PAED scale.



**Figure 1** Frequency of preferences for preanesthetic or intraoperative anesthetic drugs to prevent emergence delirium.

## Prevention

Thirty-two percent of respondents reported routinely administrating medication to prevent ED before or during anesthesia. The most commonly used drugs are displayed in Figure 1.

Fourteen percent of respondents reported using total intravenous anesthesia (TIVA) to prevent ED.

## Treatment

Participants were asked about when they treated a child with ED, and the majority reported providing treatment when the patients were agitated and did not recognize the environment or their parents (77%) or when the children displayed vigorous and potentially harmful agitation (84%). Few respondents (5%) reported providing routine treatment in accordance with hospital protocols.

After ruling out postoperative pain and other causes of agitation, thirty-five percent of respondents reported using propofol, followed by midazolam (26%) and dexmedetomidine (6%) to treat ED. A small number of respondents (4%) reported using fentanyl to treat ED. When asked about the effectiveness of the treatment, 89% reported that a single dose is usually effective.

## Discussion

This survey assessed the beliefs and practices among Brazilian anesthesiologists regarding ED. Although the majority of anesthesiologists considered ED a relevant adverse event, only 32% routinely applied preventive measures. Propofol and clonidine were the most commonly used drugs to prevent ED, and propofol and midazolam were the most frequently used drugs to treat ED.

Several meta-analyses have demonstrated that inhalation anesthetics, especially sevoflurane and desflurane, are linked to ED.<sup>8,17,18</sup> The majority of respondents reported using inhalation anesthesia for the induction and maintenance of anesthesia, similar to the German study, which found that 61% of the respondents used sevoflurane for

anesthesia maintenance.<sup>4</sup> More than a half of respondents considered sevoflurane as a risk factor for ED. Considering this information, it appears that Brazilian anesthesiologists are not always focused on the prevention of ED.

Only 14% of anesthesiologists considered TIVA as an anesthetic technique for ED prevention. This finding is different from the German and Canadian studies, which found that 60% and 38% of respondents used TIVA for ED prevention, respectively.<sup>4,9</sup> This difference may highlight the difficulty or lack of experience with the use of TIVA in children among Brazilian anesthesiologists.

One-third of respondents reported using pharmacological strategies to prevent ED. This compares with almost half of respondents from the Canadian study who reported using pharmacological strategies to prevent ED.<sup>9</sup> Clonidine and propofol were considered the first choice for prevention among Brazilian anesthesiologists. This was similar to the French study, which found that clonidine was the first choice, and to the Canadian and German studies that reported propofol as the first choice for prevention.<sup>4,9,11</sup> Previous studies have shown that propofol and alfa-2 agonists are effective in preventing ED.<sup>8,19</sup>

Many studies have shown that dexmedetomidine can be used as a proper pharmacological prevention.<sup>8,20,21</sup> Our study showed that few anesthesiologists used dexmedetomidine, similar to the Canadian and German studies; respondents in the French study did not consider dexmedetomidine.<sup>4,9,11</sup> Dexmedetomidine is relatively new for pediatric anesthesia and has not yet been approved for anesthesia procedures. The U.S. Food and Drug Administration has only approved dexmedetomidine for sedation, predominantly in intensive care units.<sup>22</sup> Being an off-label drug for anesthesia could explain the relatively low use of dexmedetomidine for ED prevention.

More than 96% of respondents reported ED as a relevant adverse event; however, only 5% reported using specific tools to measure ED. Fourteen respondents reported using the PAED scale, which is the only validated scale for assessing ED.<sup>3</sup> Although the majority considered ED a relevant adverse event, almost half of respondents reported that they were never called to the PACU to access or treat ED. One reason could be that the PAED scale is validated only in English,

making this scale more difficult to apply among Portuguese speakers. The translation and transcultural validation of the PAED scale is necessary to improve the quality of ED diagnosis in Brazil.

Untreated postoperative pain was considered a risk factor for more than 90% of respondents. This was in contrast with the German and Canadian studies, in which untreated pain was not stated as a risk factor, although an Italian survey showed that pain was considered a risk factor for ED.<sup>4,9,10</sup> Somaini et al.<sup>1</sup> conducted a prospective study and concluded that it is difficult to differentiate between ED and pain using observational scales such as the PAED scale. Locatelli et al.<sup>23</sup> also reported that the first three items of the PAED scale (eye contact, purposeful action, awareness of the surroundings) presented a higher correlation to ED compared to the PAED items that were more correlated with pain (restlessness and inconsolability). It is important to point out that pain, hypoxia, hypercapnia, anxiety, pre-existing behavior characteristics, among others, are causes of agitation, but not delirium.

When a clinician is evaluating an agitated child, pain should be ruled out or treated if it is present. Non-surgical, diagnostic procedures under general anesthesia in children also have a high incidence of ED. Costi et al.<sup>19</sup> showed that the transition to propofol in sevoflurane-based anesthesia could reduce the incidence and severity of ED in children undergoing magnetic resonance imaging (MRI) under general anesthesia. Several meta-analyses<sup>24–26</sup> have compared pharmacological strategies to prevent ED in children undergoing MRI and highlighted that procedures under general anesthesia without noxious stimulus can still lead to ED.

Brazilian anesthesiologists also considered a high level of child/parental anxiety and preschool age to be risk factors for ED. The Canadian study showed that preschool age was the most prevalent risk factor reported, followed by a previous history of ED.<sup>9</sup> The German study reported a previous history of ED and preoperative anxiety as the most common risk factors.<sup>4</sup> A survey from the UK and Italy also found that preoperative anxiety was a risk factor among respondents.<sup>10</sup> A previous history of ED was considered a risk factor for more than 70% of Brazilian respondents, similar to the Canadian and German survey.<sup>4,9</sup> The European Society of Anaesthesiology evidence-based and consensus-based guidelines on postoperative delirium state that the risk of recurrence of ED is unclear.<sup>2</sup> However, compared to the elderly, long-lasting cognitive changes studies after ED in children are scarce.<sup>2</sup> On the other hand, strong evidence showed that single exposures during a short period to general anesthetics were not related to long-term cognitive outcomes in the pediatric population.<sup>27–29</sup>

The use of midazolam as pharmacological prevention for ED is controversial. Surveys of anesthesiologists from the UK and Italy demonstrated that the majority of Italian respondents reported using midazolam as the first choice for the prevention and treatment of ED.<sup>10</sup> In contrast, few UK anesthesiologists used midazolam as the first choice. The Brazilian survey also demonstrated conflicting results, with one-third of respondents considering midazolam as a risk factor and one-third considering midazolam to be useful as a pharmacological prevention strategy.

The best approach to ED is prevention, with the majority of clinical trials related to pharmacological or nonphar-

macological strategies. Regarding ED treatment, Brazilian anesthesiologists reported using propofol as the first choice, very similar to the Canadian,<sup>9</sup> German,<sup>4</sup> British,<sup>10</sup> and French<sup>11</sup> surveys.

One of the nonpharmacological treatment options is parental presence in the PACU. The majority of Brazilian anesthesiologists reported that parents are allowed to wait for their children to awake in the PACU. This was also reported in the French, British, and Italian studies.<sup>10,11</sup> Additionally, Brazilian respondents considered the parental presence during the induction a preventive measure, in contrast with Canadian anesthesiologists, who did not find parental presence to be protective against ED.<sup>9</sup>

This study has limitations inherent to all web-based survey reports. The questionnaire was sent to all Brazilian anesthesiologists associated with the Brazilian Society of Anesthesiology (SBA). A lack of information about how many anesthesiologists received the email made it impossible to determine the response rate. We analyzed only the completed questionnaires, so we did not analyze partially completed questionnaires. Another limitation, very similar to the German study,<sup>4</sup> is that approximately only 5% of Brazilian respondents reported using the PAED scale for ED diagnosis. The absence of an adequate tool to measure ED could jeopardize proper treatment, prevent anesthesiologists from knowing the true incidence of ED, and inhibit the application of preventive measures. Additionally, the PAED scale has not been translated and cross-validated for Brazilian Portuguese, which makes its use even more difficult.

In conclusion, this study assessed the beliefs and practices among Brazilian anesthesiologists regarding ED. Although most respondents considered ED as a relevant adverse event, only one-third routinely applied preventive measures. Clonidine and propofol were the first choices for pharmacological prevention, and propofol was the first choice for pharmacological treatment. Untreated pain was considered the leading risk factor. This finding indicated that Brazilian anesthesiologists also have difficulty differentiating postoperative pain and ED, likely due to a lack of appropriate tools to measure postoperative pain and ED.

## Conflicts of interest

The authors declare no conflicts of interest.

## Acknowledgment

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.bjane.2020.12.029>.

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## ORIGINAL INVESTIGATION

### Risk factors associated with treatment of hyperactive postoperative delirium in elderly patients following hip fracture surgery under regional anesthesia: a nationwide population-based study



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#### KEYWORDS

Hip fracture;  
Anesthesia;  
Delirium

#### Abstract

**Background and objectives:** Delirium is common but is frequently undetected by clinicians, despite the fact that it can be life-threatening. This study aimed to identify the incidence of delirium and the preoperative factors associated with perioperative use of drugs to treat hyperactive delirium in elderly patients who underwent hip fracture surgery under regional anesthesia.

**Methods:** We retrospectively reviewed records of all patients  $\geq 65$  years of age who had undergone hip-fracture surgery under regional anesthesia, covered by the Korean National Health Insurance, between January 1, 2009 and December 31, 2015. A univariate and stepwise logistic regression model with the occurrence of hyperactive delirium as the dependent variable was used to identify the perioperative factors for this sample of patients.

**Results:** Among the 70,696 patients who underwent hip fracture surgery, 58,972 patients who received regional anesthesia were included in our study; of these, perioperative use of drugs to treat hyperactive delirium was diagnosed in 8,680 (14.7%) patients. Performing stepwise logistic regression, preoperative variables found to be associated with delirium were: male sex, age  $\geq 85$  years, hospital type (medical center), ICU and ventilator care, the presence of a neurodegenerative disorder, uncomplicated diabetes mellitus, peptic ulcer disease, and previously diagnosed psychoses and/or depression (OR = 1.49 [1.42–1.58], 4.7 [4.15–5.37], 13.3 [7.57–23.8], 1.52 [1.43–1.60], 1.19 [1.01–1.40], 1.20 [1.14–1.27], 1.09 [1.04–1.14], 0.87 [0.96–0.00], 2.23 [1.48–3.37], and 1.38 [1.32–1.46], respectively).

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**Conclusions:** Postoperative hyperactive delirium may affect approximately 15% of elderly patients submitted to hip fracture repair under regional anesthesia. This study has identified multiple preoperative risk factors associated with postoperative hyperactive delirium and its pharmacological management strategies.

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## Introduction

With a rapidly aging population, the incidence of hip fracture continues to increase in South Korea.<sup>1</sup> Elderly patients who fracture their hips suffer adverse complications, including mortality, thus posing a medical and financial burden on society.<sup>2</sup> Although there have been improvements in surgical and anesthetic care over time, morbidity and mortality after hip fracture remain high.<sup>3</sup> One of the most common complications following hip fracture surgery is delirium, with a reported incidence rate between 4% and 53%.<sup>4</sup>

Delirium is common but frequently remains undetected by clinicians even though it can be life-threatening and give rise to serious preventable complications.<sup>5</sup> Postoperative delirium is known to be associated with increased length of ICU and hospital stay, increased hospital costs, and mortality after surgery.<sup>6</sup>

To decrease the mortality and morbidity including postoperative delirium, it is recommended that the type of anesthesia used in hip fracture surgery should be considered. The effects of the type of anesthesia on outcomes in elderly patients are debated; some studies have reported that the use of regional anesthesia (RA) yields a more favorable outcome while other studies report no difference in the outcome. Despite the favorable results of RA in hip fracture surgery, delirium still occurs. Thus, the risk factors for delirium require investigation so that postoperative complications can be reduced in geriatric patients. The objective of this study was to identify the incidence of hyperactive delirium and the preoperative factors associated with hyperactive delirium in elderly patients who underwent hip fracture surgery under regional anesthesia.

## Methods

This study was reviewed and approved by the institutional review board (IRB N° 2019-05-005), and the need to obtain informed consent was waived because we used de-identified administrative data.

The NHIS is a single health insurer managed by the Korean government and covering approximately 97% of Koreans. The remaining 3% of Koreans are covered by the Medical Aid Program (MAP).<sup>7</sup> The National Health Information Database (NHID), created by the NHIS, is a public database composed of data obtained between 2002 and 2015 on the health care utilization, health screening, sociodemographic variables, and mortality for the entire South Korean population, composed of data obtained between 2002 and 2015. The NHID is open to all researchers whose study protocols are approved by the official review committee. The NHID pro-

vides data for research activity across various sectors, such as the social, economic, environmental, and industrial sectors, as well as for the policy and medical sectors, in the form of the Sample cohort database, Customized database, Health Disease index, and others. Among these services, our data were “customized health information data”, provided upon request specifically for our study.

## Participants

We included all patients  $\geq$  65 years old who underwent hip surgery under regional anesthesia in hospitals in Korea between January 1, 2009 and December 31, 2015 (based on admission date). The inclusion and exclusion criteria used were as follows:

### Inclusion criteria

Principal diagnosis upon admission of the femoral neck (S720) or trochanteric fracture (S721) based on the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code; admission with at least one of the following surgical operations based on procedure codes: Open Reduction of Fractured Extremity [Femur], Total Arthroplasty [Hip], or Hemiarthroplasty [Hip]; patients who received both spinal and epidural anesthesia

### Exclusion criteria

Patients with a diagnosis of multiple traumas or fractures ("S00–S70", "S73–99", "T07", or "T14"); patients who underwent more than two such operations during the same admission period; patients who had a diagnosis of psychiatric disease (F10–F29) and medication history of haloperidol, risperidone, and/or quetiapine prior to admission.

Hyperactive delirium was defined as a record of intravenous administration of haloperidol, risperidone, and quetiapine at least once during the hospitalization.

### Independent variables

The patient characteristics recorded included sex, age, comorbid conditions, and hospital type (medical center = 1, general hospital = 2, or clinic = 3). The Elixhauser Comorbidity method, which outperforms the Charlson Index in predicting inpatient death after orthopedic surgery, was used to identify patient comorbidities.<sup>8</sup> Elixhauser Comorbidity measures were calculated by the sum of weighted points based on the presence or absence of 31 different medical conditions. These include congestive

heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, complicated and uncomplicated hypertension, paralysis, other neurologic disorders, chronic pulmonary disease, complicated and uncomplicated diabetes mellitus, hypothyroidism, renal failure, liver disease, peptic ulcer disease, HIV infection/AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemia, alcohol abuse, drug abuse, psychoses, and depression. The comorbidities were followed using the list of ICD-10 codes defined by Quan et al.<sup>9</sup> Stays in the intensive care unit (ICU), as well as ventilator care, were also recorded.

## Statistical analysis

All statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC). Groups were compared using the Mann-Whitney U test; descriptive variables were analyzed by chi-squared analysis. Two-tail *p*-values were used throughout the analysis, and 95% confidence intervals were reported with relative risks and odds ratios for variables significantly associated with delirium. Using a univariate and stepwise logistic regression model with the occurrence of delirium as the dependent variable, perioperative factors were identified for this sample of patients. Stepwise logistic regression was performed with variables, which were statistically significant following the univariate logistic regression. All statistical testing was two-sided with a significance level of 0.05. For continuous variables, data are presented as the median (range).

## Results

We identified 70,696 patients who were admitted to the hospital during 2009–2015, were  $\geq 65$  years old, and underwent surgery for hip fracture under regional anesthesia; of these, 363 patients were excluded due to missing data. To reduce confounding bias, 11,361 patients with a concomitant diagnosis of psychiatric disease (F10–F29) and/or who had a medication history of haloperidol, risperidone, and/or quetiapine before admission were excluded. After these exclusions, 58,972 patients remained for inclusion in our study (Fig. 1).

The incidence of hyperactive delirium in patients who underwent hip-fracture surgery under regional anesthesia was 14.7% (8680/58972). Sex, age, Elixhauser Comorbidity score, and hospital type were different between the two groups (Delirium vs. No delirium, Table 1). Covariates including congestive heart failure, cardiac arrhythmia, peripheral vascular disorder, complicated and uncomplicated hypertension, neurologic disorder, uncomplicated diabetes mellitus, renal failure, fluid and electrolyte disorder, deficiency anemia, psychoses, and depression showed significant differences between the groups (Table 1). Additionally, ICU stays, ventilator care, and mortality were significantly different between the groups (Table 1).

Univariate factors associated with hyperactive delirium included male sex ( $OR = 1.26 [1.19–1.33]$ ), age  $\geq 85$  ( $OR = 4.5 [4.0–5.1]$ ), Elixhauser Comorbidity

score  $\geq 15$  ( $OR = 1.3 [1.14–1.48]$ ), hospital type 1 ( $OR = 26.8 [9.25–28.6]$ ), congestive heart failure ( $OR = 1.15 [1.09–1.21]$ ), cardiac arrhythmia ( $OR = 1.15 [1.09–1.21]$ ), perivascular disease ( $OR = 1.05 [1.0–1.1]$ ), uncomplicated hypertension ( $OR = 1.12 [1.05–1.19]$ ), complicated hypertension ( $OR = 1 [0.0–9.25]$ ), neurodegenerative disorder ( $OR = 1.26 [1.26–1.33]$ ), uncomplicated diabetes mellitus ( $OR = 1.02 [1.00–1.10]$ ), renal failure ( $OR = 1.15 [1.06–1.24]$ ), fluid disorder ( $OR = 1.07 [1.01–1.12]$ ), deficiency anemia ( $OR = 1.06 [1.0–1.11]$ ), psychoses ( $OR = 2.44 [1.64–3.62]$ ), and depression ( $OR = 1.33 [1.27–1.39]$ ). Duration of ICU stay ( $OR = 2.13 [2.02–2.25]$ ) and ventilator care ( $OR = 1.99 [1.7–2.3]$ ) were also significant risk factors for hyperactive delirium (Table 2).

After adjusting for other factors by stepwise logistic regression, male sex ( $OR = 1.49 [1.42–1.58]$ ), age  $\geq 85$  ( $OR = 4.7 [4.15–5.37]$ ), hospital type 1 ( $OR = 13.3 [7.57–23.8]$ ), ICU stay ( $OR = 1.52 [1.43–1.60]$ ), ventilator care ( $OR = 1.19 [1.01–1.40]$ ), neurologic disorder ( $OR = 1.20 [1.14–1.27]$ ), uncomplicated diabetes mellitus ( $OR = 1.09 [1.04–1.14]$ ), peptic ulcer disease ( $OR = 0.87 [0.96–0.00]$ ), psychoses ( $OR = 2.23 [1.48–3.37]$ ), and depression ( $OR = 1.38 [1.32–1.46]$ ) remained predictive for hyperactive delirium (Table 3).

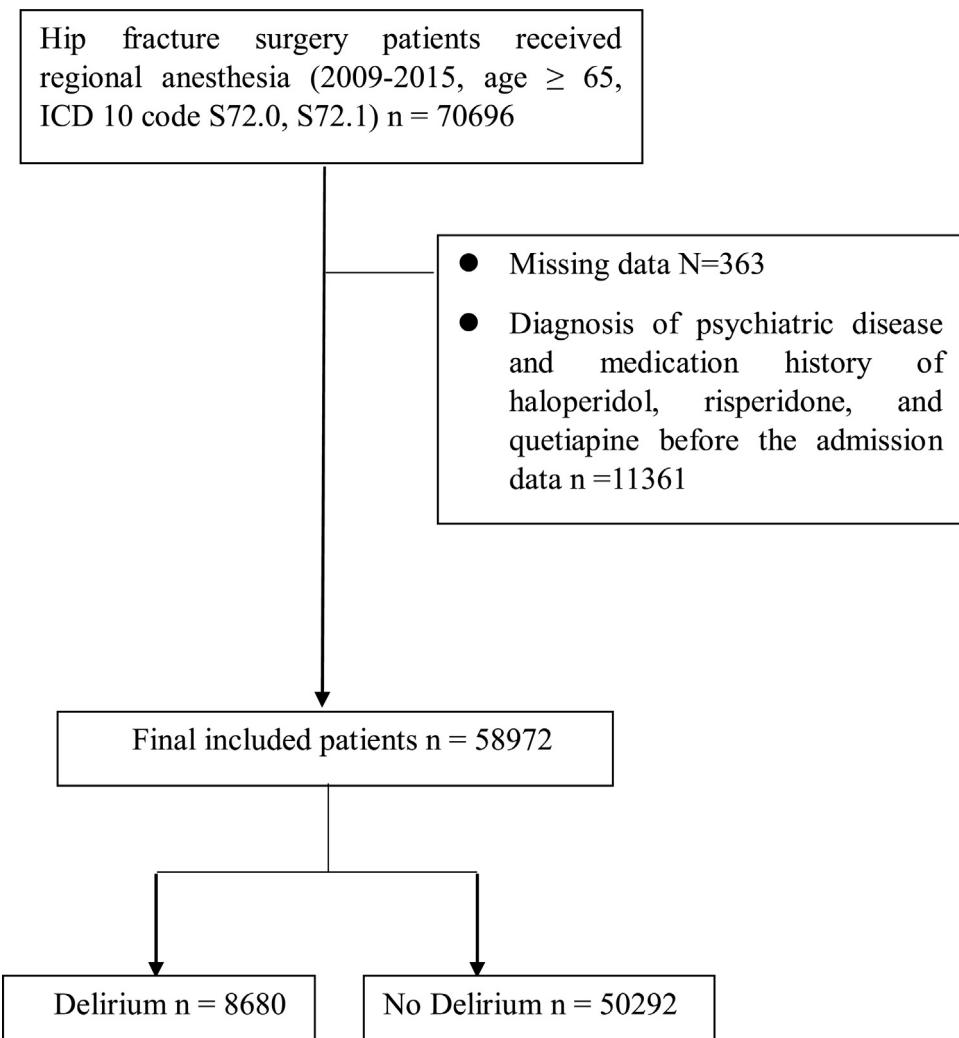
## Discussion

The present study reports that hyperactive delirium which needs pharmacologic intervention could occur in approximately 15% of elderly hip-fracture surgery cases in which regional anesthesia is used. Multiple preoperative risk factors, including male sex, age  $\geq 85$ , hospital type (medical center), ICU and ventilator care, neurodegenerative disorder, uncomplicated diabetes mellitus, peptic ulcer disease, psychoses, and depression, were associated with hyperactive delirium.

Elderly hip fracture patients require efficient, multidisciplinary perioperative evaluation and management to improve postoperative outcomes. The most common complication after hip fracture surgery is delirium, reported in up to 53% of the cases.<sup>4</sup> However, in our study, the incidence of delirium requiring pharmacological intervention in our population was 14.7%. The difference between these reported incidence rates may be related to the definition of delirium and the anesthetic method used.

Several previous reports compared the use of general anesthesia and regional anesthesia to reduce morbidity and mortality, including delirium. They reported that regional anesthesia yielded more favorable outcomes than general anesthesia.<sup>3,10,11</sup> Therefore, we selected only patients who underwent regional anesthesia to reduce selection bias. It is known that regional anesthesia is associated with shorter times for mobilization and positive outcomes.<sup>12</sup> Even regional anesthesia can cause delirium requiring pharmacological intervention to some extent. Therefore, the ability to detect patients who have a high risk of postoperative hyperactive delirium which needs pharmacologic intervention following hip surgery will reduce the incidence of delirium and help with its prevention.

Our results are consistent with those of previous studies. In line with previous reports, age  $\geq 85$  years was a

**Fig. 1** Flow diagram.

significant predictor of hyperactive delirium. It is further suggested that age  $\geq 85$  could be the cutoff for hyperactive delirium prevalence. Additionally, male patients had more developed delirium, similar to the study by Edelstein et al., which reported that the incidence of delirium in male patients was twice of that reported in females.<sup>13</sup>

Our study found that not only preoperative variables such as age, male sex, and comorbidities such as preoperative neurodegenerative disorder, diabetes mellitus, peptic ulcer disease, psychoses, and depression but also ICU stay and ventilator care may have strong associations with delirium. There are many known risk factors for delirium including the predisposing factors such as neurodegenerative disorder, depression, and comorbidity or severity of illness.<sup>14</sup> Duration of ICU stay and mechanical ventilation are also well known precipitating factors of delirium.<sup>15,16</sup> According to a recent study, peptic ulcer disease is associated with mental health problems, which suggests a possible role of the brain-gut axis system and the hypothalamic-pituitary-adrenal axis; however, further detailed evaluations are required to confirm their role.<sup>17</sup>

According to a meta-analysis of elderly hip fracture cases, patients with postoperative delirium had more than twice the risk of mortality than those without delirium.<sup>18</sup> Identification of patients who have a high risk of postoperative delirium will decrease both the prevention and treatment strategies, and help improve the hip fracture surgery outcomes.

The strength of this study was its use of anonymized data from nearly an entire country's population, which made its results less susceptible to selection bias. Additionally, we only selected patients who had received RA to reduce the influence of other types of anesthesia.

Nevertheless, this study had some limitations; first, this study used retrospective national claims data, and thus, the patient's clinical data were not included. Second, claims data can contain coding errors.<sup>19</sup> Third, information on diagnosis and disease included in the healthcare utilization database may not have sufficient validity for identifying disease occurrence and prevalence, since the data have not been analyzed and coded for research purposes, but rather for medical services claims and reimbursements. Fourth, several variables control the confounding factors which

**Table 1** Patient characteristics.

	Delirium (n = 8680)	No delirium (n = 50,292)	p-value
Sex (male/female)	2399/6281	11,718/38,574	<.0001*
Age (0/1/2/3/4)	279/835/1766/2447/3353	4426/8962/12,711/12,414/11,779	<.0001*
Elix (0/1/2/3)	1845/4020/2490/325	11,497/24,115/13,137/1543	<.0001*
Hospital type (1/2/3)	6931/1737/12	31,873/17,516/903	<.0001*
ICU care	2401(27.6)	7651(15.2)	<.0001*
Ventilator care	215(2.5)	635(1.3)	<.0001*
Congestive heart failure	2785(32.1)	14,619(29.1)	<.0001*
Cardiac arrhythmias	2259(26.0)	11777(23.4)	<.0001*
Peripheral vascular disorders	4599(52.9)	25,954(51.6)	0.0177*
Complicated hypertension	3060(35.3)	16,874(33.5)	0.002*
Neurodegenerative disorders	2151(24.8)	10,361(20.6)	<.0001*
DM, uncomplicated	4845(55.8)	27,416(54.5)	0.0242*
Renal failure	748(8.6)	3808(7.6)	0.0008*
Peptic ulcer disease, no bleeding	5453(62.8)	32,120(63.8)	0.0616
Rheumatoid arthritis/collagen vascular disease	3070(35.4)	18,303(36.4)	0.0666
Weight loss	3767(7.5)	700(8.1)	0.0619
Fluid and electrolyte disorders	13,262(23.4)	2418(27.9)	0.0038*
Psychosis	35(0.4)	84(0.17)	<.0001*
Depression	4098(47.2)	20,195(40.1)	<.0001*

Age 0, aged 65–70 years; Age 1, aged 70–75 years; Age 2, aged 75–80 years; Age 3, aged 80–85 years; Age 4, aged ≥ 85 years. Hospital type 1, medical center; Hospital type 2, general hospital; Hospital type 3, clinic. Elixhauser 1, Elixhauser < 5; Elixhauser 2, Elixhauser 5–9; Elixhauser 3, Elixhauser ≥ 10. ICU, intensive care unit. Values are expressed as absolute number (percentages), or absolute number.

\* p < 0.05 between-groups comparison.

**Table 2** Univariate analysis.

	Odds Ratio	95% confidence interval	p-value
Sex	0.794	0.754–0.836	<.0001*
Age	4.509	3.971–5.118	<.0001*
Elixhauser comorbidities	1.299	1.142–1.478	<.0001*
Hospital type	0.061	0.035–0.108	<.0001*
ICU care	2.132	2.022–2.248	<.0001*
Ventilator care	1.994	1.706–2.332	<.0001*
Congestive heart failure	1.15	1.095–1.208	<.0001*
Cardiac arrhythmias	1.148	1.09–1.21	<.0001*
Peripheral vascular disorders	1.055	1.008–1.104	0.0219*
Complicated hypertension	1.121	1.054–1.192	0.0003*
Neurodegenerative disorders	1.265	1.2–1.335	<.0001*
DM, uncomplicated	1.052	1.005–1.101	0.0313*
Renal failure	1.147	1.057–1.245	0.001*
Peptic ulcer disease, no bleeding	0.954	0.91–0.999	0.0518
Rheumatoid arthritis/collagen vascular disease	0.953	0.909–0.999	0.0478*
Weight loss	1.084	0.996–1.179	0.0607
Fluid and electrolyte disorders	1.072	1.019–1.128	0.0074*
Psychosis	2.437	1.642–3.618	<.0001*
Depression	1.33	1.27–1.392	<.0001*

ICU, intensive care unit; DM, diabetes mellitus.

\* p < 0.05 between-groups comparison.

could increase the risk of type-I error due to the multiple statistical tests. However, since the Elixhauser comorbidity score was able to determine the patient's underlying disease from the national claims data, we used the Elixhauser comorbidity score in this study. Finally, as previously stated, the definition of hyperactive delirium used in our study has its limitations; Since, neuroleptics including haloperi-

dol, risperidone, quetiapine could be used not only to treat hyperactive delirium but also as an adjuvant analgesic. Therefore, the incidence of the hyperactive delirium could have been overestimated. Also, the diagnosis of hyperactive delirium can be easily missed in a clinical setting, evaluating the nationwide claims data is difficult due to the variable incidence range. Thus, a working definition of

**Table 3** Stepwise logistic regression.

	Odds Ratio	95% confidence interval	p-value
Age	4.723	4.151–5.375	<.0001*
Hospital type	0.075	0.042–0.132	<.0001*
ICU care	1.519	1.435–1.607	<.0001*
Sex	0.669	0.634–0.706	<.0001*
Depression	1.385	1.318–1.456	<.0001*
Neurodegenerative disorders	1.206	1.139–1.276	<.0001*
Psychosis	2.232	1.476–3.375	<.0001*
Diabetes, uncomplicated	1.093	1.041–1.148	0.0013*
Peptic ulcer disease, no bleeding	0.916	0.871–0.963	0.0006*
Ventilator care	1.193	1.013–1.404	0.0343*

ICU, intensive care unit.

\* p < 0.05 between-group comparison.

hyperactive delirium is pertinent.<sup>19</sup> Further, delirium that does not require pharmacological intervention (such as the hypoactive subtype of delirium) may have been omitted in this study, so we must draw conclusions with caution.

## Conclusion

We retrospectively analyzed data of nearly 6 million elderly patients who underwent surgery for hip fracture under regional anesthesia. Hyperactive delirium requiring pharmacologic intervention patients who underwent surgery for hip fracture under regional anesthesia was associated with multiple risk factors, including male sex, old age, preoperative neurodegenerative disorder, diabetes mellitus, peptic ulcer disease, psychosis, depression, ICU stay, and ventilator care.

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## Ethical approval and consent to participate

The study was reviewed and approved by the institutional review board of Seoul Paik Hospital (IRB No 2019-05-005). The need to obtain informed consent was waived since we used de-identified administrative data.

## Availability of data and material

Data cannot be shared publicly because of confidentiality and privacy issues. Data may be available with a formal application to the institutional ethics committee (contact via <https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do>) for researchers who meet the criteria for access to confidential data.

## Conflicts of interest

The authors declare no conflicts of interest.

## Acknowledgements

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**ORIGINAL INVESTIGATION**

**Tranexamic acid in total shoulder arthroplasty under regional anesthesia: a randomized, single blinded, controlled trial**



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**KEYWORDS**

Total shoulder replacement;  
Tranexamic acid;  
Surgical blood loss;  
Blood transfusion

**Abstract**

**Purpose:** The purpose of this study was to determine whether Tranexamic Acid (TXA) can significantly reduce perioperative blood loss in Total Shoulder Arthroplasty (TSA) performed under regional anesthesia.

**Methods:** We performed a randomized, single blinded, controlled study. Forty-five patients were submitted to TSA under regional anesthesia to treat cuff tear arthropathy, proximal humeral fractures, chronic instability, primary osteoarthritis, and failures of previous prosthesis. Patients were randomized to either group TXA therapy (TXA), with 1 g intravenous (IV), or no Intervention (NTXA). Postoperative total drain output, hemoglobin variation, total blood loss, hemoglobin loss, and need for transfusion were measured. Pain-related variables were also assessed: postoperative pain assessment by visual analog scale, inpatient pain breakthrough, quality of recovery, length of stay, and coagulation function testing.

**Results:** Participants presented a mean age of 76 years, 15.6% were male, 82.2% were American Society of Anesthesiologists (ASA) physical status I or II. There were no differences between groups concerning transfusions, operative time, Post-Anesthesia Care Unit (PACU) length of stay and in-hospital stay, and QoR-15 or postoperative pain. Bleeding measured by drain output at 2, 24 and 48 hours was significantly less in the TXA group at each timepoint. There was a difference in Hb variation – TXA: median (IQR) -1.4 (1.3) g.dL<sup>-1</sup> vs. NTXA: -2.2 (1.3) g.dL<sup>-1</sup>; median difference: 0.80 (0.00–1.20);  $p = 0.047$ . aPTT was lower in TXA administered patients – TXA: median (IQR) 29.6 (14.0)s vs. NTXA: 33 (5.8)s; difference in medians: -4.00 (-6.50--1.00);  $p = 0.012$ .

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**Conclusion:** TXA use significantly decreased blood loss measured by drain output and Hb drop in TSA under regional anesthesia.

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## Introduction

Total Shoulder Arthroplasty (TSA) is associated with the risk of significant perioperative blood loss, with a rate of blood transfusions reported to be 4.3% to 43%<sup>1-3</sup> with recent transfusion rates ranging from 2.4% to 11.3%<sup>2,4,5</sup>. Although the amount of blood loss and number of necessary transfusions have been reported to be lower in TSA when compared to arthroplasties of the hip and knee, administration of erythrocyte concentrates is sometimes still indicated.<sup>2,3,6</sup> Complications of blood transfusions include allergic reactions, immunosuppression, infection and transfusion-related cardiopulmonary injury.<sup>3,7,8</sup> Moreover, perioperative blood transfusions increase the risk of medical complications such as myocardial infarction, pneumonia, sepsis and cerebrovascular accidents, as well as venous thromboembolic events and surgical complications, including periprosthetic infections, periprosthetic fractures, and mechanical complications.<sup>7</sup>

TXA is a synthetic antifibrinolytic agent which reversibly binds to plasminogen, preventing the normal cascade of fibrin clot dissolution.<sup>1,9,10</sup> The use of TXA results in less perioperative blood loss, fewer wound hematomas, and significantly lower transfusion rates.<sup>11,12</sup> TXA has demonstrated an excellent safety profile with minimal side effects and no increase in thromboembolic or cardiac events in the perioperative period, while being cost-effective in joint and hip arthroplasty, spine surgery and cardiac surgery.<sup>11,12</sup>

TXA has been validated to be effective in reducing blood transfusion requirements after hip and knee arthroplasty.<sup>13,14</sup> The efficiency of TXA in reducing blood loss following TSA has been demonstrated in small retrospective and controlled clinical trials,<sup>5,7,11,15</sup> however, their results are not consistent.<sup>4</sup> The influence of TXA in TSA due to humeral fracture was not studied. In all the papers TSA was performed under general anesthesia. We aimed to determine whether TXA can significantly reduce perioperative blood loss measured by drain output, drop in Hemoglobin (HG) and total blood loss in TSA performed under regional anesthesia.

## Methods

### Study design

We conducted a phase 3 randomized, single blinded (patient blinded), controlled trial in a tertiary hospital to assess whether TXA reduces blood loss and transfusion rate, intra- and postoperative, in patients undergoing TSA under regional anesthesia.

Patients undergoing TSA were recruited from February 2017 to May 2019. Eligibility criteria included patients with

more than 18 years of age and with the following indications for surgery: cuff tear arthropathy, proximal humeral fractures, chronic instability, primary osteoarthritis, and failures of previous prosthesis. Patients with known allergy to TXA, thromboembolic event in the previous year and refusal to be transfused, to perform regional anesthesia or give written informed consent were excluded from the study.

Sample size was calculated for a superiority trial in which hemoglobin variation differs 0.8 between groups, assuming a probability of a type II error of 0.20 and a critical alpha level of 0.05, with an expected standard deviation between groups of 1. A required sample of 20 subjects in each group was calculated. Thus, a total of 45 participants were enrolled and therefore randomized in two groups according to a computer-generated randomization list (parallel design, allocation ratio 1:1): TXA group (TXA, n = 23), where patients received an intravenous (IV) infusion of TXA 1 g immediately before surgery,<sup>5</sup> and a control group (NTXA, n = 22) where the same care was provided without the TXA infusion. The principal investigator was responsible for enrolling participants; the second and third authors generated the allocation sequence and assigned the intervention, respectively. Patients were blinded for the intervention as they were unaware of TXA administration. Moreover, participants were followed during their inpatient stay as well as 2 months postoperatively and defined primary and secondary outcomes were monitored and recorded.

### Anesthesia and surgical procedures

All patients were evaluated on a preoperative anesthesia appointment and anticoagulation therapy was stopped according to the guidelines of the European Society of Anesthesiology.<sup>16</sup>

Regional anesthesia was performed under 0.05–0.1 mg of fentanyl using an ultrasound-guided interscalene brachial block (20 mL) combined with a supraclavicular block (10 mL), in plane approach, with a mixture of ropivacaine 0.75% (135 mg), lidocaine 2% (200 mg) and dexamethasone 8 mg. Regional anesthesia was complemented with propofol sedation (1–3 mg·kg<sup>-1</sup>·h<sup>-1</sup>) in all cases.

All procedures were performed with the patient in a beach chair position, through a standard anterior deltopectoral approach. In 43 patients a reverse total shoulder arthroplasty was implanted (DePuy DELTA XTEND) and in 2 patients an anatomic arthroplasty (DePuy GLOBAL UNITE) was used. The same standard techniques and hemostasis were applied during all procedures. A medium Hemovac active drain was used in all cases placed deep into the joint space and was removed on postoperative day 2. Patients were transfused if Hemoglobin (Hb) level was < 7 g.dL<sup>-1</sup> or

if  $7.1\text{--}9 \text{ g.dL}^{-1}$  with symptoms of anemia (fatigue, hypotension, tachycardia, or tachypnea) or ischaemic heart disease.<sup>1</sup>

Postoperative analgesia was performed with paracetamol 1 g 8/8 h, tramadol 300 mg and ketorolac 60 mg in 24 hours. In case of allergic or adverse reaction to any drugs, dipyrone 2 g 12/12 h was used in substitution. For rescue analgesia it was used morphine 2 g IV. In addition, all patients received Deep Venous Thrombosis (DVT) prophylaxis with Enoxaparin 40 mg SC once a day and compression stockings on both legs until discharge from the hospital. Antibiotics prophylaxis were also performed.

## Data collection

Preoperative data regarding patient demographics and comorbidities was collected. Anemia was defined as less of  $13 \text{ g.dL}^{-1}$  for males and less of  $12 \text{ g.dL}^{-1}$  for females.<sup>17</sup> Chronic pulmonary disease included asthma, Chronic Obstructive Pulmonary Disease (COPD), and obstructive sleep apnea. Cerebrovascular disease was defined as transient ischemic attack or stroke. Postoperative platelet count and coagulation studies were performed in the first postoperative day. Hemoglobin was measured at three different timepoints – preoperatively and at 2 and 24 hours postoperatively. Hemoglobin variation, total blood loss, hemoglobin loss and total blood volume for males and females were defined as follows:

Equation1 : Hbvariation

$$= (\text{Hbat24 h[g.L}^{-1}\text{]} - \text{preoperativeHb[g.L}^{-1}\text{]})$$

Equation2 : Totalbloodlost(mL)

$$= (1000 \times \text{Hbloss[g]} / \text{Hbinitial[g]})$$

Equation3 : Hbloss = bloodvolume

$$(L \times [\text{Hbinitial.g.L}^{-1} - \text{Hbfinal.g.L}^{-1}])$$

$$+ \text{Hbtransfused[52 gofHbperunit])}$$

Equation4(males) : BloodVolume-( $0.3669 \times \text{heightinmeters}^3$ )

$$+ (0.03219 \times \text{weightinkg}) + 0.6041$$

Equation5(females) : BloodVolume-( $0.3561 \times \text{heightinmeters}^3$ )

$$+ (0.03308 \times \text{weightinkg}) + 0.1833$$

## Outcomes

Primary outcomes were blood loss-related:<sup>1,5</sup> total drain output measured at 2, 24 and 48 hours postoperatively;

hemoglobin variation, using preoperative hemoglobin levels (Equation 1), total blood loss (Equation 2), hemoglobin loss (Equation 3) and need for transfusion. Total blood volume was calculated using Equations 4 and 5 by Nadler et al.<sup>18</sup> and Good et al.<sup>19</sup>

Secondary outcomes were postoperative pain assessment by Visual Analog Scale, (VAS) measured at rest and with movement at 2, 24, and 48 hours postoperatively; inpatient pain breakthrough, defined by extra morphine prescriptions when VAS > 3; quality of recovery, measured by the Portuguese adapted version of the Quality of Recovery 15 (QoR-15) questionnaire, a validated outcome measurement instrument in clinical trials;<sup>20</sup> PACU and in-hospital length of stay and coagulation function, assessed by International Normalized Ratio (INR) and activated Partial Thromboplastin Time (aPTT).

Patients were followed two months postoperatively and complications such as hematoma, transfusion reaction, infection and thromboembolic or other adverse events were recorded.

## Statistical analysis

Intention-to-treat analysis was performed. Normally distributed continuous variables were represented as mean and Standard Deviation (SD), while non-parametric variables as median and Interquartile Range (IQR). Categorical variables were presented as number and respective percentages. Continuous variables were compared between groups using Mann-Whitney U or Student's t-test according to normality testing; effect size was reported either as differences between means or medians and respective 95% Confidence Intervals (95% CI). Chi-Squared or Fisher's exact test were used to compare categorical variables; corresponding effect size was presented as Odds Ratio (OR) and 95% CI. Statistical significance was considered when  $p < 0.05$ . Statistics Package for Social Sciences (SPSS) v.25.0 was used for all statistical analysis.

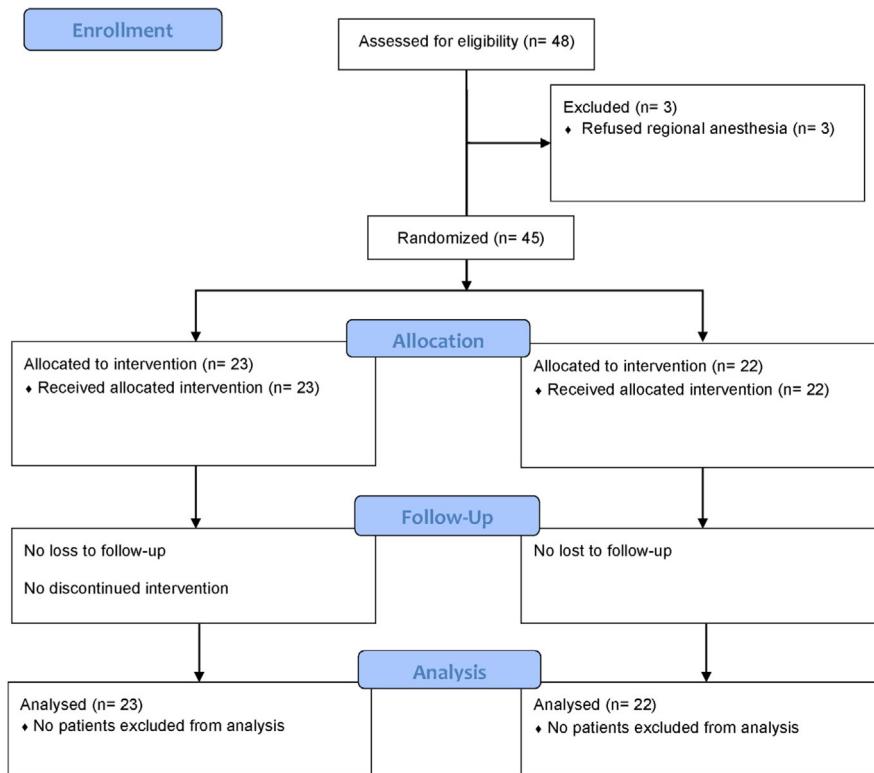
## Ethical statement

This study was approved by the hospital's Ethics Committee – Institutional Review Board. All enrolled participants signed a written informed consent and were blinded for the intervention.

## Results

### Patient characteristics

A total of 48 patients were assessed for eligibility. Three patients were excluded from the study as they were submitted to general anesthesia. Thus, 45 patients were included, of which 23 were allocated to the intervention arm (TXA) and 22 to the no intervention arm. Enrolled participants had the following surgery indications: cuff tear arthropathy ( $n = 20$ ), proximal humeral fractures ( $n = 18$ ), chronic instability ( $n = 2$ ), primary osteoarthritis ( $n = 2$ ) and failures of previous prosthesis ( $n = 3$ ). There was no exclusion

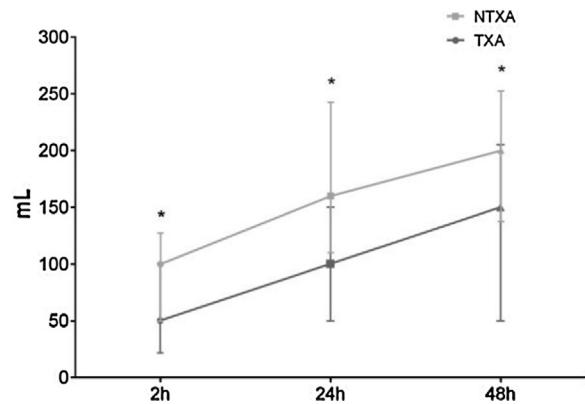
**Figure 1** Patient recruitment, randomization, and follow-up.

after randomization, contamination, or loss to follow-up in this study (Figure 1).

