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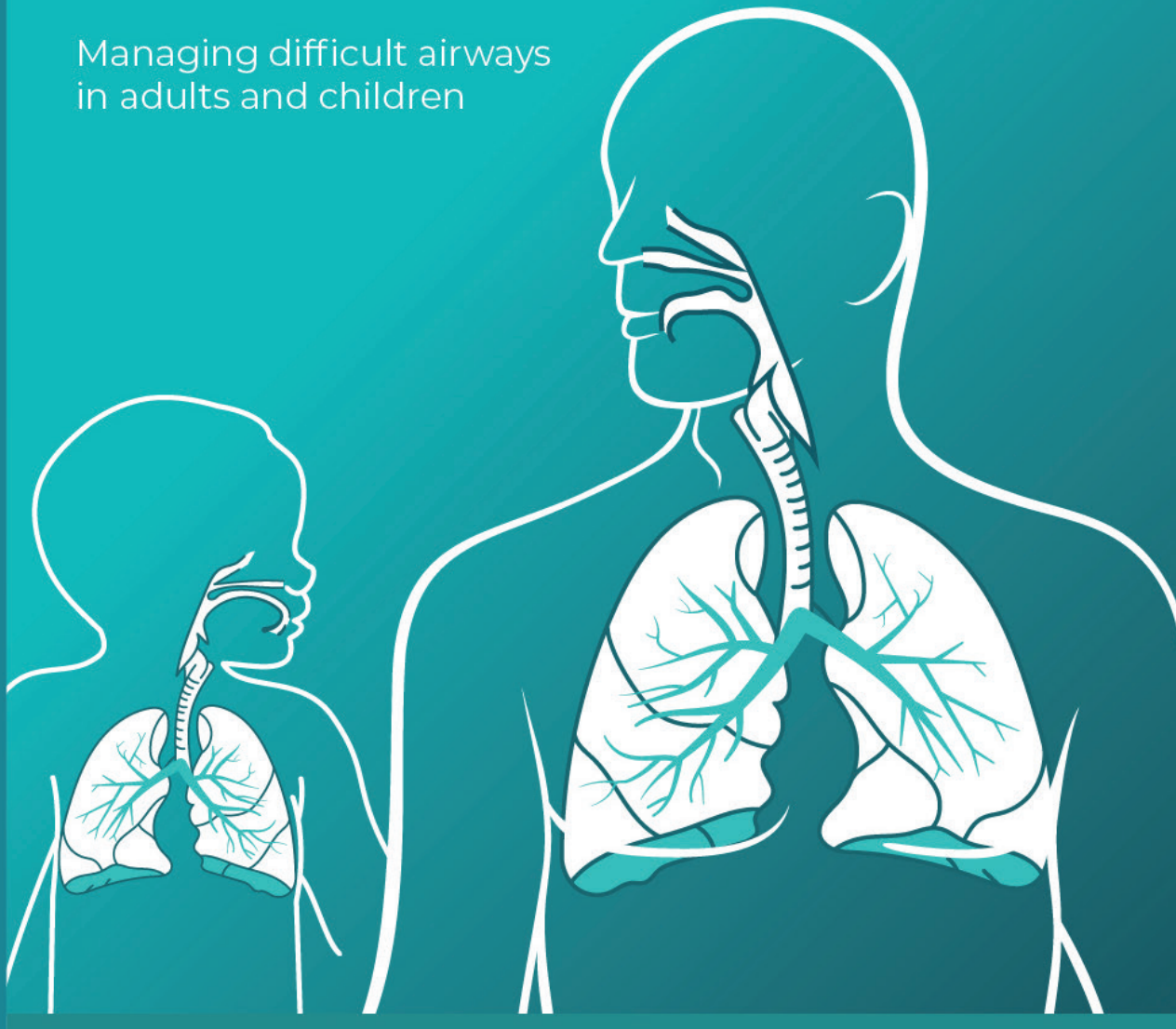
Managing difficult airways in adults and children



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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Expert recommendations for managing difficult airways in adults and children: insights from the Brazilian Society of Anesthesiology (SBA)



In the ever-evolving field of anesthesiology and critical care, the effective management of difficult airways remains a critical challenge. Published more than ten years ago, the 4th United Kingdom National Audit Project (NAP4) has estimated an incidence of major airway management complications during anesthesia to be approximately 1:22,000 with a mortality rate of 1:180,000.[1] An analysis of closed malpractice claims related to difficult intubation from 2000 to 2012 demonstrated that airway management was judged to have been inappropriate in 73 percent of 102 assessed claims and included inadequate evaluation, failure to plan for difficult intubation, failure to use a supraglottic airway for rescue, delay in calling for help, and perseveration on failed techniques.[2]

Airway management in children differs from that in adults, just as neonates and infants differ from older children. An observational study across 261 hospitals in Europe has shown that airway management practices in children vary extensively across different countries and institutions.[3] This study has demonstrated that three or more tracheal intubation attempts were necessary in 0.9% of children and the overall incidence of failed tracheal intubation was 8/10 000 (0.08%) in pediatric patients.[3] Altogether these findings reinforce the rationale that straightforward airway management techniques are essential skills for healthcare professionals.

As we delve into the latest advancements, this editorial aims to provide a comprehensive overview of the recommendations for the management of difficult airways put forth by a group of experts from the Brazilian Society of Anesthesiology (SBA) in this issue of the Brazilian Journal of Anesthesiology.[4,5] Their recommendations for both adults and children may offer invaluable insights that can shape contemporary clinical practices.

The management of the difficult airway demands a nuanced understanding of anatomical variations, patient characteristics, and the application of cutting-edge techniques. With advancements in medical technology, the landscape of airway management continues to evolve. The Brazilian Society of Anesthesiology, drawing on the collective expertise of its members, has distilled a wealth of knowledge into a set of recommendations designed to guide anesthesiologists through the complexities of adult and pediatric airway challenges. The present recommendations are extensively based on recent international guidelines,[6–8] and are specially designed to support professionals working in low and middle-income countries.