Participants' mean age was  $76.2 \pm 6.4$  years, and patients overall had excess weight ( $BMI 28.1 \pm 4.0$ ). In addition, 15.6% ( $n = 7$ ) of participants were male, 82.2% ( $n = 37$ ) were American Society of Anesthesiologists (ASA) physical status I or II, and 82.2% had a Revised Cardiac Index Risk (RCIR) of 0 ( $n = 37$ ). The most common comorbidity was arterial hypertension (68.9%,  $n = 31$ ), followed by dyslipidemia (51.1%,  $n = 23$ ), anemia (33.3%,  $n = 15$ ) and type 2 diabetes mellitus (20%,  $n = 9$ ). Hematologic disorders (8.9%,  $n = 4$ ) included thrombocytopenia ( $n = 1$ ), antiphospholipid syndrome ( $n = 1$ ), use of anticoagulants ( $n = 2$ ). Other comorbidities such as rheumatoid arthritis and peripheral artery disease were documented in 2 control group patients. There were no baseline differences between groups, either in age ( $p = 0.602$ ), gender ( $p = 0.365$ ), body mass index ( $p = 0.784$ ), ASA physical status ( $p = 0.358$ ), or RCIR ( $p = 0.473$ ). Likewise, distribution of comorbidities was similar between study arms. Patient characteristics are listed in Table 1.

### Analgesia and anesthesia assessment

Results regarding analgesia and anesthesia are depicted in Table 2. There were no differences between groups concerning operative time (TxA: mean  $113.7 \pm SD 27.7$  min; NTXA:  $107.9 \pm 35.2$  min;  $p = 0.542$ ), PACU length of stay (TxA: median 127.5 IQR (53.8) min; NTXA: 120 (60) min;  $p = 0.752$ ) and in-hospital stay (TxA: 3 (1) days; NTXA: 3 (2) days;  $p = 0.429$ ). Concerning patient postoperative recovery evaluated by QoR-15 questionnaire, no differences in score were observed between groups (TxA:  $128.2 \pm 22.3$ ; NTXA:

**Figure 2** Cumulative drain output at 2 h, 24 h, and 48 h in TXA and NTXA patients.

$121.4 \pm 23.1$ ;  $p = 0.357$ ). Moreover, pain did not vary according to TxA administration – Numeric Pain Scale (NPS) at 2, 24, and 48 hours, at rest and with motion, and the inpatient pain breakthrough were similar between study arms (Table 2).

### Blood loss and coagulation function assessment

Concerning cumulative drain output at 2, 24, and 48 hours, bleeding was significantly less for the TxA treated group at each timepoint (Figure 2). At 2 hours postoperatively, drains presented a median (IQR) of 45 (93) mL in the TxA group vs. 100 (88) mL in the control group (difference in medians: -50.0 [-70.0-0.0];  $p = 0.009$ ). Drain output at 24 hours was 112.5 (108) mL in TxA vs. 200 (100) mL in controls (-60.0

**Table 1** Patient characteristics.

	Total (n = 45)	TXA (n = 23)	NTXA (n = 22)	p-value
Age (years), mean ± SD	76.2 ± 6.4	76.7 ± 7.1	75.7 ± 5.7	0.602
Sex				
Male, n (%)	7 (15.6)	4 (17.4)	3 (13.6)	1.000
BMI, mean ± SD	28.1 ± 4.0	28.0 ± 4.1	28.3 ± 4.1	0.784
ASA classification, n (%)				0.699
I-II	37 (82.2)	18 (78.3)	19 (86.4)	
III	8 (17.8)	5 (21.7)	3 (13.6)	
RCRI, n (%)				1.000
0	37 (82.2)	19 (82.6)	18 (81.8)	
1-2	8 (17.8)	4 (17.4)	4 (18.2)	
Hypertension, n (%)	31 (68.9)	18 (81.8)	13 (56.5)	0.108
Dyslipidemia, n (%)	23 (51.1)	9 (40.9)	14 (60.9)	0.181
Obesity, n (%)	7 (15.6)	2 (8.7)	5 (22.7)	0.243
Diabetes mellitus, n (%)	9 (20)	5 (21.7)	4 (18.2)	1.000
Chronic kidney disease, n (%)	3 (6.7)	2 (8.7)	1 (4.5)	1.000
Cerebrovascular disease, n (%)	3 (6.7)	1 (4.3)	2 (9.1)	0.608
Congestive heart disease, n (%)	1 (2.2)	0 (0)	1 (4.5)	0.489
Ischemic heart disease, n (%)	1 (2.2)	1 (4.3)	0 (0)	1.000
Chronic pulmonary disease, n (%)	3 (6.7)	0 (0)	3 (13.6)	0.109
Anemia, n (%)	15 (33.3)	11 (47.8)	4 (18.2)	0.057
Other hematologic disorders, n (%)	4 (8.9)	1 (4.3)	3 (13.6)	0.346
Hypothyroidism, n (%)	4 (8.9)	2 (8.7)	2 (9.1)	1.000
Depression, n (%)	4 (8.9)	1 (4.3)	3 (13.6)	0.346
Parkinson, n (%)	2 (4.4)	2 (8.7)	0 (0)	0.489

ASA, American Society of Anesthesiologists physical status; RCRI, Revised Cardiac Risk Index; SD, Standard Deviation.

**Table 2** Analgesia/anesthesia parameters between study groups.

	TXA	NTXA	95% CI	p-value
Operative time (min), mean ± SD	113.7 ± 27.7	107.9 ± 35.2	-5.84 (-25.02–13.34) <sup>a</sup>	0.542
Length of stay (days), median (IQR)	3 (1)	3 (2)	0.0 (-1.0–0.0) <sup>b</sup>	0.429
PACU length of stay (min), median (IQR)	127.5 (53.8)	120 (60)	0 (-20.0–45.0) <sup>b</sup>	0.752
QoR-15, mean ± SD	128.2 ± 22.3	121.4 ± 23.1	-6.78 (-21.48–7.93) <sup>a</sup>	0.357
Numeric pain scale (0–10), median (IQR)				
2 h				
Rest	0	0		
Motion	0	0		
24 h				
Rest	0 (3)	0 (1)	0.0 (0.0–0.0) <sup>b</sup>	0.296
Motion	2 (5)	0 (4)	2.0 (0.0–2.0) <sup>b</sup>	0.496
48 h				
Rest	0 (0)	0 (0)	0.0 (0.0–0.0) <sup>b</sup>	0.180
Motion	0 (2)	0 (4)	0.0 (0.0–0.0) <sup>b</sup>	0.713
Inpatient pain breakthrough, n (%)	5 (25)	6 (28.6)	1.12 (0.52–2.42) <sup>c</sup>	1.000

PACU, Post-Anesthesia Care Unit; QoR, Quality of Recovery; IQR, Interquartile Range.

<sup>a</sup> 95% Confidence Interval of the mean difference.

<sup>b</sup> 95% Confidence Interval of the median difference.

<sup>c</sup> 95% Confidence Interval of the Odds Ratio.

[-110.0–20.0];  $p = 0.008$ ). Total cumulative drainage at 48 hours was 150 (155) mL in patients with TXA comparing to 210 (95) mL in the no intervention group (-50.0 [-110–0.0];  $p = 0.030$ ) (**Table 3**).

Hemoglobin was measured preoperatively and at 2 and 24 hours postoperatively. Neither individual value was different between groups – TXA: median (IQR) 12.5 (1.5) vs.

NTXA: 13.1 (1.3),  $p = 0.152$ ; 11.2 (1.9) vs. 11.8 (1.5),  $p = 0.220$  and 10.8 (1.5) vs. 10.8 (1.2),  $p = 0.993$ , respectively. However, there was a difference in Hb variation between intervention arms – TXA: median (IQR) -1.4 (1.3) g.dL<sup>-1</sup> vs. NTXA: -2.2 (1.3) g.dL<sup>-1</sup>; difference in medians: 0.80 [0.00–1.20];  $p = 0.047$  (**Figure 3, Table 3**).

**Table 3** Postoperative blood loss, platelets, and coagulation parameters between study groups.

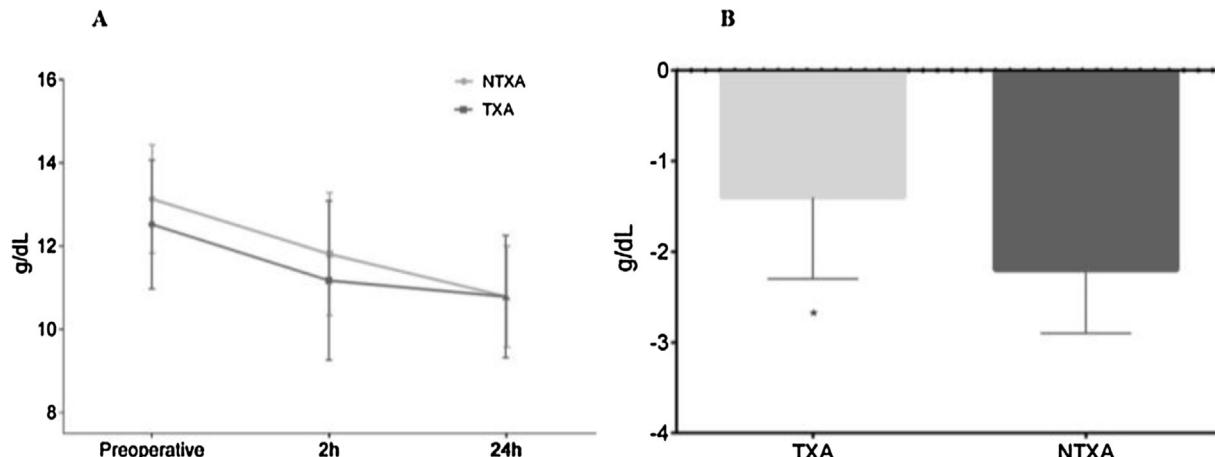
	TXA	NTXA	95% CI	p-value
Drain output (mL), median (IQR)				
2 h	45 (93)	100 (88)	-50.0 (-70.0-0.0) <sup>b</sup>	0.009
24 h	112.5 (108)	200 (100)	-60.0 (-110.0-20.0) <sup>b</sup>	0.008
48 h	150 (155)	210 (95)	-50.0 (-110.0-0.0) <sup>b</sup>	0.030
Hb (g.L <sup>-1</sup> ), mean ± SD				
Preoperative	12.5 (1.5)	13.1 (1.3)	0.62 (-0.24-1.49) <sup>b</sup>	0.152
2 h	11.2 (1.9)	11.8 (1.5)	0.64 (-0.40-1.68) <sup>a</sup>	0.220
24 h	10.8 (1.5)	10.8 (1.2)	0.004 (-0.810-0.817) <sup>a</sup>	0.993
Hb variation, median (IQR)	-1.4 (1.3)	-2.2 (1.3)	0.80 (0.00-1.20) <sup>b</sup>	0.047
Hb loss (g), median (IQR)	54.2 (64.0)	91.7 (53.6)	-33.02 (-42.82-5.15) <sup>b</sup>	0.134
Total blood loss (mL), median (IQR)	458.1 (434.6)	672.3 (382.9)	-190.30 (-280.6-48.63) <sup>b</sup>	0.166
Need for transfusion, n (%)	3 (13.0)	2 (9.1)	1.50 (0.226-9.964) <sup>c</sup>	1.000
Platelets ( $\times 10^9/L$ ), median (IQR)	243.5 (118.0)	205.0 (74.0)	17.50 (-40.00- -42.00) <sup>b</sup>	0.982
aPTT (s), median (IQR)	29.6 (14.0)	33.0 (5.8)	-4.00 (-6.50- -1.00) <sup>b</sup>	0.012
INR, median (IQR)	0.99 (0.50)	1.02 (0.08)	-0.04 (-0.07-0.04) <sup>b</sup>	0.526

Hb, hemoglobin; IQR, Interquartile Range.

<sup>a</sup> 95% Confidence Interval of the mean difference.

<sup>b</sup> 95% Confidence Interval of the median difference.

<sup>c</sup> 95% Confidence Interval of the Odds Ratio.



**Figure 3** (A) Preoperative and postoperative (at 2 h and 24 h) hemoglobin in TXA and NTXA patients. (B) Hemoglobin variation in TXA and NTXA patients.

Additionally, hemoglobin loss and total blood loss were decreased in the TXA group when compared with controls, although non-significant –  $p = 0.134$  and  $p = 0.166$ , respectively (Table 3). Regarding transfusion requirements, 3 patients (13%) were transfused in the TXA group and 2 (9.1%) in the control group ( $p = 1.000$ ).

Postoperative platelet count was unaffected by TXA administration ( $p = 0.982$ ). Regarding coagulation function assessment, aPTT was lower in TXA administered patients (TXA: median (IQR) 29.6 (14.0)s vs. NTXA: 33 (5.8)s; difference in medians: -4.00 [-6.50-1.00];  $p = 0.012$ ), despite INR not differing between study groups ( $p = 0.526$ ).

### Adverse events

Two complications were reported in the TXA group. One patient was readmitted at the hospital due to anemia (Hb: 6.1 g.dL<sup>-1</sup>) with a shoulder hematoma and was transfused

without further complications. The other patient had a postoperative delirium. In the no intervention group three complications were documented: stroke after discharge during the first postoperative week with the need for in-hospital care, a postoperative delirium, and a metabolic acidosis with admission in the intensive care unit. No other adverse events were registered during the follow-up period of 2 months (until July 31, 2019).

### Discussion

This randomized study is the first to evaluate the effect of intravenous TXA in shoulder arthroplasty under regional anesthesia (ultrasound-guided combined interscalene and supraclavicular block). As far as we are concerned this is the only article including the use of TXA in TSA for treatment of fractures and revision surgeries.

We included 45 patients in our study, regardless of the comorbidities, which included anemia, other hematologic diseases, and cerebrovascular disease. Pauzenberger et al.<sup>3</sup> excluded patients with hematologic disorders. The inclusion of these diseases adds up to the relevance of our work. Although one patient in the control group had a stroke in the follow-up period, no other complications attributable to TXA occurred.

The most important findings were that intravenous TXA is effective in reducing postoperative blood loss by evaluating drain output and hemoglobin variation after TSA. An observed 0.8 g.dL<sup>-1</sup> median difference in Hbdrop between groups is clinically significant, even more so when it can determine transfusion in a population with 33% of pre-operative anemia. Friedman's et al.<sup>12</sup> retrospective study reported a difference between groups regarding Hb variation similar to our results (TXA: 2.13 vs. NTXA: 2.63;  $p = 0,045$ ). In the meta-analysis of Randomized Controlled Trials (RCTs) and Retrospective Cohort Studies (RCS) performed by Kuo L et al.<sup>7</sup> with 677 patients a less change in haemoglobin in the TXA group of 0.64 g.dL<sup>-1</sup> was also reported.

At 2, 24, and 48 hours postoperatively, there was a statistically significant difference in drain output between the two groups. The use of TXA decreased drain output in approximately 30% at the second postoperative day. Likewise, Abildgaard et al.<sup>21</sup> retrospectively reviewed the administration of 1 g intravenous TXA in 171 shoulder arthroplasties – TXA reduced postoperative drainage by 58%, with an overall blood-saving effect of 25% in TSA.

Although there is a decrease in Hb loss and total blood loss, the difference is not statistically significant. Total blood loss in our study was approximately half of what other studies found, including Vara et al.<sup>1</sup> Our study occurred at a private hospital without residents in training and surgeries were performed by a senior shoulder surgeon with a vast experience in shoulder prostheses. This might explain the low level of lost blood and the lack of a statistically significant difference in these parameters.

Several studies of TXA in TSA show less postoperative blood loss although the route of administration and dose of TXA vary among studies. We used intravenous TXA in a dose of 1 g, while Gillespie et al.<sup>2</sup> administered a topical application of 2 g of TXA. In addition, Vara et al.<sup>1</sup> infused two doses of TXA (10 mg.kg<sup>-1</sup> before surgery and 10 mg.kg<sup>-1</sup> by the end of the surgery) and Pauzenberger et al.<sup>3</sup> used two doses of TXA but in the dose of 1 g intravenously. Kim et al.<sup>22</sup> gave only a single dose of TXA 500 mg IV before surgery, whilst Abildgaard et al.<sup>21</sup> used 1 g of TXA. Thus, more studies are needed to elect TXA ideal dose, frequency, and route of administration.

Anemia was extremely prevalent and approximately 33%, which could be due to the older age of the population (76 years) and 40% of fractures.<sup>15</sup> Transfusion was necessary in 3 patients in the TXA group (13%) and 2 in the control group (9.1%), with four patients presenting preoperative anemia and two of the transfusions occurring intraoperatively. This percentage is supported by existing literature.<sup>1</sup> However, Gillespie et al.,<sup>2</sup> Pauzenberger et al.,<sup>3</sup> Kim et al.<sup>22</sup> and Cvetanovich et al.<sup>5</sup> reported no transfusions, while Kim et al.<sup>22</sup> excluded patients who received an intraoperative transfusion. A meta-analysis of Randomized Controlled Tri-

als (RCTs) by Kuo et al.<sup>7</sup> with 677 patients suggested TXA decreases transfusion rate,<sup>23</sup> which was not found in this study.

Furthermore, Pauzenberger et al.<sup>3</sup> concluded the use of TXA decreased early postoperative pain and hematoma formation in TSA. In our study, the mean in numeric pain scale at 24 and 48 hours postoperatively, inpatient pain breakthrough, QoR-15, and length of stay in PACU and at the hospital was no different between the TXA and the control group. Our negative results regarding pain could be explained by a low overall pain score during the first postoperative days, which could be related to a better pain control associated with regional anesthesia.

Few studies evaluate the impact of TXA in coagulation parameters.<sup>24</sup> Our results demonstrate a decrease in aPTT when TXA is administered. The latter helps explain the effect of TXA in bleeding control and presents biological plausibility, since TXA is an antifibrinolytic drug. Previous randomized controlled trials in TSA have not documented the effect of TXA in coagulation parameters, which might be clinically relevant when considering treatment criteria.

The current study presents slight differences in results regarding existing literature. We included in our study all performed prostheses regardless of the indication. Theoretically, revision surgery and fractures tend to have more bleeding than cuff tear.<sup>12</sup> Since we are not a teaching hospital and surgeons were experts in shoulder interventions, the outcomes might not be applicable to every center. Moreover, our study did not present contamination between trial arms, nor did it have attrition bias, since there was no loss to follow-up. One advantage of the primary outcome is its objectivity and ease of detection in both groups. Every researcher directly involved in patient care provided the same care regardless of study group, although this randomized trial is single blinded, which could be a source of bias. Despite the limited number of patients in the study, this is the first randomized clinical trial testing TXA in TSA with broader indications and under regional anesthesia. Nevertheless, more studies are needed to clarify the effect of TXA in postoperative outcomes.

## Conclusions

TXA use (1 g IV) significantly diminished blood loss measured by drain output and Hb drop in TSA under regional anesthesia performed mainly due to cuff tear arthropathy and humeral fractures, although the number of transfusions remained similar between groups. Our results suggest the use of TXA IV does not improve the numeric analgesic scale and QoR-15, neither does it influence length of stay at the hospital or PACU. Notwithstanding, more studies are required to determine the ideal dose and route of administration of TXA in TSA and to evaluate the effectiveness of TXA in reducing transfusion requirements.

## Conflicts of interest

The authors declare no conflicts of interest.

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**ORIGINAL INVESTIGATION**

**Risk factors for failure of subclavian vein catheterization: a retrospective observational study**



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**KEYWORDS**

Subclavian vein catheterization;  
Central venous access;  
Central venous catheter;  
Catheter-related complications

**Abstract**

**Background and objectives:** The aim of this study was to analyze risk factors for failure of subclavian vein catheterization.

**Methods:** A retrospective analysis of 1562 patients who underwent subclavian vein puncture performed by the same experienced operator at Peking University Cancer Hospital from January 1, 2016 to January 1, 2019 was conducted. The success or failure of subclavian vein catheterization was registered in all cases. Various patient characteristics, including age, gender, body mass index (BMI), preoperative hemoglobin, preoperative hematocrit, preoperative mean corpuscular hemoglobin concentration (MCHC), preoperative albumin, preoperative serum creatinine, puncture needles from different manufacturers and previous history of subclavian vein catheterization were assessed via univariate and multivariate analyses.

**Results:** For the included patients, landmark-guided subclavian vein puncture was successful in 1476 cases and unsuccessful in 86 cases (success rate of 94.5%). Successful subclavian vein catheterization was achieved via right and left subclavian vein puncture in 1392 and 84 cases, respectively. In univariate analyses, age and preoperative hemoglobin were associated with failure of subclavian vein catheterization. In a multivariate analysis, aged more than 60 years was a risk factor while the central venous access with Certofix® was associated with an increased rate of success (*p*-values of 0.001 and 0.015, respectively).

**Conclusions:** This study has demonstrated that patient aged more than 60 years was a risk factor for failure of subclavian vein catheterization while the central venous access with Certofix® was associated with an increased rate of success.

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## Introduction

Central venous catheterization is one of the most helpful methods for rapid volume expansion, hemodynamic monitoring, and the administration of parenteral nutrition and chemotherapy. This procedure has been widely used in clinical practice and has been well received by most patients. Locations for central venous catheterization include the subclavian vein, the internal jugular vein, and the femoral vein. Among them, subclavian vein catheterization has the characteristics of adequate blood flow and a low incidence of catheter-related infections.<sup>1–3</sup>

Nowadays, the number of subclavian and axillary vein punctures performed with ultrasound guidance has markedly increased. However, landmark-guided subclavian vein catheterization using an infraclavicular approach is still one commonly chosen technique in China. The insertion of a catheter by a doctor who had performed 50 or more catheterizations is less likely to result in a mechanical complication than insertion by a doctor who had performed fewer than 50 catheterizations.<sup>4</sup> Hence, we defined a doctor who had performed 50 or more catheterizations as an experienced operator. Few studies have addressed risk factors for failure of subclavian vein catheterization. Prior reports regarding this topic have involved subclavian vein catheterization performed by multiple operators with different skill levels; these characteristics might influence the research results. In this study, we evaluated 1562 patients who underwent subclavian vein catheterization performed by the same experienced operator to investigate risk factors for failure of subclavian vein catheterization.

## Methods

A total of 1562 patients who underwent subclavian vein catheterization at Peking University Cancer Hospital from January 1, 2016 to January 1, 2019 were included. Exclusion criteria: patients with superior vena cava obstruction syndrome. The age, gender, body mass index (BMI), preoperative hemoglobin, preoperative hematocrit, preoperative mean corpuscular hemoglobin concentration (MCHC), preoperative albumin, preoperative serum creatinine, puncture needles from different manufacturers, and previous history of subclavian vein catheterization of the patients were collected.

All catheterization procedures were performed by the same experienced operator in our hospital's Vascular Access Center. The operator had experienced hundreds of subclavian vein puncture and usually preferred the right subclavian vein puncture. The location selected for subclavian vein puncture was approximately 1 cm to 2 cm below the midpoint of the clavicle.<sup>4</sup> Lidocaine was used for local anesthesia, and the Seldinger technique was used for subclavian vein puncture, with a central venous catheter (Certofix®, BBraun, Melsungen, Germany; or Arrow, USA) inserted at the puncture site. Previous research showed that the use of no more than three needle passes reduced the risk of complications for right infraclavicular subclavian vein catheterization.<sup>4</sup> Therefore, subclavian vein puncture was defined as a failure after three unsuccessful attempts. We

**Table 1** Patient characteristics.

Items (mean ± SD or number)	Result
Age, years	55.5 ± 12.5
Male/female	811/751
Height, m	1.65 ± 0.08
Body weight, kg	66.1 ± 12.3
BMI, kg·m <sup>-2</sup>	24.2 ± 3.7
Hemoglobin, g·L <sup>-1</sup>	130.3 ± 20.2
Hematocrit	39.0 ± 5.3
MCHC, g·L <sup>-1</sup>	333.0 ± 14.1
RDW	14.0 ± 2.3
Albumin, g·L <sup>-1</sup> <sup>a</sup>	43.3 ± 4.6
Creatinine, µmol·L <sup>-1</sup> <sup>b</sup>	66.1 ± 15.7
Prior subclavian vein puncture, yes/no	114/1448

Hemoglobin and hematocrit levels were obtained within one month prior to vein puncture. The other values were obtained within one week prior to vein puncture.

BMI, body mass index; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width.

<sup>a</sup> Data were available for 1551 patients.

<sup>b</sup> Data were available for 1555 patients.

changed the angle between the puncture needle and the clavicle but did not change the site between those attempts.

In cases involving failure of subclavian vein puncture, we performed ultrasound-guided internal jugular vein puncture, ultrasound-guided axillary vein puncture, or contralateral subclavian vein puncture. The study was approved by the Medical Ethical Committee of Peking University Cancer Hospital. All the participants gave written informed consent before the procedure itself.

Values are presented as the means ± SD or as numbers of patients, expressed as a percentage. To compare patients, average values were analyzed using *t*-tests or the Wilcoxon rank sum test, and proportions were assessed using chi-squared tests. Forward LR of logistic regression was utilized during multivariate analysis. Statistical analyses were performed using SPSS version 24.0. *P*-values less than 0.05 (two-tailed) were regarded as significant.

## Results

These patients included 473 cases of colorectal cancer, 265 cases of gastric cancer, 116 cases of ovarian cancer, 89 cases of liver cancer, 77 cases of breast cancer, 53 cases of renal cancer, 50 cases of lymphoma, 40 cases of lung cancer, 16 cases of esophageal cancer, 15 cases of pancreatic cancer, and 368 cases of other tumors. Their ages ranged from 16 to 89 years.

Major baseline characteristics of the included patients are shown in Table 1. In the 1562 included patients, subclavian vein puncture was successful in 1476 cases and unsuccessful in 86 cases. The success rate of subclavian vein puncture was 94.5%. Successful subclavian vein catheterization was achieved via right and left subclavian vein puncture in 1392 and 84 cases, respectively. In 86 cases involving failing subclavian vein puncture, ipsilateral ultrasound-guided internal jugular vein puncture, ipsilateral ultrasound-guided axillary vein puncture, and contralateral subclavian vein

**Table 2** The univariate analysis of risk factors for failure of subclavian vein catheterization.

Factors (mean $\pm$ SD or number)	Success (1476)	Failure (86)	<i>p</i> <sup>a</sup>
Age	55.2 $\pm$ 12.5	60.8 $\pm$ 11.6	0.001
Male/female	768/708	43/43	0.714
BMI	24.2 $\pm$ 3.7	23.6 $\pm$ 3.6	0.166
Hemoglobin	130.5 $\pm$ 20.3	126.9 $\pm$ 18.4	0.046
Hematocrit	39.1 $\pm$ 5.3	38.3 $\pm$ 4.9	0.080
MCHC	333.1 $\pm$ 14.1	330.9 $\pm$ 12.7	0.095
RDW	14.0 $\pm$ 2.3	14.0 $\pm$ 2.0	0.654
Albumin	43.3 $\pm$ 4.6	42.7 $\pm$ 4.7 <sup>b</sup>	0.206
Creatinine	66.1 $\pm$ 15.7 <sup>c</sup>	67.0 $\pm$ 16.4 <sup>d</sup>	0.554
Puncture needles from different manufacturers (Certofix/Arrow)	1016/460	51/35	0.065
Prior subclavian-vein puncture, yes/no	106/1370	8/78	0.462

BMI, body mass index; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width.

<sup>a</sup> We used Wilcoxon rank-sum test in the analyses of age, BMI, hemoglobin, hematocrit, MCHC, RDW and albumin; t test in the analysis of creatinine; chi-squared tests in the analyses of sex, types of puncture needle, prior history of subclavian-vein puncture.

<sup>b</sup> Data were available for 85 patients.

<sup>c</sup> Data were available for 1470 patients.

<sup>d</sup> Data were available for 85 patients.

punctures were performed for 49, 34, and 3 patients, respectively.

Chest X-rays were obtained within 48 hours after the subclavian vein catheterization procedure for 1542 patients, whereas no such X-rays were acquired for the remaining 20 patients. There were seven patients with arterial puncture, one with nerve injury, four with postoperative ectopic catheterization of the internal jugular vein, one with postoperative pneumothorax that did not need thoracic drainage, one with pinch-off syndrome, and one with postoperative catheter-related bloodstream infection.

In the univariate analysis, age and preoperative hemoglobin were associated with failure of the subclavian vein puncture (the univariate analysis of the included patients is listed in Table 2). Age, gender, preoperative body mass index (BMI), hemoglobin level, hematocrit, mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), albumin level, serum creatinine level, puncture needles from different manufacturers, and history of previous subclavian vein puncture were included in multivariate analysis, which indicated that patient aged more than 60 years was a risk factor while the central venous access with Certofix® was associated with an increased rate of success (Table 3).

## Discussion

To our knowledge, this study involved the largest reported number of subclavian vein punctures performed by the same operator. In contrast to prior studies of failure of subclavian vein puncture,<sup>5–7</sup> in this investigation, all of the patients underwent subclavian vein catheterization performed by the same experienced operator, avoiding any potential influence of differences in the technical skill levels of various operators. The success rate in our study was very high. In addition, incidences of hemothorax, ectopic catheterization and other complications were lower in this study than the other literature reported.<sup>4,8</sup>

**Table 3** Multivariate analysis of risk factors for failure of subclavian vein catheterization.

Factors	OR	95% CI for OR	<i>p</i>
Age > 60 years	1.045	1.024–1.067	0.001
Central venous access with Certofix®	0.570	0.363–0.896	0.015
Constant	0.006		0.001

We used Forward LR of logistic regression in the multivariate analysis.

In our study, we found that aged more than 60 years was a risk factor for failure of the subclavian vein puncture. We speculated that it might be related to the deterioration of venous vessels after aging. Takeyama H et al.<sup>5</sup> reported that a low BMI was associated with failure of the subclavian vein puncture but not age. Lefrant et al.<sup>7</sup> reported that more than one venipuncture and age 77 years or more were risk factors for complications of subclavian vein catheterization in critically ill patients. Another study had shown that prior major surgery in the region and BMI was associated with failure of the subclavian vein puncture,<sup>6</sup> but such association was not observed in our study. In the univariate analysis, there was a significant difference about preoperative hemoglobin in two groups but there was no significant correlation between preoperative hemoglobin and failure of subclavian vein puncture in the multivariate analysis.

We found that the central venous access with Certofix® was associated with an increased rate of success. We guessed it was related to the length of the needle. The length of the puncture needle with Certofix® was 7 cm and 6.35 cm from Arrow. A shorter needle might not get into the blood vessels in some patients. However, there was no evidence in the literature. In the future, a randomized controlled study will be needed to confirm this conclusion.

In recent years, the number of subclavian and axillary vein punctures performed with ultrasound guidance has markedly increased. However, ultrasound-guided sub-

clavian vein puncture requires special technical training.<sup>9,10</sup> Therefore, this procedure is difficult to use, especially in developing countries where ultrasound cannot be used routinely; moreover, there remains controversy regarding the use of ultrasound for subclavian and axillary vein punctures. Certain studies have suggested that ultrasound is not helpful for these procedures,<sup>6,11</sup> whereas other reports have argued that ultrasound guidance is beneficial.<sup>12–15</sup> In the cases involving failure of subclavian vein puncture, we chose ultrasound-guided axillary or internal jugular vein puncture and these might show the advantages of ultrasound-guided punctures.

Unsurprisingly, this study has shortcomings. First, this investigation is a retrospective study, and certain data, such as hemoglobin and hematocrit levels, were obtained within one month prior to vein puncture. Therefore, this study could not definitively establish positive associations between failure of subclavian vein puncture and these two test levels (hemoglobin and hematocrit); future prospective investigations are required to assess these associations. Second, we were unable to determine volume capacities of patients, but low blood volume may have been an important reason for failure of the subclavian vein puncture.

## Conclusion

This study has demonstrated that patient aged more than 60 years was a risk factor for failure of subclavian vein catheterization while the central venous access with Certofoix® was associated with an increased rate of success.

## Compliance with ethical guidelines

Our study was approved by the Medical Ethical Committee of Peking University Cancer Hospital.

## Conflicts of interest

The authors declare no conflicts of interest.

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## ORIGINAL INVESTIGATION

### Evaluation of dexmedetomidine anesthesia-related temperature changes: preliminary retrospective observational study

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#### KEYWORDS

Dexmedetomidine;  
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#### Abstract

**Introduction and objective:** Dexmedetomidine is a potent adrenergic alpha-2 agonist, and analgesic, sedative, anxiolytic and sympatholytic. Given there have been reports of dexmedetomidine associated temperature changes, in which these events have been associated with complications, our objective was to describe both temperature increase and decrease, during the intra and postoperative period (initial 24 hours), and factors associated, in patients who received dexmedetomidine for anesthesia/sedation in the surgical suite.

**Method:** Retrospective observational study, analyzing charts of patients  $\geq 18$  years submitted to anesthesia/sedation with dexmedetomidine, between 1/1/2017 and 31/12/2017. Upper temperature threshold was considered  $\geq 37.8$  °C, and lower,  $< 35$  °C. The association with dexmedetomidine was assessed by the OMS/UMC causality system and by the Naranjo algorithm.

**Results:** The sample included 42 patients who received dexmedetomidine and whose temperature data were available, with predominance of men (62%), 49.4/16.5 years old (mean/standard deviation), and weight 65/35.8 kg. None of the patients presented intraoperative temperature equal to or above 37.8 °C or below 35 °C. During the postoperative period, one patient presented an increase  $\geq 37.8$  °C (2.4%) and three, temperature decrease  $< 35$  °C (7%). Surgery/anesthesia time and exposure time to dexmedetomidine were not appropriate linear predictors of maximum temperature. Older age ( $p < 0.01$ ), longer exposure to dexmedetomidine ( $p < 0.05$ ) and shorter surgery time ( $p < 0.01$ ) were significant linear predictors for lower minimum temperature.

**Abbreviations:** MH, malignant hyperthermia; UMC, Uppsala Monitoring Centre; ICU, Intensive Care Unit; WHO, World Health Organization.

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**Conclusions:** Increase  $\geq 37.8^{\circ}\text{C}$ /decrease  $< 35^{\circ}\text{C}$  of temperature possibly associated with dexmedetomidine did not occur in the intraoperative period and had a low frequency during the postoperative period.

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## Introduction

Dexmedetomidine is an adrenergic alpha-2 agonist and is analgesic/sedative/anxiolytic/sympatholytic.<sup>1</sup> It is frequently used at the Intensive Care Unit (ICU) for mild sedation/ventilation weaning, and at the surgical suite as a sedative/adjuvant, to decrease consumption of opioid/inhalation agents.<sup>1,2</sup> Patients sedated with dexmedetomidine wake up/cooperate when asked and high doses do not result in respiratory depression.<sup>1</sup> The main side effects are hypotension/bradycardia.<sup>1</sup>

Both temperature decrease and increase have been associated with dexmedetomidine.<sup>2–8</sup> Temperature decrease would be due to the agonist action at the central alpha-2 receptor, reducing vasoconstriction/tremor thresholds and physiological responses to increase in body temperature.<sup>1,8,9</sup> Plasma concentration of dexmedetomidine of  $0.8 \text{ ng.mL}^{-1}$  reduces the tremor threshold to roughly  $34^{\circ}\text{C}$ .<sup>9</sup> Increase in temperature would result from change in thermoregulation (slight increase in sudoresis threshold) and/or from immunological response (allergic febrile reaction to drug).<sup>2–7,10</sup> Increased temperatures did not correlate to malignant hyperthermia (MH), given there were no signs of hypermetabolism; moreover, patients susceptible to MH anesthetized with dexmedetomidine did not present characteristic presentation/complications.<sup>11,12</sup> Additionally, dexmedetomidine is an option for patients susceptible to MH and allergic to egg protein, contraindicating propofol.<sup>11</sup>

Detailed data on the effect at temperature of dexmedetomidine administered during general anesthesia in adults are scarce. A Cochrane Review<sup>13</sup> on alpha-adrenergics to prevent shivering after general anesthesia emphasizes that it is not possible to establish a relationship between dexmedetomidine and temperature decrease because, of the seven articles analyzed, two did not refer temperature and only one reported the frequency of temperature decrease (44.1%).<sup>14</sup> In the four other articles, there was a decrease in temperature with dexmedetomidine, but two articles did not provide details on the statistical study,<sup>15,16</sup> one article reported no difference between groups without/with dexmedetomidine,<sup>17</sup> and another referred more pronounced decrease in temperature in the group with dexmedetomidine, only during the postoperative period.<sup>18</sup> Additionally, a retrospective study on the effect of dexmedetomidine on postoperative inflammation after percutaneous nephrolithotomy showed a significant decrease in fever/systemic inflammatory response syndrome.<sup>19</sup> Finkel (2007) reported decrease in temperature while using dexmedetomidine at the ICU on neonates.<sup>8</sup>

Regarding temperature increase associated with dexmedetomidine, data come from ICU studies<sup>2–5,7</sup> or

experimental models, in addition to a report on anesthesia of a child with suspected MH in the absence of triggering agents.<sup>6</sup> Dogs anesthetized with sevoflurane/opioid versus sevoflurane/dexmedetomidine presented both increase and decrease in temperature in both groups, but with no significant difference, both in the intra and postoperative periods.<sup>20</sup> In rodents, temperature was significantly lower with isoflurane than with dexmedetomidine/ketamine/midazolam and more animals had temperature decrease with isoflurane, leading the authors to propose that dexmedetomidine could protect against skin heat loss by peripheral vasoconstriction, and preserve central temperature by central blood redistribution.<sup>21</sup>

Thus, there is a gap in detailed studies on the effects of dexmedetomidine on temperature during the intra/postoperative period.

## Objective

To describe both increase and decrease in intra/postoperative temperature variation (initial 24 hours), and factors associated, in patients receiving dexmedetomidine for anesthesia/sedation at the surgical suite.

## Methods

The study was performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), approved by the Ethics and Research Committee (CAAE 08688512.0.0000.5505; 115.960, 05/OCT/2012), and given it was a retrospective study, informed consent was waived. Following STROBE guidelines, an observational retrospective study was performed at a tertiary hospital, on patients who received intraoperative dexmedetomidine at the surgical suite during the 01/JAN/2017–31/DEC/2017 period.

First, an author revised the electronic database of anesthesia/medical records of all patients included, registering maximum/minimum temperature/temperature amplitude during the intraoperative/initial 24 hours of the postoperative period. Intraoperative data were collected from the anesthesia record and postoperative data from nursing notes. The 24-h limit was based on detection of temperature increase, of adult ICU patients, up to 24 hours after dexmedetomidine, and normothermia up to 12 hours after discontinuation.<sup>2</sup> Inclusion criteria were using dexmedetomidine and availability of temperature control data. Exclusion criteria were age below 18 years due to the specificity of thermogenesis in children, with production of heat by brown fat, and larger body surface in relation to mass.<sup>22</sup>

The following data were collected from charts: demographics (age/gender), height-weight, history of current condition and surgical proposal, previous diseases, medications being used, type of anesthesia/sedation, anesthetic drugs used, beginning/end of procedures (anesthesia/sedation, surgery), incidents/complications from the beginning of anesthesia/sedation to discharge from post-anesthesia recovery, maximum and minimum temperature data. Daytime temperature varies between 36.5–37.5 °C and values < 36 °C and > 38 °C mark points in which thermoregulation is compromised and/or surpassed by changes in environment temperature/thermogenesis.<sup>22</sup> To amplify any possible association between dexmedetomidine and change in temperature, increase in temperature ≥ 37.8 °C and decrease in temperature < 35 °C were considered as limits. Temperature ≥ 37.8 °C was adopted to define acceptable limit for fever, while 34.6 °C was the temperature that induced thermoregulatory response of peripheral vasoconstriction in normal individuals exposed to cooling.<sup>9,23</sup>

In order to better assess the relationship between dexmedetomidine and change in temperature, possible infectious/non-infectious causes of temperature increase were considered. The association between dexmedetomidine and temperature increase/decrease was assessed by two algorithms: World Health Organization (WHO)/Uppsala Monitoring Centre (UMC) system for standardized case causality assessment and Naranjo algorithm.<sup>24,25</sup> WHO-UMC criteria compare the drug-effect relationship in question, with a table of pre-defined statements and six categories: non-classifiable, not classified, unlikely, possible, likely, and defined (Supplementary Material: Table 1).<sup>24</sup> The Naranjo scale is a point system with a questionnaire (0–13 points) that classifies the drug-effect relationship in four categories: doubtful (0), possible (1–4), probable (5–8) and definite ( $\geq 9$ ) (Supplementary Material: Table 2).<sup>25</sup> Two evaluation methods were used because the level of causality has been reported as different among several pharmacovigilance algorithms.<sup>2</sup>

To calculate the sample size, we chose the increase in temperature variable because it is less studied/frequent. Increase in temperature with dexmedetomidine was considered as occurring in up to 6.5% of patients in previous studies on adults in the ICU<sup>26</sup>; thus, in order to replicate this proportion with a maximum estimation error of 5% and 80% level of confidence, a sample of 40 patients would suffice (calculation based on simple random sample without replacement). Categorical data were described as absolute (n) and relative (%) frequency, and continuous and semi-continuous gaussian data, as mean and standard deviation. Data were checked as to normality by the K-S distance test. Non-paired *t*-test was used to compare independent samples. Correlations were calculated/tested by the Pearson test. To better check the relationship between use of dexmedetomidine and patient temperature, linear regressions were performed including variables that presented a significant correlation on the Pearson test. Based on the assumption that time of dexmedetomidine and patient temperature correlate in a linear relationship, linear regression was performed to determine how much variation in patient temperatures would be explained by time of use of dexmedetomidine, surgery time and age in

years, separately. Values of  $p < 0.05$  were considered significant.

## Results

The study included 42 patients who received dexmedetomidine during the intraoperative period and with temperature control available, 49.4/16.5 years old (mean/standard deviation; variation 19–81 years), 65/35.8 kg (data available for 39 patients; variation 42–115 Kg), and 26 (62%) men and 16 women (38%). Seven patients who received intraoperative dexmedetomidine were excluded due to unavailable temperature control data.

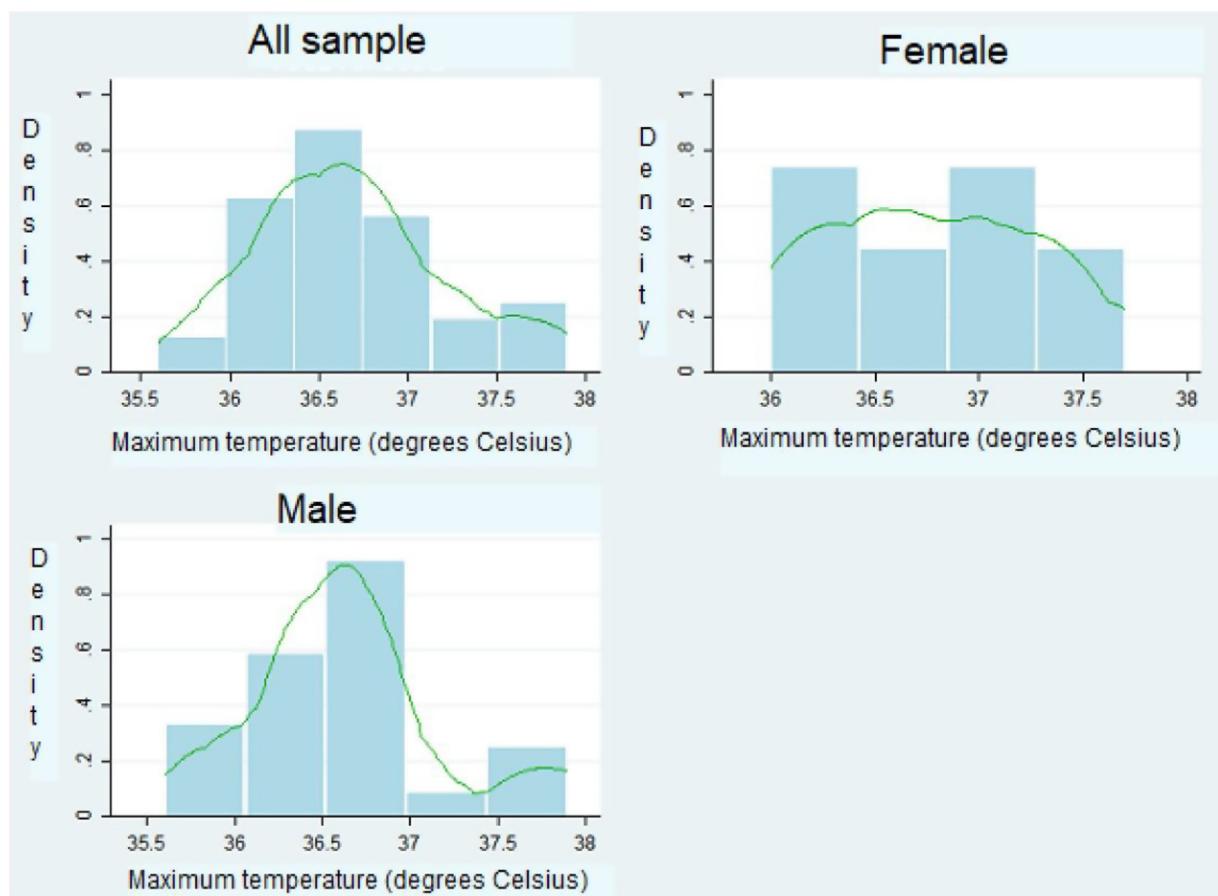
Two patients (4.76%) had baseline infectious conditions (infectious source surgically approached at pulmonary metastases and pulmonary infection). None of the patients were septic. Awake intubations were performed in 8 patients (19%). Elective procedures prevailed (36) over urgencies (6). Central nervous system surgeries were more frequent (13), followed by head/neck (8), gastrointestinal (5), orthopedic (4), ENT (3), vascular (2), urology (2), plastic (2), ophthalmology (1), gynecology (1), and heart (1). The abdominal cavity was opened in three surgeries (7.14%), and none of the thoracic cavity. None of the patients used extracorporeal circulation or had burns. One patient died at the hospital 21 days after the procedure. Mean time to discharge after surgical procedure was 3.46/3.29 days (variation 1–14 days).

Dexmedetomidine was used as sedation in nine cases (21%) and as anesthesia adjuvant in the other 33 (25 also received isoflurane, opioid and propofol; seven, opioid and propofol; and one, local anesthetic). As adjuvant, dexmedetomidine was used alone in 76.2%, associated with clonidine in 7.1%, and to ketamine in 16.7% of cases. Dexmedetomidine was used for 202.73/150.9 minutes (range 30–660 minutes), at the dose of 0.47/0.09 micrograms·kg<sup>-1</sup>·h<sup>-1</sup> (range 0.3–1).

Temperatures were measured during anesthesia/sedation with an esophageal thermometer and, at the postoperative period, with an axillary thermometer. All patients used thermal blankets adjusted to 38 °C for warming after general anesthesia induction or beginning of sedation. None of the patients were cooled down. Among maximum temperatures, highest was 37.9 °C, and lowest, 35.6 °C (mean 36.7/0.54 °C) (Fig. 1). Among minimum temperatures, highest was 36.6 °C and lowest, 34.6 °C (mean 35.6/0.56 °C). The widest temperature range (maximum temperature minus minimum temperature) on the same patient was 2.9 °C, and the lowest, 1 °C (mean 1.03/0.61 °C).

None of the patients presented temperature increase ≥ 37.8 °C during the intraoperative period, and only one patient presented temperature increase ≥ 37.8 °C in the postoperative period. The correlation between increase in temperature ≥ 37.8 °C and use of dexmedetomidine for this patient was considered as possible by the WHO-UMC causality system, and by the Naranjo algorithm (Table 1).

None of the patients had a temperature < 35 °C during the intraoperative period, but three patients (7%) did in the postoperative. For these patients, the correlation between temperature < 35 °C and using dexmedetomidine was considered as possible by the WHO-UMC causality system for three,



**Figure 1** Histogram of distribution of maximum temperature for the entire sample and by gender.

**Table 1** Patient with temperature  $\geq 37.8^{\circ}\text{C}$  or  $< 35^{\circ}\text{C}$  in postoperative period.

Patient	Change	Temp. value	Who-UMC	Naranjo <sup>a</sup>				
					Classification	Conclusive reports previous to current reaction (yes: +1, no: 0)	Adverse event emerged after medication (yes: +2; no: -1)	There were other possible causes for reaction (yes: -1, no: +2)
1	Temp. $\geq 37.8^{\circ}\text{C}$	37.9	Possible	Possible <sup>b</sup> 2 points	Yes (+1)	Yes (+2)	Yes (-1): infection	
2	Temp. $< 35^{\circ}\text{C}$	34.8	Possible	Possible <sup>b</sup> 2 points	Yes (+1)	Yes (+2)	Yes (-1): inhalation anesthetic/propofol/opioid	No (+2)
3	Temp. $< 35^{\circ}\text{C}$	34.6	Possible	Probable <sup>c</sup> 5 points	Yes (+1)	Yes (+2)	Yes (-1): inhalation anesthetic/propofol/opioid	
4	Temp. $< 35^{\circ}\text{C}$	34.8	Possible	Possible <sup>b</sup> 2 points	Yes (+1)	Yes (+2)	Yes (-1): inhalation anesthetic/propofol/opioid	

Temp., Temperature; WHO-UMC, World Health Organization (WHO)/Uppsala Monitoring Centre (UMC) system for standardized case causality assessment: “Possible” on Who-UMC is equivalent to “event or abnormal lab test with reasonable time relationship with drug ingestion, but also can be explained by other conditions or medications, and at sites where information of medication withdrawal may be absent or not very clear”.

<sup>a</sup> Naranjo: only questions that comprise point score were listed; questions that did not have points were not listed, that is, value was zero.

<sup>b</sup> “Possible” on the Naranjo scale is equivalent to 1–4 points.

<sup>c</sup> “Probable” on the Naranjo scale is equivalent to 5–8 points.

and by the Naranjo algorithm, as possible for two and likely for one (Table 1). The relationship between temperature decreases and dexmedetomidine was classified as possible when there were other medications/scenarios that could explain the increase/decrease in temperature. Additionally, none of the patients presented a temperature  $< 36^{\circ}\text{C}$  during the intraoperative period, but 20 patients presented a temperature of  $35\text{--}35.9^{\circ}\text{C}$  in the initial 24 postoperative hours.

There was no difference in maximum temperature between females ( $36.8/0.5^{\circ}\text{C}$ ) and males ( $36.6/0.5^{\circ}\text{C}$ ) (non-paired *t*-test,  $p = 0.15$ ) (Fig. 1), nor between patients aged up to 49 years ( $36.8/0.1^{\circ}\text{C}$ ) and those above 50 years or more ( $36.6/0.1^{\circ}\text{C}$ ) (non-paired *t*-test,  $p = 0.19$ ). Likewise, there was no difference between minimum temperature between sexes nor between patients above/below 50 years. There was no significant difference in minimum (respectively  $35.49/0.16^{\circ}\text{C}$  vs.  $35.68/0.93^{\circ}\text{C}$ ;  $p = 0.19$ , non-paired *t*-test) or maximum temperature ( $36.64/0.12^{\circ}\text{C}$  vs.  $36.68/0.1^{\circ}\text{C}$ ;  $p = 0.33$ , unpaired *t*-test) between the group that only received dexmedetomidine ( $n = 9$ ) and the group in which dexmedetomidine was associated with other anesthetics ( $n = 33$ ).

The period of use of dexmedetomidine presented a low positive correlation with maximum temperature (correlation coefficient  $r = 0.3$ ;  $p < 0.05$ ; Pearson correlation), and high correlation with surgical time ( $r = 0.7$ ;  $p < 0.05$ ; Pearson correlation) (Fig. 2; Table 2). Maximum temperature presented a low positive correlation with surgery time ( $r = 0.3$ ;  $p < 0.05$ ; Pearson correlation) and with minimum temperature ( $r = 0.3$ ;  $p < 0.05$ ; Pearson correlation), but a high positive correlation with temperature amplitude ( $r = 0.7$ ;  $p < 0.05$ ; Pearson correlation) (Table 2). Minimum temperature presented a low positive correlation with surgery time ( $r = 0.3$ ;  $p < 0.05$ ; Pearson correlation), low negative correlation with age ( $r = 0.3$ ;  $p < 0.05$ ; Pearson correlation) and high negative correlation with temperature amplitude ( $r = 0.7$ ;  $p < 0.05$ ; Pearson correlation) (Fig. 3; Table 2).

Linear regression of temperature as a function of time using dexmedetomidine, surgery time and age (Table 3) presented a variance inflation rate (VIF)  $< 10$  (1.04–2.44), excluding the possibility of collinearity. Analyzing first the regression in which the variable explained is maximum temperature, Table 3 shows that both surgery time and dexmedetomidine time and age did not have a statistically significant relation with maximum patient temperature. In turn, when analyzing minimum temperature of patients, time using dexmedetomidine was observed to have a negative relationship with minimum patient temperature (the more time using dexmedetomidine, lower minimum patient temperature). A similar relationship was found for age, that is, older individuals had lower temperatures. In turn, the longer surgery time, higher the minimum temperature. There was no statistically significant relationship of the variable dexmedetomidine alone/associated with minimum/maximum temperature.

## Discussion

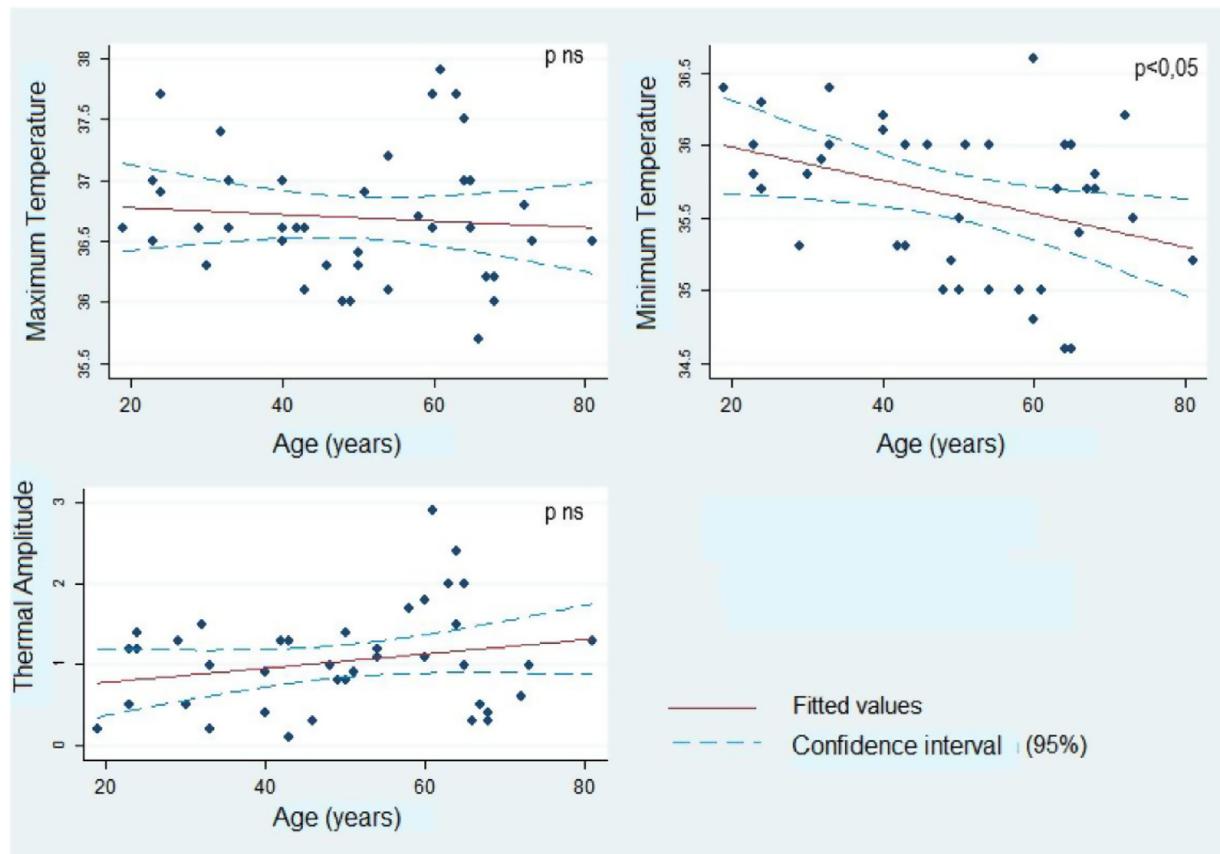
We detected both temperature  $> 37.8^{\circ}\text{C}$  and  $< 35^{\circ}\text{C}$  in less than 10% of the sample. In the present statistical modeling,

temperature decrease could, independently, be due to both older age and more time using dexmedetomidine and longer surgery time. On the other hand, increase in temperature apparently depends on joint action of dexmedetomidine and surgery time.

Sessler (2008) underscored that individuals without thermoregulation problems would not present decrease in temperature only due to factors such as low temperature of the operating room, exposure of cavities, hemorrhage/transfusion, previous conditions (ASA 3–4), malnutrition, neuropathies and older age.<sup>10,22</sup> Decrease in intraoperative temperature would imply in inhibition of thermoregulation by anesthetics such as dexmedetomidine, with consequent lower threshold for tremor and vasoconstriction, loss of heat from central compartment to periphery by vasodilation, and up to 30% decrease in metabolism.<sup>10,22</sup> This would explain our findings of lower minimum temperatures associated with longer exposure time to dexmedetomidine when we isolated the effects of surgery time and age.<sup>9</sup> Additionally, mechanisms that predisposed to temperature decrease during anesthesia apparently would stand out in relation to those that would cause temperature increase by dexmedetomidine, a different scenario from the studies performed at ICU. Prevention of temperature decrease is warranted by associated risks, such as coagulopathy (platelet/coagulation factors dysfunction), delay in anesthesia recovery, cardiac complications (increased noradrenaline, arterial hypertension, and tachycardia), shift in the hemoglobin dissociation curve to the left, and higher incidence of surgical wound infection.<sup>10</sup>

A series of 200 ICU patients on dexmedetomidine detected a temperature increase of nine, on average after six hours (range 4–10 hours) from initial dexmedetomidine at a mean dose of  $1.0 \text{ mcg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  (0.8–1.3), with a temperature decrease after discontinuation of dexmedetomidine to  $\leq 38.5^{\circ}\text{C}$ , on average in 3 hours (1–8), and to  $\leq 38.0^{\circ}\text{C}$  after 4 hours (3–9).<sup>2</sup> Authors have suggested that dexmedetomidine could be associated with occurrence of clinically relevant temperature increases.<sup>2</sup> Grayson et al. showed a significant correlation between using dexmedetomidine at the ICU and increased temperatures, mainly in the postoperative period of cardiac procedures and of the obese.<sup>27</sup> The same correlation was not found in the present study on intraoperative use of the medication, although, in agreement with Grayson et al., we also detected maximum temperature increase associated with long exposure time to dexmedetomidine.<sup>27</sup>

Malignant Hyperthermia (MH) and Neuroleptic Malignant Syndrome (NMS) should be considered as part of the differential diagnosis in any fever of unknown origin. However, temperature increase associated with dexmedetomidine is different because high creatine kinase is not always present, and symptoms tend to stop after its interruption.<sup>27</sup> Beside external factors that can increase temperature, infection can explain temperature increase, as is the case of the patient with postoperative fever and infection in cervical metastases. The relationship between temperature increases and dexmedetomidine was classified as possible in this patient, because there is another disease that could explain temperature increase. Increased temperature due to drugs is a challenge for diagnosis, that frequently is only made by exclusion, with time/resources spent in cul-



**Figure 2** Dispersion and linear prediction of maximum temperature, minimum temperature, and temperature amplitude, by age.

**Table 2** Pearson correlation matrix of variables of interest (values refer to correlation coefficients  $r$ ).

Correlation	Maximum T.	Minimum T.	Temperature amplitude	Age	Surgery time	Dexmedetomidine use time	Concentration of dexmedetomidine
Maximum T.	1	-	-	-	-	-	-
Minimum T.	0.3310 <sup>b</sup>	1	-	-	-	-	-
Temperature amplitude	0.5964 <sup>c</sup>	0.5600 <sup>c</sup>	1	-	-	-	-
Age	-0.0848	-0.3654 <sup>b</sup>	0.2291	1	-	-	-
Surgery time	0.3702 <sup>b</sup>	0.3344 <sup>b</sup>	0.0405	0.0498	1	-	-
Dexmedetomidine use time	0.3699 <sup>b</sup>	0.1185	0.2239	-0.042	0.7089 <sup>c</sup>	1	-
Concentration of dexmedetomidine	-0.0935	0.1855	-0.2291	-0.3205	-0.079	-0.2372	1

T., Temperature.

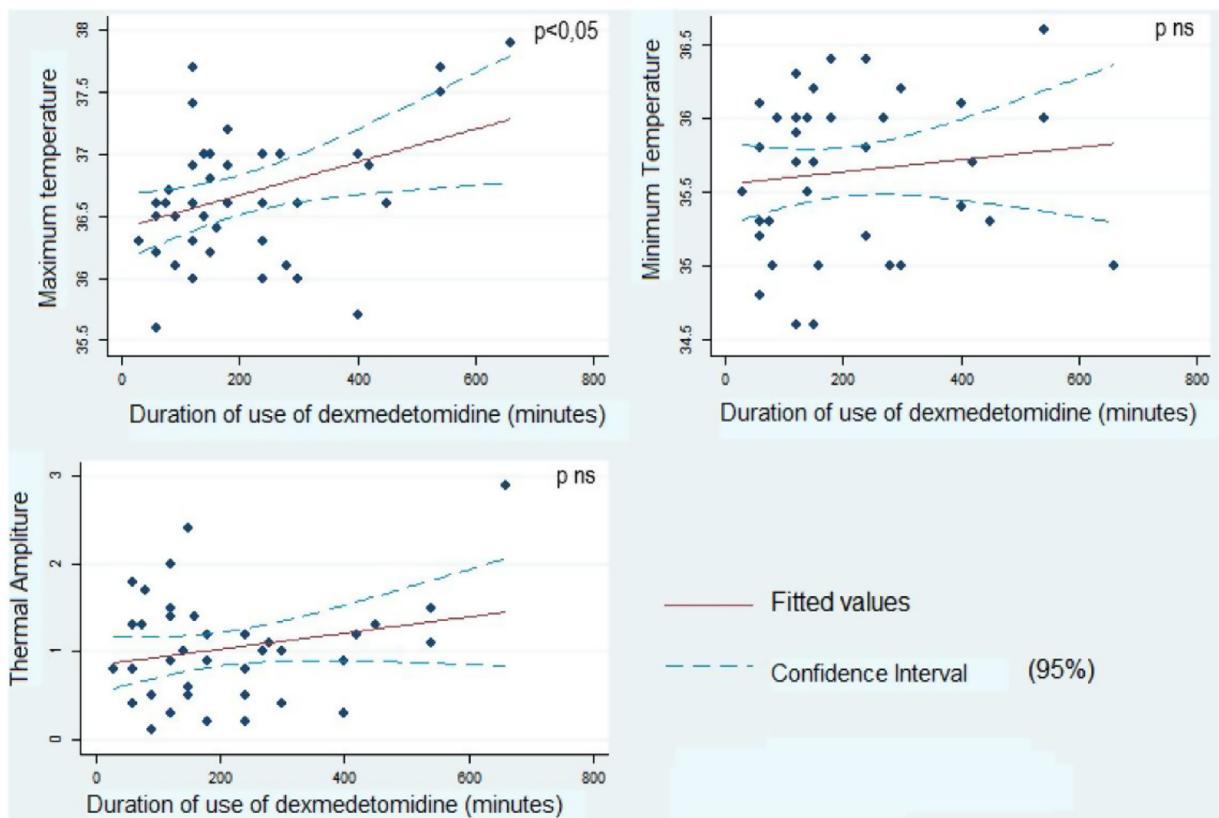
<sup>b</sup>  $p < 0.05$ .

<sup>c</sup>  $p < 0.01$ .

tures/antibiotics; with a subjacent infection, the diagnosis becomes even more difficult and sometimes is not made, even during follow-up.

Measures to minimize temperature decrease in anesthesia/sedation, such as thermal blankets, are confounding factors in the present study, by limiting the occurrence of intraoperative temperature decrease. Longer surgery time associated with higher minimum/maximum temperatures suggest that using a blanket may be a prevailing factor in this relationship. Another confounding factor in

the present study was using distinct temperature measuring methods, esophageal at the surgical suite and skin in the initial 24 postoperative hours; thus, despite the reliability of intraoperative temperatures, they can be underestimated in the postoperative period. Skin temperature has a low correspondence with esophageal temperature, more efficient because it is closer to central temperature.<sup>28</sup> Lack of data on temperature measurements in all patients who used dexmedetomidine limited our work by decreasing the number of cases analyzed. Additionally, this study has limita-



**Figure 3** Dispersion and linear prediction of maximum temperature, minimum temperature, and temperature amplitude, by time using dexmedetomidine.

**Table 3** Linear regression of maximum temperature and minimum temperature in relation to dexmedetomidine use time, surgical time, age (standard deviation between parentheses). Additionally, control was performed by variable dexmedetomidine alone or associated to other anesthetics.

Variables	Temperature (degrees Celsius)	
	Maximum	Minimum
Dexmedetomidine use time (minutes)	0.0001 (0.00079)	-0.0014 <sup>a</sup> (0.0007)
Surgical Time (minutes)	0.00143 (0.00067)	0.0018 <sup>b</sup> (0.0006)
Age (years)	-0.005 (0.0051)	-0.0139 <sup>b</sup> (0.00454)
Single/Associated Dexmedetomidine	0.1694 (0.663)	-0.471 (0.591)
Single/Associated Dexmedetomidine and Dexmedetomidine use time (minutes)	0.0041(0.005)	0.0036 (0.004)
Single/Associated Dexmedetomidine and Surgical Time (minutes)	-0.0029 (0.0024)	0.0004 (0.0021)
R <sup>2</sup>	0.23	0.36

<sup>a</sup> p < 0.05.

<sup>b</sup> p < 0.01.

tions due to its retrospective method, with a heterogeneous sample as to variables such as type of surgical procedure, without monitoring/anesthesia protocol established previously, with anesthesia/sedation performed/registered by different anesthesiologists, and without room temperature control. In order to better determine the cause-effect relationship, it would be important to perform future prospective studies, controlling all variables. However, information from the present study is important for awareness on the topic and to provide data for prospective studies to base themselves on, mainly to calculate sample size.

The major temperature variation found for patients in our study can be related to a wider interval between thresholds for response to cold/heat which is induced by anesthetics, ranging from 0.2–0.4 °C to 2–4 °C.<sup>22</sup> Temperature variations with dexmedetomidine could lead to considering monitoring temperature during its use. The Federal Medical Council recommends determining temperature and the means to assure normothermia, for procedures above 60 minutes and, regardless of procedure duration in high-risk scenarios (premature, newborn, previous history of/risk of MH and NMS).<sup>29</sup>

Although maximum temperature presented a significant positive correlation with surgical time and exposure to dexmedetomidine, these variables were not significant on the linear regression, indicating that they are not appropriate independent linear predictors of maximum temperature. On the other hand, age, surgery time and exposure time to dexmedetomidine were significant linear predictors for minimum temperature, in that older age and longer time of exposure to dexmedetomidine related to lower minimum temperatures, while longer surgery time was linked to higher minimum temperatures. These results should be seen parsimoniously, because it is not possible to infer on causality, and because the magnitude/direction of these effects can vary when controlling for other characteristics of patients/procedures. Moreover, the number of observations was low, with little variability, and the coefficients found were low, indicating a weak relationship among variables.

The significant relationship between older age and lower maximum/minimum temperature is explained by less efficient central thermoregulation for the elderly than for young adults, because of decreased baseline metabolism, muscular mass, tremors, sensitivity to cold and vasoconstrictor response.<sup>10,30</sup> The vasoconstriction threshold from 60–80 years falls 1 °C in comparison to 30–50 years.<sup>22</sup> Dexmedetomidine use may need more care in the elderly because of exacerbation of the trend to decrease temperature, especially in the postoperative period, when the patient is not subject to temperature monitoring and control implemented by the anesthesiologist.

## Conclusion

None of the patients presented increase  $\geq 37.8^{\circ}\text{C}$ /decrease  $< 35^{\circ}\text{C}$  in intraoperative temperatures. Increase  $\geq 37.8^{\circ}\text{C}$ /decrease  $< 35^{\circ}\text{C}$  in postoperative temperatures possibly associated with dexmedetomidine (OMS/ UMC causality system, Naranjo algorithm) presented a low frequency.

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## Author's contribution

**Felipe Aparecido Ferreira da Cruz:** Data acquisition, data analysis and interpretation, preparation of manuscript, final approval of version submitted.

**Luiz Fernando dos Reis Falcão:** Study conception and design, critical revision of manuscript due to important intellectual content, final approval of version submitted.

**José Luiz Gomes do Amaral:** Study conception and design, critical revision of manuscript due to important intellectual content, final approval of version submitted.

**Helga Cristina Almeida da Silva:** Study conception and design, data analysis and interpretation, preparation of manuscript, final approval of version submitted.

## Conflicts of interest

The authors declare no conflicts of interest.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: <https://doi.org/10.1016/j.bjane.2021.02.062>.

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## ORIGINAL INVESTIGATION

### The effect of alpha-2A adrenergic receptor (ADRA2A) genetic polymorphisms on the depth of sedation of dexmedetomidine: a genetic observational pilot study



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#### KEYWORDS

Adrenergic;  
Alpha-2;  
Dexmedetomidine;  
Polymorphisms;  
Sedation

#### Abstract

**Background:** The genetic polymorphisms of the alpha-2A adrenergic receptor (ADRA2A), which plays a significant role in sedation, anxiety relief, and antinociception, particularly in dexmedetomidine, may differ in the degree of sedation. This study aimed to investigate the effect of the genetic polymorphisms of ADRA2A (rs11195418, rs1800544, rs2484516, rs1800545, rs553668, rs3750625) on the sedative effects of dexmedetomidine.

**Methods:** A total of 131 patients aged 50 years or more from May 2018 to August 2019 were included in this study. The ADRA2A gene variants were evaluated using the TaqMan Assay. Dexmedetomidine diluted in normal saline to a concentration of  $4 \mu\text{g} \cdot \text{mL}^{-1}$  was infused at a dose of  $2 \mu\text{g} \cdot \text{kg}^{-1}$  to achieve procedural sedation (modified Ramsay sedation scale 4 [mRSS 4]).

**Results:** A total of 131 patients were evaluated. The genetic polymorphisms (rs11195418) of the ADRA2A receptor gene demonstrated no variation in our participants. The ADRA2A receptor gene polymorphisms (rs1800544, rs2484516, rs1800545, rs553668, and rs3750625) exhibited no differences in total dexmedetomidine doses ( $p > 0.217$ ), bispectral index at mRSS 4 ( $p > 0.620$ ), and time to obtain mRSS 4 ( $p > 0.349$ ).

**Conclusion:** This study suggested that the genetic polymorphisms of ADRA2A did not affect the sedative efficacy of dexmedetomidine.

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## Introduction

Dexmedetomidine is a selective and potent alpha-2 adrenoceptor agonist that is used for its sedative, analgesic, and anxiolytic properties. It is an effective and safe drug that is used to sedate patients during procedural sedation, regional anesthesia, and Intensive Care Unit (ICU) sedation.<sup>1</sup> A considerable advantage of dexmedetomidine-based sedation is that patients remain arousable. Along with minimal impact on breathing, dexmedetomidine is an interesting alternative in several procedures. Dexmedetomidine causes the activation of presynaptic and postsynaptic  $\alpha_2$ -receptors of the locus coeruleus, resulting in an unconscious state similar to natural sleep conditions with unique aspects that allow patients to cooperate and regain consciousness with ease.<sup>2</sup> However, high interindividual variability in dexmedetomidine pharmacokinetics has been reported, especially in the ICU population.<sup>3</sup>

The causes of high interindividual variability in the pharmacokinetics of dexmedetomidine may vary but are also found to be associated with the alpha-2 adrenergic receptor. The alpha-2 adrenergic receptor has three subtypes, namely A, B, and C. Among them, the A subtype (alpha-2A adrenergic receptor [ADRA2A]) inhibits the flow of sympathetic nerves in the central nervous system and plays a major role in sedation, anxiolysis, and antinociception.

Recently, it has been reported that there may be differences in the degree of sedation of dexmedetomidine depending on the genetic polymorphism caused by ADRA2A. Yagar et al. showed that sedation requirement with dexmedetomidine was higher in patients with the G allele than in patients with the C allele of ADRA2A, C1291.<sup>4</sup> Particularly, ADRA2A variants with rs11195418, rs1800544, rs553668, and rs10885122 were significantly related to various sympathetic drives.<sup>3,5</sup> In addition, a Single Nucleotide polymorphism (SNP) (rs11195418, rs1800544, rs2484516, rs1800545, rs34303217, rs553668, and rs3750625) of ADRA2A may be associated with cardiovascular responses to dexmedetomidine.<sup>6</sup>

Therefore, the genetic polymorphisms of ADRA2A can affect the depth of sedation or the amount of sedative required. This study aimed to investigate the effect of the genetic polymorphisms of ADRA2A (rs11195418, rs1800544, rs2484516, rs1800545, rs553668, and rs3750625) on the sedative effects of dexmedetomidine.

## Methods

### Study design

The study protocol, collection, and use of clinical data were approved by the Institutional Review Board of Pusan National University Yangsan Hospital (Yangsan, South Korea; approval n° 04-2018-010). The study was registered at the South Korean Clinical Research Information Service (trial ACTRN12616000085471). Written informed consent was obtained from all participants included in the study. Male patients with an American Society of Anesthesiologists (ASA) physical status I–III, aged over 50 years, and expected to use dexmedetomidine were recruited. Patients with psychiatric and neurological disorders and renal dysfunction or

those using tranquilizers or sedatives, which may affect the sedation level, were excluded.

After patients arrived in the operating room without any premedication, oxygen was provided via a nasal cannula at 3 L/min with routine noninvasive patient monitoring (pulse oximetry, electrocardiography, noninvasive blood pressure, and Bispectral Index [BIS]). Dexmedetomidine diluted in normal saline to a concentration of 4  $\mu\text{g}\cdot\text{mL}^{-1}$  was infused at a dose of 2  $\mu\text{g}\cdot\text{kg}^{-1}$  to achieve procedural sedation. The sedation level was assessed with the modified Ramsay Sedation Scale (mRSS), and the target sedation level was Mrss 4 (definition: appears asleep, purposeful responses to commands but at a level that is louder than the conversational level, requiring light glabellar tap, or both) in this study, which corresponds to the moderate sedation level of the ASA continuum of sedation and modified observer's assessment of alertness/sedation scale 2 (definition: responds only after mild prodding or mild shaking). The sedation level was assessed every 30-seconds after the patient appeared asleep. When bradycardia, defined as heart rate of less than 45 beats/min, was detected, 0.5 mg of atropine was administered via intravenous infusion. The study was terminated with the event of oxygen saturation below 94%, and/or alteration of heart rate or blood pressure 20% or greater from the baseline values. A standardized, general anesthesia technique was used for all patients after the target sedation level was achieved.

### DNA isolation and genotyping analysis

Ten-milliliter volume of arterial blood samples were collected from the participants of the study. Genomic DNA for genotyping was isolated from the buffy coat using the Wizard Genomic DNA Purification Kit (Promega, Madison) by an independent investigator blinded to the clinical information (Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital). The genotype was determined using polymerase chain reaction amplification, followed by restriction enzyme digestion. Validated primers were used to amplify and sequence the ADRA2A gene fragments (Macrogen, Seoul, Korea) listed in Table 1. Polymorphic changes in the ADRA2A gene were analyzed using pyrosequencing, which was performed by the PyroMark Q96 ID system (Qiagen, Korea), as described by the manufacturer.

### Statistical analysis

A prior study showed that the distribution frequency of rs1800544 alleles (CC:CG:GG) was 15%, 45%, and 45%, and the total doses of dexmedetomidine were  $108 \pm 18.14$ ,  $90.71 \pm 14.75$ , and  $90.22 \pm 17.99 \mu\text{g}$  in groups with CC, CG, and GG genotypes, respectively. The minimum sample size was determined to be 121 based on an alpha-value of 0.05 and a power of 0.80, calculated from the genotype distribution of the pilot data. Assuming a 10% loss to follow-up observations, 133 patients were calculated to be required.

Allele frequencies for a given variant were calculated by excluding samples with genotyping failure at the specific site. Data are expressed as mean  $\pm$  SD or median and interquartile range (25<sup>th</sup>–75<sup>th</sup> percentile). Deviation of the

**Table 1** Primers used for PCR amplification and pyrosequencing of regions of human ADRA2A.

SNP	Design strand	Context sequence
rs17216473	Forward	TGACCTCAGGTATCGCTGCCTC[A/G]GCCTCCCACAGTTTGATTATAG
rs11195418	Forward	AATAACTGTATCACTGGTGCAGGCT[A/G]TAGACATCAGCTGGGAATGAAGGTG
rs1800544	Forward	CCGTTGCCTCTGCTCGTGGGCC[C/G]GAGCTCATGGCCAACCTCCAGCAG
rs2484516	Forward	CTCACCCCGCCGCCGCCGCC[C/G]GAGCTCCGACAGTGTGCCCCAGCC
rs1800545	Forward	TATTAGGAGCTCGGAGCAAGAAGGC[A/G]CCCACCGAGAGCGTCTGAAGCGCGA
rs3750625	Forward	TTTAAAGAAAATGCTAAGGGCAGC[A/C]CTGCCCTGCCATCCCCCGCT
rs553668	Reverse	CATTCCTAACCTCTCTCTCTTTT[A/G]AAGAAAATGCTAAGGGCAGCCCTG

SNP, Single-Nucleotide Polymorphism; B, Biotinylated on the 5'-end of the primer.

frequency of polymorphisms from the Hardy-Weinberg equilibrium was assessed using the Chi-Square ( $\chi^2$ ) test. The median differences in the total dose of dexmedetomidine, time to reach mRSS 4, and BIS value when the target sedation level was achieved with various ADRA2A polymorphisms were evaluated using the Kruskal-Wallis test. The Mann-Whitney *U* test was performed to evaluate differences between the A/A, G/A, and G/G genotypes, and *p*-values were corrected with the Bonferroni correction according to the number of comparisons.

Statistical significance was set at *p* < 0.05 for all observations. All calculations were performed with the SPSS® software, version 20.0 (SPSS Inc., Chicago, IL, USA), for IBM computers (IBM, Armonk, NY, USA). Calculations of heterozygosity and allele frequency using the Hardy-Weinberg equilibrium test were performed using the R software, version 2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria).

## Results

A total of 133 male patients of Korean nationality, aged 50 years or more, who underwent elective surgery in our institution from May 2018 to August 2019 were included in this study. A flow diagram of the progression through the study is shown in Fig. 1. The composition of body fluids, muscle mass, body fat percentage and blood volume vary depending on the sex, which was fixed to account for any variability. One female patient and one patient with missing data were excluded (*n* = 2). The characteristics of the patients are presented in Table 2. The total median dose of dexmedetomidine was 98.4 (82.6–123) mcg, and the median time to obtain Mrss 4 for dexmedetomidine sedation was 7.5 (6.5–9) min.

The genotype and allele frequencies of the ADRA2A gene polymorphisms are shown in Table 3. The gene polymorphisms (rs11195418) of the ADRA2A receptor gene showed no variation in our participants. The allele frequencies (rs1800544, rs2484516, rs1800545, rs553668, and rs3750625) of the genetic polymorphisms assessed in the study population were within the Hardy-Weinberg equilibrium.

Table 4 shows the total dose of dexmedetomidine, BIS at mRSS 4, and time to obtain mRSS 4 across the SNP genotypes. The ADRA2A receptor gene polymorphisms exhibited no differences in the total dexmedetomidine doses (*p* > 0.217), BIS at mRSS 4 (*p* > 0.620), or time to obtain mRSS 4 (*p* > 0.349).

**Table 2** Characteristics of the patients enrolled in this study.

	Overall (n = 131)
Age	71.0 ± 7.4
Body weight (kg)	66.0 ± 9.2
Height (cm)	166.1 ± 5.4
BMI (kg m <sup>-2</sup> )	23.9 ± 2.9
Comorbidities	
Hypertension	92 (70.2%)
Diabetes mellitus	53 (40.5%)
Cardiovascular disease	44 (33.6%)
Respiratory disease	17 (13.0%)
Chronic kidney disease	13 (9.9%)
Cerebrovascular disease	20 (15.3%)
Others	6 (4.6%)
Total dexmedetomidine dose (mcg)	98.4 (82.6–123)
Dexmedetomidine dose (mcg·kg <sup>-1</sup> )	1.6 ± 0.4
BIS value at mRSS4	87 (82–91)
Time to obtain mRSS4 (min)	7.5 (6.5–9)

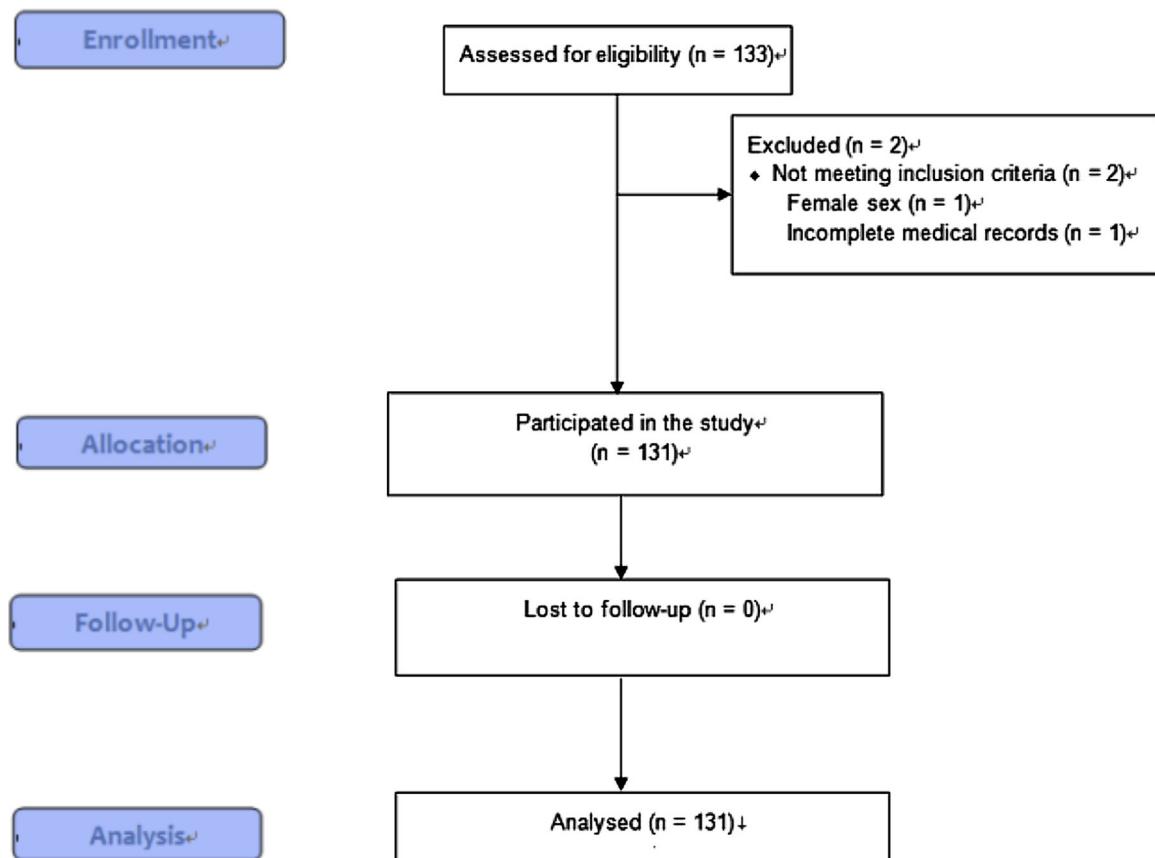
Values are shown as mean ± standard deviation, median (quartile) or number (%).

BMI, Body Mass Index; BIS, Bispectral Index value when target sedation level is achieved; mRSS, Modified Ramsay Sedation Scale.

## Discussion

The effect of the genetic polymorphisms of the ADRA2A gene on the sedative effects of dexmedetomidine was evaluated in this study. Only male patients were enrolled because sex has been reported to affect the pharmacokinetics of dexmedetomidine. The polymorphisms of the ADRA2A gene (rs1800544, rs2484516, rs1800545, rs553668, and rs3750625) did not have any significant association with the sedative effects of dexmedetomidine.

Dexmedetomidine is highly preferred because of its combined sedation, anxiolytic, and analgesic properties with limited respiratory depression.<sup>7</sup> It has a high alpha-2 adrenoceptor affinity and locus coeruleus activity, which has been shown to reduce the duration of mechanical ventilation compared with midazolam and shorten the extubation time compared with propofol and midazolam.<sup>8</sup> Dexmedetomidine decreases analgesic and opioid requirements, does not induce clinically significant respiratory depression, and has little effect on weaning from mechanical ventilation and extubation. Patients on dexmedetomidine can be eas-

**Figure 1** Flow diagram of the participants in this study.**Table 3** Genotype with allele frequencies and heterozygosity of  $\alpha_2$ -adrenergic receptor A subtype polymorphisms.

SNP	Genotype	Frequency	Allele	Frequency	<i>p</i> -value of Hardy-Weinberg equilibrium	Hetero-zygosity
rs1800544	C/C	18 (14.06)	C	91 (35.55)	0.562	0.502
	C/G	55 (42.97)	G	165 (64.45)		
	G/G	55 (42.97)				
rs2484516	C/C	98 (74.81)	C	229 (87.40)	0.2202	0.490
	C/G	33 (25.19)	G	33 (12.60)		
	A/A	7 (5.34)	A	45 (17.18)	0.0629	0.455
rs1800545	G/A	31 (23.66)	G	217 (82.82)		
	G/G	93 (70.99)				
	A/A	7 (5.34)	A	44 (16.79)	0.05376	0.497
rs3750625	C/A	30 (22.90)	C	218 (83.21)		
	C/C	94 (71.76)				
	A/A	26 (19.85)	A	123 (46.95)	0.3816	0.502
rs553668	G/A	71 (54.20)	G	139 (53.05)		
	G/G	34 (25.95)				

Values are described as number (%).

SNP, Single-Nucleotide Polymorphism.

ily awakened and tend to cooperate better with nursing and radiologic procedures in the ICU, which facilitates spontaneous awakening trials.<sup>9</sup> Based on European clinical trials), which proved the noninferiority of dexmedetomidine to propofol and midazolam in achieving the target sedation levels in mechanically ventilated patients in the ICU,

dexmedetomidine is considered as an economical option with lower ICU costs than standard sedatives.<sup>8,10</sup>

On the other hand, the use of dexmedetomidine alone is known to have different sedation levels among individuals using the same dose of the injected drug. In reality, the MIDEX and PRODEX clinical trials demonstrated inadequate

**Table 4** Evaluation of the equivalence of the population medians of total dexmedetomidine dose, BIS at mRSS4, and time to obtain mRSS4 across the SNP genotypes using the Kruskal-Wallis test.

SNP	Geno-type	Total dose of dexmedetomidine (mcg)	p-value	BIS at mRSS4	p-value	Time to obtain mRSS4 (min)	p-value
rs1800544	C/C	108.64 ± 39.25	0.684	85.17 ± 11.94	0.669	7.64 (6.48–8.55)	0.967
	C/G	103.60 ± 29.67		85.69 ± 7.20		7.27 (6.38–9.37)	
	G/G	100.68 ± 26.50		86.85 ± 7.53		7.58 (6.54–8.38)	
rs2484516	C/C	101.83 ± 28.96	0.313	85.66 ± 8.62	0.620	7.46 (6.52–8.62)	0.924
	C/G	108.55 ± 33.91		86.45 ± 7.63		7.68 (5.76–9.92)	
	A/A	94.46 ± 25.21		87.86 ± 8.32		7.53 (6.68–8.46)	
rs1800545	A/G	97.33 ± 23.27	0.217	84.90 ± 9.48	0.702	7.49 (6.67–8.29)	0.837
	G/G	106.27 ± 32.43		86.03 ± 8.03		7.57 (6.45–9.44)	
	A/A	94.46 ± 25.21		87.86 ± 8.32		7.53 (6.68–8.46)	
rs3750625	A/C	98.64 ± 22.47	0.322	84.73 ± 9.59	0.665	7.53 (6.79–8.29)	0.950
	C/C	105.75 ± 32.63		86.07 ± 7.99		7.47 (6.34–9.40)	
	A/A	94.46 ± 25.21		87.23 ± 5.89		7.39 (6.31–7.96)	
rs553668	A/G	97.33 ± 23.27	0.544	85.68 ± 7.78	0.506	7.78 (6.54–9.45)	0.349
	G/G	106.27 ± 32.63		85.21 ± 10.91		7.31 (6.38–8.46)	

Values are shown as mean ± standard deviation.

BIS, Bispectral Index; mRSS, Modified Ramsay Sedation Scale.

sedation (undersedation) with dexmedetomidine in at least one out of eight patients.<sup>8</sup> Additionally, previous studies have reported a lack of efficacy as high as 21% and 50%.<sup>11,12</sup> In clinical practices, patients receiving sedatives frequently develop side effects that are either ineffective or difficult to tolerate. Consequently, different drugs or additional dosages are repeatedly administered until an appropriate drug or concentration is determined. This is not only inefficient, but it also poses risks to a patient's safety.

Clinically, we have observed that there is heterogeneity in the response to dexmedetomidine, for example, no sedation or excessive hypertension and severe bradycardia with the same dosage. Dexmedetomidine recipients required significantly more rescue sedation than midazolam recipients.<sup>13</sup> Study drug discontinuation occurred in 24% of the dexmedetomidine recipients and 20% of the midazolam recipients in MIDEX and in 28% of the dexmedetomidine recipients and 23% of the propofol recipients in PRODEX. Significantly more patients receiving dexmedetomidine versus midazolam (9% vs. 4%) or propofol (14% vs. 5%) had their treatments discontinued because of lack of efficacy in these studies.<sup>8</sup>

There can be several reasons why the sedative effects of dexmedetomidine differ at the same dosage. The effect of physiological factors such as age, sex, and pathological conditions can contribute to individual responses against sedative drugs. According to recent studies, the individual variability of the effectiveness of a drug can often be associated with genetically determined variations. Especially, the polymorphisms of drug metabolizing targets, carriers, and enzymes can have a significant impact on individual dose-response relationships.<sup>14</sup> Likewise, the genomic polymorphisms of ADRA2A can contribute to individual responses to dexmedetomidine.

In case of dexmedetomidine, the polymorphism of ADRA2A, a major implication associated with the sedative effect, may lead to differential effects on sedation lev-

els. Previously, Yağar et al.<sup>4</sup> investigated the relationship between the effect of gene polymorphism of ADRA2A, C-1291 G in the promoter region of the candidate gene and the clinical characteristics of dexmedetomidine. Patients with the variant genotype demonstrated higher BIS and Ramsay sedation scores, indicating that higher drug doses were required to reach the same depth of sedation, and the use of the same dosage results in a longer duration of sleep.<sup>4,15</sup> Hunter et al.<sup>16</sup> hypothesized that the ADRA2A genes with rs1800545, rs1800035, rs1800038, rs11195418, rs1800544, rs2484516, +1483T > A, rs553668, and rs3750625 would cause different cognitive tasks and pain perceptions before and after three different dexmedetomidine doses were administered. Although the ADRA2C del322–325 variant was shown to affect pain perception, the ADRA2A gene polymorphism has not been observed to be correlated with pain perception and cognitive tasks at the three different doses.

A limitation of this study is that dexmedetomidine stimulates a spindle-type Electroencephalogram (EEG) activity, as in physiological sleep.<sup>17</sup> Dexmedetomidine induces sleep by activating endogenous nonrapid-eye movement sleep pathways and reduces the firing of noradrenergic locus coeruleus neurons in the brain stem.<sup>18</sup> Dexmedetomidine produces a state equivalent to physiological stage 2 sleep, with an abundant sleep-spindle activity corresponding to a transient EEG activation and a slight-to-moderate amount of slow-wave activity. The abundant sleep-spindle activity may be misinterpreted by the BIS algorithm as light anesthesia because spindles mimic arousal and an alpha-pattern EEG.<sup>19</sup> Thus, in this study, mRSS was used to assess the depth of sedation periodically.<sup>20</sup> The depth of sedation assessment methods, including mRSS, requires the periodical stimulation of patients, which can interfere with the depth of sedation itself.<sup>21,22</sup> We attempted to minimize and standardize the stimulation by providing verbal commands in a conversational level at 30-seconds intervals after the patients appeared to be asleep.