A revision of the practice guidelines for the management of the difficult airway by the American Society of Anesthesiologists (ASA) Task Force has been recently published,[6] long expected in order to include techniques that greatly evolved in the last decade. The ASA guidelines differ from previous publications since they were developed by an international task force representing several medical organizations. Other societal and international guidelines addressing the management of difficult airways have been published, but according to AGREE II criteria for the quality of the guideline creation process, the most recent ASA guideline outperforms its predecessors.[9] Although all guidelines proceed with the same purpose, some discrepancies have been highlighted between the different societal recommendations,[10] and local practices, availability of resources and recent technologies may be related to some of these differences.

Both articles are structured around pertinent questions and answers, offering straightforward tools to assist clinicians in making crucial decisions when managing the difficult airway. These resources are designed to ensure gradual and objective approaches to the difficult airway. Importantly, decision-making relies on a rational approach, the expertise and skills of the airway operator, and the specific clinical context in which airway management is undertaken. These documents aim to standardize the approach to both anticipated and unanticipated difficult airway management regardless of the different expertise of the professionals

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involved. The authors emphasize the need for cautious preanesthetic airway assessment and adequate preparation before patient induction. This preparation includes adopting a strategy before approaching the airway, immediate availability of airway devices, and adequate patient positioning and monitoring. Significant attention is given to the use of ultrasound to evaluate the airway and its role in identifying the cricothyroid membrane. Furthermore, these recommendations emphasize the pivotal role of preoxygenation and oxygen administration (including apneic oxygenation) throughout the entire airway management procedures, including extubation.

In adults, the experts strongly recommend performing awake tracheal intubation in case of suspected difficult laryngoscopy, associated with suspected difficulty with facemask or supraglottic ventilation, increased risk of aspiration, decreased apneic tolerance, or suspected difficulty with emergency invasive airway rescue.[4] If the strategy adopted is to proceed with intubation after induction of general anesthesia, the guidelines recommend identifying a preferred sequence of airway devices, being aware of elapsed time and oxygen saturation, and limiting the number of attempts to prevent potential complications. In this context, the most recent evidence regarding the use of videolaryngoscopy, its advantages, indications, and limitations are further discussed. The experts overall agree that videolaryngoscopy has clear advantages over direct laryngoscopy for tracheal intubation, especially when the first attempt is unsuccessful, or when the airway is known to be difficult. Despite some unanswered questions, the available evidence supports the safety and efficacy of videolaryngoscopes when compared to direct laryngoscopes.[11,12]

The airway strategy should be based not only on the clinician's experience but also on the accessibility of the equipment and the context in which airway management is performed. Unexpected difficult airway management represents a challenging scenario and the authors emphasize the importance of asking for help, aiming to optimize the patient's oxygenation, and considering the possibility of waking the patient before an invasive approach to the airway is warranted. The document places specific emphasis on the confirmation of tracheal intubation, emphasizing the guidance provided by capnography. Additionally, updated recommendations for the extubation of difficult airway cases are highlighted.

In terms of airway management in children,[5] considerable attention has been dedicated to defining a difficult airway within the pediatric population and assessing a child's airway. The discussion delves into specific insights on managing a recognized difficult airway, including the criteria for choosing between videolaryngoscopy or fiberoptic bronchoscopy in children. Recognizing the pivotal importance of ensuring adequate oxygenation during pediatric anesthesia induction and airway management, additional insights are provided, focusing on the restoration of ventilation and oxygenation in scenarios involving anatomical obstructions and on the options of low- and high-flow apneic oxygenation. This encompasses optimizing face mask ventilation, appropriately indicating and utilizing supraglottic devices, and selecting the correct anesthetic drugs, depth of anesthesia, and use of neuromuscular blockers. Finally, experts offer further commentary on various pertinent topics. These encompass a robust recommendation to restrict the number of intubation attempts, potential strategies for optimizing laryngoscopy, confirming tracheal intubation, ensuring the safe extubation of pediatric patients with a difficult airway, and addressing the procedures for an emergency pathway in the challenging scenario of "cannot intubate, cannot ventilate".

A notable feature of both documents is the customized approach to handling difficult airways in both adults and children. Recognizing the distinctive anatomical and physiological aspects in pediatric patients, the recommendations offer insights into the nuances specific to this population. By addressing challenges across various age groups, these recommendations guarantee a comprehensive and adaptable strategy, including a more in-depth discussion about human factors and non-technical skills, elucidating their role in the management of a difficult airway.

Remarkably, the two documents presented by the Brazilian Society of Anesthesiology are not formulated as guidelines, as they do not adhere to international guideline recommendations. Instead, they take the form of narrative articles crafted to review the latest information derived from recent guidelines and references in the field. The objective is to tailor these recommendations to the context of Brazil and other comparable low- and middle-income countries, acknowledging the constraints imposed by limited healthcare resources in these regions. The experts emphasize the importance of adapting guidelines to the local reality, particularly in consideration of the availability of new technologies, including supraglottic devices, videolaryngoscopes, fiberoptic bronchoscopes, and ultrasound devices. Of note, Portuguese translations of the 2022 ASA practice guidelines for managing difficult airways are now officially accessible.[13,14] This marks a noteworthy stride in disseminating knowledge across our country and other nations should consider adopting similar strategies to enhance adherence to these protocols.

In summary, as we navigate the dynamic landscape of anesthesiology and critical care, the expert recommendations provided by the Brazilian Society of Anesthesiology,[4,5] in association with recent international guidelines,[6,13,14] emerge as a beacon of knowledge in the realm of difficult airway management. By synthesizing the most up-to-date information, this editorial aims to not only shed light on the airway expert's insights but also encourage a continued dialogue within the medical community, fostering a collaborative and ever-improving approach to the challenges posed by difficult airways in adults and children. Ultimately, the effectiveness of any set of recommendations lies in its real-world impact on patient outcomes.

Conflicts of interest

The authors declare no conflicts of interest.

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EDITORIAL

Fatigue in anesthesia workers



One of the inescapable elements of medical practice is long hours and night work. In recent years, research has demonstrated the impacts of fatigue on our clinical work and on our health. We know from experience that as we become more tired, we find it harder to take in and learn new information, to think flexibly and do complex calculations. We might notice lapses in vigilance and concentration, that we are less dextrous at practical procedures, and that we are less empathic.[1] Our teams might notice our mood getting worse or that we are more likely to take risks. All of these are well recognized signs of fatigue, and they all have detrimental effects on the care we deliver to patients.