## Conclusions

Based on the high interindividual variability in dexmedetomidine pharmacokinetics, this study attempted to evaluate the effect of the genetic polymorphisms of the ADRA2A on the pharmacodynamics of dexmedetomidine. The ADRA2A gene polymorphism (rs1800544, rs2484516, rs1800545, rs553668, and rs3750625) has not been observed to be correlated with the sedative effects of dexmedetomidine in this study.

## Conflicts of interest

The authors declare no conflicts of interest.

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**ORIGINAL INVESTIGATION**

**Comparison of Proseal LMA with i-Gel in children under controlled ventilation: a prospective randomised clinical study**

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**KEYWORDS**

Laryngeal masks;  
Airway management;  
Pediatrics;  
Anesthesia;  
General

**Abstract**

**Background:** Supraglottic airway device is presently the most common modality of airway management in children for short surgical procedures. The i-gel is one such novel supraglottic airway device with a non-inflatable cuff. The objective of the present study was to evaluate the efficiency of i-gel compared to LMA Proseal regarding oropharyngeal leak pressure, insertion time, ease of insertion, and fiberoptic view of larynx.

**Methods:** After obtaining ethical clearance and parental consent, 70 children aged 2–10 years, weighing 10–30 kg were randomised to receive LMA Proseal or i-gel for airway management. Data with respect to oropharyngeal leak pressure, insertion time, ease of insertion, number of attempts, and fiberoptic score were collected. The primary outcome was the oropharyngeal leak pressure with the two supraglottic airway devices measured by manometric stability.

**Results:** Demographic data were comparable between the two groups. The oropharyngeal leak pressure (LMA Proseal vs. i-gel,  $20.51 \pm 4.71 \text{ cmH}_2\text{O}$  vs.  $19.57 \pm 5.71 \text{ cmH}_2\text{O}$ ), ease of insertion, number of attempts, and fiberoptic view score was similar between the two groups. The insertion time was faster with i-gel ( $22.63 \pm 5.79 \text{ s}$ ) compared to LMA Proseal ( $43.26 \pm 7.85 \text{ s}$ ).

**Conclusion:** I-gel was similar to LMA Proseal with respect to oropharyngeal leak pressure in children under controlled ventilation.

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**Introduction**

Supraglottic Airway Device (SAD) is presently the common modality of airway management in children for short surgical procedures under general anesthesia.<sup>1</sup> It not only provides adequate ventilation, oxygenation, and delivery of anesthetic agents, but has lower risk of respiratory adverse

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events, thus replacing the need for conventional tracheal intubation. To overcome the risk of regurgitation and aspiration of gastric contents with the first-generation SAD, several second generation SADs with a gastric drain tube have been introduced.<sup>2</sup> LMA Proseal and i-gel are two such second-generation SADs. LMA Proseal with its unique design specifications is regarded as a state-of-the-art SAD and is compared with all latest SADs.<sup>3</sup>

Several studies have established the efficiency of both devices, however i-gel has been studied broadly in adults with limited literature on their use in children.<sup>4–6</sup> It was assumed i-gel to be more effective than LMA Proseal with respect to Oropharyngeal Leak Pressure (OLP) in children. The study intended to compare the efficacy of i-gel and LMA Proseal under controlled ventilation in children undergoing elective surgeries. The primary objective was to evaluate the efficiency of i-gel compared to LMA Proseal in terms of oropharyngeal leak pressure under controlled ventilation in children undergoing short elective surgeries.

## Methods

The study was conducted after obtaining Institutional Ethical Committee clearance and informed consent from the parents/guardians of the children in a tertiary care hospital (mono center study). The study was also registered in the Clinical Trial Registry (CTRI/2018/03/012287).

Children scheduled for elective short duration surgeries (< 2 h), aged between 2 and 10 years, weighing 10–30 kg and with American Society of Anesthesiologists (ASA) physical status I and II were included. Children with a history of obstructive sleep apnea, laparoscopic surgeries, intraoral surgeries, risk of aspiration of gastric contents, anticipated difficulty in the airway, and children who were to be operated in prone positions were excluded from the study. Eligible patients were randomly assigned to either group LMA Proseal or group i-gel by computer-generated random number table and concealed in a sequentially numbered sealed envelope by an anaesthesiologist not involved in the study. The sealed envelopes were opened to reveal the group allocation just before induction of anaesthesia by another anaesthesiologist, who had the sealed envelopes in his safe keeping. The size of each SAD was selected based on the bodyweight of children (LMA Proseal: 10–20 kg: size 2; 20–30 kg: size 2.5; i-gel: 10–20 kg: size 2; 25–30 kg: size 2.5).

All the children were fasting as per the ASA fasting guidelines and were premedicated with oral Phenergan 0.5 mg.kg<sup>-1</sup> on the morning of surgery. An intravenous line was secured in the ward under EMLA cream (lidocaine 2.5% and prilocaine 2.5%) analgesia as per institutional practice. Following minimal mandatory monitoring, anaesthesia was induced with fentanyl 2 mcg.kg<sup>-1</sup> and propofol 2 mg.kg<sup>-1</sup>. After ensuring bag-mask ventilation, atracurium 0.5 mg.kg<sup>-1</sup> was administered to achieve neuromuscular blockade and after attaining adequate jaw relaxation, an appropriate size SAD was inserted as per the manufacturer's recommendation. The cuff of LMA Proseal was inflated to achieve 60 cmH<sub>2</sub>O pressure with a cuff pressure monitor. Later, the SAD was connected to a circle breathing system and appropriate placement was confirmed by movements of chest wall, aus-

culation of breath sounds, an absence of gastric insufflation (determined by epigastric auscultation), and a square-wave capnograph. The OLP was measured with head in the neutral position, under manual ventilation by closing the expiratory valve of the circle system at a fixed gas flow of 3 L.min<sup>-1</sup> and documenting the airway pressure at equilibrium.<sup>7,8</sup> To avoid barotrauma during measurements, the peak airway pressure was limited to 40 cmH<sub>2</sub>O. After the OLP measurement, a flexible fibreoptic scope was guided through the airway tube and the visualization of the glottis was scored<sup>9</sup> as follows: (1) vocal cords not seen; (2) vocal cords + anterior epiglottis seen; (3) vocal cords + posterior epiglottis seen; (4) only vocal cords are seen.

A lubricated gastric tube was then guided through the drainage channel, and the number of attempts at placement was recorded. Gastric tube placement was checked by auscultation of injected air over the epigastrium. Insertion time was defined as the time between picking up the device and obtaining an effective airway with capnograph trace on the monitor. Failed device placement was defined as being unable to observe a smooth square-wave capnograph, inadequate ventilation, no rise of the chest wall, and significant leakage from the gastric drain tube. Patients with three failed attempts at device insertion were intubated and omitted from the study. While placing the device, the following manoeuvres were done to achieve correct placement: movement of device upwards and downwards, jaw lift-jaw thrust, and head extension-neck flexion. Ease of device placement was graded<sup>5</sup> from 1 to 3 on a scale: 1 – very easy (no maneuver), 2 – easy (one maneuver), 3 – difficult (requiring more than one maneuver). Following the surgery, patients were examined for any perioperative complications such as coughing, bronchospasm, laryngospasm, hiccup, blood on the device after removal, injury to lips, teeth or tongue, and sore throat.

## Statistical analysis

The sample size was obtained using R software. In the hypothesis, it was assumed that i-gel is more effective than LMA Proseal in terms of the oropharyngeal leak pressure. With power 80%, 95% confidence level, assuming large effect size as 0.6 and for one-tailed test, minimum sample size required was 34.03 per group. Hence, the minimum sample size required for each group was 35 subjects. SPSS v.15 (SPSS Inc., Chicago, Illinois, USA) was used to analyse the data. Descriptive and inferential statistics were used to analyse the data. Continuous data were presented as mean  $\pm$  SD and assessed using Student's *t*-test. Categorical data were presented in frequency (%) and assessed using Chi-Square and Fisher Exact tests. Significance was assessed at 5% level of significance.

## Results

Among the 85 children who were assessed for eligibility for the study, 15 were excluded (6 did not meet inclusion criteria, 6 declined to participate, and 3 underwent laparoscopic surgery). Of the 70 children who were randomized, all completed the study and were included for analysis (Fig. 1). Demographic characteristics and opera-

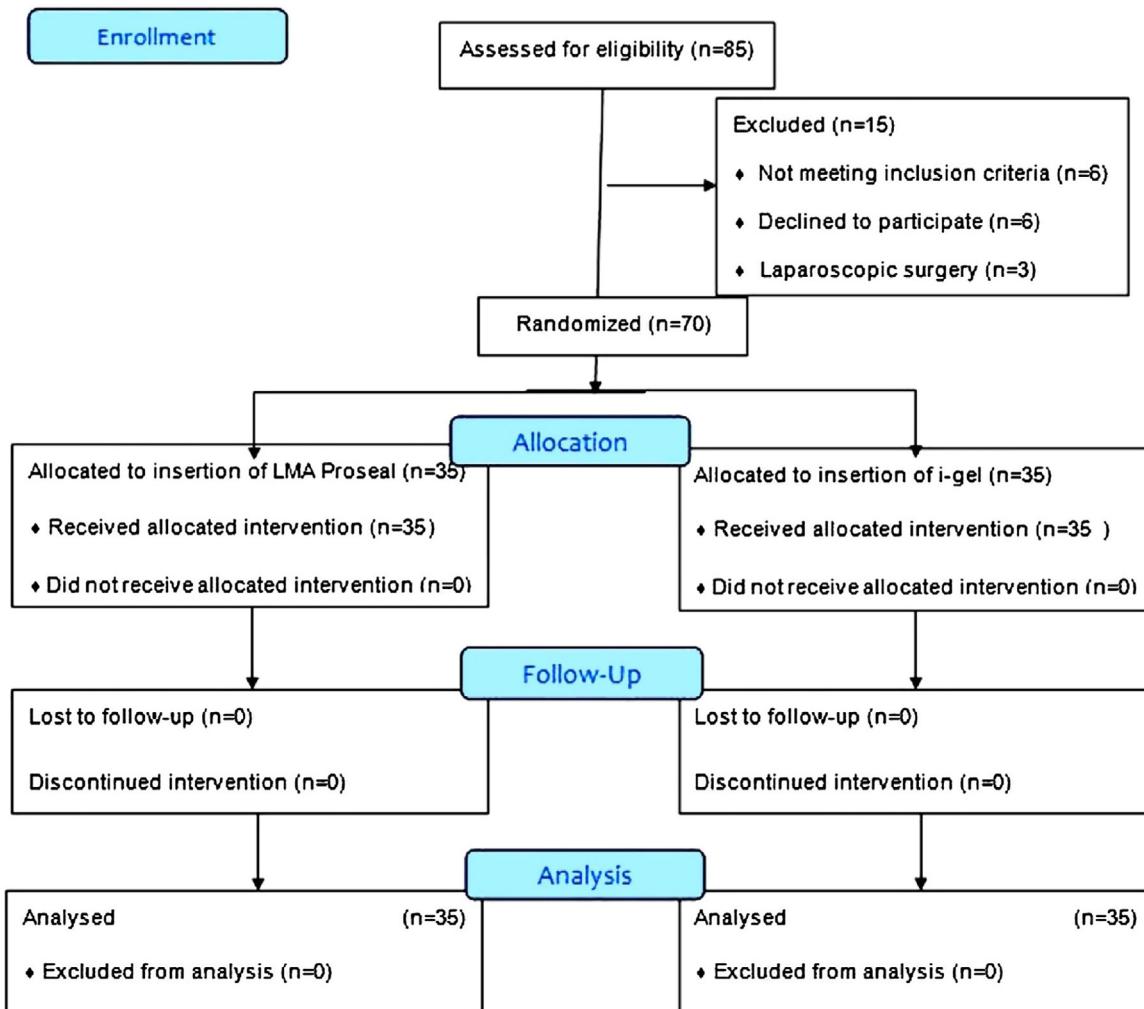


Figure 1 CONSORT 2010 Flow Diagram.

Table 1 Patient baseline characteristics and operative data.

Variables	Group LMA Proseal	Group i-gel	p-value
Age (years) <sup>a,b</sup>	4.87 ± 2.89	4.86 ± 3.01	0.984
Gender <sup>c</sup>			
Male	30 (85.7%)	29 (82.8%)	1.000
Female	5 (14.3%)	6 (17.2%)	
Weight (Kg) <sup>a,b</sup>	16.09 ± 5.18	16.37 ± 5.53	0.824
BMI (Kg.m <sup>-2</sup> ) <sup>a,b</sup>	14.57 ± 2.29	15.13 ± 1.50	0.232
Type of surgery			-
Cervical lymph node excision	13 (37.1%)	11 (31.4%)	
Circumcision	7 (20%)	12 (34.3%)	
Herniotomy	5 (14.3%)	3 (8.6%)	
Hypospadias repair	3 (8.6%)	1 (2.9%)	
Miscellaneous	7 (20%)	8 (22.9%)	

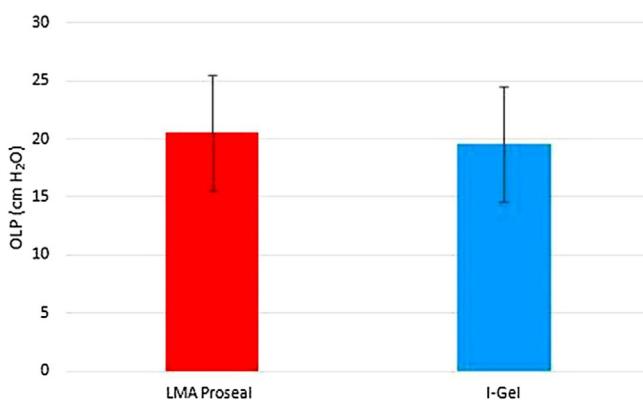
<sup>a</sup> Data expressed in terms of Mean ± SD.<sup>b</sup> Student t-test.<sup>c</sup> Chi-Square test.

tive data of the patients are summarised in Table 1. Most of the children in this study were aged between 2 and 5 years (Group LMA Proseal: 57.1%; Group i-gel: 60%) with striking

male predominance (Group LMA Proseal: 85.7%; Group i-gel: 82.8%). No significant difference was observed between the groups in terms of age, gender, Body Mass Index (BMI),

**Table 2** Comparison of clinical performance of LMA and i-gel.

Variables	Group LMA Proseal	Group i-gel	p-value
<b>Size of SAD<sup>a</sup></b>			
2	25 (71.4%)	30 (85.7%)	0.145
2.5	10 (28.6%)	5 (14.3%)	0.145
<b>Insertion time (s)<sup>b,c</sup></b>			
	43.26 ± 7.85	22.63 ± 5.79	0.0001
<b>Ease of insertion<sup>a</sup></b>			
Grade 1	32 (91.4%)	28 (80%)	0.172
Grade 2	3 (8.6%)	6 (17.1%)	0.284
Grade 3	0	1 (2.9%)	1.000
<b>Number of attempts<sup>d</sup></b>			
1	35 (100%)	33 (94.3%)	0.493
2	0	2 (5.7%)	
<b>Gastric tube placement<sup>a</sup></b>			
	35 (100%)	35 (100%)	1.000
<b>Oropharyngeal leak pressure (cmH<sub>2</sub>O)<sup>b,c</sup></b>			
	20.51 ± 4.71	19.57 ± 5.71	0.453
<b>Fibroscopic view score<sup>a</sup></b>			
1	5 (14.3%)	9 (25.7%)	0.232
2	11 (31.4%)	15 (42.9%)	0.322
3	0	1 (2.9%)	1.000
4	19 (54.3%)	10 (28.6%)	0.029

<sup>a</sup> Chi-Square test.<sup>b</sup> Data expressed in terms of Mean ± SD.<sup>c</sup> Student t-test.<sup>d</sup> Fischer Exact test.**Figure 2** Mean oropharyngeal leak pressure between the two groups.

height, and weight. ASA status was comparable between the groups ( $p = 1.00$ ). Most of the patients in group LMA Proseal underwent cervical node excision (37.14%) whereas group i-gel underwent circumcision (34.28%). The mean duration of surgery in group LMA Proseal was higher as compared to group i-gel; however, statistically insignificant ( $p = 0.203$ ).

Size 2 device was used in most of the children in both groups. In most of the children, LMA Proseal or i-gel insertion was achieved in the first attempt. Ease of insertion was graded as "very easy" in most children of both groups. Size of the device, ease of insertion and number attempts were comparable between the groups. The OLP was similar between the two groups and the difference was not statistically significant (LMA Proseal vs. i-gel,  $20.51 \pm 4.71$  cm H<sub>2</sub>O vs.  $19.57 \pm 5.71$  cm H<sub>2</sub>O;  $p = 0.453$ ); (Fig. 2). The mean insertion time was faster in group i-gel as compared to group LMA Proseal and the difference was statistically significant

**Table 3** Profile of perioperative complications.

Variables	Group LMA Proseal	Group i-gel	p-value
Blood on device	1 (2.9%)	0	1.000
Sore throat	2 (5.7%)	3 (8.6%)	
Post-extubation cough	1 (2.9%)	0	

( $p = 0.0001$ ). The fibroscopic view was comparable in both the groups, where most of the cases in group LMA Proseal (54.3%) had grade 4 view while most cases in group i-gel (42.9%) had grade 2 view. Gastric tube placement was 100% successful in both groups (Table 2). Perioperative complication was comparable between the groups (Table 3). The sore throat was the commonest complication observed in both groups.

## Discussion

The study found that the OLP immediately following insertion of i-gel was similar to LMA Proseal and hence the superiority hypothesis cannot be adopted. Similarly, the ease of placement of the device, first insertion attempt success, and the fiberoptic visualization of the glottis was comparable between the two devices. However, the time to successful placement of i-gel was significantly shorter than LMA Proseal.

A higher OLP is required to ensure positive pressure ventilation with SADs. It was speculated that i-gel with its soft, non-inflatable, gel-like cuff designed to mirror the pharyngeal structures may result in a higher OLP than LMA Proseal. Although there was no significant difference in OLP immediately after device insertion, the results of the present

study should be interpreted with caution. The finding with respect to OLP in the present study is similar to studies of Gasteiger et al.<sup>10</sup> and Saran et al.,<sup>4</sup> who observed that the OLP between the two devices was similar. In contrast, the OLP with i-gel was significantly higher than LMA Proseal in a few studies.<sup>6,11–14</sup> The comparison of OLP between various studies is complicated by the difference in the methodology adopted, such as under spontaneous ventilation, presentation of results, and the size of the device employed in the study. The studies by Acharya R et al.<sup>11</sup> and Goyal R et al.,<sup>12</sup> employed spontaneous ventilation, whereas in the present study children were paralysed, which might explain the difference in the results. OLP is difficult to perform accurately in spontaneously ventilating patient, since a constant airway pressure cannot be obtained, as the seal probably varies throughout the respiratory cycle due to changes in pharyngeal wall tone, as opined by Brimacombe.<sup>15</sup> In the study by Mitra S et al.,<sup>13</sup> the device size used was only 2.5. In the present study, although the devices of size 2 and 2.5 were used, the predominant size of device used was number 2 in more than 70% of children, which might explain the difference in the results. The sealing pressure of i-gel has been suggested to improve over time as it may conform to the upper airway anatomy better as it approaches body temperature due to the thermoplastic nature of the material.<sup>16</sup> In the present study the OLP was measured in both groups immediately following device insertion, and may be another reason for similarity in the OLP in the two groups.

Fibrooptic visualization of glottis used to assess appropriate placement of SAD was comparable between the two devices and was consistent with previous studies.<sup>4,6,10,14</sup> The incidence of complications in the present study was low in both groups, however no statistical inference about the same can be drawn as it is not powered to study the same.

The present study had a few limitations that need to be acknowledged. First, unblinded observers collected the data. Blinding was not possible as i-gel appears different from LMA Proseal. Second, the study was performed in children with normal airway and hence the findings cannot be inferred to those with difficult airway or abnormal upper airway anatomy. Third, insertion of devices was performed by a single experienced user and hence the findings may not apply to inexperienced users, such as residents. Finally, the number of children receiving 2.5-size device was relatively small.

## Conclusion

The present study showed that the OLP with i-gel was similar to LMA Proseal immediately following insertion of the device under controlled ventilation in children. In addition, the two devices were similar with respect of ease of insertion, number of attempts, and fiberoptic view of glottis. The i-gel demonstrated a shorter time to successful placement compared with LMA Proseal.

## Author's contributions

Study conceptualization and designing have been done by Dr. Tejesh CA. Data acquisition, analysis and interpretation of

the data have been performed by Dr. Praveen. The first draft of the manuscript has been prepared by Dr. Praveen. Draft is revised by Dr. Tejesh CA. Both the authors have approved the final manuscript and are the grantor for this study.

## Conflicts of interest

The authors declare no conflicts of interest.

## Acknowledgments

Both the authors have contributed equally in the development of manuscript.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.bjane.2021.02.042>.

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## ORIGINAL INVESTIGATION

### Comparison between epidural technique and mid-axillary ultrasound-guided TAP block for postoperative analgesia of laparoscopic radical prostatectomy: a quasi-randomized clinical trial<sup>☆</sup>



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#### KEYWORDS

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after surgery

#### Abstract

**Background:** Our goal was to evaluate whether TAP block offers the same analgesic pain control compared to epidural technique in laparoscopic radical prostatectomy surgery through the morphine consumption in the first 48 hours.

**Methods:** In this study, 45 patients were recruited and assigned to either TAP or epidural. The main study outcome was morphine consumption during the first 48 hours after surgery. Other data recorded were pain at rest and upon movement, technique-related complications and adverse effects, surgical and postoperative complications, length of surgery, need for rescue analgesia, postoperative nausea and vomiting, start of intake, sitting and perambulation, first flatus, and length of in-hospital stay.

**Results:** From a total of 45 patients, two were excluded due to reconversion to open surgery (TAP group = 20; epidural group = 23). There were no differences in morphine consumption (0.96 vs. 0.8 mg;  $p = 0.78$ ); mean postoperative VAS pain scores at rest (0.7 vs. 0.5;  $p = 0.72$ ); or upon movement (1.6 vs. 1.6;  $p = 0.32$ ); in the TAP vs. epidural group, respectively. Sitting and perambulation began sooner in TAP group (19 vs. 22 hours,  $p = 0.03$ ; 23 vs. 32 hours,  $p = 0.01$ ; respectively). The epidural group had more technique-related adverse effects.

**Conclusion:** TAP blocks provide the same analgesic quality with optimal pain control than epidural technique, with less adverse effects.

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<sup>☆</sup> The study was carried out in Hospital Sant Joan Despí Moisès Broggi, Barcelona, Spain.

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## Introduction

The purpose of enhanced recovery programs pathways combined with laparoscopic techniques is to reduce post-operative stress and complication rates, shorten the length of hospital stay, and provide an optimal anesthesia avoiding high opioid doses.<sup>1</sup> Good results were obtained in colorectal surgery,<sup>2</sup> and they have become extensive to various surgical procedures,<sup>3–5</sup> with the aim of improving postoperative recovery.<sup>6–8</sup> However, bibliography is scarce regarding urological surgery.<sup>5,9–11</sup>

Multimodal pain management is essential to enhanced recovery programs.<sup>7</sup> Epidural analgesia has been established as the most adequate analgesic technique for this type of surgery,<sup>12</sup> as it allows for proper pain management<sup>8</sup> without the adverse effects of other analgesics such as morphine, and a decrease in complications.<sup>13,14</sup> However, it is not free of side effects or complications.<sup>15,16</sup> All of these can affect early patient mobilization, satisfaction, and increase hospital stay.<sup>7,8</sup> These aspects go against the enhanced recovery programs, hence various studies have been published recommending other analgesic techniques such as the transversus abdominis plane (TAP) block in abdominal surgeries.<sup>17,18</sup> The TAP block is an interfacial plane block based on the injection of local anesthetic in the neurofascial space between the internal oblique muscle and the transversus abdominis muscle. Within this space run the nervous fibers that gather abdominal wall sensitivity. The clinical effectiveness of TAP block versus epidural technique or other analgesic techniques have been studied.<sup>19</sup> However, there are no direct comparisons between both techniques regarding the degree of analgesia provided in laparoscopic radical prostatectomy. Specific bibliography considering the analgesic effect of the TAP blockade in laparoscopic radical prostatectomy is scarce, and mostly refers to robot-assisted surgeries.<sup>11,20,21</sup> To our knowledge, no study has been published evaluating TAP vs. epidural in laparoscopic radical prostatectomy in the enhanced recovery programs context, evaluating both analgesia and enhanced recovery programs-related outcomes.

Our main objective was to compare morphine consumption and analgesic efficacy between epidural technique and TAP block in the first 48 hours after laparoscopic radical prostatectomy.

## Methods

### Patient selection

The study was a controlled, quasi-randomized, non-blinded, single center trial with two parallel arms. The study protocol was reviewed and approved by our local ethics committee (approval number 16/42) and was conducted in accordance with the Declaration of Helsinki. The results are reported according to current TREND guidelines. The allocation procedure was performed using a 1:1 sequential assignment, to either TAP or epidural group, by the anesthesiologist at the preoperative visit, where the patients were recruited. Informed consent was obtained from all those patients who underwent laparoscopic radical prostatectomy between October 2016 and May 2018 before entering the study. The

study was registered in Clinicaltrial.gov with the number 03884335.

Exclusion criteria were age below 18 years old; anesthesia ASA (American Society of Anesthesiologists) score  $\geq$  IV; body mass index (BMI)  $\geq$  30 kg.m $^{-2}$ ; history of local anesthetic allergies; chronic opioid use, coagulopathy; peripheral neuropathy; reconversion to open surgery; or patient's refusal.

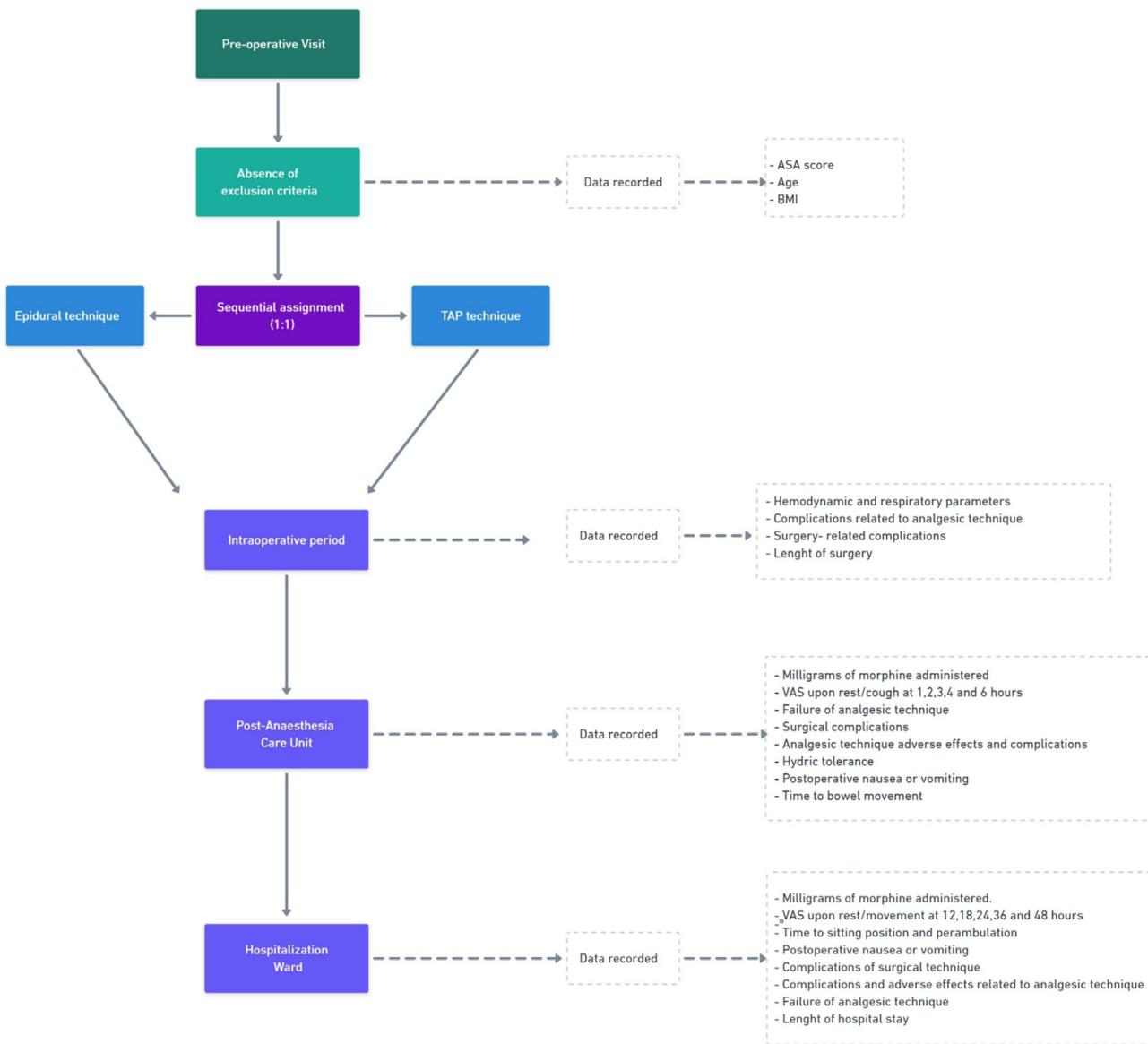
Secondary outcomes registered were technique-related complications and adverse effects, surgical and postoperative complications, length of surgery, need for rescue analgesia, postoperative nausea and vomiting, start of intake, sitting and perambulation, first flatus; and length of in-hospital stay.

Data was recorded at different time points (Figure 1): *Pre-operative visit*: age, anesthesia ASA score and BMI; *Intraoperative period*: complications related to analgesic technique (vascular puncture, peritoneal or intestinal puncture in the TAP block, number of attempts, impossibility to perform technique), surgery-related complications (bleeding, intestinal, bladder or diaphragmatic perforation), and length of surgery; *Postanesthesia care unit*: milligrams of administered morphine, pain as evaluated by the visual analogue scale (VAS) upon rest (VASr) and movement – cough – (VASm) at 1, 2, 3, 4, and 6 hours; failure of analgesic technique (need of morphine PCA), surgical complications, analgesic technique adverse effects (motor blockade, paresthesia, accidental catheter disconnection) and complications (spinal hematoma, infection, postdural-puncture headache, nerve lesions), hydric tolerance, postoperative nausea or vomiting, and time to bowel movement (first flatus after surgery); *Hospitalization ward*: milligrams of administered morphine; VASr and VASm at 12, 18, 24, 36, and 48 hours; time to sitting position and perambulation; postoperative nausea or vomiting; complications of surgical and analgesic technique (including infection at this point) and adverse effects related to analgesic technique; failure of analgesic technique (need of morphine PCA); and length of in-hospital stay.

All recorded parameters were registered prospectively and stored in an IRB-approved database.

### Intraoperative management

All patients underwent combined anesthesia: either general anesthesia + epidural (epidural group); or general anesthesia + TAP block (TAP group). Patients were pre-medicated with intravenous midazolam 0.05 mg.kg $^{-1}$ . In the epidural group, the catheter was inserted 4–5 cm into the epidural space at L1–L2 level. Three milliliters (mL) lidocaine 2% were injected as a testing dose to exclude intrathecal placement prior to induction. Induction was performed intravenously with fentanyl (1.5 mcg.kg $^{-1}$ ), propofol (1.5–2 mg.kg $^{-1}$ ), and rocuronium (0.6 mg.kg $^{-1}$ ). Orotracheal intubation was performed. Prior to skin incision 8 mL of 0.25% levobupivacaine were administered epidurally, and a continuous perfusion of 0.125% levobupivacaine at 5 mL.h $^{-1}$  was started. In the TAP group, a bilateral, ultrasound-guided mid-axillary TAP block was performed immediately after induction (which was the same as described in the epidural group) but prior to surgery. The high-frequency lineal



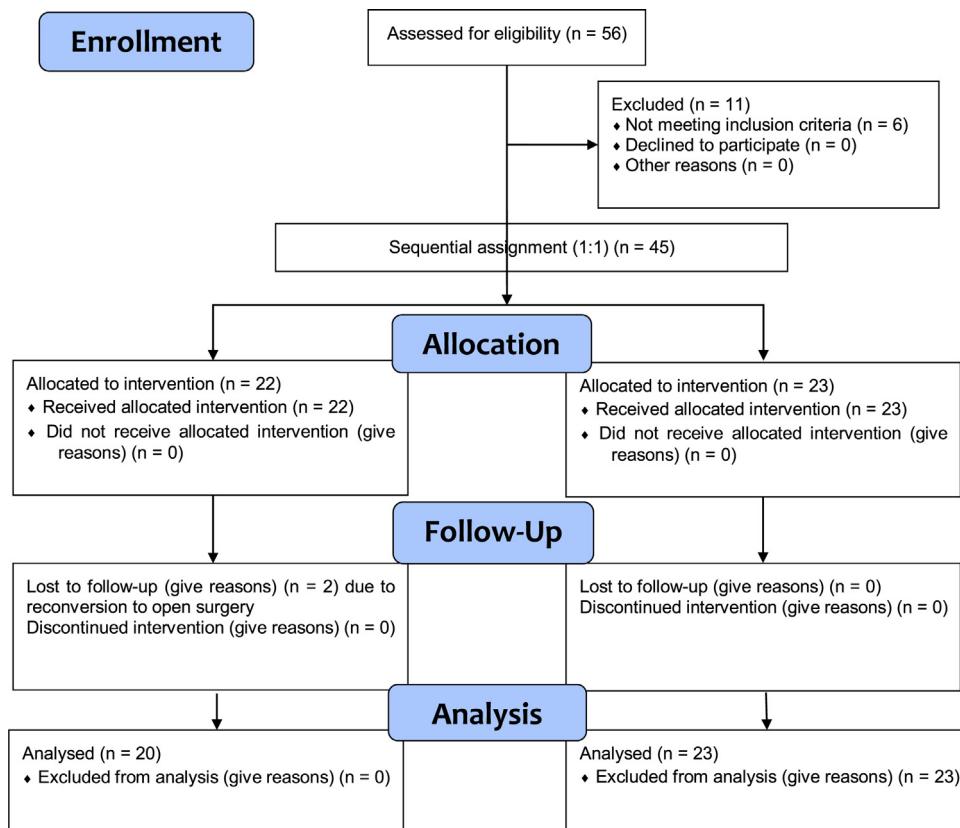
**Fig. 1** Flowchart of this study.

probe (Sonosite MicroMAXX<sub>TM</sub>) was placed midway between the costal margin and iliac crest, and transversus abdominis muscle located behind the rectus abdominis and below the internal oblique muscle. Twenty mL of local anesthetic (bupivacaine 0.375%) was administered via a 22G Quincke spinal needle inserted in-plane on each side of the abdomen. We considered a successful block if ultrasound vision evidenced interfacial local anesthetic spread.

A laparoscopic radical prostatectomy was performed. Intraoperative anesthetic maintenance was performed with propofol target-controlled infusion for BIS between 40 and 60. Net zero fluid therapy was maintained, as well as normothermia and normotension following enhanced recovery programs criteria.<sup>1</sup> After surgery, patients were awoken from general anesthesia and transferred to the postanesthesia care unit for a 6-hour follow-up prior to transfer to conventional ward and optimal postoperative analgesia.

### Postanesthesia care unit management

In the postanesthesia care unit, the patient was kept under observation for 6 hours for pain and bleeding control, as well as hemodynamic and respiratory management. Besides epidural or TAP blockade, standard analgesia was maintained with paracetamol 1 g/8 h IV (intravenous) alternate with metamizole 2 g/8 h IV, as well as 2 mg bolus of morphine, if required. If pain was unmanageable, in the epidural group the first option was administration of 8 mL of 0.125% levobupivacaine; next catheter was repositioned, and if these options failed catheter was removed, and a morphine infusion was begun. In the TAP group, if rescue morphine bolus (of up to 10 mg) was not enough, TAP-block was repeated. If after 20 minutes, the patient showed no improvement, morphine infusion was begun. In these cases (both epidural and TAP groups), data was recorded as analgesic technique failure.



**Fig. 2** Flow Diagram of this study.

## Hospitalization ward management

After postanesthesia care unit, patients were transferred to conventional hospital ward. During this period, they were followed-up by our hospital's acute pain team, formed by an anesthesiologist and a specialized nurse. Epidural infusion and catheter removal was performed when VASm were consistently < 3 in patients with continuous perfusion of 0.125% levobupivacaine at 3 mL.h<sup>-1</sup>, if coagulation parameters and heparin regime permitted.

## Statistical analysis

Previous studies reported minimal morphine consumption differences at 48 hours being of mean (standard deviation [SD]) 26.8 (19.8 mg).<sup>22</sup> Aiming to detect a reduction in two thirds or morphine consumption as compared these previously published results, and in order to increase the study's potency, sample size was calculated with a confidence interval of 99%, a two-tailed alpha set at 0.01 and a beta of 0.1; sample size was established as 17 per group. An increase of 20% (22 patients) to be recruited for each arm was established to minimize effects secondary to patient losses.

Results are reported as mean and standard deviation (SD) in quantitative data and percentage or rank in qualitative data. Kolmogorov-Smirnov test was run to evaluate data distribution.

For normally distributed numerical data, the independent samples' Student *t*-test was used to compare the

difference in the means between the two study groups. For skewed numerical data, the Wilcoxon rank sum test was applied. The Pearson chi-square test was used for comparison of the two groups as regards differences in categorical data. Fisher's exact test was applied in place of the chi-square test when cell count is less than 5. All *p*-values are two-sided. A *p* < 0.05 is considered statistically significant. Statistical analyses were carried out using SPSS v 22.0 (SPSS, Chicago, IL, USA).

## Results

A total of 45 patients were recruited, two of which (from the epidural group) were excluded due to surgical reconversion from laparoscopy to open surgery due to technical difficulties. From the 43 remaining patients, 20 were allocated in the epidural and 23 in the TAP group (Figure 2). There were no differences between groups regarding patient characteristics (Table 1).

## Intraoperative results

Regarding complications related to analgesic technique, in the epidural group there were 2 cases of dural puncture (technique was repeated at a higher level); and one case of paresthesia when the catheter was being introduced. No complication was registered in the TAP group. No statistically significant differences were found between groups and appearance of complications (*p* = 0.09).

**Table 1** Patient characteristics.

Variable	TAP	Epidural	P
Age (years)	65.6 (4.8) (54–71)	65.9 (5.4) (54–71)	0.84 <sup>a</sup>
ASA physical status score			0.43 <sup>b</sup>
I	2	3	
II	21	16	
III	0	1	
BMI ( $\text{kg} \cdot \text{m}^{-2}$ )	27.3 (2.2)	27.7 (3.3)	0.47 <sup>a</sup>
Length of surgery (minutes)	241 (48)	246 (58)	0.46 <sup>a</sup>

Age, BMI and length of surgery were expressed as mean (standard deviation (SD)). ASA physical status score was expressed as number (n). P-value for significant differences between TAP group and epidural group.

Statistical test used: <sup>a</sup> T-test; <sup>b</sup> Chi-square.

As for surgical complications, there were no differences between groups in appearance of these ( $p = 0.85$ ). Of note, there were four bladder perforations, three of which (two from the epidural and one from the TAP group) requiring simple suture as a solution, and one (epidural group) requiring suprapubic cystectomy.

### Postoperative results (postanesthesia care unit and hospitalization ward)

No statistically significant differences were found between analgesic techniques in VASr (Figure 3), VASm (Figure 4) during postanesthesia care unit and conventional ward follow-up; and morphine administration during hospitalization. Morphine consumption at postanesthesia care unit, was 0.87 (1.57) mg in the TAP group vs. 0.65 (2.06) mg in the epidural group ( $p = 0.66$ ). At hospitalization ward, morphine consumption was 0.09 (0.41) mg vs. 0.15 (0.48) mg ( $p = 0.65$ ); and total morphine administered was 0.96 (1.58) mg vs. 0.8 (2.07) mg ( $p = 0.65$ ), respectively. There was no case either in the epidural or in the TAP group, at any point (postanesthesia care unit or ward follow-up) that required conversion to intravenous continuous analgesia (morphine infusion).

The two study groups were equivalent in postoperative nausea or vomiting appearance at postanesthesia care unit and ward hospitalization, oral tolerance, first flatus and length of in-hospital stay. In the TAP group, 8.9% patients presented the first flatus in the postanesthesia care unit (within the first 6 hours), as compared to 2.2% of the patients in the epidural group. Also, in the TAP group, sedestation and perambulation happened sooner than in the epidural group, being statistically significant (Table 2).

Concerning specific analgesic technique complications there were none in any group. However, regarding specific analgesic technique adverse effects, there were three cases of unilateral lower limb motor block (these reverted when catheter was partially withdrawn), one case of bilateral lower limb motor block (which reverted with a decrease in velocity of anesthetic infusion); and one case that required repetition of technique in the postanesthesia care unit, due to uncontrollable pain in the epidural group. There were no analgesic technique complications related to TAP block ( $p = 0.01$ ). At postoperative 24 hours, adverse effects were also statistically significant in the epidural group ( $p = 0.03$ ),

**Table 2** Follow-up outcomes in TAP and epidural group.

	TAP	Epidural	P
PONV PACU/ward	0	3	0.06 <sup>a</sup>
PONV ward	1	3	0.25 <sup>a</sup>
Oral tolerance < 6 h	12	12	0.49 <sup>b</sup>
First flatus (hours)	18 (9)	22 (12)	0.55 <sup>c</sup>
Time to Sitting (hours)	19 (5)	22 (6)	0.03 <sup>c</sup>
Time to Perambulation (hours)	23 (8)	32 (11)	0.01 <sup>c</sup>
Length of stay (days)	4 (2.75)	3 (3)	0.35 <sup>d</sup>

Data expressed as number (n) or mean (standard deviation [SD]), except length of stay which was expressed as median (interquartile range).

TAP, transversus abdominis plane group; PONV, postoperative nausea and vomiting; PACU, postanesthesia care unit.

P-value for significant differences between TAP and epidural group.

Statistical test used: <sup>a</sup> Fisher test; <sup>b</sup> Chi-square; <sup>c</sup> T-test; <sup>d</sup> U-Mann Whitney

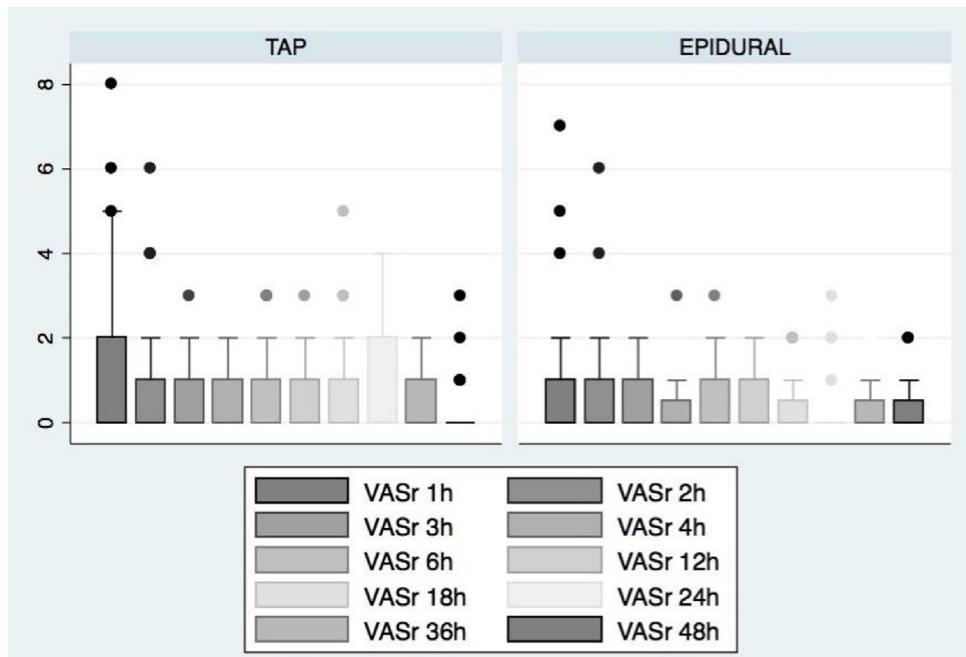
which presented with three cases of lower limb motor block and one case of paresthesia, all of which improved with decrease in infusion rhythm. At the 48-hour follow-up there was one case of accidental catheter extraction, but pain was correctly controlled with morphine bolus. Differences between TAP and epidural group were not statistically significant ( $p = 0.46$ ) at 48-hour follow-up.

Finally, four surgical complications were detected. There were three cases of bladder perforation (two in the epidural and one in the TAP group), and one case of anastomosis leakage (in the epidural group). Differences between groups were not statistically significant ( $p = 0.36$ ).

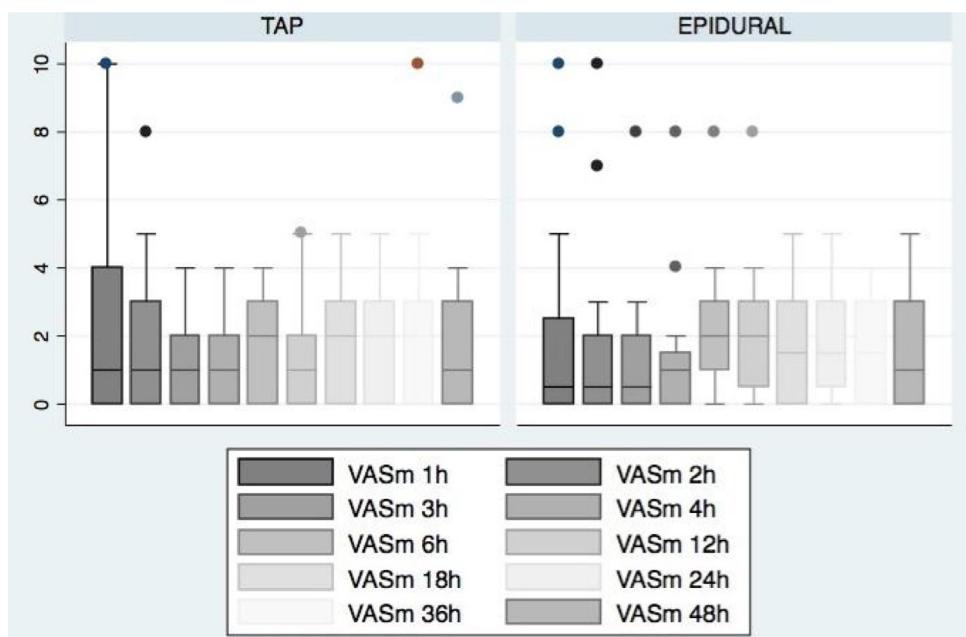
### Discussion

This study was conducted in the setting of an enhanced recovery program and aimed to analyze the effect of TAP block compared to epidural technique in the management of postoperative pain.