But night shift work has negative impacts on our own health as well. Hypertension, myocardial infarction, stroke, type II diabetes, breast, bowel and prostate cancer, and depression are all more common in night shift workers and we are more prone to accidents.[2,3] We are twice as likely to have a car crash driving home after a 12-hour shift than an 8-hour shift. If we drive after being awake for 18–20 hours our performance behind the wheel is as bad as if our blood alcohol is over the legal limit for driving.[4] Fatigue induces spontaneous, unrecognized "sleep lapses" or "microsleeps", and doctors, nurses and other healthcare workers have had serious accidents or died as a result of a microsleep when driving. In many European countries it is illegal to drive when critically tired; why do the same rules not apply to clinical practice?

Night working, acute sleep deprivation, chronically shortened sleep, and high work intensity all cause fatigue and impact on the safety and effectiveness of the care we deliver.[5] There are physiological reasons for this. Two processes control sleep, one homeostatic and one circadian. While we are awake, substances called somnogens such as adenosine build up in our brains, promoting sleep. This is counteracted by the circadian alerting signal during daylight hours. We have two circadian nadirs, one at about 3–4 pm and one at night between 3 and 6 am when we are most likely to make errors. After dark, the effects of increasing levels of somnogens makes us increasingly tired, to a point where we need to sleep.[6] If we ignore this, our ability to function effectively deteriorates; this reduced physiological performance is called fatigue. Left unchecked this eventually leads to exhaustion, an inability to respond to emotional or physical stressors.[7] Emotional exhaustion is one part of the triad of burnout, together with depersonalization and a reduced sense of personal accomplishment, an increasingly common condition affecting healthcare workers.

Many organs other than the brain have circadian processes, such as the pancreas, kidneys and cardiovascular system, and these are active during the day (diurnal). This may be why night-shift workers are more prone to the diseases mentioned above; for instance, we are less able to metabolize a high calorie meal at night.[8] To shift our internal body clock "phase" by 1 hour takes about 24 hours, so rotating day and night shift work is difficult, and we are often tired on night shifts and struggle to sleep during the day.[9]

As we age, the quality of our sleep can become poorer and we may sleep for less time.[10] However our need for sleep does not diminish, and we find night shift work more difficult. Responsibilities grow as we become more senior and have families; mothers of young children are some of the most sleep-deprived workers.[11]

Until now, healthcare has seen tiredness and fatigue as occupational hazards, not recognizing their impacts on our clinical performance and on driving home safely. Management of fatigue has been left up to the individual. In contrast, other high-hazard industries such as airline and petrochemical have regulations requiring good fatigue risk management, so organizations have to identify fatigue-related errors, provide rest facilities and run safe rotas. We need to learn from other high-hazard industries and establish good fatigue risk management as part of our overall safety culture in healthcare.

Several strategies used in other safety-critical industries can also work in clinical practice. Examples include 20-minute "power naps" taken during a quiet spell or a break during a long shift or a night shift. You need 15 minutes to get to sleep, and somewhere quiet dark, safe and flat to lie down. Some airlines advise their workers to have a cup of coffee before going to sleep as the caffeine will be taking effect as

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you wake from the nap. Caffeine works by blocking the effects of adenosine, a key somnogen, on our brain.

Good teams discuss how tired each person is at the start of a night shift and make sure those who are the most tired get their power naps early in the shift. They are especially vigilant at the circadian nadir (3—6 am and 2—4 pm) double checking critical decisions and drugs with other team members. And they support each other, watching out for signs of fatigue, and encouraging a culture where this is discussed and seen as part of safe practice.

Rotas are also carefully managed; those on night shifts never work more than 12 hours and never more than 3 nights in a row. Rolling rotas always work forward, so everyone works early shifts then late shifts, then nights, with enough time to recover after a shift. For those on call, the maximum length of work is 24 hours and there are contingency plans in place to call others in if they are working for 16—18 hours continuously.

In Europe we are beginning to put some of these practices into action as we recognize the impacts staff fatigue has on patient safety and on our own safety and well-being. Brazil may be ahead of us here, with regulatory frameworks that make 12-hour shifts the norm and facilities provided for sleep during the night shift. This is part of a bigger European project, raising awareness, identifying good practice from other industries, and developing effective fatigue risk management systems through organizations and influencers, including patient groups.

Fatigue Risk Management Systems are frameworks and formal processes designed to systematically identify areas where fatigue poses a risk and to manage the risk effectively through appropriate control measures. Principles of systems-based thinking typically used in health safety and well-being management systems are applied to fatigue risk management. Successful implementation of a risk management system requires planning, commitment, consultation, clarity of roles and responsibilities, documentation, monitoring, review, and evaluation.[12]

In Europe, we realized that many clinicians and managers know little about circadian physiology and the scientific basis for good fatigue risk management. We started to raise awareness with surveys of trainees and trainers.[13,14] These showed that many of us are chronically sleep restricted and have examples of fatigue related errors and near misses from our own practice. Ninety two percent of the 1500 consultants who responded to our survey, from 32 European countries, experienced work-related fatigue.[14] Causes included their working patterns, clinical and non-clinical workload, staffing issues and excessive hours worked. Over 70% reported that work-related fatigue negatively impacted physical and mental health, personal well-being, and safe commuting. Other impacts described by trainees included effects on their ability to do their job (53%) to study (88%), manage exam revision, do projects (82%), and on their job satisfaction (61%).[13] Most consultants and trainees did not feel supported by their organization to maintain good health and well-being, including a lack of support from hospitals and management for recovery during and after night shifts.

In Europe, 37% of trainees have had an accident or near miss driving home, and although 40% describe feeling too tired to drive, some do so anyway. Seventy percent have access to post-shift rest facilities for a power nap before driving home but 40% do not use these as they "prefer to get home". Earlier UK studies showed that 57% of trainees and 45% of consultants described accidents or near misses driving tired, 75% used cars or motor bikes, 84% of trainees and 60% of consultants knew they were too tired to drive but did so because they had limited access to on shift rest facilities.[15]

Realizing we have a big problem, the European Board and the European Society of Anaesthesiology and Intensive Care are working to address this. We provide educational material and do talks and workshops to help anesthesiologists to understand the problem and identify ways of mitigating its impact. Each one of us has a part to play. We should adopt good sleep hygiene principles as individuals, making sure we rest before and between night shifts, having power naps during nightshift breaks, talking about fatigue, and double checking any work we have to do during our circadian nadir [3—6 am]. Teams and departments should discuss fatigue, especially during night shift ward rounds, watch out for colleagues who are getting tired and make sure everyone gets breaks. They should ensure there are facilities available for people to lie down somewhere quiet dark and private for power naps, and that during the night, only life or limb saving surgery is done, and no routine work or stocking up is permitted. Organizations should ensure staff are educated about fatigue and how to mitigate its impacts, and provided with the resources and facilities to ensure both patients and staff are safe when working long hours and overnight. We should regard fatigue as a patient and staff safety risk, have it on the risk register, implement and promote strategies that mitigate its impact.

Conflicts of interest

The authors declare no conflicts of interest.

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EDITORIAL

Greening the operating room



"Nature does nothing in vain" Aristotle in *On the Soul*

Since Swedish scientist Svante Arrhenius first estimated the extent of warming from widespread coal burning in 1896, climatologist Wallace Broecker coined the term "global warming" in the late 1970s, and the Meadows Report was published in 1972, several meetings have been held on the links between the ecological consequences of economic growth, resource limitation, and demographic trends.[1]

The French Economic Transformation Plan, launched in March 2020, aims to offer pragmatic solutions to decarbonize the economy in each sector. Regarding healthcare, in-depth work will be launched to educate the healthcare sector on its greenhouse gas emissions and the pathway to decarbonization.[2] Indeed, the healthcare sector provides 2.6 million jobs or more than 9% of the active population with emission levels between 40 and 61 $MtCO_2e$ (Metric tons of Carbon Dioxide equivalent), i.e., between 6.6% and 10% of France's carbon footprint.[1,2]

At the global level, according to the nongovernmental organization Health Care Without Harm, the climate footprint of the health sector represents 4.4% of net global emissions, or the equivalent of 2 gigatons of Carbon Dioxide (CO_2).[1] This climate footprint of the global health sector is equivalent to the annual greenhouse gas emissions of 514 coal-fired power plants.[1]

It is therefore imperative that this sector do its part to reduce emissions by 5% per year by 2050 to stay below 2°C.[1,2]

The operating room alone accounts for 40% of these emissions. The three main components of this carbon footprint are: waste production, energy demand, and anesthetic gas emissions.[3–5]

Greenhouse gases, which include water vapor, carbon dioxide, nitrous oxide, halogenated fluorocarbons, and hydrofluorocarbons (HFCs), absorb infrared radiation in the atmosphere, warming the Earth.[5–9] Halogenated chlorofluorocarbons (halothane, enflurane, isoflurane) or fluorinated hydrocarbons (sevoflurane and desflurane) are therefore potentially harmful to the Earth's ozone layer.[5–9] The physicochemical properties of these gases give them the ability to warm the climate because they meet the three characteristics of greenhouse gases: significant infrared absorption throughout their lifetime, long atmospheric lifetime, and the amount or concentration present in the atmosphere.[5–9]

Global Warming Potential (GWP) was developed to allow comparison of the effects of different gases on global warming.[1,2] It is a measure of how much energy emissions from one ton of a gas absorb over a period of time, compared to emissions from one ton of Carbon Dioxide (CO_2).[1,2,5-9] The higher the GWP value, the more a particular gas warms the earth compared to CO_2 over that time period.[1,2] The time period commonly used for GWPs is 100 years.[1,2] The power with which halogenated fluorocarbons contribute to global warming is equal to 1. For example, a single anesthesiologist administering N_2O or desflurane can cause the CO_2 equivalent of more than 1000 km of driving in an average workday.[6]

Developing new methods to reduce resource use, CO_2 emissions, and waste (including toxic byproducts), ranging from minimizing hospitalizations (improving primary care and expanding outpatient procedures) to reducing the use of medications and devices, could help promote a healthy and sustainable future.[5–9]

In 2022, the French Society of Anesthesia and Intensive Care Medicine, in collaboration with the French Society of Hospital Hygiene and the French Society of Clinical Pharmacy, proposed a reference system to reduce the environmental impact of general anesthesia in the operating room.[7]

This work has formulated recommendations to reduce the environmental impact of general anesthesia in the operating room, which we summarize below:[7]

- Considering the same clinical benefit to the patient, anesthesiologists should prefer sevoflurane to desflurane or isoflurane and not use nitrous oxide. They should also limit fresh gas flow during inhalation anesthesia to a maximum of 1 $L.min^{-1}$ and consider the frequency that anesthetic circuits require washing to reduce the environmental impact of general anesthesia.[6,5,8,9]

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- Experts suggest that anesthesiologists use monitoring of anesthetic depth in combination with the fraction of anesthetic vapor exhaled during inhalation anesthesia to reduce anesthetic vapor consumption and thus environmental impact.[10]
- From the point of view of environmental impact, inhaled general anesthesia or total intravenous general anesthesia with propofol could be used indiscriminately; the former has environmental impact due to emission of greenhouse gases, but the latter has ecotoxicity to soil and water.[11,12] Metabolites of intravenous general anesthesia may enter the hospital wastewater system. It is possible that degradation products such as phenol are formed from propofol, but it is not known whether there is significant accumulation in the food chain.[11,12]
- Experts recommend that anesthesiologists give preference to reusable medical devices over disposable ones and choose models that do not contain Di(2-Ethylhexyl) Phthalate (DEHP). Consider other reusable items such as laryngoscope blades, laryngeal masks, scissors, etc. For the same patient, consider the minimum number of syringes required.[6] When using reusable medical devices, inventory procedures should be established to ensure that devices are reused as much as possible to reduce the environmental impact and financial costs.[13–15]
- Concerning healthcare waste in the operating room some actions are proposed:[6,7]
  - Identify your waste and ask the question: can I avoid it, reuse it or recycle it? If not, can I rethink my practices or purchases?
  - Collaborate with the department responsible for waste management and the hospital hygiene team.
  - Integrate selective sorting into the waste management process and in the evaluation of professional practice.
  - Optimize the ergonomics of sorting: choice of bins and their position.
  - Inform and create awareness among staff to sorting at source.
  - Evaluate the financial benefits of sorting at source and recycling sorted waste so that the administration can fund future sustainable development projects (virtuous cycle).
- Last but not least, the health sector cannot be considered in isolation and depends on other sectors, such as:[2]
  - The energy sector, which supplies electricity, oil, and gas to all machines, whether inside facilities (heating, appliances, robotic mixers, and kitchen stoves, etc.) or outside, such as cars and trucks that provide transportation for patients, employees or even supplies.
  - The area of daily mobility, which allows the movement of patients and professionals in this area, and which affects the general health of the population through daily physical activity and air pollution.
  - The agricultural sector, which both provides communal catering in health facilities and influences the general health of the population through daily nutrition.
  - The construction industry to build, maintain and renovate health care facilities, medico-social facilities, nursing homes and medical practices.
  - The area of urban planning that determines the relationship of health facilities to their territory and population.
  - The digital sector, which supports all digital transformations in the health sector, both in the medical field (technological medical devices, patient monitoring, telemedicine) and in administration.
  - The industrial sector to produce the various drugs and medical devices consumed by users in the health sector.[2] For example, the Halogenated Drug Recovery unit was developed by Class 1 Inc. of Cambridge, Ont. It collects anesthetic gases after they leave hospital surgical rooms, strips out the gas molecules and stores them.