Literature comparing TAP vs. epidural technique is available for different types of surgeries,<sup>5,9,10,17,18</sup> but scarce when referring to the enhanced recovery programs



**Fig. 3** VAS at rest during postanesthesia care unit stay and ward follow-up in the TAP and epidural groups. Median (line within box), interquartile range (box) and range (error bars) are shown. No statistically significant differences were found between groups and analgesic efficacy.



**Fig. 4** VAS at movement during postanesthesia care unit stay and ward follow-up in the TAP and epidural groups. Median (line within box), interquartile range (box) and range (error bars) are shown. No statistically significant differences were found between groups and analgesic efficacy.

scenario,<sup>23,24</sup> and absent when considering the specific laparoscopic radical prostatectomy situation.

In our study, we observe that both techniques are equally useful for postoperative pain management. There were no statistically significant differences regarding VAS at rest and upon movement in any time point, nor in milligrams of administered morphine. In the TAP group, mobilization and

perambulation began sooner; however, length of stay was similar in both groups. Our results are similar to those published in the colorectal surgery setting, where it has been already reported that both techniques are similar as to analgesic quality.<sup>24,25</sup> Published results regarding length of hospital stay are at odds.<sup>23,24</sup> Porrera and cols. found no difference in length of stay,<sup>24</sup> whereas Torgeson and col. found

a significant decrease of hospital stay, from 3.3 days in the epidural to 2.8 in the TAP group.<sup>23</sup>

Studies specifically evaluating laparoscopic radical prostatectomy in enhanced recovery programs are scarce. Magheli and cols.<sup>6</sup> reported that the patients that followed the enhanced recovery programs had peristalsis and perambulation sooner than conventional program patients. It is of note that the analgesic protocol used in these cases was COX2 for the enhanced recovery programs group (dosage unreported) and opioid PCA for the conventional group, the latter of which goes against enhanced recovery programs.

Regarding the analgesic effect of TAP block in laparoscopic prostatectomy, only results in robot-assisted, but not conventional laparoscopy surgeries have been published,<sup>11,20</sup> with just one of the studies performed in an enhanced recovery program setting.<sup>11</sup> Sternlicht and colleagues evaluated analgesic quality according to different dosages of local anesthetic in the TAP group, finding no differences.<sup>20</sup> Cacciamani and col. compared TAP plus wound infiltration against wound infiltration alone in the enhanced recovery programs context; with shorter length of hospital stay and better pain control in the TAP group.<sup>11</sup>

Another important parameter in enhanced recovery programs is the favoring of bowel movements. This can be evaluated by postoperative nausea or vomiting and first flatus. Our own results and those published by other authors<sup>24,25</sup> found no differences between the incidence of postoperative nausea or vomiting and analgesic technique used. Similarly, the data published by Pirrera found statistically significant differences between the first flatus (which came sooner in the patients with TAP than those with epidural),<sup>24</sup> whereas other studies found none.<sup>23</sup> Again, our results show no statistically significant differences between start of peristalsis and analgesic technique. This could be due to the fact that laparoscopic radical prostatectomy is not an intra-abdominal technique, and thus excludes bowel manipulation, decreasing the incidence of ileus and aiding prompt intake.<sup>26</sup>

Following our hospital's protocol, we used levobupivacaine at 0.125% for the epidural technique. This low concentration allows for a differential neuraxial blockade, with sensory fibers being blocked, but with preservation of motor function.<sup>27</sup> Despite this, various patients presented adverse effects associated to motor blockade. These could be solved by standard methods, although they might be the cause of a longer time to sitting and perambulation, which was significantly greater in the epidural group. Our results are similar to those found by Pirrera and cols.<sup>24</sup>

The use of bupivacaine in the TAP group was chosen as it is the most potent local anesthetic,<sup>28,29</sup> and toxic doses were not exceeded. Approach was always ultrasound-guided, reducing the risk of complications due to vascular injection or peritoneal puncture, as well as intoxication due to local anesthetic.<sup>30</sup>

## Limitations

One of the limitations of our study is that it was not designed as a double-blind study, as the personnel could know to which group the patient belonged to if the epidural catheter was in place. This study is a quasi-randomized

clinical trial – not a randomized clinical trial –, as assignment to each treatment group was sequential. This could be a risk of bias. Another limitation could be the lack of catheter placement in the TAP block group, for continuous medication administration. Our study protocol opted for single-dose local anesthetic administration based on previously published studies.<sup>19</sup> However, compared groups were homogeneous in terms of demographic and clinical data and we used the same postoperative analgesia protocol for both groups. Another limitation is the exclusion of patients with a BMI > 30 kg.m<sup>-2</sup>, as TAP technique might be harder to perform in these patients, as well as success of surgery itself. Our study is based on a small sample size, powered to evaluate specifically analgesic quality, secondary outcomes related to these techniques might warrant studies with a greater sample size.

## Conclusions

In an enhanced recovery program, TAP block offers the same postoperative analgesia quality as compared to the continuous epidural technique in laparoscopic radical prostatectomy, with the possibility of early patient mobilization.

## Conflict of interest

The authors declare no conflicts of interest.

## Acknowledgements

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## ORIGINAL INVESTIGATION

### Comparison of the influence of low dose etomidate and propofol as priming dose on the incidence of etomidate induced myoclonus: a randomised, double-blind clinical trial

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#### KEYWORDS

Myoclonus;  
Priming;  
Etomidate;  
Propofol

#### Abstract

**Background:** Though hemodynamically stable, etomidate is known for its myoclonus side effect following induction. The main aim of this study is an effective attempt to decrease the incidence of myoclonus with a priming agent.

**Methods:** A prospective, double-blind study was carried out on 50 adults posted for elective surgery. After premedication, priming was done with etomidate  $0.03 \text{ mg} \cdot \text{kg}^{-1}$  (Group E) and propofol  $0.2 \text{ mg} \cdot \text{kg}^{-1}$  (Group P), i.e., 1/10th of induction dose. After 60 seconds of priming, patients were induced with etomidate by titrating dose over 60 seconds until loss of verbal command and eyelash reflex. The grading of myoclonus, induction dosage, and hemodynamics for 10 minutes post induction were recorded.

**Results:** In the study, only 4 cases had myoclonus. Grade 1 myoclonus was encountered in three cases of etomidate group, while only one case in the propofol group had grade 2 myoclonus which was not statistically significant ( $p$ -value: 0.12). There was a significant reduction in the etomidate induction dosage in both groups.

**Conclusion:** Priming with etomidate and propofol is equally effective in reducing myoclonus with the added benefit of hemodynamic stability and reduction of an induction dose of etomidate (> 50%).

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## Introduction

Etomidate as compared with other induction agents is associated with less hemodynamic changes, less pain during injection with lipid formulation,<sup>1</sup> less histamine release, and high therapeutic index.<sup>2</sup> Therefore, etomidate is the preferred induction agent for rapid sequence induction during emergency situations in view of hemodynamic instability.<sup>3</sup> Etomidate use has been limited since it has shown to cause adrenocortical suppression, myoclonus, and pain on injection.<sup>3</sup> Single-induction dose of etomidate has not shown any deleterious effects; rather, hemodynamic stability has increased due to its usage in the intraoperative management of emergency and sick cardiac cases. Thus, etomidate has seen a resurgence in its usage in anesthesia practice. Myoclonus, the side effect of etomidate is not desired in situations where there are closed globe injuries to eye and penetration trauma of the abdomen. Prevention of myoclonus by pretreatment with midazolam, magnesium sulphate, opioids, gabapentin, ketamine, propofol, and priming dose of etomidate has been studied.<sup>4-7</sup> Both etomidate and propofol in induction dosages are known to cause myoclonus. Etomidate in low priming doses and propofol in different doses has been studied for the prevention of myoclonus induced with etomidate induction. But none of the studies compared etomidate with propofol. This study attempted to compare myoclonus incidence with a priming dose of etomidate, and propofol as both the drugs in induction dosage is known to cause myoclonus.<sup>8</sup>

## Methods

The study is registered in the Clinical Trial Registry of India. REF/2015/03/008627. The study has approval from NIEC [NIMS (Nizam's Institute of Medical Sciences, Hyderabad) Institutional ethical committee] with approval no. EC/NIMS/1672/2015. After ethics committee approval and informed consent of patients, 50 American Society of Anesthesiologists (ASA) I and II physical status patients, of either sex, aged between 20 to 65 years, with Mallampati grading I and II, scheduled for lumbar laminectomy under general anaesthesia were prospectively enrolled in the study. Patients were randomly allocated in two groups. This was accomplished with RAND (0,1) [Microsoft. (2010). Microsoft Excel [computer software] Redmond, Washington], and the study was conducted in a double-blind fashion. Patients with a history of epilepsy, alcoholics, those with endocrine disorders – Cushing's syndrome, pituitary disorders, and immunosuppressed patients were excluded.

This study adhered to CONSORT guidelines (<http://www.consort-statement.org>). The study drugs were prepared by an anesthesia technician who was aware of the randomization number allotted and the demographic profile of the patient. The study participants and investigator collecting the data were blinded to the treatment group. Baseline parameters heart rate (HR), blood pressure (BP), oxygen saturation by pulse oximetry (SPO<sub>2</sub>), and entropy were noted. All patients were premedicated with midazolam 0.02 mg.kg<sup>-1</sup> + fentanyl 2 µg.kg<sup>-1</sup> intravenously. The above parameters were again noted after 5 minutes of premedication. Patients were ventilated with 100% oxygen

if SPO<sub>2</sub> falls to < 97% or the patient becomes apneic. After 5 minutes of premedication, etomidate (E) group of patients received priming dose of etomidate 0.03 mg.kg<sup>-1</sup> and propofol (P) group of patients with 0.2 mg.kg<sup>-1</sup> (1/10th of induction dose). After 60 seconds of priming, patients were induced with etomidate by titrating dose over 60 seconds until loss of verbal command and eyelash reflex. Entropy was used for monitoring depth of anesthesia. Patients were observed during induction and 1 minute following induction for myoclonus and grades of myoclonus. This was the primary objective of the study. The myoclonus grades used were<sup>9</sup>: Grade 0, no myoclonus; Grade 1, mild myoclonus (Small movements in 1 body segment, such as finger or wrist); Grade 2, moderate myoclonus (Slight movements in 2 or more muscle areas, such as face or shoulder); Grade 3, severe myoclonus (intense movements in 2 or more muscle areas, sudden adduction of an extremity). The dose of etomidate required for each patient for loss of verbal command and eyelash reflex was noted.

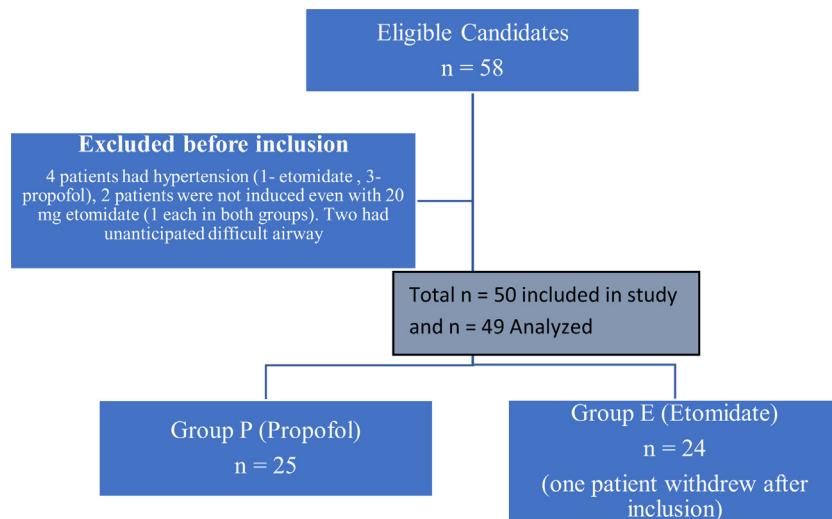
After confirming for mask ventilation, neuromuscular blockade was achieved with atracurium 0.5 mg.kg<sup>-1</sup>, and trachea was intubated with an appropriate sized endotracheal tube around 4 minutes after induction. Entropy was maintained between 40–60 following induction for 10 minutes. The ventilation was done with 100% O<sub>2</sub>, and blood pressure and heart rate were recorded every 1 minute till 10 minutes following induction. The supplemental doses of etomidate were used to intubate if entropy was more than 60. The endpoint of the study was 10 minutes past induction after recording the hemodynamic parameters. The post inclusion exclusion criteria included patients with an unanticipated difficult airway sustained tachycardia or rise in BP (> 40% baseline), bradycardia (< 50 bpm) requiring atropine, and hypotension requiring vasopressor administration.

The primary objective of this study was to compare the incidence of myoclonus and its severity with a priming dose of etomidate, and propofol during induction with etomidate. The secondary objectives included the induction dosage of etomidate and hemodynamic changes following induction.

## Statistical analysis

Sample sizes of 21 in group 1 and 21 in group 2 achieved to detect a non-inferiority margin difference between the group proportions of -0.3000. The reference group proportion is 0.5000. The treatment group proportion is assumed to be 0.2000 under the null hypothesis of inferiority. The power was computed for the case when the actual treatment group proportion is 0.6000. The test statistic used is the one-sided Z test (unpooled). The significance level of the test was targeted at 0.0500. The significance level actually achieved by this design is 0.0542. As dropout of cases would be expected, the total sample size of 50 (25 in each group) was taken for undertaking this study. PASS software (PASS 13 Power Analysis and Sample Size Software (2014). NCSS, LLC. Kaysville, Utah, USA, [ncss.com/software/pass](http://ncss.com/software/pass)) was used for estimating the sample size for conducting this study.

NCSS version 9 statistical software (NCSS 9 Statistical Software (2013). NCSS, LLC. Kaysville, Utah, USA, [ncss.com/software/ncss](http://ncss.com/software/ncss)) was used for statistical analysis. Data was presented as the mean ( $\pm$  S.D.). Categorical data

**Figure 1** Flow chart of participants in the study.

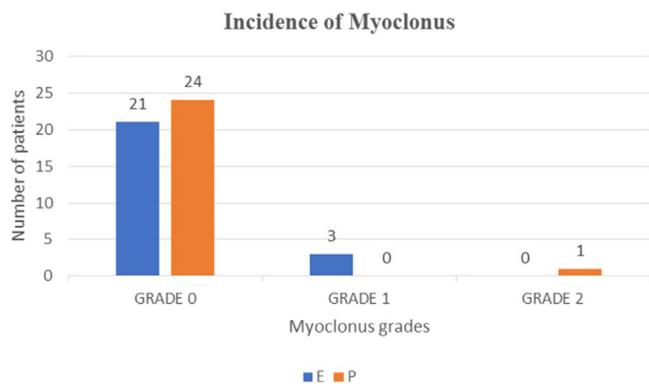
was described as the number of patients (n). Normality of the data was tested using the Kolmogorov-Smirnov test. Categorical variables were compared with the chi-square test. Continuous variables were compared using independent sample *t*-test. Within the group and intergroup comparison of hemodynamic variables was done using ANOVA. A *p*-value < 0.05 was considered as significant.

## Results

Fifty adults aged 20 to 65 years were studied. One patient who was randomly allotted to etomidate group voluntarily withdrew from the study after inclusion (Fig. 1), thus only 49 were analyzed. The demographic data was comparable in both groups (Table 1). The propofol group had 5 ASA II patients (20%), and etomidate group had only one ASA II patient (4.16%) with *p*-value of 0.05. There was no significant difference in state entropy (SE) and response entropy (RE) in between the two groups (baseline, 5 minutes following premedication and following induction). This suggests that the depth of anesthesia was maintained in both groups without significant difference. The data was found to be normally distributed with respect to demographic and other control parameters.

After induction, 3 patients (12.5%) in the etomidate group had myoclonus of grade 1, and 1 patient (4%) in the propofol group had myoclonus of grade 2 (Fig. 2). Overall, only 4 patients had myoclonus out of 49 included (8.16%). There was no significant difference between the groups (*p* = 0.12). The dose of etomidate needed for loss of eyelash reflex was  $3.96 \pm 1.62$  mg, and  $4.42 \pm 2.12$  mg in propofol and etomidate group respectively (*p*-value 0.40). Similarly, the dose of etomidate needed for loss of verbal commands was  $3.98 \pm 1.86$ , and  $4.40 \pm 1.63$  mg in propofol and etomidate group, respectively (0.88) as shown in Table 2.

The changes in heart rate and MAP were comparable between the groups (*p* = 0.8) and also within the groups (Figs. 3 and 4).

**Figure 2** Incidence of myoclonus occurrence in the two groups. E, Group etomidate; P, Group propofol (*p* = 0.12).

## Discussion

Our study findings did not reject the null hypothesis, thus stating that both etomidate and propofol in low doses are effective in attenuating the myoclonic movements following induction with etomidate. Only 4 patients out of 50 had myoclonus (8.16%).

In the study by Isitemiz et al., the incidence of myoclonus was reduced significantly with fentanyl  $1 \text{ mcg} \cdot \text{kg}^{-1}$  (40%) and the combination of midazolam  $0.15 \text{ mg} \cdot \text{kg}^{-1}$  + fentanyl  $0.5 \mu\text{g} \cdot \text{kg}^{-1}$  (25%).<sup>9,10</sup> The incidence of myoclonus with a combination of midazolam and fentanyl was 25%, which is quite high and still distressing for any patient. Fentanyl is routinely used as an analgesic as a standard protocol in all the recentres, including ours. Induction with etomidate with fentanyl as an analgesic used in routine basis showed a significant increase in the incidence. A trial study was conducted with fentanyl  $2 \mu\text{g} \cdot \text{kg}^{-1}$  and midazolam  $0.02 \text{ mg} \cdot \text{kg}^{-1}$ , and noticed a significant incidence of myoclonus almost with all the cases which appeared ethically unacceptable. The intensity of pain with a priming dose of propofol injection is expected to be less, and this combination was helpful in combating this.<sup>11</sup> Hence, to avoid this bias, we standardized

**Table 1** Comparison of demographic and control parameters in both groups.

Variable	Mean $\pm$ SD Group P (n = 25)	Mean $\pm$ SD Group E (n = 24)	p-value
Age	37.32 $\pm$ 9.07	38.79 $\pm$ 10.79	0.6
Sex			
Male	13 (52%)	11 (45.83%)	0.77
Female	12 (48%)	13 (54.16%)	
Height (cm)	162 $\pm$ 10.3	157 $\pm$ 13.1	0.2
Weight (kg)	63.28 $\pm$ 10.6	61 $\pm$ 9.4	0.44
ASA			
I	20 (80%)	23 (95.83%)	0.05
II	5 (20%)	1 (4.16%)	
Response entropy (baseline)	96.9 $\pm$ 2.03	97.2 $\pm$ 2.1	0.67
State entropy (baseline)	88.24 $\pm$ 2.5	88.3 $\pm$ 4.2	0.86
Response entropy (5 min after premed)	93 $\pm$ 3.456.07	93.3 $\pm$ 7	0.34
State entropy (5 min after premed)	84.7 $\pm$ 5.5	85.8 $\pm$ 6.4	0.5
Response entropy (induction)	54.24 $\pm$ 14.4	50.7 $\pm$ 13.4	0.37
State entropy (induction)	51.8 $\pm$ 14.4	48.4 $\pm$ 14.6	0.4

SD, standard deviation; P, propofol group; E, etomidate group.

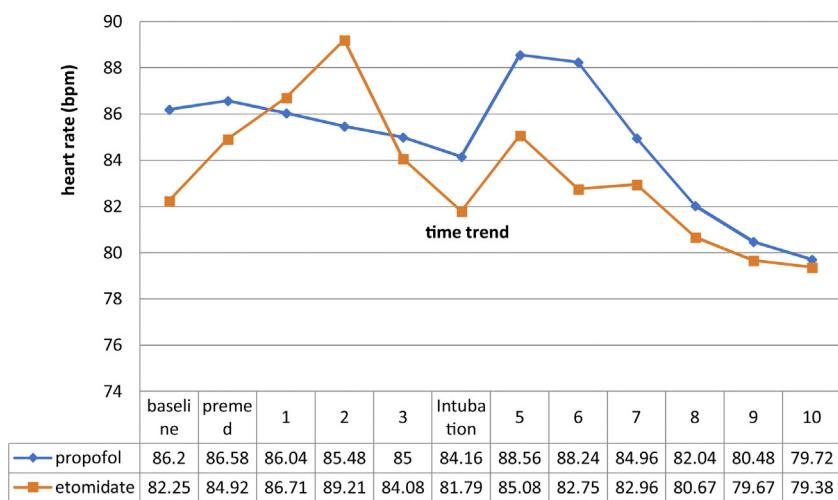
Data represented as n or mean  $\pm$  SD.**Table 2** Induction dose in both the groups.

Dose	Group P	Group E	p-value
Loss of eyelash reflex in mg $\pm$ SD (mg.kg $^{-1}$ $\pm$ SD)	3.96 $\pm$ 1.62 (0.06 $\pm$ 0.03)	4.42 $\pm$ 2.12 (0.07 $\pm$ 0.04)	0.40
Loss of verbal commands in mg $\pm$ SD (mg.kg $^{-1}$ $\pm$ SD)	3.98 $\pm$ 1.86 (0.07 $\pm$ 0.03)	4.40 $\pm$ 1.63 (0.07 $\pm$ 0.03)	0.4
			0.3

SD, standard deviation.

Data represented as n or mean  $\pm$  SD.

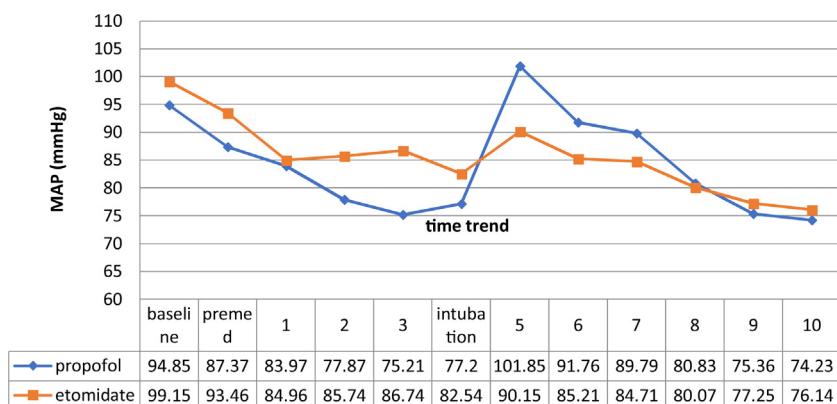
### Heart Rate changes in the two groups

**Figure 3** Heart rate changes in the two groups. Premed, 5 minutes following premedication; 1, 1 minute following induction; 2, 2 minutes following induction; 3, 3 minutes following induction; 5, 5 minutes following induction; 6, 6 minutes following induction; 7, 7 minutes following induction; 8, 8 minutes following induction; 9, 9 minutes following induction; 10, 10 minutes following induction.

the combination of midazolam and fentanyl as a premedication regime for both the groups along with study drugs for conducting this study.

Etomidate, the preferred agent for induction in view of hemodynamic stability,<sup>12</sup> myoclonus the main side effect associated with its use cannot be neglected.<sup>13</sup> The incidence

### Mean Arterial Pressure Trends in the two groups



**Figure 4** Mean arterial pressure trends in the two groups. MAP, mean arterial pressure; premed, 5 minutes following premedication; 1, 1 minute following induction; 2, 2 minutes following induction; 3, 3 minutes following induction; 5, 5 minutes following induction; 6, 6 minutes following induction; 7, 7 minutes following induction; 8, 8 minutes following induction; 9, 9 minutes following induction; 10, 10 minutes following induction.

of involuntary myoclonic movements (MM) after induction of anesthesia is higher compared with propofol, though the incidence may vary from 0 to 70%.<sup>9,14,15</sup> Myoclonus is caused by transient disinhibition of subcortical structures due to difference in cerebral blood flow. Another explanation is the difference of GABA-A receptor subunits within the central nervous system. The significant reduction of myoclonus occurs with drugs (benzodiazepines or opioids) and with pre-treatment with low dose etomidate, and propofol is known to inhibit the subcortical neuronal activity, or through enhancement of  $\gamma$  aminobutyric acid type A receptor.<sup>4,9,16,17</sup> In this study by Doenicke et al. on EEG with etomidate, it was hypothesized that inhibitory circuits are depressed earlier and with low dose compared to excitatory circuits. This was the basis for using a low dose of etomidate as priming dose before induction with etomidate for reduction of myoclonus. They found that the myoclonus incidence decreased with 0.03 and 0.05 mg.kg<sup>-1</sup> priming with etomidate (i.e., low dose), and the incidence increased with 0.075 mg.kg<sup>-1</sup> priming dose (i.e., higher dose). Slow induction with etomidate 0.3 mg.kg<sup>-1</sup> by infusion over 90 seconds without pre-treatment reduced incidence of myoclonus to 28% compared to 84% with faster induction over 10 seconds in a study by Do et al.<sup>18</sup>

Etomidate and propofol are known to cause myoclonus though the incidence of myoclonus with propofol is very minimal (1:10,000). The mechanism for propofol-induced myoclonus was proposed to be subcortical disinhibition similar to etomidate.<sup>19,20</sup> They also act on GABA-A receptors on excitatory and inhibitory neural circuit mechanisms. A recent study by Jinfeng et al. have shown a considerable decrease in the incidence of myoclonus with different doses of propofol following etomidate induction. There was decreasing incidence with increasing doses of propofol.<sup>5</sup> Therefore, priming with low-dose propofol and etomidate were studied and compared along with fentanyl and midazolam to see its effectiveness in preventing myoclonus with etomidate induction.

The induction dose of etomidate is 0.3 mg.kg<sup>-1</sup> (0.2 to 0.6 mg.kg<sup>-1</sup>). For an average 60 kg adult, this will be around 18 mg. The loss of eyelash reflex and verbal commands were achieved with hardly 4.42  $\pm$  2.12 mg dose of etomidate. The use of premedication and priming with propofol or etomidate has significantly reduced the induction dose of etomidate by more than 50%. Similar results were recorded in studies where priming was used in different doses and have shown a significant reduction in the induction dosage requirements of propofol.<sup>21,22</sup> But etomidate induction dosage was not studied. Rather, a combination of etomidate-lipuro and propofol 1:1 (etofol) was found to be an effective induction regime with decreased dose requirement and decreased incidence of adverse reactions.<sup>23</sup>

Etomide has been the agent of choice for induction in view of hemodynamic stability.<sup>3</sup> Next, etofol (1:1 admixture of etomidate-lipuro and propofol) was associated with best hemodynamic stability compared to etomidate and propofol group.<sup>23</sup> In this study by Saricaoglu et al., the 90 patients were randomly assigned to three groups in which induction was performed with etomidate-lipuro, propofol, or etomidate-lipuro-propofol admixture. The best hemodynamic stability with the least incidence of myoclonus and injection pain etofol group with least BIS value of 40 was observed. We could also get similar results with etomidate group as patients were hemodynamically stable. The group primed with etomidate and further induction with etomidate caused the least changes in hemodynamics. As the primed dose of propofol used was 1/10th of induction dose, least likely to cause hemodynamic instability. This property of hemodynamic stability would explain the response characteristics of ASA II patients in this study. As 5 patients of p primed group were ASA II and expected to be on a few disease control drugs, could lead to induction changes in hemodynamics. Though there were fluctuations but are not critical to cause compromise and all changes recovered back with intubation.

## Limitations

There are some limitations to our study. Most of the studies have compared fentanyl and midazolam as counterparts for attenuation of myoclonus. Rather, we have used these drugs in both groups as a standard and routine practice. This is done especially to create a practical atmosphere for using these drugs to get their maximum beneficial effect. Even duration of myoclonus was not recorded.

## Conclusion

Priming with etomidate and propofol are equally effective in reducing myoclonus with the added benefit of almost halving the induction dose of etomidate and hemodynamic stability.

## Conflicts of interest

The authors declare no conflicts of interest.

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**ORIGINAL INVESTIGATION**

**Comparison of different local analgesia protocols in postoperative pain management after total knee arthroplasty**



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**Abstract**

**Objectives:** This study was to compare the effects of different local analgesia protocols on osteoarthritis patients undergoing total knee arthroplasty (TKA).

**Methods:** Medical records of 148 osteoarthritis patients who underwent unilateral TKA between October 2016 and October 2017 in our hospital were retrospectively analyzed. All these patients were divided into three groups according to the pain management protocol (morphine, morphine + cocktail [100 mg ropivacaine, 10 mg morphine, and 30 mL 0.9% sodium chloride solution containing 2 mL betamethasone (4 mg)], or cocktail). The postoperative visual analog scale (VAS) score, muscle strength, and complications were compared between the groups.

**Results:** At 6 and 12 hours post-operation, the VAS score in group C was significantly higher than that in group A or group B. In addition, the muscle (quadriceps femoris) strength score of group C ( $3.7 \pm 2.8$ ) was significantly higher than that in groups A and B at 6 and 12 hours post-operation. The VAS score and muscle strength score showed no significant differences among the three groups at 24 and 36 hours post-operation. The time of postoperative first void of group C was significantly shorter than that of groups A and B. Groups A or B had a significantly higher incidence of nausea and emesis compared with group C. The incidence of pruritus was higher in groups A or B than that in group C.

**Conclusion:** Epidural anesthesia combined with local analgesic cocktail injection is a preferable effective multimodal analgesia for TKA.

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## Introduction

Total knee arthroplasty (TKA) is known to be a very successful procedure for advanced osteoarthritis. However, persistent pain after TKA can hamper rehabilitative exercise and functional recovery.<sup>1</sup> Various postoperative pain control protocols have been suggested, each with its pros and cons. For example, orally, intramuscularly, or intravenously administered opioid plays a pivotal role in postoperative pain relief because of their effectiveness in relieving moderate to severe pain, however, opioids may cause respiratory depression, sedation, renal impairment, nausea, emesis, and inhibition of smooth muscle contraction.<sup>2</sup> Femoral nerve block, one of the commonly used pain control method after TKA, was demonstrated to provide effective analgesia but may lead to muscle weakness, with a possible increase in fall risk.<sup>3</sup> In recent years, as surgeons have become more aware of postoperative pain, preemptive analgesia and multimodal analgesia have been widely used in a clinical setting. The multimodal analgesia typically includes a combination of several different pain-alleviating medications, which provide successful pain management, prevent addiction to a single component, and reduce the incidence of side effects associated with high dose analgesia.<sup>4</sup> Current Enhanced Recovery after Surgery (ERAS) protocols for TKA focus mainly on perioperative care, which includes optimized pain and sleep management, and optimized drainage and urinary catheterization protocol.<sup>5-7</sup> To improve perioperative management, enhance postoperative recovery, increase overall satisfaction in TKA patients, we conducted this retrospective clinical study. We reviewed the clinical data of 148 patients who underwent primary TKA surgery and compared the effects of different intraoperative analgesic administration protocols on the postoperative recovery in TKA patients.

## Methods

This study was approved by the ethics committee of our hospital. Written informed consent was not required from each patient, as per the institutional review board of our hospital, for this is a retrospective study.

### Study subjects

The medical records of osteoarthritis patients who underwent unilateral TKA in our hospital between October 2016 and October 2017 were retrospectively analyzed. Inclusion criteria: (1) age below 80 years; (2) BMI < 35; (3) definite diagnosis of knee osteoarthritis before TKA (Kellgren-Lawrence Grade III-IV), symptoms mainly in one knee and did not respond to non-surgical treatment; (4) overall physical status were I or II according to American Society of Anesthesiologists (ASA) score; (5) TKA approaches were simple midline skin incision or medial parapatellar incision; (6) used stable prostheses without posterior cruciate ligament retention. Exclusion criteria: (1) severe disease in both knees; (2) previous narcotics addiction, history of drug abuse, or current hormonal or opioid treatment; (3) liver or kidney dysfunction before surgery; (4) history of stroke or neurological or psychiatric disorders; (5) uncontrollable

angina or bundle branch block; (6) abnormal coagulation; (7) severely deformed knees or ligamentous instability; (8) postoperative complications, e.g., common peroneal nerve injury; (9) benign prostatic hyperplasia.

All the patients showed similar clinical manifestations, which included severe pain in the affected knee joint, and the inability to walk or stand for long periods. In these patients, the pain worsened when they stood up or climbed stairs. The knee joint had varying degrees of deformity and restricted activity. Preoperative X-ray examination showed significant narrowing of the joint space, subchondral sclerosis, and the formation of osteophytes. The articular valgus deformity was not observed. No patient had a history of knee surgery or knee instability.

In this study, all the selected patients were divided into three groups based on the pain management protocol. The detail grouping information is as follows: patients who received morphine (3 mg) via epidural anesthesia catheter before catheter extraction were assigned to group A, patients who received morphine (3 mg) via epidural anesthesia catheter before catheter extraction plus local analgesic cocktail injection at the knee were assigned to group B, and patients who received epidural anesthesia plus local analgesic cocktail injection at the knee were assigned to group C.

### Preoperative care

Before the operation, all the patients were explained to in detail about pain management and trained for pain assessment using VAS. In addition, patients received oral administration of celecoxib once a day for three days at a time of 200 mg.

### Surgery

All the surgeries were performed by the same surgeon from a four-member surgical team. During surgery, peripheral intravenous access was established, and vital signs including blood pressure, peripheral capillary oxygen saturation ( $\text{SpO}_2$ ), respiratory rate, and end-tidal carbon dioxide/ $\text{ETCO}_2$  ( $\text{PetCO}_2$ ) were monitored. All the patients received the same epidural anesthetic. Continuous epidural anesthesia was given at  $L_{2-3}$  or  $L_{3-4}$  interspaces to achieve bilateral sensory block between  $T_8$  and  $T_{10}$ . An intraoperative ropivacaine infusion was used to maintain sedation during surgery, and the anesthesia depth was adjusted according to blood pressure, heart rate, bispectral index, and other parameters. All surgeries were conducted using a standard medial parapatellar arthrotomy with an inflatable tourniquet with pressure set as a patient's systolic pressure plus 100 mmHg (1 mmHg = 0.133 kPa).<sup>8</sup>

A femur resection was performed using the intramedullary alignment technique followed by a four-surface osteotomy of the femur. Tibia resection was performed using the extramedullary alignment technique. The prosthesis was inserted after size measurement. Posterior stabilized knee prosthesis fixed with bone cement (Zimmer Biomet, US) was used in all TKAs. For group A, morphine (3 mg) was administered via the epidural catheter, which was withdrawn at the end of the surgery.

**Table 1** Characteristic data of patients who underwent TKA (mean  $\pm$  SD).

Variables	Group A (n = 50)	Group B (n = 46)	Group C (n = 52)	$\chi^2/F$ -value	p-value
Gender (male/female, n)	20/30	16/30	18/34	0.4025	0.8177
Age (years)	65.3 $\pm$ 8.3	66.8 $\pm$ 7.9	65.5 $\pm$ 8.1	0.44	0.6413
BMI ( $\text{kg} \cdot \text{m}^{-2}$ )	25.3 $\pm$ 2.3	24.3 $\pm$ 2.7	24.3 $\pm$ 3.1	0.29	0.7486
Kellgren-Lawrence Grade (III/ IV, n)	19/31	17/29	19/33	1.3488	0.5095
Osteoarthritis site (left/right)	27/23	20/26	25/27	1.0772	0.5085
Osteoarthritis type (traumatic/degenerative, n)	2/48	3/43	4/48	0.6628	0.7179
KSS score	52.2 $\pm$ 7.1	53.8 $\pm$ 7.9	54.4 $\pm$ 6.8	1.80	0.1652
VAS score	4.2 $\pm$ 3.2	4.3 $\pm$ 3.5	4.0 $\pm$ 3.1	0.79	0.4549
Tibiofemoral angle (°)	14.3 $\pm$ 5.6	15.6 $\pm$ 6.0	15.7 $\pm$ 5.7	1.64	0.1938
Knee flexion contracture angle (°)	14.2 $\pm$ 8.3	13.5 $\pm$ 8.8	13.9 $\pm$ 7.9	0.85	0.4267

For group B, morphine (3 mg) was administered via the epidural catheter which was withdrawn at the end of the surgery. In addition, before the prosthesis was inserted, an analgesic cocktail was injected into a periarticular capsule of the knee joint, medial collateral ligaments, peripatellar soft tissue, infra-patella fat pad, and posterior articular capsule. For group C, the patients received an equal volume of saline instead of morphine via the epidural catheter and periarticular injection of the drug cocktail (same as group B). The drug cocktail consisted of 100 mg ropivacaine, 10 mg morphine, 30 mL 0.9% sodium chloride solution containing 2 mL betamethasone (4 mg).

### Postoperative care

No intravenous patient-controlled analgesia pump was used. Instead, all patients received intramuscular administration of ondansetron hydrochloride (4 mg). After surgery, the patients received intermittent cooling using an icepack at the incision area during the first 24 hours. A dose of 5 mg dezocine was administrated at midnight when VAS > 5. They were asked to raise the affected leg. Meanwhile, patients were asked to start isometric quadriceps exercise, and ankle pumps immediately after surgery. Parecoxib (40 mg) was administered 2 times per day for the first 3 days post-surgery. Then oral celecoxib (200 mg) was administered daily (twice per day) until discharge.

### Postoperative evaluations

Postoperative evaluation included the following items: (1) pain level: pain level at 6, 12, 24, and 36 hours post-operation, both at rest and with activity (straight leg raising, bending and flexing the knee in the supine position), were assessed using VAS at each time point. (2) Quadriceps femoris muscle strength: the patients were asked to complete isometric quadriceps exercise and the muscle strength score which was divided into five grades (0-5) were estimated at 6, 12, 24, and 36 hours post-operation. Grade "0" represents absolutely no visible contraction; grade "1" means there was visible contraction but no movement; grade "2" represents some movement but insufficient to counteract gravity; grade "3" represents barely against gravity (inability to resist any additional force); grade "4" represents less than normal (but enough to resist

gravity); grade "5" represents normal. (3) Postoperative complications: the incidence of postoperative nausea, emesis, pruritus, and urinary retention. (The foley catheter was removed 4 hours after surgery. The period during which the patient emptied his or her bladder for the first time after surgery was recorded as postoperative first void. If the post-operative first void was longer than 10 hours, the catheter was reinserted.)

### Statistical analysis

Data were analyzed using SPSS 22.0 software. The numerical data were presented as mean  $\pm$  SD, and categorical variables were expressed as the frequency (%). The inter-group comparison was conducted using paired t-test. The multiple means comparison was conducted using F-test when normal distribution was achieved, followed by SNK-q test for post hoc comparisons. If the normal distribution was not achieved, Kruskal-Wallis test was used. The comparison of categorical data was conducted using  $\chi^2$  test. A p-value less than 0.05 was considered significantly different.

### Results

#### Baseline characteristics of osteoarthritis patients undergoing TKA in each group

A total of 148 osteoarthritis patients were finally included in our study. Baseline characteristics of each group were summarized in Table 1 and described in detail as follows:

Group A: There were 50 patients consisted of 20 men and 30 women in this group. The average age was  $65.3 \pm 8.3$  years old (ranges from 52 to 78 years). The average body mass index (BMI) was  $25.3 \pm 2.3 \text{ kg} \cdot \text{m}^{-2}$  (ranges from 22.3 to  $28.5 \text{ kg} \cdot \text{m}^{-2}$ ). Among all the cases, 27 were left knees and 23 were right knees. Two patients had traumatic osteoarthritis and 48 had degenerative osteoarthritis. Nineteen patients were categorized to Kellgren-Lawrence grade III and 31 were categorized to Kellgren-Lawrence grade IV. The mean pre-operative VAS score was  $4.2 \pm 3.2$  (ranges from 3 to 5). The mean knee society score (KSS) was 52.2 (ranges from 40 to 68). Mean tibiofemoral angle (varus deformity) was  $14.3 \pm 5.6^\circ$  (ranges from 0 to  $25^\circ$ ) and mean knee flexion contracture angle (flexion deformity) was  $14.2 \pm 8.3^\circ$  (ranges from 0 to  $29^\circ$ ).

**Table 2** Comparison of pain level and Dezocine use among patient groups receiving different pain management protocols (mean  $\pm$  SD).

Group	N	6 h VAS ( $x \pm s$ )		12 h VAS ( $x \pm s$ )		24 h VAS ( $x \pm s$ )		36 h VAS ( $x \pm s$ )		Dezocine use (n, %)
		At rest	With activity	At rest	With activity	At rest	With activity	At rest	With activity	
Group A	50	2.1 $\pm$ 0.6	2.3 $\pm$ 0.7	2.2 $\pm$ 0.6	3.0 $\pm$ 0.7	2.4 $\pm$ 0.7	4.5 $\pm$ 0.9	3.8 $\pm$ 0.7	4.8 $\pm$ 0.9	6 (12.0)
Group B	46	1.5 $\pm$ 0.6	1.8 $\pm$ 0.5	1.8 $\pm$ 0.6	2.1 $\pm$ 0.7	2.2 $\pm$ 0.7	2.7 $\pm$ 0.8	2.5 $\pm$ 0.7	3.0 $\pm$ 1.1	4 (8.7)
Group C	52	2.9 $\pm$ 0.6	3.0 $\pm$ 0.8	2.8 $\pm$ 0.9	3.4 $\pm$ 1.0	3.0 $\pm$ 1.1	4.1 $\pm$ 0.9	3.8 $\pm$ 1.0	4.7 $\pm$ 1.2	6 (11.5)
$\chi^2/F$ value		12.56	13.34	15.23	11.65	2.11	3.02	1.83	1.27	2.48
p-value		< 0.05	< 0.05	< 0.05	< 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Group A: Patients received morphine (3 mg) via epidural anesthesia catheter before catheter extraction. Group B: Patients received morphine (3 mg) via epidural anesthesia catheter before catheter extraction and local analgesic cocktail injection. Group C: Patients received epidural anesthesia and local analgesic cocktail injection. VAS, visual analogue scale; SD, standard deviation.

Group B: There were 46 patients consisted of 16 men and 30 women in this group. The average age was  $66.8 \pm 7.9$  years old (range from 51 to 79 years). The average BMI was  $24.3 \pm 2.7 \text{ kg.m}^{-2}$  (ranges from 22.2 to 27.4  $\text{kg.m}^{-2}$ ). Among all the cases, 20 were left knees and 26 were right knees. Three patients had traumatic osteoarthritis and 43 had degenerative osteoarthritis. Seventeen patients were categorized to Kellgren-Lawrence grade III and 29 were categorized to Kellgren-Lawrence grade IV. The mean average preoperative VAS score was  $4.3 \pm 3.5$  (ranges from 3 to 5). The mean KSS score was  $53.8 \pm 7.9$  (range 43–67). The mean tibiofemoral angle (varus deformity) was  $15.6 \pm 6.0^\circ$  (ranges from 0 to  $23^\circ$ ). The mean knee flexion contracture angle (flexion deformity) was  $13.5 \pm 8.8^\circ$  (ranges from 0–27°).

Group C: There were 42 patients consisted of 18 men and 34 women in this group. The average age was  $65.5 \pm 8.1$  years old (ranges from 52 to 77 years). The average BMI was  $24.3 \pm 3.1 \text{ kg.m}^{-2}$  (range from 23.4–28.4  $\text{kg.m}^{-2}$ ). Among all the cases, 25 were left knees and 27 were right knees. Four patients had traumatic osteoarthritis and 48 had degenerative osteoarthritis. Nineteen patients were categorized to Kellgren-Lawrence grade III and 33 were categorized to Kellgren-Lawrence grade IV. The average preoperative visual analog scale (VAS) score was  $4.0 \pm 3.1$  (ranges from 3 to 5). The mean KSS score was  $54.4 \pm 6.8$  (ranges from 41–69). The mean tibiofemoral angle (varus deformity) was  $15.7 \pm 5.7^\circ$  (ranges from 0–25°). The mean knee flexion contracture angle (flexion deformity) was  $13.9 \pm 7.9^\circ$  (ranges from 0–26°).

No significant differences were found in terms of all the variables mentioned above among the three groups.

### Pain level and dezocine use after unilateral KTA

The VAS scores, both at rest and with activity, at 6 and 12 hours post-operation, were significantly different among the three groups ( $p < 0.05$ ). Further q-test showed no difference in VAS score between groups A and B ( $p > 0.05$ ), however, the VAS in group C was significantly higher than that in group A or B ( $p < 0.05$ ). The VAS scores at 24 and 36 hours post-operation were not different among the three groups ( $p > 0.05$ ). The use of dezocine did not differ among the three groups ( $p > .05$ ) (Table 2).

### Muscle strength score in patients underwent unilateral TKA

The muscle strength score at 6 and 12 hours post-operation differed significantly among the three groups ( $p < 0.05$ ). Further q-testing showed no difference in muscle strength between groups A and B ( $p > 0.05$ ), while muscle strength in group C was significantly higher than that in groups A or B ( $p < .05$ ). Muscle strength at 24 and 36 hours post-operation were not different among three groups ( $p > 0.05$ ) (Table 3).

### Postoperative complications after unilateral TKA

The incidences of postoperative complications, including urinary retention, nausea, emesis, and pruritus, differed

**Table 3** Comparison of muscle strength of the affected leg among patient groups receiving different pain management protocols (mean  $\pm$  SD).