Hence, it is imperative for the healthcare sector to actively contribute to preserving a healthy environment and combatting global warming.[1,2] The instances elucidated by expert associations underscore the importance of healthcare professionals embracing this responsibility.

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ORIGINAL INVESTIGATION

Recommendations from the Brazilian Society of Anesthesiology (SBA) for difficult airway management in pediatric care

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Abstract
Difficult airway management in pediatrics during anesthesia represents a major challenge, requiring a careful approach, advanced technical expertise, and accurate protocols. The task force of the Brazilian Society of Anesthesiology (SBA) presents a report containing updated recommendations for the management of difficult airways in children and neonates. These recommendations have been developed based on the consensus of a panel of experts, with the objective of offering strategies to overcome challenges during airway management in pediatric patients. Grounded in evidence published in international guidelines and expert opinions, the report highlights crucial steps for the appropriate management of difficult airways in pediatrics,

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encompassing assessment, preparation, positioning, pre-oxygenation, minimizing trauma, and, paramountly, the maintenance of arterial oxygenation. The report also delves into additional strategies involving the use of advanced tools, such as video laryngoscopy, flexible intubating bronchoscopy, and supraglottic devices. Emphasis is placed on the simplicity of implementing the outlined recommendations, with a focus on the significance of continuous education, training through realistic simulations, and familiarity with the latest available technologies. These practices are deemed essential to ensure procedural safety and contribute to the enhancement of anesthesia outcomes in pediatrics.
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Difficult airway management in pediatrics presents unique clinical challenges, requiring a careful approach and precise protocols. Rapid assessment and interventions are crucial in this scenario, which can arise in a variety of clinical situations, from elective procedures to emergency cases. Continuous education, training in realistic simulations, and familiarity with the latest technologies are vital when dealing with a difficult airway in pediatrics. A multidisciplinary approach and collaboration among healthcare professionals, including anesthesiologists, surgeons, and nursing staff, play a crucial role in the successful management of the difficult airway in pediatric patients.

The present article primarily aims to provide a comprehensive framework of practical recommendations for the effective management of difficult airways in pediatric cases, covering everything from initial assessment to intervention strategies. The recommendations are based on a synthesis and analysis of the current literature and their goal is to assist the decision-making process in the context of pediatric anesthesiology.

Importantly, the recommendations developed by the Brazilian Society of Anesthesiology (SBA) do not seek to establish absolute standards, and their use cannot assure specific outcomes. The present recommendations may be implemented, adapted, or rejected according to the clinical scenario and the document can be revised as necessary to keep pace with evolving medical evidence.

Pediatric airway management

Airway management in children differs from that in adults, just as neonates and infants differ from older children when it comes to the management of difficult airways. An epidemiological study revealed that the incidence of difficult intubation was 0.28% in pediatric patients, being higher in neonates (1%) and children under 1 year of age (1.1%). In children aged 1 to 5 years, the incidence was 0.2%, while for children aged 6 to 12 it was 0.1%, and for those over 12 years of age, 0.1%.[1]

The strategy to ensure a safe airway must focus on the only true objective which is to ensure survival without causing harm but guaranteeing adequate oxygen supply to the brain and other organs and tissues. The current approach must incorporate oxygenation as the primary target, abandoning attempts to intubate at any cost in favor of oxygenating at any cost.[2]

The evidence for pediatric airway management is still scarce, and although recent studies have provided some guidelines, most of the studies lack methodology rigor.[3]

How to define difficult airway in children

Similarly to adults, a difficult airway in pediatrics is defined by a clinical situation, previously identified or not, in which a skilled anesthesiologist has to deal with one or more of the following difficulties: maintaining adequate ventilation; placing the laryngoscope in the correct position; visualizing the vocal cords; inserting the tracheal tube.[4,5]

Anatomical characteristics that make it difficult to approach the airway

The inherent anatomical features of the pediatric age group may, by themselves, cause difficult airway situations in neonates and children. As the child grows up to 10 years of age, the respiratory system undergoes size, shape, position, and constitution changes.[6] The smaller the child, the greater the airway differences compared to adults.[7]

Table 1 describes the most important pediatric anatomical features that make pediatric airway management more challenging.[8-10] Likewise, the anesthesiologist's expertise can be a factor for pediatric airway management failure.

Acquired clinical conditions

Airway patency and/or access are influenced by several clinical conditions that affect anatomical structures, leading to a variable degree of ventilation obstruction. Among them, we highlight congenital, inflammatory, metabolic, neoplastic, and traumatic conditions.[10] The children's larynx is a cartilaginous skeleton. Fracture of airway structures is uncommon, but as ligaments and membranes connecting cartilaginous structures are immature, laryngotracheal separation is more frequent after trauma.[10]

Penetrating trauma is associated with different injuries, due to the nature of the tissues that enclose the larynx. Edema and hematoma formation adjacent to the vocal cords are fairly common, in addition to lacerations, displacement of the arytenoids, cricoid separation, and vocal cord paralysis, all factors that combined make tracheal intubation more cumbersome[11] (Table 2).

Table 1 Airway anatomical features associated with challenging airway management in pediatric care.

Anatomical region	Feature	Risks
Head	Relatively large in relation to neck and chest. Greater prominence of the occipital region.	It favors flexion of the neck over the chest when in the supine position, making it challenging to align the airway axes and visualize structures. Facilitates upper airway obstruction.
Nose	Presents relatively more mucosa and lymphoid tissue. Smaller nostril diameters.	Increased risk of edema, obstruction, and bleeding during nasal intubation.
Nasopharynx	Adenoid is hypertrophied in early childhood, and it is located in the roof and posterior wall of the nasopharynx.	Greater risk of obstruction to nasal air flow. Risk of bleeding, edema, and tissue detachment during nasal intubation.
Anterior mandibular space (space to which the tongue is displaced during laryngoscopy)	Until approximately 2 years of age, the mandible is relatively hypoplastic, with consequent reduction in the anterior mandibular space.	Airway obstruction occurs and direct visualization of glottic structures is challenging due to the disproportion between tongue size and oral cavity size. Any other condition making the anterior mandibular space even smaller will make laryngoscopy and intubation difficult.
Genioglossus muscle	It is smaller and its insertion is more posterior.	Passive airway obstruction, particularly in the supine position.
Larynx — ligaments	Ligaments and membranes connecting the cartilaginous structures are immature.	Greater risk of separation of structures in trauma. Greater susceptibility to dynamic airway collapse in the presence of respiratory obstruction.
Larynx — location	More cephalad position (C3-C4), making the distances between tongue, hyoid bone, epiglottis, and rim of the mouth shorter.	Upper airway obstruction when tongue is pushed into the oral cavity.
Larynx — angle between the base of the tongue and the glottic cleft	The angle between the base of the tongue and the glottal cleft is more acute.	Makes direct visualization of structures problematic.
Larynx — mucosa and submucosa	Tissues are abundantly vascularized, and have abundant lymphatic tissue, conferring an appearance of engorgement to the region.	Edema and bleeding of the laryngeal fossa, epiglottis, and glottis during airway handling. Difficult visualization of the vocal cords when using straight blades.
Epiglottis — anatomy and location	In newborns, the epiglottis is narrow, longer, less tonic, omega shaped (Ω), and is located more angled to the axis of the trachea.	Elevating the epiglottis during laryngoscopy is problematic.
Vocal cords	They are more cartilaginous, inserted more anteriorly and have a more inferior closure.	Edema formation during tracheal cannula insertion or using a tracheal cannula of inadequate size can make it difficult to maintain adequate ventilation after tracheal extubation. More susceptible to trauma.
Trachea	Variable diameter (around 3 to 6 mm).	Greater risk of airway obstruction when edema is present, which can occur when an inadequate size tracheal cannula is chosen, facilitating extubation failure.
Cricoid cartilage	The cricoid cartilage forms a complete ring in the airway. The cricoid cartilage, that rests on a basement membrane, is almost devoid of elastic fiber, thus it is not an expandable or mobile structure. Until the age of 10 to 12, it is considered the greatest narrowing point of the larynx.	Prolonged tracheal intubation or using a cannula with an inadequate diameter increases the risk of cricoid compression injury, the likelihood of edema formation, reduction in tracheal lumen to a critical diameter and extubation failure. The injury may later progress to subglottic stenosis.

Table 2 Clinical conditions that can make pediatric airway management difficult according to etiology and anatomical structure.[10]

Etiology	Affected anatomical structure				
	Nasopharynx	Tongue	Mandible/ Maxilla	Pharynx/ Larynx	Trachea
Congenital				Laryngomalacia Stenosis Laryngocele Laryngeal membrane	Vascular ring Tracheomalacia Stenosis
Inflammatory	Adenoid hypertrophy Nasal congestion		Juvenile rheumatoid arthritis	Granuloma Epiglottitis Amygdalitis Abscess Diphtheria pseudomembrane Laryngeal polyps	Laryngotracheobronchitis Bacterial tracheitis
Metabolic		Mucopolysaccharidosis Hypothyroidism Glycogen disease		Laryngospasm associated to hypocalcemia	
Neoplastic	Teratoma	Teratoma Hygroma Hemangioma	Bone tumors	Tumors	Mediastinal tumor Neurofibroma Paratracheal nodules
Traumatic	Foreign body Burns Trauma	Lacerations Venous obstruction Lymphatic obstruction	Fractures Neck retracted scars	Fractures Separation of structures Inhalation injury Foreign body Post intubation stenosis Epidermolysis Bullosa	Post intubation stenosis

Congenital airway malformations

The most frequent syndromes and malformations that determine anatomical abnormalities that can result in a difficult airway are cleft palate and craniofacial dysostoses.[10,12] In some syndromes, the defects undergo changes during the child's growth or development, increasing the level of difficulty.[12] Maxillary hypoplasia often occurs associated with choanal atresia and/or some degree of nasal obstruction. These patients are mouth breathers and suffer from respiratory obstruction when the mouth is closed. Hypoplasia of the maxilla and mandible and tongue hyperplasia reduce the volume of the oral cavity, causing upper airway obstruction.[10] Micrognathism is an important and reliable risk factor for predicting difficult laryngoscopy, particularly in children under 6 months of age.[7]

Temporomandibular joint (TMJ) disorders prevent inferior and/or anterior displacement of the jaw, restricting mouth opening and making airway handling difficult. The fixed causes (congenital or traumatic conditions) of these defects do not change with anesthesia. Conversely, non-fixed causes (inflammatory processes or abscesses that cause trismus) are eased allowing patients to open their mouths completely under the effect of general anesthesia. Diseases reducing cervical spine mobility (vertebral and hemivertebrae fusions, arthropathies, etc.) make airway management and tracheal intubation challenging or even impossible.[9,10]

Clinical conditions presenting cervical spine instability have a greater risk of spinal cord injury, making it difficult to optimize the patient's position to access the airway.[9,10] The mass effect caused by soft tissue accumulation can also limit cervical mobility, mouth opening, and eventually airway management. The most commonly encountered mass effect is macroglossia, followed by tumors and arteriovenous malformations[9,13] (Table 3).