Group	N	Muscle strength at 6 h	Muscle strength at 12 h	Muscle strength at 24 h	Muscle strength at 36 h
Group A	50	2.2 $\pm$ 1.2	2.4 $\pm$ 0.8	3.7 $\pm$ 1.1	4.2 $\pm$ 2.6
Group B	46	1.9 $\pm$ 0.7	2.1 $\pm$ 1.2	3.5 $\pm$ 1.9	4.2 $\pm$ 2.7
Group C	52	3.2 $\pm$ 1.9	3.7 $\pm$ 2.8	4.1 $\pm$ 2.1	4.5 $\pm$ 0.9
F-value		8.82	12.23	3.63	2.46
P-value		< 0.05	< 0.05	> 0.05	> 0.05

Group A: Patients received morphine (3 mg) via epidural anesthesia catheter before catheter extraction. Group B: Patients received morphine (3 mg) via epidural anesthesia catheter before catheter extraction and local analgesic cocktail injection. Group C: Patients received epidural anesthesia and local analgesic cocktail injection. SD, standard deviation.

**Table 4** Comparison of complications among different patient groups after TKA.

Group	N	Postoperative first void (urinary retention) (mean $\pm$ SD, min)	Nausea and emesis (n, %)	Pruritus (n, %)
Group A	50	442 $\pm$ 112	39 (78)	29 (58)
Group B	46	463 $\pm$ 98	32 (69)	32 (69)
Group C	52	269 $\pm$ 107	12 (23)	20 (38)
$\chi^2$ /F-value		9.39	12.76	10.48
P-value		< 0.05	< 0.05	< 0.05

Group A: Patients received morphine (3 mg) via epidural anesthesia catheter before catheter extraction. Group B: Patients received morphine (3 mg) via epidural anesthesia catheter before catheter extraction and local analgesic cocktail injection. Group C: Patients received epidural anesthesia and local analgesic cocktail injection. TKA, total knee arthroplasty; SD, standard deviation.

significantly among groups A, B, and C ( $p < 0.05$ ). Further q-testing showed that all the incidences of postoperative complications between groups A and B were not significantly different ( $p > 0.05$ ). In addition, all the incidences of postoperative complications in group C were significantly lower than those in groups A or B ( $p < 0.05$ ) (Table 4).

## Discussion

The conception of ERAS has drawn more and more attention in total joint arthroplasty.<sup>9,10</sup> ERAS programs aim to reduce postoperative complications, reduce the stress response to surgical trauma, improve surgical safety, and improve overall patient satisfaction. At present, the perioperative analgesia approaches for patients undergoing TKA include nonpharmacological methods, pharmacological methods, intraspinal analgesia, peripheral nerve blocking, injection of analgesic cocktail around the incision site, and patient-controlled analgesia (PCA). Intrathecal administration of opioids is still the mainstay in postoperative pain management. The common side effects of opioid analgesics are concentrated in the gastrointestinal tract and central nervous systems.<sup>11</sup> These side effects include nausea, emesis, constipation, drowsiness and excessive sedation, and respiratory depression. In addition, opioids may cause pruritus, urinary retention, and low blood pressure. Moreover, locally administered anesthetics may block motor neurons and thus affect postoperative rehabilitation exercises. ERAS programs in TKA mainly focus on perioperative care which includes optimization of pain management, prevention of infection and deep vein thrombosis, and optimization of bladder catheterization.<sup>5–7</sup> In this study, we compared the effects of a local analgesic cocktail injection on the effects

of epidural morphine injection in pain control. The results showed that local analgesic cocktail injection is more conducive to muscle strength recovery in the first 24 hours post-operation, reducing urinary retention, and lowering the risk of postoperative complications including nausea, emesis, and pruritus.

Pain is considered the fifth vital sign. TKA patients' acute uncontrollable postoperative pain hampers early functional training,<sup>12</sup> which is usually recommended as early as possible after the operation. In our study, epidural morphine and/or local analgesic cocktail injection were/was administered to the patients undergoing total knee arthroplasty. VAS scores, which represent pain levels, were compared among different groups and different time points. VAS scores at 36 hours post-operation, both at rest and with activity, were significantly higher than that at 6, 12, and 24 hours post-operation. The delayed pain may be associated with icepack usage and intravenous administration of parecoxib. The VAS score differed significantly among groups A, B, and C. Further comparison was conducted between pairs of groups. The VAS of groups A and C differed significantly at 6 and 12 hours post-operation, both at rest and with activity, but it did not differ at 24 and 36 hours post-operation. In contrast, the VAS of groups A and B did not differ at any of the time points, either at rest or with activity. These results were consistent with the previous observation that morphine remained within the cerebrospinal fluid for at least 20 hours,<sup>13</sup> and demonstrated that epidural morphine administration could effectively relieve acute postoperative pain. Among the three groups, patients in group B got maximum pain relief at 6 and 12 hours, followed by group A, and the percentage of dezocine use in group B was the lowest, suggesting that morphine performed better in relieving pain than a cocktail.

Husted et al.<sup>6</sup> reported that muscle weakness after TKA surgery is positively correlated with the length of stay (LOS). Delayed discharge and prolonged recovery will increase medical expenses. Yan et al.<sup>14</sup> found that epidural morphine administration affects early muscle strength recovery. In this study, the muscle strengths of groups A and B at 6 and 12 hours were significantly lower than those at 24 and 36 hours. In group C, the muscle strength at 6 hours post-operation was significantly lower than that at 12, 24, and 36 hours. Most researches suggested that adding glucocorticoid into the local analgesic cocktail can reduce the time to postoperative straight leg raise and improve the post-operative joint movement.<sup>15–19</sup> The individuals in group C had significantly greater muscle strength at 6 and 12 hours post-operation than those in groups A and B, although the differences at 24 and 36 hours were not significant. These results suggested that a local analgesic cocktail without epidural morphine administration could facilitate early muscle strength recovery after TKA.

As proposed by current ERAS, no catheterization, no emesis, higher patients' satisfaction, and lower risk of post-operative complications are the future development trend in perioperative care. Indwelling bladder catheter causes patients' discomfort, prevents them from early mobility, prolongs the length of hospital stay, and increases the risk of postoperative venous thrombosis.<sup>20</sup> In our study, patients in groups A and B who received morphine administration had a significantly higher incidence of urinary retention, emesis, and pruritus, suggesting local analgesic cocktail injection is superior to morphine administration via epidural anesthesia catheter.

Despite the interesting findings, our study still contains limitations. First, we did not include a non-treatment control group due to ethical reasons. Second, this is a retrospective study with a limited sample size. A further multi-center prospective clinical study with a larger sample size is needed to validate our results.

## Conclusion

In summary, both pain protocols, epidural anesthesia plus morphine and epidural anesthesia plus local analgesic cocktail injection, provide satisfactory pain relief. However, within the first 24 hours after operation, epidural anesthesia plus morphine protocol causes reduced muscle strength and higher incidence of urinary retention, nausea, emesis, and pruritus compared with the protocol of epidural anesthesia plus local analgesic cocktail injection. Local analgesic cocktail injection provides better pain relief, prevents the occurrence of postoperative complications, improves patients' early satisfactory rate, and facilitates recovery. Therefore, epidural anesthesia combined with local analgesic cocktail injection is a preferable effective multimodal analgesia for TKA.

## Conflict of interest

The authors declare no conflicts of interest.

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**ORIGINAL INVESTIGATION**

**Predictors of success of immediate tracheal extubation  
in living donor liver transplantation recipients** 



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**KEYWORDS**

Living donors;  
Liver transplantation;  
Tracheal extubation

**Abstract**

**Background:** Early tracheal extubation of recipients following liver transplantation (LT) has been gradually replacing the standard postoperative prolonged mechanical ventilation, contributing to better patient and graft survival and reduced costs. There are no universally accepted predictors of the success of immediate extubation in LT recipients. We hypothesized several potential predictors of successful immediate tracheal extubation in living donor liver transplantation (LDLT) recipients.

**Aim:** Evaluation of the validity of the following hypothesized factors: model for end-stage liver disease (MELD) score, duration of surgery, number of intraoperatively transfused packed red blood cells (RBCs) units, and end of surgery (EOS) serum lactate, as predictors of success of immediate tracheal extubation in living donor liver transplantation (LDLT) recipients.

**Methods:** In this prospective clinical investigation, perioperative data of adult living donor liver transplantation (LDLT) recipients were recorded. "Immediate extubation" was defined as tracheal extubation immediately and up to 1 hour post-transplant in the operating room. Patients were divided into the extubated group who were successfully extubated with no need for reintubation, and the non-extubated group who failed to meet the criteria of extubation, or were re-intubated within 4 hours of extubation.

**Results:** We enrolled 64 patients candidates for LDLT; 50 patients (76.9%) in group 1 were extubated early after LDLT while 14 patients (23.07%) in group 2 were transferred to the intensive care unit intubated. After data analysis, we found that EOS serum lactate, duration of surgery and number of packed RBCs units transfused intraoperatively were good predictors of success of immediate extubation ( $p < 0.001$ ). MELD scores did not show any significant impact on the results ( $p = 0.54$ ). Other factors such as EOS urine output and blood gases indices were shown to have a significant effect on the decision of extubation ( $p = 0.03$  and  $0.006$ , respectively).

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**Conclusions:** EOS serum lactate, duration of surgery and number of packed RBCs units transfused were potential predictors of post-transplant early extubation.

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## Introduction

Orthotopic liver transplantation (LT) is the definitive treatment for acute liver failure, end-stage liver disease (ESLD), advanced liver cirrhosis, and liver tumors.<sup>1</sup> In our center we previously encouraged that leaving the patient sedated on mechanical ventilation is the standard care following LT. Clinicians believe that this type of clinical management improves outcomes by providing a smooth transition to the recovery phase and reducing physiological stress caused by awakening and spontaneous ventilation. This had remained the common practice despite the lack of evidence that routine postoperative ventilation or intensive care unit (ICU) admission prevents perioperative complications or benefits donor organ function.<sup>2</sup> Developments in the preoperative assessment, surgical techniques, and postoperative care made immediate extubation following LT a feasible and safe procedure for a significant number of patients.<sup>3</sup> Immediate extubation in LT recipients was reported in the early 1990s. Nowadays, early extubation after LT has been successful in many patients and is gradually being adopted in more and more hospitals.<sup>4</sup>

However, the determination of the appropriate tracheal extubation timing and conditions remains important in securing safe and reasonable patient recovery after LT. No definitive or universal criteria have yet been established regarding the predictors of early tracheal extubation in LT patients.<sup>5</sup> Although immediate extubation variables are the same as those for any other surgery, it is a complex decision for patients who have undergone LT, and there is a learning curve, as it can take some time to increase the immediate extubation success rate.<sup>3</sup>

In 2014, Lee and colleagues demonstrated that several factors, including model for end-stage liver disease (MELD) score, lung disease, encephalopathy, ascites, surgical time, transfusion of packed red blood cells (RBCs), urine output, vasopressors, and serum lactate all may affect the decision of early extubation. However, after multivariate analysis, only packed RBC transfusion and end-of-surgery (EOS) serum lactate were selected as predictors of early extubation after living donor liver transplantation (LDLT).<sup>5</sup> Elnour and Milan,<sup>3</sup> reviewed 32 controlled trials on early extubation following LT, and listed factors affecting early extubation, which included: primary liver disease, age, gender, body mass index (BMI), comorbidities, MELD score, encephalopathy, previous abdominal surgery, graft function, duration of anhepatic phase, amount of intraoperative blood replacement, duration of surgery, inotropes at the end of the surgery, lactate at the end of surgery, and temperature. They mentioned factors that were not considered because they were not easily measurable, but may have a significant impact, such as the medical centers' experience, the quality of teamwork, local protocols, and supporting services,

such as nutritionists, social workers, physiotherapists, and recovery room/high dependency unit/ICU settings, therefore mentioning that clinical judgment remains an important factor in decision-making.<sup>3</sup>

Based on previous clinical experience at our center and relevant publications, we aimed to investigate potential predictors of successful immediate tracheal extubation in LDLT recipients, including MELD score, length of surgery, the number of units of packed RBCs transfused intraoperatively, and EOS serum lactate.

## Methods

The academic and ethical committee of the faculty of medicine, Ain-Shams University, approved the study with approval no. FMASU MD 92/2017. The total sample size was 64 patients. All patients enrolled in this study were recipients of LDLT admitted to Ain Shams Center for Organ Transplant (ASCOT). Written informed consent was obtained from every patient or legal guardian after having explained the procedure.

### Type of the study

Prospective observational clinical investigation on recipients of living donor liver transplantation. Adult patients aged 18–60 years, of both sexes, with ESLD scheduled to receive LDLT. Exclusion criteria were emergency transplant, encephalopathy at the time of surgery, re-transplant and the presence of major intraoperative surgical complications such as massive bleeding and injury of major vascular structures or diaphragm.

### Anesthetic technique

Preoperative assessment and preparation were performed according to the institutional protocol. General anesthesia was started with a modified rapid sequence induction. Intraoperative monitoring included: 5-lead ECG, invasive arterial blood pressure, noninvasive blood pressure, continuous central venous pressure (CVP), body temperature, oxygen saturation (SaO<sub>2</sub>), capnometry (EtCO<sub>2</sub>), and urine output (mL). Anesthesia was maintained with a balanced anesthetic technique, consisting of a volatile agent (Isoflurane or Sevoflurane) and a mixture of air and oxygen (FiO<sub>2</sub> 0.5), atracurium infusion at a dose of 0.25 mg·kg<sup>-1</sup>·h<sup>-1</sup> and fentanyl infusion at a dose of 1–2 mcg·kg<sup>-1</sup>·h<sup>-1</sup>. Patients were mechanically ventilated, with ventilator parameters adjusted to achieve normocarbia with an inclination to hyperventilation and hypocapnia during the anhepatic phase to correct metabolic acidosis without resorting to chemical buffers such as sodium bicarbonate.

At the end of the surgery, all patients were prepared for the emergence and tracheal extubation. Fentanyl and atracurium infusions were discontinued 45 minutes before the expected time of extubation. The inhaled anesthetic was stopped at the beginning of skin closure, when patients were awake and able to follow commands and regaining full muscle strength (neuromuscular monitoring: train of four more than 1/4 was satisfactory for extubation). Additionally, the usual criteria for extubation was adopted, including hemodynamic stability with no or minimal vasopressor support (noradrenaline  $< 0.1 \text{ mcg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ), normothermia (temperature  $> 36^\circ\text{C}$ ), a positive gag response, spontaneous breathing with sufficient tidal volume ( $5\text{--}8 \text{ mL} \cdot \text{kg}^{-1}$ ), and respiratory rate of less than 20 breaths/min, normocarbia (evaluated by end-tidal carbon dioxide analysis), and satisfactory arterial blood gas analysis (ABG). pH less than 7.2, PO<sub>2</sub> less than 80 mmHg and PCO<sub>2</sub> more than 45 mmHg were against trials of extubation.<sup>3</sup> In the event of fulfilling all the criteria, endotracheal and oral suctioning was done, followed by extubation. Oxygen therapy was started in the form of an oxygen mask or nasal prongs. Patients were monitored for any sign of respiratory distress, desaturation, or disturbed consciousness level that may require reintubation. Failure of immediate extubation included patients who did not meet the stated criteria and those who were reintubated within 4 hours after extubation. Thirty minutes following skin closure was considered a time limit for failure of extubation and no further trials of extubation were performed in the operation theatre.

## Measurements

Intraoperatively: Serum lactate ( $\text{mmol} \cdot \text{L}^{-1}$ ) and pH from arterial blood gas (ABG) analysis were recorded immediately at four different timings; T1, after insertion of an arterial cannula, T2, during the anhepatic phase, T3, 30 minutes after reperfusion, T4, at the end of surgery (EOS). Blood product requirements were recorded as the number of units of packed RBCs transfused intraoperatively. Duration of surgery (hours) calculated from induction of anesthesia until the end of skin suturing. Vital data at the end of surgery such as mean arterial blood pressure (MABP) (mmHg), heart rate (HR) (beats/min, BPM), body temperature ( $^\circ\text{Celsius}$ ), hemodynamic support at the end of surgery Noradrenaline ( $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ), urine output (UOP) ( $\text{mL} \cdot \text{h}^{-1}$ ) recorded during the last hour of surgery before recovery.

## Endpoints

The primary endpoint was the success of immediate extubation with no need for reintubation within 4 hours after extubation.

## Statistical methods

The statistical analysis was performed using a standard SPSS software package version 22 (SPSS Inc., Chicago, IL, USA). Normally distributed numerical data are presented as mean  $\pm$  SD, and differences between groups were compared using the independent Student's *t*-test. Data not normally

distributed were compared using the Mann-Whitney test and are presented as median (IQR). Categorical variables were analyzed using the  $\chi^2$  test or Fisher's exact test and are presented as number (%). The odds ratio was used to assess the predictors for extubation. All *p*-values are two-sided  $< 0.05$  is considered statistically significant. The sensitivity and specificity of possible predictors were evaluated by the area under the receiver operating characteristic (ROC) curve (AUC).

## Results

We enrolled 64 ESLD patients' candidates for living donor liver transplantation; demographic data were recorded and compared for patients of both extubated and the non-extubated groups (Table 1). There was a significant difference between the two study groups (*p* = 0.013) concerning the pathology of ESLD.

Preoperative MELD scores showed no statistical difference (*p* = 0.54) in the decision of extubation of the patients.

Of the total sample size of 64 patients, 50 patients (76.9 %) met the criteria for successful extubation with no need for reintubation within 4 hours of extubation: Extubated group. On the other hand, 14 patients (23.1 %) did not meet the extubation criteria and so remained intubated after the operation and were transferred to the ICU with their endotracheal tubes in place: Non-extubated group.

At the end of surgery all 64 patients were assessed for the possibility of extubation, and evaluated for possible predictors for extubation. Fifty patients (76.9 %) were extubated successfully, no patients (0%) required re-intubation within the first 4 hours, 14 patients (23.1 %) were not extubated; 5 patients from both groups (7.6%) developed postoperative respiratory complications in the form of Pneumonia (*n* = 3), lung collapse (*n* = 2) all these patients were among the non-extubated group.

Higher EOS serum lactate was found among the non-extubated group of patients ( $11.4 \pm 3.49$ ) when compared to the extubated group ( $5.39 \pm 2.9$ ) (*p* < 0.001). Lactate measured 30 minutes after reperfusion was also reduced (*p* = 0.014) but to a lesser extent than at the end of surgery. On the other hand, when comparing the two groups as regards lactate measured after induction and during the anhepatic phase, no difference was detected (*p* = 0.34 and 0.94 respectively) (Table 2). There was a difference when comparing both groups in regard to pH during the an-hepatic phase (*p* = 0.001) and also at the end of surgery (*p* = 0.006). There was also a high statistical difference between groups 30 minutes after reperfusion (*p* < 0.001) (Table 2).

As noted in Table 2, Patients of the non-extubated group received higher amounts of blood products (*p* = 0.004). Duration of surgery was found to be longer in the non extubated group ( $11.6 \pm 2.67$  hrs) than in the extubated group ( $9.74 \pm 1.35$ ) (*p* = 0.056) with Odd's ratio 0.611. Hemodynamic support (defined by high doses of norepinephrine) is lower in the extubated group 0 (0–0.05)  $\text{microgram} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , than in the non extubated group 0.065 (0.02–0.14)  $\text{microgram} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (*p* = 0.001).

EOS urine output in  $\text{mL} \cdot \text{hr}^{-1}$  showed higher values among the extubated group (*p* = 0.03) especially during the last hour of the operation ( $231.8 \pm 75.43 \text{ mL} \cdot \text{hr}^{-1}$ ).

**Table 1** Comparing the extubated and non-extubated groups regarding age, sex, Body mass index (BMI), diagnosis, and Child-Pugh class.

	Extubated		Non extubated		p-value
Age (years, mean ± SD)	48.88 ± 8.92		46.67 ± 11.04		0.11
Sex	Male 27	Female 23	Male 9	Female 5	0.377
BMI (kg.m <sup>-2</sup> )	28.33 ± 3.04		27.04 ± 4.64		0.21
Diagnosis -ESLD, HCV	24		3		0.013*
-ESLD, HCV, HCC	3		3		
-ESLD, HBV	8		0		
-ESLD, HCV, Previous HBV	3		1		
Child-Pugh class					0.258
-C	27		7		
-B	23		7		
MELD Score	17 (13-21)		16 (14-19)		0.54

ESLD, End stage liver disease; HCV, Hepatitis C virus; HCC, Hepatocellular carcinoma; HBV, Hepatitis B virus; MELD, Model for end stage liver disease.

p < 0.05 is considered statistically significant.

**Table 2** Comparing the extubated and non-extubated groups with respect to serum lactate, pH packed RBCs transfused at different intraoperative stages.

Serum lactate (mmol.L <sup>-1</sup> )	Extubated (n = 50)	Non-extubated (n = 14)	p-value
Baseline	1.24 ± 0.54	1.35 ± 0.46	0.34
Anhepatic	4.8 ± 1.92	4.84 ± 2.5	0.94
30 min after reperfusion	5.5 ± 2.31	7.4 ± 3.3	0.014*
EOS	5.39 ± 2.9	11.4 ± 3.49	< 0.001**
PH	Extubated (n = 50)	Non-extubated (n = 14)	p-value
Baseline	7.42 ± 0.05	7.43 ± 0.056	0.32
Anhepatic	7.33 ± 0.08	7.2 ± 0.11	0.001*
30 min after reperfusion	7.27 ± 0.07	7.18 ± 0.127	< 0.001**
EOS	7.3 ± 0.89	7.24 ± 0.08	0.006*
Number of packed PRBCs	Extubated	Non-extubated	
No. of units	1 (0-2)	3 (2-4)	0.004*

EOS, end of surgery.

Data are presented as mean ± SD.

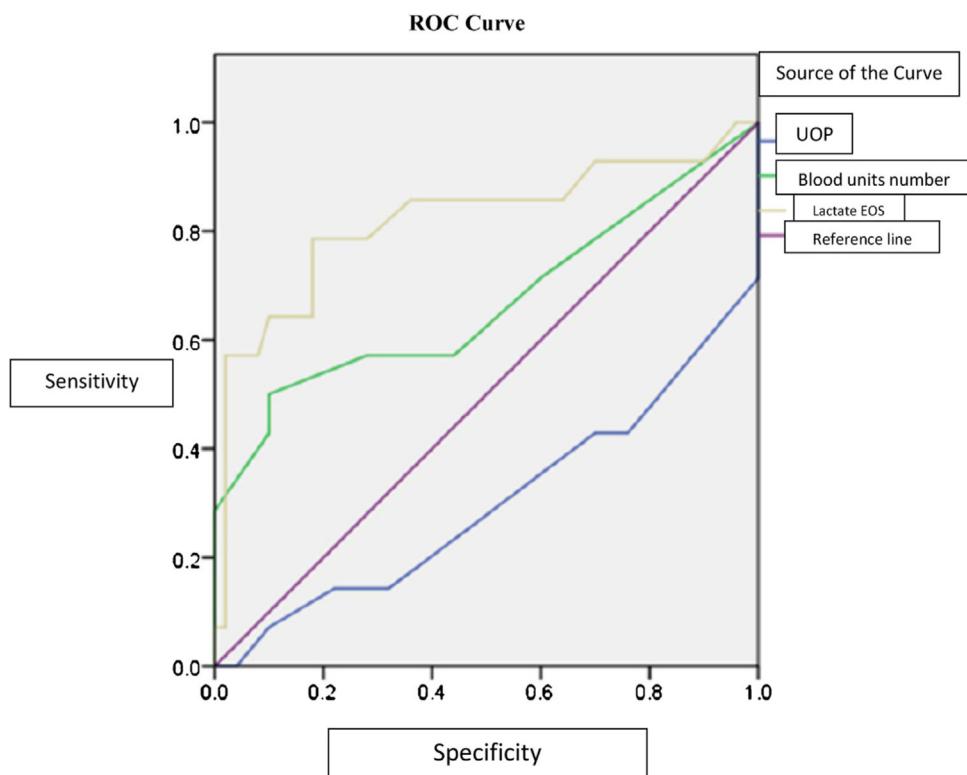
p < 0.05 is considered statistically significant.

Values shown to have high significance were chosen as common indicators for early extubation. These included blood products, UOP and EOS serum lactate. They were represented in the ROC curve to show their sensitivity and specificity as follows in [Figure 1](#).

## Discussion

The definition of "Early" extubation following LT is tracheal extubation immediately or within 1 hour post-transplant in the operating room.<sup>7</sup> If a patient who undergoes early post-transplant extubation is transferred directly to a surgical ward without an ICU stay, the expression "fast-tracking" may be used in place of early extubation. Early extubation

is an essential component of fast-tracking, and the patient undergoes major recovery in the post anesthesia care unit.<sup>5</sup> Most studies about fast-tracking have discussed the pros and cons of fast-tracking. However, limited studies have been performed on how and when to extubate a patient who has undergone LT in the operating theatre, and which factors affect the decision-making process.<sup>3</sup> The current study was conducted on a total of 64 adult patients aged 18–60 years, of both sexes, with ESLD. All of which were candidate recipients of living donor liver transplantation admitted to Ain Shams Center for Organ Transplant (ASCOT). Of the 64 patients, 50 patients (76.9 %) were successfully extubated, while 14 (23.1 %) patients remained intubated postoperatively.



	AUC	Sensitivity	Specificity
<b>UOP</b>	0.301	71.4%	36%
<b>Blood transfusion</b>	0.669	30%	100%
<b>EOS Serum lactate</b>	0.821	85.7%	74.4%

UOP, urine output; EOS, end of surgery.

**Figure 1** Receiver operating characteristic (ROC) curve of the two study groups.  
UOP, urine output; EOS, end of surgery.

When analyzing the proposed predictors of the success of immediate extubation, our study surprisingly showed no significant difference when comparing MELD between the extubated and non-extubated groups, indicating that MELD scores may not be an accurate predictor for early extubation after surgery. These results were supported in a remarkable case report by Li et al., of a 48-year-old male patient with ESLD secondary to Hepatitis B with a documented MELD score of 41 who was successfully extubated in the operating room at the end of LT surgery.<sup>8</sup> Interestingly Lee and colleagues, while performing another study on 107 patients of which 66 were extubated early after LDLT, noticed the significant difference in the MELD score between patients who were successfully extubated (lower MELD score) and those who remained mechanically ventilated. However, after multivariate adjustment with intraoperative factors in their study, the role of MELD scores as a predictor of early tracheal extubation in LT has disappeared.<sup>5</sup> In contrast to our study, Bulatao and colleagues, in a single-variable analysis found that successful fast-tracking was significantly more likely for patients with lower MELD scores.<sup>9</sup> Similarly, in a prospective analysis of 354 patients by Biancofiore et al., a MELD score < 11 was reported to have predictive power for

identifying subjects with a higher likelihood of immediate extubation.<sup>6</sup>

In our study, baseline and anhepatic phase serum lactate levels showed no significant variation between the two groups, while when measured 30 minutes after reperfusion and at EOS, a highly statistically significant difference was demonstrated. Similar to our study, Elnour and Milan, in their review, concluded that EOS serum lactate is of high significance when comparing extubated and non-extubated groups of patients.<sup>3</sup> Also, Unlukaplan and colleagues found that a higher mean intraoperative lactate level was a predictor of mechanical ventilation need in patients after liver transplantation.<sup>10</sup> The same way, Skurzak et al. assigned serum lactate as one of the major criteria in the "Safe Operating Room Extubation after Liver transplantation" (SORELT) criteria, with a cut-off value of < 3.4 mmol.L<sup>-1</sup>.<sup>11</sup> This lower value may be attributed to the use of cadaveric whole grafts and different surgical techniques.

Concerning blood product utilization, patients of the non-extubated group had higher transfusion rates, demonstrated by the number of intraoperatively transfused packed RBCs units. Blaszkzyc et al. mentioned that the decision regarding immediate extubation can be aided by considering the number of units of packed RBCs and fresh frozen

plasma transfused during surgery.<sup>12</sup> Hoffmeister and colleagues found a highly significant difference in the amount of intraoperative transfused blood products between the extubated and non-extubated groups.<sup>1</sup> Zeyneloglu et al., when comparing extubated with non-extubated patients, found that those extubated had lower transfusion requirements.<sup>13</sup> Blood transfusion requirements were lower in our study, which may be attributed to the routine use of cell salvage, lower triggers for transfusion and different surgical techniques.

In our study, we observed a trend of longer duration of surgery among the non-extubated group, but it was not statistically significant, probably reflecting the greater difficulty in the surgical procedure. In a similar study, Bulatao and colleagues demonstrated that successful fast-tracking was significantly more likely for patients with a shorter operative time.<sup>9</sup> Khosravi and colleagues when conducting their study on 200 patients undergoing liver transplantation, also found a significant difference between the extubated and non-extubated groups when comparing their operative times.<sup>14</sup> In contradiction to our study, Hoffmeister and colleagues declared no statistically significant difference between the two groups as regards the duration of surgery.<sup>1</sup> Also, Biancofiore et al. found that the duration of surgery had no significant influence on the time of extubation.<sup>6</sup>

This study presents some major limitations, including the small sample size and the lack of investigation of additional potential predictors such as cold ischemia time, living donor age, graft size and any previous abdominal operations.

Altogether, our findings indicate that immediate extubation after liver transplantation is possible and can be safely done in a substantial percentage of cases after evaluating major factors that may affect the decision. Anesthesiologists ought to be encouraged to extend this practice to the largest possible number of patients. Successful immediate extubation may be an important indicator of the perioperative quality of care in liver transplantation.<sup>7</sup> Our study demonstrated that EOS serum lactate, number of packed RBCs units transfused intra-operatively and the UOP at the neohepatic phase are good predictors of the success of immediate tracheal extubation in LDLT recipients, while MELD score has no predictive value in this matter.

### Conflict of interest

The authors declare no conflicts of interest.

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**ORIGINAL INVESTIGATION**

**Determination of the minimum effective volume of bupivacaine for ultrasound-guided infraclavicular brachial plexus block: a prospective, observer-blind, controlled study**



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**KEYWORDS**

Brachial plexus block;  
Bupivacaine;  
Drug dose-response  
relationship;  
Regional anesthesia

**Abstract**

**Background:** We aimed to determine the minimum effective volume (MEV) of 0.5% bupivacaine for infraclavicular brachial plexus block.

**Methods:** We assigned patients to volume groups consisting of five consecutive patients. Local anesthetic was sequentially reduced from a starting dose of 30 mL by 2 mL to form the volume groups. Five patients were included in each volume group, and at least 3 of 5 injections had to be successful to consider the volume of the anesthetic as sufficient. The study ended when the anesthetic volume of a group was determined to be unsuccessful (two or fewer successful blocks). Block was successful if the patient reported a sensorial block score of 7 or more on an 8-point scale and sensorial and motor block's total score of 14 on a 16-point scale.

**Results:** The MEV of 0.5% bupivacaine for infraclavicular brachial plexus block was 14 mL. A successful block was achieved in all patients ( $n = 45$ ) in 9 volume groups, which received 30 mL down to 14 mL. Three blocks were unsuccessful in the 12-mL group. Time to onset of block and time to first postoperative anesthetic administration was 15 (10–15) min and more than 24 h in the 30-mL bupivacaine group, but 40 (30–45) min and 14 (10–24) h were determined for the 14-mL group, respectively.

**Conclusions:** The MEV of 0.5% bupivacaine for ultrasound-guided infraclavicular brachial plexus block was 14 mL. However, this low-dose block has a long onset time of 40 (30–45) min on average.

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## Introduction

Several blocks can be performed without ultrasound guidance, but the use of ultrasonography has become standard. Ultrasonography has various advantages, including reduced local anesthetic (LA) requirement, better visualization of patient anatomy, and the possible identification of anatomical variations that would otherwise be overlooked.<sup>1</sup>

A small LA volume is preferred owing to the possibility of systemic anesthetic toxicity with high doses.<sup>2</sup> The incidence of systemic toxicity due to peripheral block is low (0.18–0.2%), but such toxicity is a serious complication that may be fatal.<sup>3–5</sup> Reducing the volume of LA in routine practice can play a crucial role in preventing complications in rare situations, such as the administration of bilateral blocks when the LA volume should be reduced.<sup>4</sup> Thus, the minimum effective volume (MEV) of any anesthetic administered with any approach is important. When the MEV of a procedure is determined, the procedure can be safely performed without excessive anesthetic. To our knowledge, few studies have investigated the MEVs of various LAs administered for infraclavicular blocks with different approaches.<sup>6,7</sup> We aimed to determine the MEV of bupivacaine for ultrasound-guided (USG) infraclavicular brachial plexus block.

## Methods

This study was performed in accordance with the ethical standards of our institution, the national research committee (Ankara Numune Training and Research Hospital Clinical Research Ethical Committee; Reference No. 646, approved November 11, 2015), the 1964 Declaration of Helsinki and its later amendments, and other comparable ethical standards.

The study was registered at ClinicalTrials.gov (No. NCT03838120). Informed consent was obtained from all patients before inclusion in this controlled, patient- and observer-blind, single-center study. We included patients between 18 and 70 years of age with American Society of Anesthesiologists (ASA) physical status I–III who underwent upper limb surgery from November 2015 through November 2016.

We excluded patients who refused to participate; those with ASA physical status IV or V; those with serious cardiac,

respiratory, hepatic, or renal comorbid conditions; those with neuromuscular and/or neurological disease, mental disorders, and coagulopathy; those who were pregnant; and those with an allergy to LA and infection at the injection site. We excluded eight patients (two because of coagulopathy, three because of respiratory disease, and three who refused to participate) during the preoperative evaluation period.

All procedures were performed by the same physician (S.B.). Routine anesthesia monitoring was performed, and each patient was administered  $0.03 \text{ mg} \cdot \text{kg}^{-1}$  of midazolam and  $1 \mu\text{g} \cdot \text{kg}^{-1}$  of fentanyl for sedation. The injection site was prepared according to aseptic and antiseptic guidelines.

We performed the lateral sagittal infraclavicular block technique, as reported by Klaastad.<sup>8</sup> The technique was modified to include ultrasound guidance, which was performed with a 6–12 MHz linear ultrasound probe. The patient was placed in the supine position, with the head turned away from the application side and the shoulder relaxed. The arm on the operative side was slightly abducted; the elbow was flexed 90° and placed on the patient's torso. The anesthesiologist was positioned beside the head of the patient. The ultrasound probe was placed 1 cm inferior to the intersection of the clavicle and the coracoid process on the sagittal axis. The in-plane technique was used, and a 21G, 5-cm needle (Locoplex, Vygon, Ecouen, France) was visualized at all times. To obtain appropriate anesthetic spread, the LA (0.5% [5 mg·mL<sup>-1</sup>] bupivacaine) was applied in a U-shaped pattern from 3 to 11 o'clock around the axillary artery; if this spread could not be achieved, the needle was repositioned as necessary (0.5% bupivacaine, which is the only long-acting LA available in our hospital).

The patients were assigned to the groups in order of admission, and the volume of LA was reduced from a starting dose of 30 mL in the first group. Five patients were included in each volume group, and at least 3 of 5 injections had to be successful to consider the volume of LA as sufficient. If the previous group's anesthesia was successful, the anesthesiologist reduced the dose by 2 mL every five patients. We ended the study when the anesthetic dose of a group of patients was insufficient (two or fewer successful blocks) (Table 1).

**Table 1** Volume groups and outcomes.

Volume group	Volume, mL	Patients, n	Outcome
1	30	5	$\geq 3$ Patients with successful block
2	28	5	$\geq 3$ Patients with successful block
3	26	5	$\geq 3$ Patients with successful block
4	24	5	$\geq 3$ Patients with successful block
5	22	5	$\geq 3$ Patients with successful block
6	20	5	$\geq 3$ Patients with successful block
7	18	5	$\geq 3$ Patients with successful block
8	16	5	$\geq 3$ Patients with successful block
9	14	5	$\geq 3$ Patients with successful block
10	12	5	$\leq 2$ Patients with successful block (end of study)
1–9	14–30	45 (93.8% of total)	Successful block
10	12	3 (6.3% of total)	Unsuccessful block

X, the first group in which anesthetic dose is insufficient; Y, the first volume of anesthetic dose which is insufficient.

The researcher who determined whether the block was successful (N.A.E.) was blind to the study protocol. We evaluated sensorial and motor blocks to determine block success. To measure sensorial block, we used touch and cold sensation tests to evaluate these sensations in each region innervated by the musculocutaneous, median, radial, and ulnar nerves. Touch sensation was evaluated with the cotton wool test, and cold sensation was evaluated with ice packs. Each region was compared with the corresponding contralateral region. A score of 0 indicated no block; 1, some analgesia achieved (touch sensation present, but temperature sensation absent); and 2, complete sensorial block in that specific region.

Motor block was graded on a 3-point scale: 0, no block; 1, partial motor block; and 2, complete motor block. To evaluate motor block, we evaluated motor responses in the muscles innervated by the musculocutaneous, median, radial, and ulnar nerves. Lack of movement indicated complete block, slight movements indicated partial motor block (i.e., initiation of motor block), and normal movements indicated an absence of motor block.

Evaluations were performed every 5 minutes during the first 60 minutes after injection. The maximum total score of sensorial and motor block was 16. Anesthesia and block were considered unsuccessful if the score was less than 14. Furthermore, a sensorial block score of at least 7 on an 8-point scale was required for a successful block.

If the block was unsuccessful during the first 60 minutes after the procedure, we administered laryngeal mask airway anesthesia.

We defined initiation of motor and sensorial block as the time at which the score on the Bromage scale changed from 0 to 1, and we defined time of regression as the time at which this score decreased to less than 1. Postoperative pain was evaluated with a visual analogue scale (VAS) at 2, 4, 8, 12, 16, and 24 hours. VAS was assessed with a 10-cm ruler, with numbers ranging from 0 to 10. Additional analgesic was administered when the VAS score increased to greater than 4.

Statistical analysis was performed with IBM SPSS 21.0 (IBM Corp., Armonk, NY) and MedCalc 15.11.4 (MedCalc Software bv, Ostend, Belgium; <https://www.medcalc.org>). Descriptive statistical methods (frequency, percentage, mean, standard deviation, median, min–max) were used to evaluate study data. Normality was evaluated with the Shapiro-Wilk test, skewness-kurtosis, and graphical methods (histogram, Q-Q Plot, Stem and Leaf, Boxplot). In the study, categorical variables were presented as n/%, normally distributed quantitative data as mean  $\pm$  SD, and non-normally distributed data as median (min–max). The Kruskal-Wallis test was used to compare volume groups. In cases where there was a difference, the (post-hoc) Tukey HSD test was used to find out which volume(s) caused the difference. The relationship between local anesthetic volume and the different times evaluated as outcomes (onset of successful block, regression of sensory and motor block, and first operative analgesic rescue) were evaluated by the Spearman correlation test. This test yields values (rho) between -1.00 (perfect negative correlation or inverse relationship) and +1.00 (perfect positive correlation or direct relationship) with a value of 0.00 representing the absence of correlation. In this study,  $p \leq 0.05$  was considered significant.

## Results

The mean age of our patient group was  $37.3 \pm 13.7$  years, 66.7% were men, the mean weight was  $73.4 \pm 11.8$  kg, the mean height was  $171.3 \pm 10.8$  cm, the mean body mass index was  $25.0 \pm 3.3$ , and 83.3% had ASA II physical status. Block was successful in 93.8% of patients (Tables 1 and 2).

The overall median time to onset of successful block was 20 (10–45) min, the median sensorial block regression time was 18 (10–24+) h, the median motor block regression time was 18 (8–24+) h, and the median time of first postoperative analgesic administration was 24 (10–24+) h. Consistently reducing the LA volume from 30 to 14 mL increased the time to onset of successful block from 15 to 40 minutes and shortened the time required for sensory and motor block regression from more than 24 hours to 12 hours. Patients in groups that received decreased LA required additional analgesia at an earlier time (Table 3).

Volume was negatively associated with time to onset of successful block ( $r = -0.89$ ) but positively associated with sensorial and motor block regression times ( $r = 0.80$  and  $r = 0.77$ , respectively), and positively associated with time to first postoperative analgesic administration ( $r = 0.77$ ). These relationships were statistically significant ( $p < 0.05$ ). The MEV of 0.5% bupivacaine for brachial plexus block was 14 mL (Table 4).

## Discussion

The administration of a brachial plexus block with USG techniques has important positive effects, such as a reduced number of needle passes, less pain during the procedure, and higher success and lower complication rates.<sup>7,9</sup>

The incidence rates of complications such as systemic toxicity,<sup>3</sup> phrenic paralysis,<sup>10</sup> and Horner syndrome<sup>11</sup> are low in patients who receive infraclavicular block, but these serious complications may be fatal. Reducing the volume of LA in routine practice can play a crucial role in preventing complications, especially in rare situations such as bilateral block administration<sup>4</sup> and the treatment of patients with comorbid conditions that require a reduced dose (e.g., those with renal failure).

**Table 2** Patient characteristics.

Variable	n (%) or mean $\pm$ SD
Sex <sup>a</sup>	
Female	16 (33.3%)
Male	32 (66.7%)
Age <sup>b</sup>	$37.3 \pm 13.7$
Weight, kg <sup>b</sup>	$73.4 \pm 11.8$
Height, cm <sup>b</sup>	$171.3 \pm 10.8$
BMI <sup>b</sup>	$25.0 \pm 3.3$
ASA <sup>a</sup>	
I	8 (16.7%)
II	40 (83.3%)

ASA, American Society of Anesthesiologists physical status; BMI, body mass index; SD, standard deviation.

<sup>a</sup> n/%.

<sup>b</sup> Mean  $\pm$  SD.

**Table 3** Anesthetic duration according to volume, median (minimum to maximum).

Volume	Time to onset of successful block, min	Time to regression of sensorial block, h	Time to regression of motor block, h	Time to first additional postoperative analgesic, h
12 mL	—	—	—	—
14 mL	40 (30–45) <sup>a</sup>	12 (10–18) <sup>a</sup>	12 (8–18) <sup>a</sup>	14 (10–24) <sup>a</sup>
16 mL	35 (25–40) <sup>a,b</sup>	16 (10–18) <sup>a,b</sup>	14 (10–18) <sup>a,b</sup>	16 (12–24) <sup>a,b</sup>
18 mL	30 (20–35) <sup>b,c</sup>	12 (10–24) <sup>a,b</sup>	12 (10–20) <sup>a,b</sup>	20 (14–24) <sup>a,b,c</sup>
20 mL	25 (20–30) <sup>c,d</sup>	18 (12–24) <sup>a,b</sup>	18 (12–22) <sup>a,b,c</sup>	22 (16–24) <sup>a,b,c,d</sup>
22 mL	25 (20–25) <sup>c,d</sup>	18 (10–24) <sup>a,b</sup>	18 (10–24) <sup>a,b,c</sup>	22 (15–24+) <sup>b,c,d</sup>
24 mL	20 (20–25) <sup>d</sup>	18 (12–24) <sup>b,c</sup>	18 (12–24) <sup>b,c</sup>	24 (16–24+) <sup>c,d</sup>
26 mL	20 (15–20) <sup>e</sup>	24 (18–24+) <sup>c,d</sup>	19 (18–24) <sup>c,d</sup>	24 (18–24+) <sup>d,e</sup>
28 mL	15 (15–20) <sup>e</sup>	24+ (24–24+) <sup>d</sup>	24 (20–24+) <sup>d,e</sup>	24+ (24+–24+) <sup>e</sup>
30 mL	15 (10–15) <sup>e</sup>	24+ (24+–24+) <sup>d</sup>	24+ (24+–24+) <sup>e</sup>	24+ (24+–24+) <sup>e</sup>

The same letters denote the lack of a significant difference between rows.

Bupivacaine is a widely studied, long-acting, high-quality, cheap LA for brachial plexus block. It is commonly administered because of its strong sensorial block properties but has several disadvantages.<sup>12</sup> Studies have reported that at least 25 to 30 mL of bupivacaine is required to achieve anesthesia.<sup>13,14</sup> However, conflicting results have been reported. In a study that decreased the volume of 0.5% bupivacaine to 1 mL for each nerve,<sup>12</sup> 50% of patients had a successful block and the MEV was 9.6 mL.<sup>6</sup>

In our study, the MEV of 0.5% bupivacaine was 14 mL. Few studies have investigated the MEV of bupivacaine.<sup>6,12</sup> Tran et al.<sup>7</sup> reported that 90% of patients administered 1.5% lidocaine had successful brachial plexus block and the MEV was 30 mL. Although lidocaine and bupivacaine are amino-amide anesthetics, bupivacaine is more potent owing to its higher lipid solubility and may be administered in lower concentrations (usually 0.5% bupivacaine vs. 2% lidocaine).<sup>15</sup> Thus, this comparison should be cautiously considered, and the longer onset time of bupivacaine (median of 40 min in our study) compared with that of lidocaine should be kept in mind, too. Bupivacaine for brachial plexus block reportedly has a block duration of 9 to 12 hours,<sup>16</sup> which agrees with our finding of 10 hours in the 14-mL volume group. However, we found that a greater volume also increased the block duration. Thus, the MEV of bupivacaine may be an important consideration in clinical evaluations of postoperative recovery and pain management.

In the present study, the median time to onset of sensorial block was 40 minutes in the 14-mL group vs. 15 minutes

in the 30-mL group. Our results are greater than those in the literature. Pongraweewan et al.<sup>17</sup> reported a time to onset of 6.68 minutes for 30 mL of 0.5% bupivacaine. Another study reported a median (range) time to onset of 6 (3–12) minutes for 40 mL of 0.5% bupivacaine.<sup>18</sup> However, these studies did not compare different volumes; thus, the evaluation of time to onset may have been less strict than in the present study. Indeed, the evaluation of sensory block in the latter study depended on the patients reporting a “different” (as opposed to the “same”) sensation during the touch test. Pedro et al.<sup>13</sup> reported a time to onset of 5 to 15 minutes for 30 mL of 0.5% bupivacaine administered with the supraclavicular approach; this finding is similar to ours.

A broad range of times to first postoperative analgesic administration has been reported. Liisanantti et al.<sup>19</sup> reported a mean of 17.8 hours after 45 mL of 0.5% bupivacaine, whereas Ozmen et al.<sup>20</sup> reported a mean of 4.4 hours after 20 mL of 0.5% bupivacaine. In the present study, the time to first postoperative analgesic administration was 14 hours after 14 mL of 0.5% bupivacaine, and this time increased to greater than 24 hours with 30 mL. These differences may be due to variations in LA volume and application; however, the pain scoring scales and the value at which additional analgesics were considered necessary could have affected the results. Liisanantti et al.<sup>19</sup> did not use a scoring system to evaluate pain, and Ozmen et al.<sup>20</sup> did not define a specific pain value at which additional analgesics would be administered. In our study, a VAS score greater than 4 indicated that additional analgesics were required.