Assessment of the child's airway

Despite lacking validated criteria to identify difficult airway in a pediatric patient, airway assessment should comprise the following topics:

Table 3 Congenital airway malformations.[12]

Malformation	Characteristics	Associated risks
Cleft palate	Cleft palate is associated with other malformations, such as macroglossia, mandibular or maxillary hypoplasia.	Challenging both to adapt facial mask and insert oropharyngeal cannula (Guedel) When the clefts are bilateral, they generate angulation in the airway axes, and the insertion of the laryngoscope blade is problematic.
Craniofacial dysostoses/ premature closure of skull bones	Hypoplasia of facial bones, predisposing to a small jaw, high palate, and decreased development of paranasal sinuses. Modified tongue volume/oral cavity volume ratio.	Optimizing patient position for airway management is problematic. Restricted cervical mobility. Properly adapt mask to face is challenging. Increased risk of oral cavity occlusion.

Clinical history

It is important to identify the following information:[7,13,14] diseases or syndromes associated with difficult airway (Table 4); previous anesthesia with reports of struggle during airway management; acquired conditions with airway changes (examples: radiotherapy to the face and neck, inflammatory processes, burns or trauma); history suggesting respiratory obstruction (examples: choking, hoarseness, snoring, apnea, stridor, changes in sucking or swallowing); possible postural changes facilitating sleeping or improving respiratory condition.

Physical examination

It is necessary to evaluate:[5,7,14,15] abnormal movement, size, and aspect of the head (examples: low-set ears, facial asymmetries, limited range of movement of temporomandibular joint); mouth opening, palate shape, prominent upper incisors, and tongue size; changes in the maxilla, mandible, and submandibular region (for example: range of movement and presence of retrognathia); cervical changes and cervical range of movement; hyomental distance > 1.5 cm (neonates) and > 2.0 cm (infants) are associated with appropriate visualization of glottis structures; occurrence of scars, deviations, hematomas, tumors and subcutaneous emphysema; lung auscultation, chest expansion and use of accessory muscles.

The different methods used to detect a difficult airway in adults are not validated for the pediatric population.[7,16] The Mallampati classification can be useful in children over 5 years of age who can cooperate during the test.[17] In children between 0 and 2 years of age, an association is described between difficult laryngoscopy and body mass index (< 15.10 $kg.m^{-2}$), thyromental distance (< 3.55 cm, a more specific parameter), mandibular length (< 6.5 cm), tragus to mouth distance (< 7.75 cm) and age less than 1 year.[18] In children under 5 years of age, the combined assessment of the lower lip-to-chin distance (< 2.2 cm), the tragus-to-mouth distance (< 3.9 cm), and low body mass index (< 12.17 $kg.m^{-2}$) correlate with difficult glottis visualization during laryngoscopy, with high specificity and sensitivity.[15]

Retrognathism and micrognathism are associated with difficult laryngoscopy. Likewise, the inter-incisor distance, sternomental distance, and thyromental distance are predictive of difficulty in laryngoscopy. (7) In children under 2 years of age, the major predictors of difficult laryngoscopy viewing are age < 6 months, weight < 5 kg, and height < 61 cm.[19]

Mnemonic methods, such as ABCDE, aid airway assessment (Table 5). Complementary tests, such as x-Ray and CT scan help to elucidate data from medical history and physical examination suggestive of anatomical airway changes. Sublingual ultrasonography is accurate in predicting difficult tracheal intubation when the hyoid bone is not visualized, with sensitivity and specificity of 73% and 97%, respectively.[20]

Maintenance of adequate oxygenation during intubation

Apnea in the pediatric population causes oxygen saturation (SpO_2) to drop more quickly than in the adult population. This is due to a combination of physiological features of the child, such as high oxygen consumption (5 to 8 $mL.kg^{-1}.min^{-1}$), making children more dependent on normal ventilation to keep tissue oxygenation. Children's high minute volume (130 $mL.kg^{-1}.min^{-1}$) reveals this dependence. Early arterial desaturation onset is the lower functional residual capacity compared to minute volume, causing lower lung oxygen reserve at the end of expiration and during apnea.[8]

Thus, during a child's apnea, there is less available time for managing the airway, explaining the high incidence of hypoxemia during pediatric tracheal intubation, that is in up to 13% of tracheal intubations, and in up to half of difficult intubation cases.[8]

In newborns, hypoxemia events are even more frequent, reaching 75% of difficult tracheal intubation cases, and 42% of cases in which tracheal intubation was not deemed difficult.[21] Thus, it is critical to implement approaches to reduce the occurrence of hypoxemia, mainly: pre-oxygenation and oxygenation during intubation. Apneic oxygenation or

Table 4 Syndromes favoring the occurrence of a difficult airway situation.[10]

	Choanal defects	Micrognathia	Micro-stomia	Macro-glossia	Larynx defects	Palate defects	Cervical spine defects	Cardiac defects
Down's syndrome				X	X	X	X	X
CHARGE syndrome	X	X			X			X
Pierre-Robin syndrome	X	X		X		X		
Treacher-Collins syndrome	X	X	X		X			
Edwards syndrome	X	X	X		X		X	
Goldenhar syndrome		X			X		X	
Beckwith-Wideman syndrome				X				X
Klippel-Feil syndrome							X	
Freeman-Sheldon syndrome			X		X			
Apert syndrome	X	X						
Crouzon syndrome	X	X						
Pfeiffer syndrome	X	X						
Progressive fibrodysplasia ossificans		X					X	
Mucopolysaccharidosis				X	X			X

Table 5 ABCDE mnemonic method for airway assessment.

A. Congenital (syndromes) or acquired (tumors, burns, trauma, infections, trismus) anomalies;
B. Mouth (opening, tongue, tooth, hypoplasia);
C. Neck (cervical range of movement, deformities, TMJ);
D. Dysphagia, dysphonia;
E. Stridor and stenosis.

spontaneous breathing oxygenation are the recommended strategies during tracheal intubation of children.[22]

Evidence for pre-oxygenation in children

Previous studies suggest that administering tidal volume breathing for 3 minutes or 8 respiratory cycles at vital capacity, with the use of 100% oxygen, constitutes adequate strategies to extend safe apnea time.[23]

Apnea time with $SpO_2 > 95\%$ is shorter the younger the child, in line with the expected physiological development during childhood. In children of 2 months of age undergoing laryngoscopy for tracheal intubation, paralyzed and exposed to apnea, the time for oximetry to decrease from 100% to 95% is longer in those previously ventilated with 100% oxygen compared to those ventilated with a 40% oxygen mixture with nitrous oxide or air.[24]