**Table 4** Associations between anesthetic volume and duration of anesthesia.

Variable	(1)	(2)	(3)	(4)	(5)
(1) Volume, mL	1.00				
(2) Time to onset of successful block, min	−0.89 <sup>a</sup>	1.00			
(3) Time to regression of sensorial block, h	0.80 <sup>a</sup>	−0.55 <sup>a</sup>	1.00		
(4) Time to regression of motor block, h	0.77 <sup>a</sup>	−0.48 <sup>a</sup>	0.90 <sup>a</sup>	1.00	
(5) Time to first postoperative analgesic, h	0.77 <sup>a</sup>	−0.50 <sup>a</sup>	0.90 <sup>a</sup>	0.94 <sup>a</sup>	1.00

Spearman rho values are shown.

<sup>a</sup>  $p < 0.001$

The numbers 1 to 5 represent the different analyzed variables, as seen in the rows of the first column. Correlations are presented with their respective Spearman rho values using those numbers as references of relationships throughout the table. Values of 1.00 are seen as perfect positive correlation when those variables are correlated to themselves, as expected.

We did not observe any procedure-related complications. Studies have reported Horner syndrome (3.2%), phrenic nerve palsy (3%), pneumothorax (1–4%), and hematoma (2–3%), in addition to rarely observed complications such as venous puncture,<sup>21,22</sup> in patients who underwent infraclavicular brachial plexus block. Studies on the complication rates of brachial plexus block techniques mostly report low complication rates, mild complications, and complete recovery (barring rare cases).<sup>14,23,24</sup>

We did not consider the effects of body mass index or type of surgery, which may be limitations. However, the strengths of our study include our use of objective evaluation criteria, blind evaluators, and non-biased patient selection. The lowest effective dose was 14 mL, but because the volume groups were formed by sequentially decreasing the dose of LA by 2 mL from a starting point of 30 mL, successful doses between 12 mL and 14 mL could not be evaluated.

Few studies have determined the MEVs of various LAs administered with various anatomical approaches for USG infraclavicular brachial plexus block.<sup>6,7,12,25</sup> Although the methodologies and results of these studies differ, the aims were similar: to reduce the dose of LA administered for brachial plexus block. We concluded that brachial plexus block can be successfully performed with a low bupivacaine dose, albeit with a long time of onset. When elective surgery requires a brachial plexus block, a low dose of LA may be used without compromising safety. Additional studies with more patients are needed to determine the MEVs of LAs.

## Conclusion

We determined that the MEV of 0.5% bupivacaine for USG lateral sagittal infraclavicular brachial plexus block was 14 mL. However, this low-dose block has a long onset time of 40 (30–45) minutes on average. Future studies should investigate the MEV of low-dose bupivacaine.

## Conflicts of interest

The authors declare no conflicts of interest.

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**ORIGINAL INVESTIGATION**

**Location of motor branches of tibialis posterior muscle and its relation in treatment of spastic equinovarus foot: a cadaveric study**



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**KEYWORDS**

Tibial nerve;  
Posterior tibial tendon dysfunction;  
TARP syndrome

**Abstract**

**Background and objectives:** Nerve block or neurolysis is an important approach in the treatment of spastic equinovarus foot. To illustrate the accurate location of the nerve branch to the tibialis posterior muscle (TP) in clinical practice, 21 adult cadavers were dissected and 14 complete both lower limb specimens were obtained. A total of 28 lower limbs were included.

**Methods:** We measured the length of the motor branch nerve (LM) of the tibialis posterior muscle, the length of the fibula (LF), the vertical distance (D1) from the midpoint of LM to the fibula tip as well as the horizontal distance (D2) from the midpoint of LM to the inner edge of the fibula.

**Results:** The LM was higher ( $35.74 \pm 7.28$  mm) in male than in female ( $30.40 \pm 6.88$  mm) specimens but there was no significant correlation between LM and gender ( $p > 0.05$ ). Additionally, among male specimens, the LM on the right side was longer than that on the left ( $p \leq 0.05$ ) while among female specimens, the D1 on the left side was longer than that on the right ( $p \leq 0.05$ ). The LF in male specimen was significantly longer than that in female ( $p \leq 0.05$ ). The midpoint of the nerve to the motor branch of the tibialis posterior muscle was about 50 mm distal to the fibular head and 10 mm at the inner edge of the fibula.

**Conclusion:** Using this coordinate, the midpoint of the nerve branch to the TP could be accurately located.

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## Introduction

Spastic equinovarus foot (SEF) is a frequent deformity, with an estimated incidence of between 18–56%, among patients suffering from spastic hemiplegia following a stroke.<sup>1,2</sup> The condition is characterized by spasticity of the triceps surae and tibialis posterior muscles (TP).<sup>3–6</sup> Various approaches have been applied in the treatment of SEF including: physiotherapy, muscle stretch training, use of orthosis, alcohol or phenol neurolysis, botulinum toxin injection, selective neurotomy, tendon transfer, and Achilles tendon lengthening. Effective neurolysis involving the use of phenol or alcohol requires the accurate location of the motor nerve branches of the triceps surae and TP muscle responsible for SEF. Botulinum toxin, phenol or alcohol injection can be used in the treatment of spastic clubfoot, and the treatment effect can be maintained for 6 months, so it is an ideal treatment choice.<sup>7</sup>

Anatomically, the TP muscle originates from the posterior fibula, the posterior tibia and the interosseous membrane, below the soleus muscle line. The attendant tendon is subdivided into anterior, middle, and posterior parts, ending at the sole of the foot.<sup>8</sup> The main function of the TP muscle is to maintain the medial arch of the foot and to make the foot varus.<sup>9</sup>

Several studies have been conducted on the motor nerve branches of the triceps surae muscle but, in contrast, not much attention has been given to studying the location of the motor branches of the TP muscle.<sup>10–13</sup> Nihal and colleagues used the tip of the fibular head as the location of the tibial nerve branch. The position of the tibial nerve from the tibial nerve to the tibial posterior muscle was 7.6 cm away from the tip of the fibula, the length of the branch was 7.8 cm, and the average terminal branch was 3.7 branches.<sup>14</sup> However, it is difficult to apply it in clinical practice. Bodily and colleagues<sup>15</sup> used the tibial plateau as a reference point to determine the location of the origin of muscular motor branches in the posterior compartment of the leg. It is difficult to accurately locate the motor branch of posterior tibial muscle due to the lack of specific location of tibial plateau. Baroncini and colleagues<sup>16</sup> measured the distance from the femoral tibial joint line of the knee joint to the origin point of the posterior tibial nerve branch of the tibial nerve. Because it is difficult to reach the posterior popliteal fossa of the knee joint, the anterior knee joint line as a reference, clinical application is more difficult. Because the motor branches of soleus and tibialis posterior muscles are too small to be identified in imaging, we must use related muscles to locate these branches indirectly. The motor branches of posterior tibialis muscle are located at the starting point of posterior tibial muscle. These localization methods are difficult to be accurately applied in clinic. The purpose of this study was, therefore, to find a simple and reliable method of locating the motor branch (LM) of the TP using adult cadaveric specimens.

## Methods

A total of 21 adult cadaver specimens soaked in 10% formalin were collected from the Department of Anatomy, Qingdao University. The inclusion criteria involved the cadavers hav-

ing complete lower limbs and no trauma or deformity in the lower limbs. Cadavers were excluded if they lacked one or both calves, if calves had features of previous calf injuries, if there were noticeable deformities of the calves or ankles, or if there was evidence of previous surgery. Some 14 cadavers, with a total of 28 legs, were eventually included in the study. The gender distribution was 8 male and 6 female cadavers. The specimens were placed in the prone position on the anatomical table with the knee joint flat and straight, in an extended position. An incision was made on the posterior median section of the calf, from the top of the popliteal fossa to the back of the ankle. The skin and subcutaneous tissue were cut open to expose the triceps surae muscle. The Achilles tendon was then cut off at the distal end and the triceps surae muscle turned to the proximal end and removed to carefully expose the posterior deep chamber while minimizing interference to the deep tissue. The tibial nerve, popliteal artery and vein, as well as the distal posterior tibial artery and vein were exposed from the proximal end. The medial edge of the lateral fibula and the full length of the fibula (LF) were similarly exposed. The length of the fibula was measured and recorded. To the TP muscle and the entry point to the TP muscle were located and dissected carefully under a 4-fold microscope, avoiding traction of the nerve. An electronic digital Vernier caliper (Sino-foreign joint venture Jingjiang measuring tools Co., Ltd., accuracy of 0.01 mm, corrected reading before use), was used to measure the length of the nerve branch of the TP muscle, marked as LM. The length of the fibula was marked as LF. The vertical distance from the midpoint to the nerve branch of the TP muscle to the fibula tip was marked as vertical distance from the midpoint of the motor branch of the tibial nerve supplying the TP to the fibula tip (D1). The horizontal distance from the midpoint of the nerve branch of the TP muscle to the inner edge of the fibula was marked as horizontal distance from the midpoint of the motor branch of the tibial nerve supplying the TP to the inner edge of the fibula (D2). Pictures (camera model, Sony α-77) of the images were also captured. This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (Fig. 1).

## Statistical analysis

All measured data was expressed as mean  $\pm$  standard deviation ( $X \pm s$ ). Comparison between groups was performed using the Student's *t*-test for independent samples while correlation analysis between variables was performed using the Pearson test. Differences between entities were considered statistically significant when the value of  $p \leq 0.05$ .

## Results

In all specimens, the nerve branch of the TP muscle of the tibialis posterior muscle was found to originate from the fibular side of the tibial nerve trunk distal to the fibular head. The LM was  $35.74 \pm 7.28$  mm in male and  $30.40 \pm 6.88$  mm in female specimens; the difference in length was, however, not statistically significant ( $p > 0.05$ ). Equally, the values obtained for D1 ( $47.57 \pm 8.65$  mm in male and  $51.98 \pm 12.92$  mm in female) and D2 ( $10.93 \pm 3.31$  mm in male and  $11.14 \pm 2.84$  mm in female)



**Figure 1** A, Image of motor branches of the tibial nerve supplying the TP muscle. B, Length of the fibula. The red dot is the midpoint of the trunk of the motor branch of the tibial nerve innervating the TP. D1 represents the distance between the superior edge of the tip of the fibula and the midpoint of the main motor branch of the tibial nerve that supplies the TP; D2 represents the distance between the midpoint of the main motor branch of the tibial nerve supplying the TP and the inner edge of the fibula.

**Table 1** Comparison of LM, D1 and D2 values between Male and Female specimen.

	Female (n = 12)	Male (n = 16)	t	p
LM	30.40 ± 6.88	35.74 ± 7.28	1.968	0.60
D1	51.98 ± 12.92	47.57 ± 8.65	-1.085	0.29
D2	11.14 ± 2.84	10.93 ± 3.31	-0.18	0.86
LF	340.58 ± 14.91	377.32 ± 37.71	-3.18	0.004

Note: Values are in mm and represent the mean ± SD.  
LM, Length of the motor branch of the tibial nerve of the tibialis posterior muscle; LF, Length of the fibula; D1, Vertical distance from the midpoint of the motor branch of the tibial nerve of the tibialis posterior muscle to the fibula tip; D2, Vertical distance from the midpoint of the motor branch of the tibial nerve of the tibialis posterior muscle to the inner edge of the fibula.

did not differ significantly ( $p > 0.05$ ). The LF was higher in male ( $377.32 \pm 37.71$  mm) compared to that in female ( $340.58 \pm 14.91$  mm) specimens,  $p < 0.05$  (Table 1).

As summarized in Table 2, no significant differences were found between the left and right sides among female specimens in the values of LM, D2 and LF. To the contrary, the D1 was longer on the left compared to the right side ( $p < 0.05$ ). Considering male specimens, the only significant differences recorded between the left and right sides was in the value of LM ( $p < 0.05$ ). For the other parameters: D1, D2 and LF, the

**Table 2** Comparison of LM, D1 and D2 values between left and right sides of female specimen.

	Left (n = 6)	Right (n = 6)	t	p
LM	30.35 ± 7.81	30.44 ± 6.56	-0.021	0.98
D1	59.91 ± 9.91	44.06 ± 10.88	2.639	0.025
D2	10.21 ± 3.05	12.08 ± 2.53	-1.156	0.275
LF	338.00 ± 16.15	343.17 ± 14.57	.58	0.573

Note: Values are in mm and represent the mean ± SD.  
LM, Length of the branch nerve to the tibial nerve of the tibialis posterior (TP) muscle; LF, Length of the fibula; D1, Vertical distance from the midpoint of the branch nerve of the TP to the fibula tip; D2, Horizontal line from the midpoint of the nerve branch to the tibial nerve of the TP to the inner edge of the fibula.

differences between left and right sides did not meet the threshold to be considered statistically significant (Table 3). Further analysis failed to show a relationship between LF and either LM, D1 or D2 (Table 4).

## Discussion

Patients who have suffered from a stroke episode are at risk of developing SEF.<sup>17</sup> With SEF, affected patients often must contend with curtailed walking speed and distance. More-

**Table 3** Comparison of LM, D1 and D2 values between left and right sides in male specimen.

	Left (n = 8)	Right (n = 8)	t	p
LM	31.52 ± 6.32	39.97 ± 5.73	-2.802	0.014
D1	51.31 ± 9.16	43.83 ± 6.68	1.866	0.083
D2	10.28 ± 3.89	11.59 ± 2.71	-0.782	0.447
LF	376.28 ± 38.40	378.38 ± 39.62	-0.108	0.916

Note: Values are in mm and represent the mean ± SD.

LM, Length of the branch nerve to the tibial nerve of the tibialis posterior (TP) muscle; LF, Length of the fibula; D1, Vertical distance from the midpoint of the branch nerve of the TP to the fibula tip; D2, Horizontal line from the midpoint of the nerve branch to the tibial nerve of the TP to the inner edge of the fibula.

**Table 4** Pearson correlation test of LM, LF, D1 and D2 between genders.

	Female (n = 12)	Male (n = 16)	p
LM	30.40 ± 6.88	35.74 ± 7.28	0.067
D1	51.98 ± 12.92	47.57 ± 8.65	0.097
D2	11.14 ± 2.84	10.93 ± 3.31	0.243
LF	340.58 ± 14.91	377.32 ± 37.71	

Note: Values are in mm and represent the mean ± SD.

LM, Length of the branch nerve to the tibial nerve of the tibialis posterior (TP) muscle; LF, Length of the fibula; D1, Vertical distance from the midpoint of the branch nerve of the TP to the fibula tip; D2, Horizontal line from the midpoint of the nerve branch to the tibial nerve of the TP to the inner edge of the fibula.

over, there is functional restriction of the affected foot that may impair the ability to execute normal daily activities.<sup>18</sup> Most patients, especially those who present with early phase spasticity, can respond to physiotherapy, muscle stretch training, and neurolysis using substances such as alcohol, phenol, or injection with botulinum toxin.<sup>19,20</sup> The main side effect of alcohol or phenol neurolysis is hypoesthesia, with an incidence of 2–32%. However, it has the advantages of no immune response and lower price compared with botulinum toxin.<sup>21</sup>

Oral drug therapy, like the use of baclofen, although employed in the treatment of extensive spasm, has registered poor efficacy dotted with unpleasant side effects. This has made it unsuitable for the treatment of focal SEF. On the other hand, spasticity ( $\geq 6$  months) is often associated with muscle and tendon contracture and require tendon lengthening surgery.

Although potentially helpful, ultrasound-assisted block of the main trunk of the tibial nerve can lead to the loss of plantar sensation. Consequently, patients may lose balance, further aggravating postural and walking capabilities, increasing risks of falls. Applying selective motor branch blockade significantly reduces this risk. The precise and selective blockade of the LM of the TP muscle can clarify the role of the nerve in causing foot varus. In addition, it can provide important information in guiding the treatment of SEF. For foot varus caused by TP muscle spasticity, neu-

rolysis, or neurotomy of the motor branches of this muscle can be performed to relieve the spasticity.<sup>22</sup>

The selective blockade of the nerve branch of the TP muscle requires that it should be accurately and precisely located. This way, it can be useful in the diagnosis or treatment of spasticity arising from the TP muscle. In a study by Apaydin and coworkers, the average distance between the entry point of the nerve branch of the TP and the tip of the fibula was 7.6 cm.<sup>22</sup> In contrast, our study, in which we followed the midpoint of the motor branch of the TP muscle, obtained a much lower value (male 47.57 mm, female 51.98 mm). In another study, Picelli and colleagues used an ultrasound technique to measure the distance between the nerve branch of the TP and the tip of the fibula.<sup>4</sup> The distance of 4.3 cm which they obtained more closely approximates the result of the current study as compared to the earlier findings by Apaydin et al. However, it is important to note that in their work, Picelli and colleagues did not indicate the exact location of the motor branch of the tibial nerve. In another study, Deltombe et al applied the computed tomography (CT) coordinate system to locate the motor nerve branches of the TP muscle in adult hemiplegic patients. And their study determined the location of the motor nerve branches to the soleus and tibialis posterior muscles in relation to anatomic surface landmarks for selective motor branch blocks and neurolytic procedures. And the result shows that the mean coordinates ± standard deviation for the soleus motor branch were 10 ± 5 mm (vertical), 17 ± 9 mm (horizontal), and 30 ± 4 mm (deep); for the tibialis posterior motor branch they were 45 ± 6 mm (vertical), 17 ± 8 mm (horizontal), and 47 ± 4 mm (deep). These coordinates allowed people to perform selective motor blocks without CT scan.<sup>23</sup> Other researchers have defined the precise locations of the muscular branches and motor points of triceps surae muscles in relation to the bony landmarks.<sup>24</sup>

Deltombe and Gustin's measurement with CT found that the nerve branch of the TP muscle was located 47 ± 4 mm deep.<sup>3</sup> On the other hand, Picelli et al found a depth of the tibialis posterior motor branch was 42 ± 8 mm by using ultrasound measured.<sup>4</sup> The observations by these researchers can thus provide a suitable reference for clinical operation. The main purpose of the current study was to provide a reference for the localization of the motor branch block or neurolysis of the tibial nerve of the TP. In clinical practice, it is necessary to include the electrical stimulation technique to determine the location of the nerve. Since the thickness of superficial structures of the body surface vary greatly, the measurement of depth may also vary similarly. We, therefore, recommend using electrical stimulation during motor branch blockade of the tibial nerve to compensate for the limitations of this two-dimensional localization. Obesity has a great influence on the depth, and hence localization, of the nerve branch of this muscle. For some obese patients, the inner edge of the fibula is difficult to reach, and therefore localization using ultrasound is preferable. The findings of this study provide a basis for ultrasonic localization of the motor nerve branch of the tibial nerve that supplies the TP muscle.

Since the specimens in our study were soaked in formalin, making it difficult to obtain the height accurately, we measured and expressed the length of the fibula as a ratio. Thus, the LM, the D1, and the D2 were not related to the length of

the fibula. In our study, the average length of the LM of the TP was 35.74 mm in men and 30.40 mm in women. Injection at the midpoint of the motor branch can prevent alcohol or phenol from spreading to the main trunk of the tibial nerve. This can help avoid the negative effects of impairing sensation of the sole of the foot and the walking capabilities of the patient. This assertion, however, needs to be confirmed by further clinical research.

Our study, although providing important insights into the localization of the LM of the TP, is beset by some limitations which require consideration. First, as the cadaver specimens were soaked in formalin, the tissues may have been dehydrated and denatured; this could potentially affect the accuracy of measured values. Secondly, although great care was taken during the procedure, the removal of superficial tissue structures may still affect the position of the nerve. It is critical to retain the integrity of the tissue around the tibial nerve and minimize the impact on the position of the tibial nerve and its branches. For clinical validation, it is necessary to confirm the location of the LM of the TP by electrical stimulation; this can make up for the shortcomings of this anatomical study. Third, it is impossible to measure the depth of the motor nerve branches of the tibial nerve in the current study due to procedural limitations that required the removal of superficial tissue structures. Therefore, this study can only locate the motor branches of the tibial nerve in two dimensions.

## Conclusion

Treatment of TP spasticity using injection with botulinum toxin or neurolysis of motor branches is beset by the need for high technical skills. This study has demonstrated that it is feasible to locate the motor branch nerve of the TP whose blockade can help to relieve spasticity in the treatment of spastic equinovarus foot. Further validation of this approach should provide a clinically viable intervention in managing this condition.

## Conflicts of interest

The authors declare no conflicts of interest.

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## SYSTEMATIC REVIEW

### Tracheal intubation while wearing personal protective equipment in simulation studies: a systematic review and meta-analysis with trial-sequential analysis

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#### KEYWORDS

Direct laryngoscopy;  
Videolaryngoscopy;  
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Time to intubation;  
Success rate

#### Abstract

**Background:** Tracheal intubation in patients with coronavirus disease-19 is a high-risk procedure that should be performed with personal protective equipment (PPE). The influence of PPE on operator's performance during tracheal intubation remains unclear.

**Methods:** We conducted a systematic review and meta-analysis of simulation studies to evaluate the influence of wearing PPE as compared to standard uniform regarding time-to-intubation (TTI) and success rate. Subgroup analyses were conducted according to device used and operator's experience.

**Results:** The TTI was prolonged when wearing PPE (eight studies): Standard Mean Difference (SMD) -0.54, 95% Confidence Interval [-0.75, -0.34],  $p < 0.0001$ . Subgroup analyses according to device used showed similar findings (direct laryngoscopy, SMD -0.63 [-0.88, -0.38],  $p < 0.0001$ ; videolaryngoscopy, SMD -0.39 [-0.75, -0.02],  $p = 0.04$ ). Considering the operator's experience, non-anesthesiologists had prolonged TTI (SMD -0.75 [-0.98, -0.52],  $p < 0.0001$ ) while the analysis on anesthesiologists did not show significant differences (SMD -0.25 [-0.51, 0.01],  $p = 0.06$ ). The success rate of tracheal intubation was not influenced by PPE: Risk Ratio (RR) 1.02 [1.00, 1.04];  $p = 0.12$ ). Subgroup analyses according to device demonstrated similar results (direct laryngoscopy, RR 1.03 [0.99, 1.07],  $p = 0.15$ , videolaryngoscopy, RR 1.01 [0.98, 1.04],  $p = 0.52$ ). Wearing PPE had a trend towards negative influence on success rate in non-anesthesiologists (RR 1.05 [1.00, 1.10],  $p = 0.05$ ), but not in anesthesiologists (RR 1.00 [0.98, 1.03],  $p = 0.84$ ). Trial-sequential analyses for TTI and success rate indicated robustness of both results.

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**Conclusions:** Under simulated conditions, wearing PPE delays the TTI as compared to dressing standard uniform, with no influence on the success rate. However, certainty of evidence is very low. Performing tracheal intubation with direct laryngoscopy seems influenced to a greater extent as compared to videolaryngoscopy. Similarly, wearing PPE affects more the non-anesthesiologists subgroup as compared to anesthesiologists.

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## Introduction

At the beginning of May 2021 the coronavirus disease 2019 (COVID-19) pandemic has approached almost 165 million diagnosed cases in 191 countries/regions, causing over 3.300.000 deaths according to the data from the Center for Systems Science and Engineering at Johns Hopkins University.<sup>1</sup> It has been estimated that around 2% of patients with COVID-19 will eventually require tracheal intubation for acute respiratory failure.<sup>2</sup>

A cornerstone in the management of COVID-19 pandemic has been the use of personal protective equipment (PPE) in order to ensure adequate protection to healthcare staff. Indeed, COVID-19 is a highly contagious disease and all maneuvers spreading aerosol particles (such as tracheal intubation) are considered as high-risk procedures for contamination of healthcare personnel. During the 2003 Severe Acute Respiratory Syndrome epidemic, Loeb et al. identified the following activities at high-risk for contagion in healthcare professionals: performing and assisting for tracheal intubation, suctioning before intubation, manipulating the oxygen mask.<sup>3</sup> Such risks were subsequently confirmed by a systematic review.<sup>4</sup>

In the attempt to safely manage airways of COVID-19 patients and to minimize the risk of viral transmission, several recommendations have been issued in the course of the current pandemic.<sup>5-7</sup> Among these, experts have suggested to wear full PPE and to use a videolaryngoscope (VLS) already at the first tracheal intubation attempt, possibly using a device with distant screen in order to enable further distancing of the operators from the patient's mouth. Of note, these recommendations are mostly based on a theoretical background and on the experience acquired during present<sup>5</sup> and previous<sup>8</sup> pandemics. However, there is currently no strong evidence supporting these recommendations and it remains unclear if VLS is truly the best choice. Moreover, it remains uncertain if the use of PPE has different impact on tracheal intubation according to the operator's experience. Therefore, several aspects pertaining the approach to tracheal intubation during a pandemic need to be systematically addressed.

Whilst it seems likely that the indispensable use of PPE under hazardous conditions may render airway management more challenging due to operator's constraints, one study reported faster performance by operators wearing PPEs as compared to their results whilst dressing in standard uniform.<sup>9</sup> Moreover, several other studies showed neutral findings.<sup>10-12</sup> In light of the above considerations, we thought it was urgent to pool the results of the available evidence. Therefore, we conducted a systematic review and a meta-

analysis of simulation studies to evaluate the impact of wearing PPE as compared to standard uniform, both in term of time to intubation (TTI) and of success of the procedure, with sub-analyses conducted according to the type of device used or to the operator's experience.

## Methods

This systematic review and meta-analysis is reported in accordance with PRISMA guidelines.<sup>13</sup> A protocol was written before starting the current review but the registration with the international prospective register of systematic reviews (PROSPERO) was not feasible as the register itself does not currently consider systematic reviews and meta-analyses on simulation studies.

### Eligibility criteria

We included prospective studies conducted in simulated adult scenarios where participants with any level of experience in airway management performed tracheal intubation both under standard uniform dressing and whilst wearing any level of PPE. Regarding the simulation scenarios, we decided to include prospective simulated studies performed both on manikins or cadavers, and irrespectively of a normal or difficult airway scenario. The outcomes of interest were TTI and success rate (see Supplementary Digital Content 1 for PICOS criteria – Population, Intervention, Comparison, Outcomes, Study design).

### Exclusion criteria

Studies including a population below 10 participants were considered for sensitivity analyses only. Paediatric studies were excluded. We applied a language restriction and only articles providing an abstract and published in the English language were considered for inclusion.

### Search strategy

Two systematic independent literature searches of the electronic databases were performed through the NHS Healthcare Databases Advanced Search. We systematically searched the PubMed, MedLine, and EMBASE databases with the last update on September 3<sup>rd</sup>, 2020; the searches consisted of the combination of the MESH term "airway" with at least one term from each of two groups: 1) "simulat\*" or "manikin\*" or "mannequin\*", and 2) "protective equipment" or "CBRN" (Chemical, Biological, Radiological, and

Nuclear hazards) or “protective clothing” or “PPE” or “biohazard” or “protective gear” for the second group. A further independent manual search was performed by two authors (ST, VLR).

### Study selection and data extraction

Two pairs of assessors screened the titles and abstracts for suitability (FS, ST, VLR, PM), with a fifth assessor (MA) arbitrating any disagreements. Full text articles identified as potentially relevant were assessed against PICOS criteria. Discrepancies were resolved by consensus and/or by involving another author (MA). All the authors conducted also an independent search on PubMed to check for further evidence. Two reviewers (ST, VLR) independently extracted data from individual studies and entered information into a pre-designed data collection form, which was cross-checked by two other authors (FS, PM). If needed, we planned to contact the corresponding authors to get more data.

### Synthesis of evidence and outcomes of interest

The two primary outcomes were time-to-intubation (TTI) and success rate of the intubation procedure. These outcomes were considered for participants performing tracheal intubation wearing any type of PPE as compared to standard work dressing. In this regard, it must be noted that the level of protection offered by PPEs varies. In fact, PPEs have been classified by the Environmental Protection Agency and by the Occupational Safety and Health Administration into four levels of protection,<sup>14,15</sup> each one identified by a capital letter (A, B, C, D). The level A PPE offers the highest protection, whilst level D identifies the standard uniform (standard precautions for healthcare professionals as gloves, splash protection, etc.). Details of PPE level are provided as Supplementary Digital Content 2. For each study, we evaluated in detail the equipment worn by participants before confirming the level of PPE. Despite apparent differences in PPE levels and in the protection offered, they all increase constraints and discomfort for the operator. For such reason, and because we expected a relatively low number of prospective studies with a heterogeneous design regarding devices and operator’s experience,<sup>16</sup> we preventively decided to perform the primary analysis grouping all the PPE levels (A, B, and C) as compared to standard uniform (level D).

### Subgroup and secondary analyses

Subgroup analyses of the outcomes of interest (TTI, success rate) were conducted separating studies results according to: a) the type of device used, or b) the operator’s experience. Regarding the type of device, we divided data of participants in those performing tracheal intubation with direct laryngoscopy (DL, with or without the use of aids) or with a VLS. In case of studies where DL was performed both alone or with the use of aids (i.e., stylet, bougie), we included only the DL without use of aids. In the second subgroup analysis, we separated studies where all participants were anaesthesiologists (or anesthesiology residents) from

those where the population was mostly represented by non-anaesthesiologists. In particular, in the case of a study with a mixed population, it was classified in the subgroup of non-anaesthesiologists if the anaesthesiologists were less than 50% of the study population.

We also performed secondary analyses. As discussed, PPEs are classified into 3 levels (A, B, C). In the secondary analyses, we repeated the analyses for TTI and success rate separating studies according to the type of PPE. Thus, we performed three secondary analyses. Another secondary analysis was performed pooling together the PPE of level A and B, as we judged similar the level of discomfort/constraint caused by them (main difference is that PPE level A is fully encapsulating, while B is not).

### Statistical analysis, heterogeneity, risk of bias, quality of assessment, and publication bias

Number of participants, mean values, and standard deviation were collected for the outcome analysis of TTI. If data were reported only as median and interquartile range or confidence interval (CI), we followed the approaches suggested by Luo et al.<sup>17</sup> and Wan et al.<sup>18</sup> For the analysis of the success rate, we collected the number of attempts and the success at first attempt. A random effect model was used, the continuous outcome (TTI) and the categorical variable (success rate) differences were analyzed using the inverse variance method with a 95%CI. Values for TTI are reported as standard mean difference (SMD), while success rate is reported according to Risk Ratio (RR); *p*-values were two-tailed and considered significant if *p* < 0.05.

The presence of statistical heterogeneity was assessed using the  $\chi^2$  (Cochran Q) test. Heterogeneity was likely if  $Q > df$  (degrees of freedom) and confirmed if  $p \leq 0.10$ . Quantification of heterogeneity was performed using  $I^2$  statistic. Values of 0–24.9%, 25–49.9%, 50–74.9%, and > 75% were considered as none, low, moderate, and high heterogeneity, respectively. Meta-analysis was performed using review manager (Revman, Version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

As already performed in other meta-analyses in the field of anesthesiology,<sup>19,20</sup> we conducted trial-sequential analyses (TSAs) and assessment of the quality of evidence of our findings. In particular, we performed the TSA in order to evaluate the effect of random error and calculate the information size (the power of the meta-analysis) for the overall analyses of TTI and success rate. We used the freely-available TSA Software (Copenhagen Trial Unit’s TSA Software®; Copenhagen, Denmark). The information size was computed assuming an alpha risk of 5%, a beta risk of 20%. The estimated effects (RR and SMD) were computed averaging results of the classical meta-analysis method. Further details on TSA and its interpretation are available elsewhere.<sup>21</sup>

There were no deviations from the protocol. The risk of bias was performed using the RoB 2.0 for “*Individually-randomized, cross-over trials*”<sup>22</sup> which was deemed the most appropriate after consultation with senior statisticians. Publication bias was investigated by visual inspection of funnel plots for the primary outcomes. The quality of evidence was generated in accordance with the Grading

of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group. Using the GRADEpro online software, we performed a summary of the overall analyses in order to assess the quality and certainty of evidence for each outcome (pooled data expressed as SMD or RR).<sup>23–25</sup> The flow of references was managed with the Endnote X7 citation manager.

## Results

The two independent literature searches produced 31 titles on Medline, 48 on PubMed, and 51 on EMBASE. The PRISMA flowchart of the systematic search and qualitative synthesis is reported as Figure 1. After removal of duplicates and after screening of titles and abstracts, 17 articles were considered of interest. Six were excluded because participants performed simulated tracheal intubation wearing PPEs but not under a standard uniform (missing control group). Two other studies were excluded for not reporting the data required (we contacted twice the corresponding author without success). Therefore, we finally included 9 studies. Of these, one was a four-arm study (controls, PPE A, B, and C),<sup>10</sup> another evaluated tracheal intubation with both levels B and C PPEs as compared with controls.<sup>9</sup> Of the remaining seven studies, five compared level C PPEs to standard uniform,<sup>11,12,26–28</sup> and two involved the use of level A PPEs.<sup>29,30</sup> All studies performed tracheal intubation with DL ( $\pm$  aids), one included also attempts with a McCoy laryngoscope,<sup>30</sup> and five performed tracheal intubation with VLS(s).<sup>9,11,27,28,30</sup> As shown in Table 1, data extracted from each study included the PPE level, the type of device(s) used for tracheal intubation, operator's experience, and the outcome(s) of interest reported.

### Outcome analyses – TTI

Eight studies reported the TTI comparing simulated procedure performed both dressing standard uniform (controls) and wearing PPE.<sup>9–12,26,28–30</sup> In particular, regarding the intervention group, seven studies reported data on level C PPE, two with level B, and three level A.

The primary outcome analysis (pooling together results from all levels of PPEs) showed that tracheal intubation was significantly shorter wearing standard uniform (SMD -0.54, 95%CI [-0.75, -0.34],  $p < 0.0001$ ,  $I^2 = 69\%$ ; 19 studies, 1306 procedures; very low certainty of evidence). As shown in Fig. 2, we found no subgroup differences according to the device used for tracheal intubation, being TTI shorter with standard uniform using both DL (SMD -0.63, 95%CI [-0.88, -0.38];  $p < 0.0001$ ,  $I^2 = 69\%$ ) or VLS (SMD -0.39, 95%CI [-0.75, -0.02];  $p = 0.04$ ,  $I^2 = 72\%$ ). As shown in Supplementary Digital Content 3, when dividing subgroups according to the operator's experience, anesthesiologists had a non-significant trend towards shorter TTI whilst wearing standard uniform (SMD -0.25, 95%CI [-0.51, 0.01];  $p = 0.06$ ,  $I^2 = 72\%$ ). Conversely, in the subgroup of non-anesthesiologists (which included also Garner et al.<sup>10</sup> where 2 out of 16 participants were anesthesiologists) the TTI was significantly shorter wearing standard uniform as compared to PPE (SMD -0.75, 95%CI [-0.98, -0.52];  $p < 0.0001$ ,  $I^2 = 61\%$ ).

In order to provide more clinical sense of potential delay of intubation under the constraints of wearing PPE, we also calculated the weighted means from the groups. We found that weighted TTI was on average prolonged by 11.3 seconds when wearing PPE uniform (38.8 vs. 27.5 seconds in the standard uniform).

### Outcome analyses – success rate

Seven studies reported the success rate during simulated attempts of tracheal intubation performed by participants dressing standard uniform (controls) and wearing PPE(s).<sup>9,11,12,27–30</sup> We pooled data from five studies where participants worn level C PPE, one where they dressed level B PPE and two with level A PPE. The primary outcome analysis showed that wearing PPE did not significantly influence the success rate of tracheal intubation (RR 1.02, 95%CI [1.00, 1.04];  $p = 0.12$ ,  $I^2 = 25\%$ ; 17 studies, 1192 procedures; very low certainty of evidence; Fig. 3). This finding was valid for both the use of DL (RR 1.03, 95%CI [0.99, 1.07];  $p = 0.15$ ,  $I^2 = 49\%$ ) or VLS [(RR 1.01, 95%CI [0.98, 1.04];  $p = 0.52$ ,  $I^2 = 0\%$ )].

When the analysis was performed dividing subgroups according to the operator's experience, we found that success rate in anesthesiologists was not influenced by wearing PPEs as compared to standard uniform (RR 1.00, 95%CI [-0.98, 1.03];  $p = 0.84$ ,  $I^2 = 0\%$ ). Conversely, the subgroup of "non-anesthesiologists" had a trend towards lower success rate when wearing PPEs (RR 1.05, 95%CI [1.00, 1.10];  $p = 0.05$ ,  $I^2 = 57\%$ , Supplementary Digital Content 4).

In order to provide more clinical understanding on the impact of wearing PPE on success rate at first attempt of the intubation procedure, we calculated the weighted success rates, which was, on average, almost 5% lower when wearing PPE uniform (93.6% vs. 98.5% in the standard uniform).

### Trial-sequential analyses

The two TSA performed for the overall TTI and success rate showed similar results (Supplementary Digital Content 5 and 6, respectively). The TSA on the overall TTI crossed the trial sequential monitoring boundary, showing that meta-analysis results are well-powered. Indeed, the two-sided alpha-spending boundary according to O'Brien-Fleming method showed that the number of intubation procedures needed to be included in the meta-analysis to reach the desired level of significance and power was 148, which was passed very early by the z-curve. Therefore, the result on TTI seems very robust and unlikely to be biased.

The z-curve on the overall success crossed the futility boundary and almost reached the required sample size of 1243 procedures. This indicates that the finding of no difference in success rate between standard uniform and PEE is robust and no further studies are needed.

### Secondary analyses

Table 2 shows the results of the primary analyses on TTI and success rates together with the findings of the analyses conducted according to the level of PPE used. As the studies of

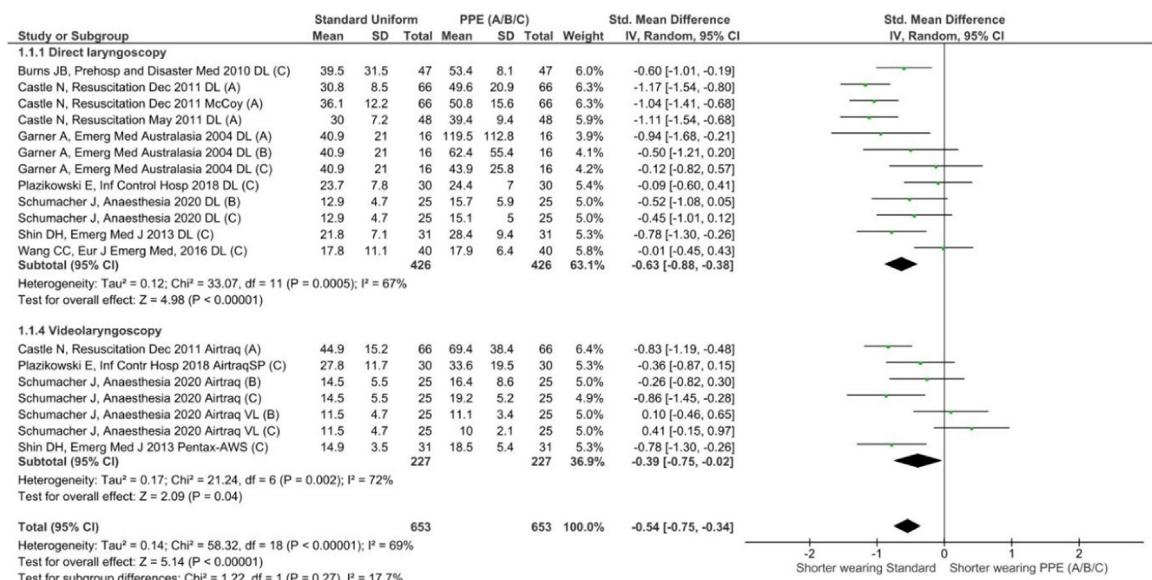


Figure 1 PRISMA flowchart.

Table 1 Characteristics of the included studies.

First Author, Year Journal	PPE(s) level	Device(s) for tracheal intubation Operator's experience	Outcome reported
Schumacher, 2020 Anaesthesia	B, C	DL; VLSs 25 Anaesthesiologists	TTI, Success rate
Plazikowski, 2018 Inf Control and Hosp	C	DL; VLS 30 Anaesthesiologists	TTI, Success rate
Taylor, 2018	C	DL; VLS	-
Am J Emerg Med		19 (15 EM residents; 4 EMS personnel)	Success rate
Wang, 2016	C	DL+stylet	TTI, Success rate
Eur J Emerg Med		40 EM residents	Success rate
Shin, 2013 Emerg Med J	C	DL+stylet; VLS 31 medical doctors passing the national boards exam	TTI, Success rate
Castle, 2011 Dec Resuscitation	A	DL, DL+stylet, DL+bougie; McCoy; VLS 66 final-year paramedic students	TTI, Success rate
Castle, 2011 May <sup>a</sup> Resuscitation	A	DL 48 final-year paramedic students	TTI, Success rate
Burns, 2010 Prehosp and Disaster Med	C	DL 47 EMS personnel	TTI
Garner, 2004 Emerg Med Australasia	A, B, C	DL 16 mixed (3 paramedics; 8 prehospital doctor; 3 EM physicians; 2 anaesthesiologists)	TTI -

DL, direct laryngoscopy; EM, emergency medicine; EMS, emergency medical service; PPE, personal protective equipment; TTI, time-to-intubation; VLS, videolaryngoscope.

<sup>a</sup> This study evaluated the tracheal intubation in four different manikin's positions. We used the values reported in the ambulance trolley (60 cm height) position and discarded results reported regarding the intubation performed lying prone, kneeling and sitting.

Schumacher et al.<sup>9</sup> and Garner et al.<sup>10</sup> compared the control group with two and three level of PPE respectively, we also conducted further post-hoc analyses of the primary outcomes considering one level of PPE only (vs. control group) for these two studies. None of these analyses changed the results.

### Risk of bias, publication bias, and quality of evidence assessment

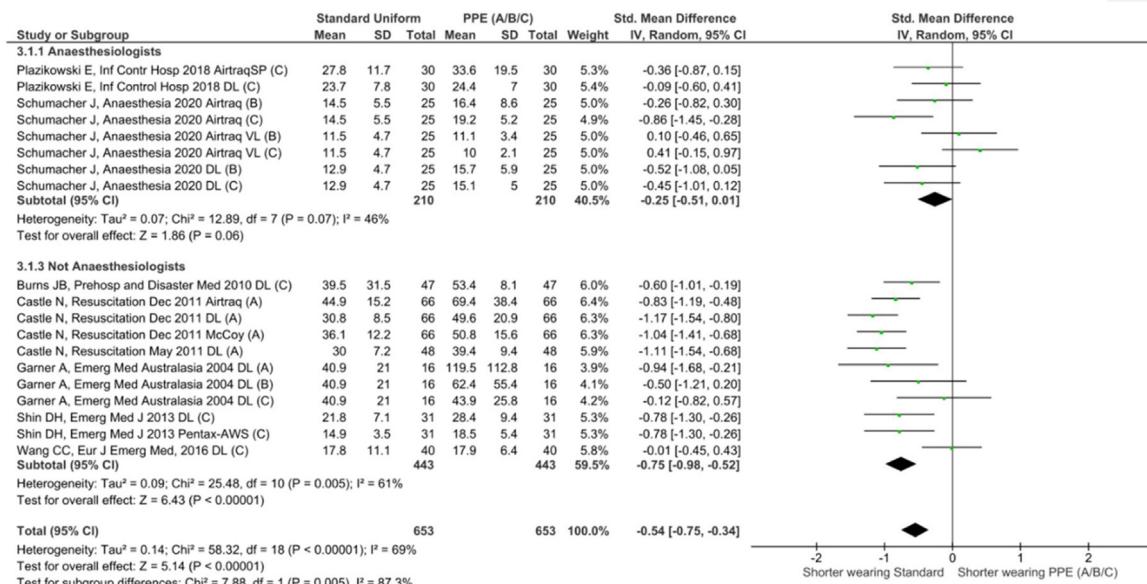
The assessment of the risk of bias performed with the RoB 2.0 showed that all studies were at high-risk (Supplementary Digital Content 7).

**Table 2** Summary of the results of the primary and secondary analyses comparing tracheal intubation wearing personal protective equipment (PPE) vs. standard uniform (control group).

Outcome and type of PPE	Overall	DL	VLS	Anesthesiologists	Non-anesthesiologists
TTI	<b>SMD -0.54 [-0.75, -0.34]</b> <i>p &lt; 0.00001; I<sup>2</sup> = 69%</i>	<b>SMD -0.63 [-0.88, -0.38]</b> <i>p &lt; 0.0001; I<sup>2</sup> = 67%</i>	<b>SMD -0.39 [-0.75, -0.02]</b> <i>p = 0.04; I<sup>2</sup> = 72%</i>	<b>SMD -0.25 [-0.51, 0.01]</b> <i>p = 0.06; I<sup>2</sup> = 46%</i>	<b>SMD -0.75 [-0.98, -0.52]</b> <i>p &lt; 0.00001; I<sup>2</sup> = 61%</i>
PPE all types (n = 19)					
TTI	<b>SMD -0.37 [-0.62, -0.12]</b> <i>p = 0.004; I<sup>2</sup> = 56%</i>	<b>SMD -0.35 [-0.61, -0.09]</b> <i>p = 0.008; I<sup>2</sup> = 37%</i>	<b>SMD -0.40 [-0.95, 0.15]</b> <i>p = 0.16; I<sup>2</sup> = 76%</i>	<b>SMD -0.27 [-0.66, 0.13]</b> <i>p = 0.19; I<sup>2</sup> = 62%</i>	<b>SMD -0.47 [-0.79, -0.15]</b> <i>p = 0.005; I<sup>2</sup> = 52%</i>
PPE C (n = 10)					
TTI	<b>SMD -0.27 [-0.56, -0.02]</b>	<b>SMD -0.51 [-0.95, -0.07]</b>	<b>SMD -0.08 [-0.47, 0.31]</b>	<b>SMD -0.22 [-0.57, 0.12]</b>	not reported as based on one study only
PPE B (n = 4)	<i>p = 0.07; I<sup>2</sup> = 0%</i>	<i>p = 0.02; I<sup>2</sup> = 0%</i>	<i>p = 0.69; I<sup>2</sup> = 0%</i>	<i>p = 0.21; I<sup>2</sup> = 14%</i>	
TTI	<b>SMD -1.03 [-1.21, -0.84]</b>	<b>SMD -1.09 [-1.31, -0.88]</b>	not reported as based on one study only	no studies on anesthesiologists	<b>SMD -1.03, [-1.21, -0.84]</b>
PPE A (n = 5)	<i>p &lt; 0.00001; I<sup>2</sup> = 0%</i>	<i>p &lt; 0.00001; I<sup>2</sup> = 0%</i>			<i>p &lt; 0.00001; I<sup>2</sup> = 0%</i>
TTI	<b>SMD -0.74 [-1.01, -0.46]</b>	<b>SMD -0.97 [-1.18, -0.76]</b>	<b>SMD -0.36 [-0.94, 0.21]</b>	<b>SMD -0.22 [-0.57, 0.12]</b>	<b>SMD -0.99 [-1.17, -0.82]</b>
PPE A/B (n = 9)	<i>p &lt; 0.00001; I<sup>2</sup> = 65%</i>	<i>p &lt; 0.00001; I<sup>2</sup> = 15%</i>	<i>p = 0.22; I<sup>2</sup> = 77%</i>	<i>p = 0.21; I<sup>2</sup> = 14%</i>	<i>p &lt; 0.00001; I<sup>2</sup> = 0%</i>
Success rate	RR 1.02 [1.00, 1.04]	RR 1.03 [0.99, 1.07]	RR 1.01 [0.98, 1.04]	RR 1.00 [0.98, 1.03]	RR 1.05 [1.00, 1.10]
PPE all types (n = 17)	<i>p = 0.12; I<sup>2</sup> = 25%</i>	<i>p = 0.15; I<sup>2</sup> = 49%</i>	<i>p = 0.52; I<sup>2</sup> = 0%</i>	<i>p = 0.84; I<sup>2</sup> = 0%</i>	<i>p = 0.05; I<sup>2</sup> = 57%</i>
Success rate	RR 1.01 [0.98, 1.04]	RR 1.01 [0.97, 1.05]	RR 1.02 [0.97, 1.06]	RR 1.00 [0.97, 1.04]	RR 1.04 [0.97, 1.11]
PPE C (n = 10)	<i>p = 0.43; I<sup>2</sup> = 0%</i>	<i>p = 0.59; I<sup>2</sup> = 0%</i>	<i>p = 0.52; I<sup>2</sup> = 21%</i>	<i>p = 0.79; I<sup>2</sup> = 0%</i>	<i>p = 0.28; I<sup>2</sup> = 44%</i>
Success rate	RR 1.00 [0.96, 1.04]	not reported as based on one study only	RR 1.00 [0.95, 1.06]	RR 1.00 [0.96, 1.04]	no studies on non-anesthesiologists
PPE B (n = 3)	<i>p = 1.00; I<sup>2</sup> = 0%</i>		<i>p = 1.00; I<sup>2</sup> = 0%</i>	<i>p = 1.00; I<sup>2</sup> = 0%</i>	
Success rate	RR 1.06 [0.98, 1.15]	RR 1.07 [0.96, 1.20]	not reported as based on one study only	no studies on anesthesiologists	RR 1.06 [0.99, 1.14]
PPE A (n = 4)	<i>p = 0.15; I<sup>2</sup> = 73%</i>	<i>p = 0.20; I<sup>2</sup> = 82%</i>			<i>p = 0.09; I<sup>2</sup> = 71%</i>
Success rate	RR 1.03 [0.99, 1.08]	RR 1.05 [0.97, 1.14]	RR 1.01 [0.96, 1.06]	RR 1.00 [0.96, 1.04]	RR 1.06 [0.99, 1.14]
PPE A/B (n = 7)	<i>p = 0.19; I<sup>2</sup> = 53%</i>	<i>p = 0.21; I<sup>2</sup> = 75%</i>	<i>p = 0.75; I<sup>2</sup> = 0%</i>	<i>p = 1.00; I<sup>2</sup> = 0%</i>	<i>p = 0.09; I<sup>2</sup> = 71%</i>

Results of Time-To-Intubation (TTI) are reported as Standardized Mean Difference (SMD, with in square brackets the 95% confidence interval), followed by *p*- value and statistical heterogeneity ( $I^2$ ). Results of success rate are reported as Risk Ratio (RR, with in square brackets the 95% confidence interval), with *p*-value and statistical heterogeneity ( $I^2$ ). Results are in bold font if statistically significant. Results with a trend towards statistically significant finding are indicated in italic font.

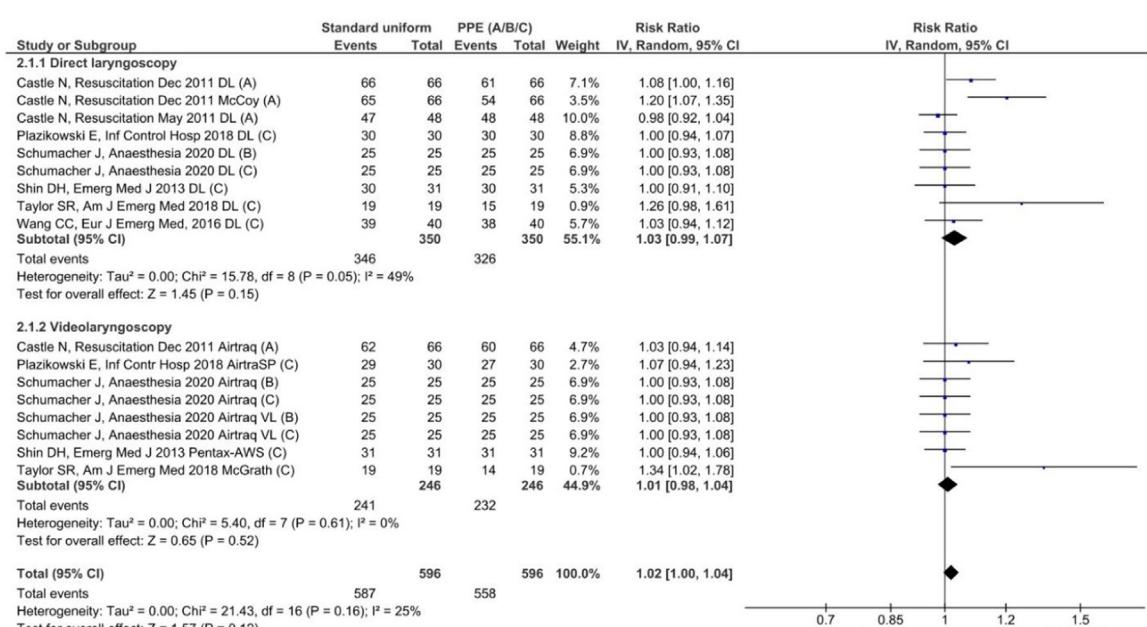
DL: direct laryngoscopy; VLS: videolaryngoscope.



**Figure 2** Forest plot comparing the Time to Intubation wearing standard uniform as compared with personal protective equipment (PPE) of level A, B, or C. Subgroups are divided according to the type of device used for the tracheal intubation.

CI, confidence interval; DL, direct laryngoscopy; IV, inverse variance; SD, standard deviation; VLS, videolaryngoscopy.

For each study, we indicated the first author, the journal and year of publication, the type of device used for tracheal intubation, and the level of PPE worn (in brackets).



We investigated publication bias by visual inspection of funnel plots for the primary outcomes (Supplementary Digital Content 8). We found no evidence of publication bias

regarding the TTI outcome. The success rate included a total of seventeen comparisons, with ten of them reporting a RR value of 1.00 and similar sample size. Therefore, several

studies had an overlap on the funnel plot. Only one comparison of the three reported by Castle et al.<sup>30</sup> behaved as outlier (RR = 1.20, intubation with McCoy DL). Its exclusion did not change the overall and the subgroups' results.

Quality of evidence generated in accordance with the GRADE Working Group resulted *very low* for both outcomes (Table 3), suffering from the high-risk of bias in the included studies and the indirectness of the simulation scenarios.

## Discussion

We conducted a systematic review and meta-analysis with the aim of investigating whether performing tracheal intubation under the constraints of wearing PPE may worsen the operator's performance, both in terms of TTI and success rate. The most important finding of our meta-analysis is that wearing PPE significantly prolonged the TTI without affecting the overall success rate of tracheal intubation as compared with standard uniform. The two TSAs showed that both analyses reached the appropriate information size. Therefore, wearing PPE prolongs the TTI without worsening the success rate of intubation with no further research required to confirm these findings. However, the high risk of bias in the included studies, the inconsistency due to the different level of experience in airway management across studies' participants and the indirectness of findings due to the simulation environment contributed to the very low certainty of evidence for the two primary outcomes as assessed with the GRADEpro software. The larger effect size found for TTI allowed an upgrade of certainty of evidence.

From a clinical perspective, as the use of SMD and the RR are not entirely intuitive in describing to what extent PPE hinders tracheal intubation, we calculated the weighted means of TTI and success rate. On average, we found that PPE increased the TTI of about 11 seconds, whilst decreasing 5% the probability of success at first attempt. As guaranteeing the operators' safety during intubation is certainly of utmost importance, our meta-analysis numerically supports that wearing PPE has a mild clinical impact on intubation practice.

We also performed subgroup analyses according to the device used for tracheal intubation or to the operator's experience. The first subgroup analysis (taking into account the type of device used) confirmed that wearing PPE increases the TTI regardless of the device used. However, the delay in achieving tracheal intubation was longer using DL as compared with VLS (see values of SMD and relative 95%CI – weighted means around 13 s for DL and 9 s for VL). The success rate was not different between subgroups.

The other subgroup analysis was performed considering the experience in airway management. In this analysis, the TTI was significantly prolonged in operators with lower experience in airway management, whilst the impact on anesthesiologists did not reach a statistically significant result ( $p = 0.06$ ). Regarding the success rate at first attempt, wearing PPE did not influence the performance of anesthesiologists, whilst a trend towards lower success rate in non-anesthesiologists was noted ( $p = 0.05$ ).

Noteworthy, one should keep in mind that, among several limitations of pooling evidence from simulated scenarios, the included studies were not set up for difficult intubation.

This setting deserves further investigations as, theoretically, the constraints of wearing PPE may further worsen performances in difficult airway scenarios. Nonetheless, despite these and other limitations (see dedicated paragraph), our meta-analysis provides some support to the current (and possibly future) guidelines developed on the airway management in highly hazardous conditions,<sup>5–7</sup> such as in COVID-19 patients. Current guidelines suggest that tracheal intubation procedure should be performed from the beginning with a VLS, also suggesting the use a VLS equipped with a distant screen to enable greater distance between the operator's face and the patient's mouth. As we did not find enough studies evaluating the use of VLS with distant screen, we could not investigate if this type of VLS offers better performances as compared to VLS with "screen-on-blade". Indeed, there was a large heterogeneity regarding the devices for tracheal intubation in the included simulation studies. Therefore, a quantitative analysis comparing the performances of each device was not reasonable, and we rather pooled studies in broad subgroups according to the type of device (DL or VLS). This results in a certain degree of clinical heterogeneity as in the subgroup DL were also included procedures performed with the aid of a stylet,<sup>12,28</sup> as well as results obtained with the use of McCoy blade.<sup>30</sup> Similarly, we included in the VLS subgroup both studies performed with the device with screen attached (Pentax AWS<sup>28</sup> and Airtraq VL<sup>9</sup>) or distant from the blade (Airtraq VL<sup>9</sup>). We acknowledge the heterogeneity of pooling together different levels of PPE, but this choice was justified by the expected (and confirmed) relatively low number of studies.

Though some analyses were not feasible due to the low number of studies, in the attempt to look for difference between PPE levels, we performed secondary analyses in this regard confirming the results of the primary outcomes. In particular, wearing PPE delays the TTI but does not affect the overall success rate of tracheal intubation. Moreover, the findings of subgroup analyses also seemed similar, with greater delay when tracheal intubation is performed with DL or by less experienced operators (non-anesthesiologists).

Of note, we excluded one study where the participants (anesthesiology consultants and residents) performed tracheal intubation with DL wearing various PPEs but the study did not include a control group (lower level of protection was equivalent to PPE level C<sup>31</sup>).

## Limitations

Our meta-analysis has several limitations. First, the studies presented heterogeneity in the definition of TTI, and the chronometer count did not have the same start-point for all the studies. Moreover, not all studies were clear on the TTI calculation in case of failure. In such instance, authors have two main options: 1) calculate the TTI averaging only the time taken for successful intubations, or 2) also counting the time for failed procedures attributing a "failure time" (pre-established cut-off) for each failed procedure. In other words, some studies explicitly reported in their design a predefined cut-off time to declare a failed tracheal intubation attempt (i.e., 120 seconds). In these cases, authors may have either counted the cut-off time for each failed attempt, or rather discarded the case. As in most cases

**Table 3** Evaluation of quality of evidence according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group.

Does wearing PPE compared to standard uniform influence the operator's performances during tracheal intubation? <b>Patient or population:</b> Operators performing tracheal intubation <b>Intervention:</b> Wearing PPE					<b>Setting:</b> Simulation studies <b>Comparison:</b> Wearing standard uniform
Outcomes	Difference wearing PPE as compared to standard uniform	Relative effect (95% CI)	N. of participants (studies)	Certainty of the evidence (GRADE)	Comments
Time to intubation	SMD 0.54 SD lower (0.75 lower to 0.34 lower)	-	1306 (19 RCTs)	⊕○○○ VERY LOW <sup>a,b,c</sup>	Quality of evidence was downgraded because the high-risk bias in included studies, the inconsistency due to the different level of experience in airway management across studies' participants, and the indirectness of findings due to the simulation environment. Result of the trial sequential analysis shows that the meta-analysis is well-powered.
Success rate	19 more per 1.000	RR 1.02 (1.00 to 1.04)	1192 (17 RCTs)	⊕○○○ VERY LOW <sup>a,b,c</sup>	Quality of evidence was downgraded because the high-risk bias in included studies, the inconsistency due to the different level of experience in airway management across studies' participants, and the indirectness of findings due to the simulation environment. Result of the trial sequential analysis shows that the meta-analysis is well-powered.

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; SMD, standardised mean difference; RR, risk ratio.

<sup>a</sup> As per RoB 2.0.

<sup>b</sup> Different levels of operator's experience.

<sup>c</sup> Findings are from simulation studies.

authors were unclear in this regard, we preferred to use the overall number of participants for the calculation of the TTI. Since the success rates were similar between groups, we think that it is unlikely that the analysis was significantly biased by this reporting issue.

Second, the validity of subgroup analyses according to the operator experience is probably limited. Indeed, the group of anesthesiologists consisted of 55 participants only, whilst the experience in the remaining non-anesthesiologist participants was highly variable. Moreover, the between-study heterogeneity cannot be fully corrected using a random-effects analysis. In this regard, one way to investigate the influence of factors contributing to the variability of study findings would have been to perform a meta-regression analysis accounting for operator experience (anesthesiologist or non-anesthesiologist), type of model for performing intubation (manikin or cadaver), positioning of the operator (lying or in upright position), and possibly others. We unfortunately don't have the required skills to perform such advanced analysis and lack of meta-regression analysis is one limitation of our study.

Third, we investigated simulation studies and the included studies cannot account for all the human factors involved in the airways management of patients with highly infectious diseases, such as COVID-19. Indeed, while some factors are potentially accounted also in simulation studies as related to the uniform itself, other issues that may influence the operator performance (such as the fear of self-contamination with a highly infectious disease)<sup>32,33</sup> are probably not well-replicated by simulation environment. Moreover, in a computed tomography study, Schebesta et al. showed that manikins do not fully reflect the upper airways anatomy of actual patients.<sup>34</sup> Therefore, the generalizability of our findings and those of all manikin studies is certainly limited.

Fourth, from a statistical perspective, the decision to pool together the studies regardless the level of PPE was dictated by the expectation of a low number of studies.<sup>35</sup> This means that for the two studies exploring more than one level of PPE,<sup>9,10</sup> the performances of tracheal intubation with each PPE level were plotted against the same control group. However, post-hoc analyses ruled out this issue.

Fifth, we found some difficulties in finding the best scale of evaluation for the risk of bias. After consultation with a senior statistician, we agreed that the ROB 2.0 for "Individually-randomized, cross-over trials" was the most appropriate.

## Conclusion

In conclusion, under simulated conditions, wearing PPE prolongs the time to achieve successful tracheal intubation as compared to dressing in standard uniform, without influence on the success rate of the procedure. The influence of wearing PPE seems greater when performing tracheal intubation with DL as compared with VLS. The performance of anesthesiologists seem less influenced than of non-anesthesiologists. Although, the overall analyses are well-powered according to the TSA, the strength of our findings is heavily weakened by the high risk of bias in the included studies and the very low/low certainty of evidence

found in the GRADE assessment. The clinical impact of our meta-analysis is weakened by the variability in the included studies regarding providers, PPE used, operator experience, and by the indirectness of findings due to the simulation setting.

The PRISMA checklist is provided as supplementary material.

## Conflicts of interest

The authors declare no conflicts of interest.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.bjane.2021.08.017>.

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**SHORT COMMUNICATION**

**A cross-sectional study analyzing the quality of YouTube videos as a source of information for COVID-19 intubation**

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Airway management;  
COVID-19;  
Coronavirus;  
Hand washing;  
Intubation

**Abstract**

**Introduction:** There are many possible sources of medical information; however, the quality of the information varies. Poor quality or inaccurate resources may be harmful if they are trusted by providers. This study aimed to analyze the quality of coronavirus disease 2019 (COVID-19)-related intubation videos on YouTube.

**Methods:** The term “COVID-19 intubation” was searched on YouTube. The top 100 videos retrieved were sorted by relevance and 37 videos were included. The video demographics were recorded. The quality of the videos was analyzed using an 18-point checklist, which was designed for evaluating COVID-19 intubation. Videos were also evaluated using general video quality scores and the modified Journal of the American Medical Association score.

**Results:** The educational quality was graded as good for eight (21.6%) videos, moderate for 13 (35.1%) videos, and poor for 16 (43.2%) videos. The median safe COVID-19 intubation score (SCIS) was 11 (IQR = 5–13). The SCISs indicated that videos prepared in an intensive care unit were higher in quality than videos from other sources ( $p < 0.05$ ). The length of the video was predictive of quality (area under the curve = 0.802, 95% CI = 0.658–0.945,  $p = 0.10$ ).

**Conclusions:** The quality of YouTube videos for COVID-19 intubation is substandard. Poor quality videos may provide inaccurate knowledge to viewers and potentially cause harm.

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YouTube ([www.youtube.com](http://www.youtube.com)) is the second most visited website in the world behind Google.<sup>1</sup> Free and easy access to YouTube makes it one of the most popular sources of information. Considering its popularity and easy accessibility,

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YouTube offers invaluable opportunities for dissemination of medical information. However, the quality of unfiltered information may be unscientific, misleading, or even harmful.<sup>2,3</sup> Intubation in a patient with COVID-19 carries a high risk to healthcare providers because of the highly contagious nature of the disease, which is transmitted by droplets or aerosols. Although there are some videos on YouTube about COVID-19 intubation, the quality of these videos has not been evaluated. We therefore aimed to assess the quality of COVID-19 intubation videos that are accessible on YouTube.

The term “COVID-19 intubation” was searched on YouTube on May 9, 2020. The only search filter used was the “sort by” filter of “relevance”, which is the default filter for a typical YouTube search. Using methods previously described, on the assumption that it is rare for users to go beyond the first 100 videos for a specific search term, only the first 100 videos were evaluated.<sup>2</sup> The search was performed using a cleared-cache web browser that consists of the most current version of Google Chrome in incognito mode with all available updates enabled. The main researcher prescreened the top 100 videos and created a watch list. First, two of the researchers (BA, TS) independently reviewed and scored the videos, then a third researcher (OC) reviewed and resolved any final discrepancies between the first two researchers. Only videos in English (or with comments or subtitles in the English language) were included, as English is a global language. Duplicates and irrelevant videos were excluded. Videos without a demonstration of intubation or that were unrelated to COVID-19 were also excluded. Videos that met the study criteria were assessed in terms of video length, total number of views, days online, daily views, likes, dislikes, upload source, video recording place, general video quality, JAMA, and COVID-19 intubation score. The upload source was classified as an intensive care unit, an emergency room, or an operating room. When the upload source could not be determined, it was classified as “other”. Approval by the Institutional Review Board for this report was unnecessary because only publicly accessible data were used.

There were no validated evaluation tools available to assess online information regarding COVID-19 patients’ intubation. Thus, to determine the educational quality of video content, the authors BA and TS created a novel 18-point Safe COVID-19 Intubation Score (SCIS) based on a recently published clinical consensus statement and current recommendations.<sup>4,5</sup> The SCIS consists of 18 items including preparation, equipment, number of staff members, prevention measures, and precautions related to COVID-19 intubation recommendations. One point was assigned for each item fulfilled resulting in a maximum possible score of 18 points (Table 1). The quality of videos was graded based on the SCIS as (1) good, if SCIS > 13; (2) moderate, if SCIS 13 ≤ but > 7; and (3) poor, if SCIS ≤ 7. The reliability of the videos was assessed using the modified JAMA benchmark criteria.<sup>6</sup> The JAMA benchmark assesses the reliability of online knowledge based on four parameters: authorship, attribution, disclosure, and currency. One point is given for each parameter. Four points indicate the information with the highest quality.

To evaluate the general video quality, the authors used a variation of the parameters defined in the Evaluation of the

**Table 1** Safe COVID-19 Intubation Score.

1. Hand hygiene
2. Double gloves
3. Goggles or face shield
4. N95 respirator or powered air-purifying respirator device
5. Gown
6. Most experienced/skilled intubator to perform the intubation
7. Number of healthcare providers in the room
8. Drugs
9. Avoidance of aerosolization
10. Plan for difficult intubation and ventilation
11. Plan for rapid sequence induction
12. Preoxygenation with 100% oxygen
13. Use of a high-efficiency hydrophobic filter
14. Use of videolaryngoscope
15. Inflation cuff before ventilation
16. Clamping the endotracheal tube
17. Confirmation of the correct position of the tracheal tube
18. Doffing of personal protective equipment

Video Media Guidelines. This tool consists of four sections (content, production, users, and presentation free of bias). The authors chose only the first three for the current study. These sections were previously used in another similar study.<sup>7</sup> Each parameter was evaluated with a Likert-type scale from 0–5: 0 = does not apply; 1 = very unsatisfying; 2 = unsatisfying; 3 = regular; 4 = satisfying; and 5 = very satisfying. Therefore, each video could reach a maximum score of 70.

Data were analyzed using IBM SPSS statistics version 21.0 software (IBM Co., Armonk, NY, USA). The data distribution was assessed using a Shapiro-Wilk test. Numerical variables are presented as median values (IQR interquartile ratios) and categorical variables are reported as frequencies. Pairwise group comparison of numeric variables was performed by using Mann-Whitney U tests, while Kruskal-Wallis tests were used for comparisons of three or more groups. Categorical data were analyzed using Fisher’s exact test. Spearman’s rho correlation test was used to assess the correlation between the parameters. Interrater reliability (IRR) was separately calculated for the SCIS using Cohen’s kappa coefficient ( $\kappa$ ). Kappa values were interpreted according to criteria defined by Landis and Koch.<sup>8</sup> The cutoff points were obtained by evaluating the best Youden index (sensitivity + specificity – 1) and the maximum area under the receiver operating characteristic (ROC) curve. A  $p$ -value < 0.05 was considered significant.

Among the 100 videos identified, irrelevant videos ( $n = 50$ ), duplicates ( $n = 9$ ), and non-English-language videos ( $n = 4$ ) were excluded. A total of 37 videos were included in the study (available at <http://dx.doi.org/10.17632/5nd4bv3dpk.2>). The median video length was 5:31 minutes (IQR = 3:22–5:08). The median number of views was 2,734 (IQR = 730–20,377) and the median number of likes was 28 (IQR = 10–108). Of the videos included in the analysis, the first was uploaded on February 25, 2020, while the most recent was uploaded on April 19, 2020.

Regarding the SCIS, the median score was 11 (IQR = 5–13). The IRR was calculated for SCIS’ parameters. The

**Table 2** Analysis of the content covered in 37 YouTube videos about safe COVID-19 intubation.

Categories	Total (n = 37), n (%)	Operation room (n = 8), n (%)	Intensive care unit (n = 12), n (%)	Emergency room (n = 6), n (%)	Others (n = 11), n (%)
Hand hygiene	6 (16.2)	2 (25)	4 (66.7)	0 (0)	0 (0)
Double gloves	9 (24.3)	3 (37.5)	6 (50)	0 (0)	0 (0)
Goggles or face shield	26 (70.3)	8 (100)	11 (91.7)	1 (16.7)	6 (54.5)
N95 respirator or powered air-purifying respirator device	25 (67.6)	8 (100)	11 (91.7)	1 (16.7)	5 (45.5)
Gown	28 (75.7)	8 (100)	11 (91.7)	3 (50)	6 (54.5)
Most experienced intubator to perform the intubation	11 (29.7)	2 (25)	8 (66.7)	1 (16.7)	0 (0)
Number of healthcare providers	17 (45.9)	5 (62.5)	9 (75)	1 (16.7)	2 (18.2)
Drugs	20 (54.1)	7 (87.5)	11 (91.7)	0 (0)	2 (18.2)
Avoidance of aerosolization	16 (43.2)	3 (37.5)	10 (83.3)	3 (50)	0 (0)
Plan for difficult intubation and ventilation	14 (37.8)	3 (37.5)	8 (66.7)	1 (16.7)	2 (18.2)
Rapid sequence induction	16 (43.2)	5 (62.5)	9 (75)	1 (16.7)	1 (9.1)
Preoxygenation with 100% oxygen	26 (70.3)	7 (87.5)	11 (91.7)	2 (33.3)	6 (54.5)
Use of high-efficiency hydrophobic filter	30 (81.1)	8 (100)	9 (75)	5 (83.3)	8 (72.7)
Use of videolaryngoscope	30 (81.1)	8 (100)	10 (83.3)	5 (83.3)	7 (63.6)
Inflation cuff before ventilation	31 (83.8)	8 (100)	11 (91.7)	5 (83.3)	7 (63.6)
Clamping of the endotracheal tube	8 (21.6)	2 (25)	4 (33.3)	1 (16.7)	1 (9.1)
Confirmation of the correct position of the tracheal tube	22 (59.5)	5 (62.5)	12 (100)	1 (16.7)	4 (36.4)
Doffing personal protective equipment	4 (10.8)	2 (25)	2 (16.7)	0 (0)	0 (0)

kappa scores were between 0.81 and 1.00 (perfect agreement) for 10 parameters, between 0.61 and 0.80 (substantial agreement) for six parameters, and between 0.41 and 0.60 (moderate agreement) for two parameters. The highest and lowest kappa scores were 1.00 and 0.54 respectively for SCISs. Of the 37 videos, 31 (83.8%) mentioned cuff inflation before ventilation. Thirty videos (81.1%) demonstrated the use of high-efficiency hydrophobic and video laryngoscopes (Table 2). The majority of videos mentioned the need for goggles (or face shields), an N95 respirator (or powered air-purifying respirator device), and clothing. Hand hygiene, use of double gloves, and doffing of personal protective equipment (PPE) were covered in fewer than one-third of the videos. According to the SCIS, 8 videos (21.6%) were graded as good, 13 (35.1%) as moderate, and 16 (43.2%) as poor. There was no statistically significant difference in the number of views ( $p = 0.22$ ), daily views ( $p = 0.20$ ), likes ( $p = 0.23$ ), or the number of days online ( $p = 0.81$ ) between those graded as good, moderate, and poor quality. The only variable that showed a significant difference was the length of the video ( $p = 0.005$ ). ROC analysis showed that video duration could predict a good-quality video (area under the curve = 0.802, 95% CI = 0.658–0.945,  $p = 0.10$ ). The cutoff value for predicting good quality was 5:50 minutes. This value had a sensitivity of 87.5%, and a specificity of 65.5%, for predicting good quality.

The SCIS positively correlated with the general video quality score, JAMA score, and length of the videos ( $\rho = 0.875$ ,  $p < 0.001$ ;  $\rho = 0.552$ ,  $p < 0.001$ ;  $\rho = 0.508$ ,  $p = 0.001$ , respectively). The recording location of the video was an intensive care unit for 12 (32.4%) videos, an operation room for eight (21.6%) videos, an emergency room for six (16.2%) videos, and other places for 11 (29.7%) videos. The SCIS and general video quality scores were significantly higher for

intensive care unit-based videos than for the other videos ( $p < 0.05$ ).

The main finding of this study was that YouTube videos do not provide sufficient, and comprehensive educational information for COVID-19 intubation. Poor results were found twice as often as good results in terms of SCIS. More importantly, hand hygiene, double gloving, and doffing (16.2%, 24.3%, 10.8% of videos, respectively) – which are key steps to preventing contamination – were demonstrated only in a limited number of videos. The median SCIS of the videos was 11, which also shows low-quality. Our findings are consistent with the results of previous studies. Keelan et al. first analyzed the content of YouTube-related immunization videos and found low-quality scores for various medical conditions.<sup>3</sup> A report evaluating the quality of regional anesthesia videos found that half of the videos were of poor quality in relation to the procedure technique.<sup>9</sup> Similarly, a study on the brachial plexus also showed low-quality scores.<sup>7</sup> Umut et al. recently assessed endotracheal intubation videos on YouTube using their specific intubation score system, which included 15 items. They reported a mean score of 4.6/15 ( $\pm 2.7$ ) among videos posted by academics.<sup>10</sup>

The study demonstrates that most of the videos related to COVID-19 intubation on YouTube is of poor quality, as many omit key steps to prevent COVID-19 transmission during procedure. Also, there was no correlation between the number of views and the quality of the content. As such, many viewers may obtain information from low-quality materials.

## Conflicts of interest

The authors declare no conflicts of interest.

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**CLINICAL IMAGES**

**Dilated esophagus on a preoperative chest radiograph:  
an easily missed risk factor for aspiration**



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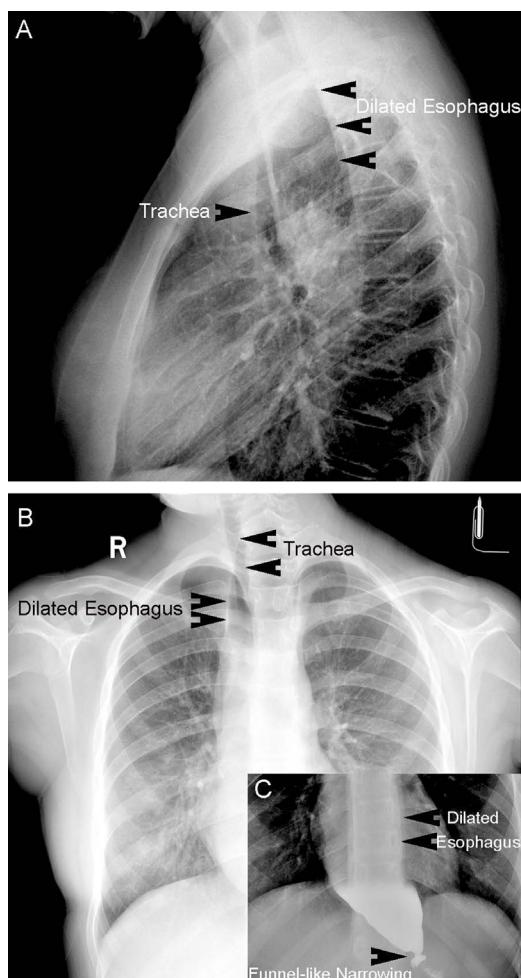
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Chest radiography, used as a preoperative screening tool for COVID-19 in high-risk children during the COVID-19 pandemic,<sup>1</sup> is relatively less sensitive for detecting esophageal anomalies due to the lack of contrast observed when the esophagus is empty and close. The images from a girl for tonsillectomy revealed an abnormal distension of the esophagus, indicating a potential narrowing of the lower esophagus prompting further examination (Fig. 1A-B). However, the diagnosis of dilated esophagus was initially overlooked due to no specific clinical manifestations. Reflux and aspiration during anesthesia induction were observed. Esophageal achalasia, a rare disease in children,<sup>2</sup> was post-operatively diagnosed (Fig. 1C).

Emptying of the esophagus prior to intervention is essential to prevent aspiration during anesthesia induction in patients with esophageal achalasia.<sup>3</sup> Diagnosis of esophageal achalasia may easily be missed if symptoms are not evaluated by well-trained clinicians. Furthermore, the gas-filled esophagus shaded in the mediastinum can be neglected on chest radiograph if unsuspected, particularly in the postero-anterior view. Normally, gas-like low density in the mediastinum is only found in the trachea on chest radiograph. It is important for an anesthesiologist to understand the various differential diagnoses on a chest radiograph if another gas-like density in the mediastinum is seen.

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**Figure 1** A, Lateral view shows abnormal dilated esophagus with air (arrow) behind the trachea in the posterior mediastinum; B, Postero-anterior view shows an easily - missed distension of the esophagus (arrow) in the upper mediastinum and lower esophagus is covered by heart and great vessels; C, Upper gastrointestinal radiography using iohexol on postoperative day 1 shows distal funnel-like narrowing and proximal dilation of the esophagus.

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**CLINICAL IMAGES**

**Ulcer due to prolonged use of high-flow nasal oxygen**

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The prolonged administration of high-flow nasal oxygen (HFNO) can create friction between the nose and the cannula. This causes trauma to the skin and can lead to the formation of ulcers. Continuing the Coronavirus disease-2019 (COVID-19) pandemic, patients may require prolonged usage of HFNO therapy. It is noninvasive, simple to use (needing a fraction of inspired oxygen [ $\text{FiO}_2$ ] and flow setting only), and delivers heated and humidified oxygen. It is also beneficial for patients since people who receive HFNO therapy are awake and can speak, eat, and drink.<sup>1</sup> Generally, it does not have to be interrupted or discontinued as a result of intolerance. But it can also lead to pressure ulcers, if used for a prolonged period (Fig. 1). The first patient received HFNO therapy with  $\text{FiO}_2$  of 90–100% and 60 liters per minute flow for 11 days. The second patient received HFNO therapy with  $\text{FiO}_2$  of 100% and 70 liters per minute flow for nine days. Sterile dressings were applied to the ulcer, and good hygiene was maintained. In the next couple of days, the ulcer showed healing.

It is advised to observe frequently for the occurrence of these ulcers during HFNO therapy. If ulcers develop, one should avoid infection by applying the sterile dressing, maintaining good hygiene, proper caring for wounds, managing discomfort, and ensuring adequate nutrition.



**Figure 1** Arrows show ulcers due to prolonged use of high flow nasal oxygen in COVID-19 patients.

**Conflicts of interest**

The authors declare no conflicts of interest.

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## LETTER TO THE EDITOR

### A converted spray device for topical pharyngeal anesthesia in awake intubation



Dear editor,

Ankylosing Spondylitis (AS) is a common inflammatory arthritis with progressive reduced spinal mobility.<sup>1</sup> Difficult airway exists in those patients with restricted neck movement, in which scenario awake intubation before anesthesia induction is suggested. Adequate topical anesthesia of oropharyngeal/nasopharyngeal and subglottic tracheal mucosa is required for airway instrumentation and patient comfort during this procedure.

Traditional device for topical pharyngeal anesthesia, like laryngotracheal topical anesthesia kit, is widespread but its effectiveness is not always ideal. Other techniques are soon proposed, for example, both ultrasonic nebulization and spray-as-you-go techniques provide acceptable conditions for awake intubation.<sup>2</sup> However, ultrasonic nebulizer is time consuming (usually needs 10–15 min) and spray-as-you-go technique is perceived difficult. Ultrasound-guided superior laryngeal nerve block is a hot topic, but it is invasive and required bilateral block.<sup>3</sup> Here we reported our successful experience for awake intubation through a new spray device easily converted from a spray bottle and oxygen delivery device. This converted spray device was consisted of three main parts, i.e., a glass bottle with a special spray nozzle, a simple humidifier, and a pipe for oxygen delivery (Fig. 1).

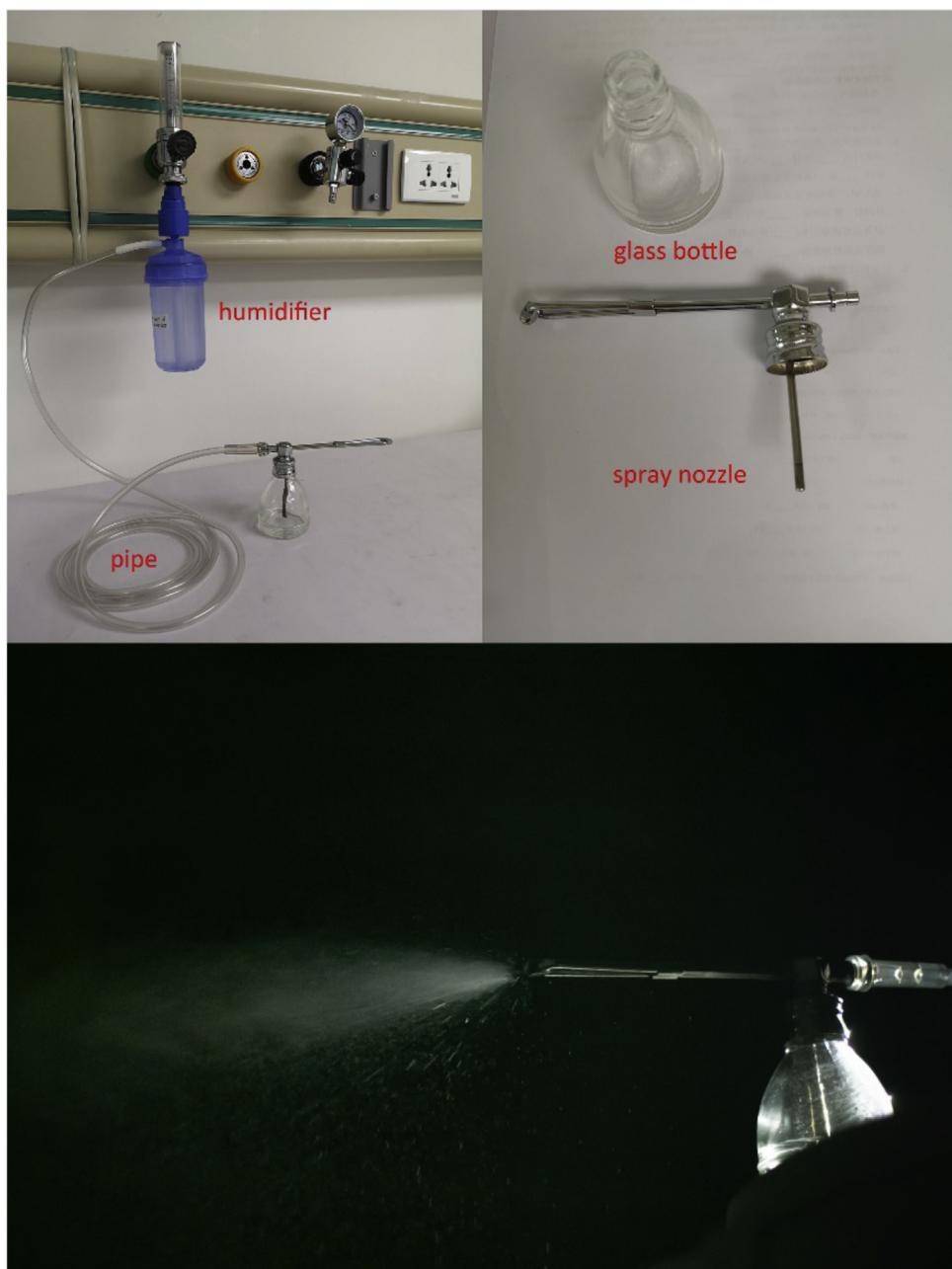
From October 8, 2020 to November 30, 2020, 5 patients aged 29–49 years, diagnosed with AS undergoing spinal deformity surgery received the awake intubation. After intravenous cannula insertion, patients were connected to routine monitors and received supplemental oxygen ( $5\text{ L} \cdot \text{min}^{-1}$ ) via ventilation mask. Intravenous sedation consisted of  $0.8\text{--}1\text{ }\mu\text{g} \cdot \text{kg}^{-1}$  dexmedetomidine with remifentanil infusion (target effect-site concentration  $0.5\text{--}1.5\text{ ng} \cdot \text{mL}^{-1}$ ) to keep the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score between 3 to 5.<sup>4</sup>

About 10 minutes after administering dexmedetomidine, we used this converted spray device driven by oxygen

( $5\text{ L} \cdot \text{min}^{-1}$ ) to anesthetize pharyngeal mucosa (Fig. 1). We firstly instructed the patient to open their mouth loudly, stick out their tongue as far as possible and sprayed 1% tetracaine solution into oropharynx for 3–5 seconds, then we sprayed the tetracaine solution into nasopharynx when they took a deep breath for 2–3 seconds bilaterally as well. Two minutes later, we repeated these steps. Another 1 minute later, we used a 5-mL syringe for thyrocricocentesis after identifying the cricothyroid membrane by landmark palpation and sterilizing the local area, 3 mL 2% lidocaine was given for subglottic tracheal mucosa anesthesia once the tip of needle located in the trachea, as signaled by a sudden loss of resistance and freely air withdrawing.

We performed awake intubation by flexible fiberscope with the endotracheal tube in-situ through the most patent nostril. After passing through the choana and identifying the epiglottis and glottis, the fiberscope was moved slowly into the trachea until the tracheal carina was visualized. Then the endotracheal tube was railroaded through the flexible fiberscope into the trachea. After reconfirming the position of the tube by mainstream capnograph, the cuff was inflated. During the procedure, glottis opening was fine when the fiberscope advanced into the glottis and trachea, and no intolerance symptoms such as cough, vomit, movement were found. Besides, MAP, HR, and  $\text{SpO}_2$  were all stable. Patients were all satisfied about the procedure. General anesthesia was induced by propofol, remifentanil and rocuronium bromide. The anesthesia maintenance and surgery of those patients were all uneventful.

This converted spray device for topical pharyngeal anesthesia has several advantages. First, it is noninvasive and is more acceptable to patient; Second, it is easily converted from routine clinical devices and is very simple to use; Third, the consumed tetracaine is very small (median dose of these 5 patients is 35 mg), thus the risk of local anesthetic systemic toxicity is relatively low; Last and most important, it is more timesaving. Generally speaking, it only takes us 3–5 minutes to get sufficient topical anesthesia both for oropharynx and nasopharynx. Thus, it is a promising device for awake intubation in clinical practice.



**Figure 1** Converted spray device and beautiful sprayed solution.

### Conflicts of interest

The authors declare no conflicts of interest.

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## LETTER TO THE EDITOR

### Acute hospital oxygen shortage during COVID-19 pandemic surge: how can we prevent the apocalypse?



Dear Editor,

The 2019 novel coronavirus disease, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has caused not only 3 million deaths worldwide, but also crumbled the healthcare system of various countries. One such country facing this grim reality is India. Almost 15% of patients are likely to develop severe illness while 5% may develop critical disease requiring invasive mechanical ventilation.<sup>1</sup> Oxygen therapy is one of the few known and accepted treatments for COVID-19. Catastrophic shortage of oxygen in various parts of the world has urged us to introspect whether we are equipped enough to deal with this crisis.

Prevention of an apocalyptic disaster in the face of oxygen shortage entails measures at all levels. One important measure is augmenting oxygen production to match usage. A technical guidance by the World Health Organization (WHO) says that oxygen can be generated at Pressure Swing Adsorption (PSA) in oxygen plants and liquid oxygen plants, that can or cannot be located at a medical facility respectively. Oxygen concentrators are another portable means, which use PSA technology to draw air from the environment and remove nitrogen to deliver around 90% concentrated oxygen. They work on the principle of fractional distillation. They are safe and cost-effective but require continuous source of power. Another limitation is that the flow may be less than the requirement of the hospital.

The WHO also recommends development of an "oxygen surge plan" to ensure readiness to tackle a surge in cases. Establishment of more PSA plants in hospitals can be done. Urgent installation of oxygen concentrators with PSA technology especially in rural India may save the day and brace us for the rising COVID-19 cases. A team of doctors, biomedical engineers, and technicians should oversee the safe working of oxygen supply plants.

Another challenge is of oxygen supply that can be done by means of primary, secondary, and reserve components. Primary consists of liquid oxygen and cylinder manifold while secondary supply comprises a manual cylinder system of another vessel of liquid oxygen. Most

hospitals that use a cylinder manifold as reserve need to have two storage banks of around 20 cylinders each to ensure a reserve of 4 days at least. The reserve supply means an automated cylinder manifold stored at a location different from that of the primary site.

One vital measure that we may incorporate in practice is judicious use of oxygen by meticulously defining target goals for oxygen saturation. Surviving sepsis guidelines for COVID-19 have recommended a "conservative oxygen strategy" with target oxygen saturation ( $\text{SpO}_2$ ) of 92–96%. They strongly recommend against a  $\text{SpO}_2$  of > 96%.<sup>2</sup> The same has been justified to avoid a scenario of depletion of oxygen resources by liberal use. We recommend that a tailored approach weighing benefits of oxygen therapy versus available resources for individual patients be utilized. Srinivasan and colleagues proposed the use of "Oxygen Extraction Ratio ( $\text{O}_2\text{ER}$ )" in conjunction with arterial blood gas and central venous oxygen ( $\text{ScVO}_2$ ).<sup>3</sup> The Improving Oxygen Therapy in Acute-illness (IOTA) systematic review and meta-analysis reported a significantly high 30-day mortality in the liberal oxygen therapy group and they concluded that supplemental oxygen was no longer beneficial in patients with an  $\text{SpO}_2$  above 94–96%.<sup>4</sup>

Unwarranted oxygen wastage in the form of circuit leaks must be anticipated and avoided. Nursing officers and technicians should be educated in this regard. Lastly, in the event of an unwarranted surge in COVID-19 cases, all elective procedures must be suspended. A "contingency plan" for such a crisis management must be put together by governments.<sup>5</sup> To conclude, these measures are indeed need of the hour to help us stay afloat in this COVID-19 tsunami.

## Conflicts of interest

The authors declare no conflicts of interest.

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