Evidence for low- and high-flow apneic oxygenation in children

Apneic oxygenation during the management of the pediatric airway has become the standard technique both when the difficult airway is expected and when greater safety is required during the apnea period of elective tracheal intubation.[4]

Low-flow techniques

Low-flow techniques ($< 2\ L.kg^{-1}.min^{-1}$) include oxygenation through nasal or pharyngeal cannulas or a laryngoscope. Studies evaluating pharyngeal cannula with or without administration of supplemental oxygen during direct laryngoscopy revealed a decrease in desaturation incidence when oxygen is administered.[25] Experimental data have suggested that administering oxygen through an oropharyngeal cannula or a direct laryngoscopy blade has an advantage when compared to a nasal cannula.[26]

A randomized study comparing three techniques of administering supplemental oxygen to apneic children (nasal cannula supplying 100% O_2 at $0.2\ L.kg^{-1}.min^{-1}$; transnasal humidified rapid insufflation ventilatory exchange (THRIVE) supplying 100% O_2 at $2\ L.kg^{-1}.min^{-1}$ and THRIVE supplying 30% O_2 at $2\ L.kg^{-1}.min^{-1}$), showed that children receiving 100% O_2 perform better than those receiving 30% O_2.[27]

There have been reports describing gastric rupture associated with nasal or nasopharyngeal cannulas supplying gas at $3\ L.min^{-1}$ or more, although cannula location was checked, supporting the recommendation of using low gas flow rates. Using a cannula is safe when the following conditions are observed: administration for a short period, the child's mouth is kept open, the pharyngeal location of the cannula is confirmed, frequent gastric palpation is performed, and the cannula in the maxillary region is secured.[28]

Table 6 Flow rate values for high-flow systems according to weight.

Up to 3 kg	6 L.min^{-1}
3 to 5 kg	10 L.min^{-1}
5 to 10 kg	20 L.min^{-1}
10 to 20 kg	35 L.min^{-1}
20 to 40 kg	40 L.min^{-1}
40 to 60 kg	50 L.min^{-1}
Adults	70 L.min^{-1}

Apneic oxygenation with a nasal or pharyngeal cannula makes ventilation with a face mask difficult, due to the impossibility of maintaining the facial seal, requiring cannula removal for effective face mask ventilation.

High-flow techniques

During the past decade, we have observed increased use of apneic oxygenation with a high-flow nasal cannula (> 2 L.kg^{-1}.min^{-1}) aiming to reduce the incidence of hypoxemia during airway management.[21,29] High-flow systems consist of a gas mixer connected to the oxygen and compressed air high-pressure outlets, enabling titration of the fraction of inspired oxygen (FiO_2); heater; humidifier; circuit, and high-flow nasal cannula or mask. The high-flow technique allows administering up to 80 L.min^{-1} flow rate, generates airway positive pressure, reduces respiratory effort, and optimizes oxygenation.

In children, it is recommended to adjust the flow rate according to weight (Table 6), as excessive flow rates cause airway mucosa injury and are associated with gastric inflation and pneumothorax.[21]

To date, however, no robust evidence has been found showing the superiority of high-flow nasal cannula techniques for apneic oxygenation in pediatric intubation when compared to low-flow techniques.[21,29] The high-flow technique reduces alveolar CO_2 concentration, and decreases hypercapnia and respiratory acidosis in adults, findings that have not been reported in children.[27,30]

Children's physiological and anatomical features, such as high metabolic rate and small airway caliber increased flow resistance, are believed to prevent adequate elimination of CO_2. Moreover, the gas flow rates studied so far in children may be insufficient to overcome the high airway resistance and reduce CO_2.[21]

However, the advantage of the high-flow nasal cannula technique is that enables humidifying and warming the administered gas, lowering the risk of airway mucosal damage triggered by administering dry gases. Conversely, some disadvantages of high-flow systems must be pointed out, such as high cost, requirement of specific equipment not yet easily accessible in the operating room, and difficult face mask ventilation.[21]

Oxygenation with spontaneous breathing

For children with documented difficult airway, it is possible to choose an anesthetic technique that combines sedation and spontaneous breathing, especially when flexible bronchoscopy is planned. Also, when managing an apneic child, it is essential to maintain an O_2 supply as it optimizes oxygenation and minimizes adverse events. In these cases, oxygenation techniques with low and high O_2 flow can be used.[31] Comparing high-flow nasal cannulas with low-flow nasal cannulas in healthy, sedated and spontaneously breathing children has not revealed significant differences in hypoxemia, hypercapnia, and apnea rates.[31,32]

Summary of oxygenation recommendations in children

- Pre-oxygenation with 100% O_2 should be routinely used for airway management of every child, observing the patient's acceptance;
- When opting for intubation post-anesthetic induction (apneic child), apneic oxygenation is recommended, particularly when higher hypoxemia risk is identified;
- Whenever opting for apneic oxygenation, use the technique you feel more comfortable with, as no superiority between low- or high-flow techniques has been found;
- When opting for tracheal intubation under sedation and spontaneous breathing, the recommendation is to maintain oxygenation using the technique you feel more comfortable with (low or high-flow techniques);
- When using low-flow techniques, limit flow rate to 0.2 L.kg^{-1}.min^{-1}, optimize cannula position, and frequently palpate the abdominal region for early detection of gastric distension;
- When using a high-flow nasal cannula technique, adjust the flow rate according to weight and plan a prompt switch to a face mask and breathing circuit system, when required.

How to manage an anticipated difficult airway

Anticipated pediatric difficult airway is performed under general anesthesia or sedation. It requires skills, detailed care, and an experienced professional.[4] Difficult airway management training emphasizes the importance of spontaneous breathing to maintain oxygen saturation and airway tone during the procedure. Moreover, it provides the patient with continuous oxygenation and fast recovery if tracheal intubation fails.[33] Thus, it is critical to maintain oxygen supply at all stages of airway handling.[4] Airway handling under an insufficient anesthesia depth is one of the major causes of laryngospasm and other adverse events during intubation.[34]

Sedatives, analgesics, and even neuromuscular blockers are indicated in most cases. They provide comfort, enable to optimize patient position, minimize sympathetic responses, facilitate glottis exposure, and make the procedure safe.[35]

How to choose drugs and techniques for sedation or general anesthesia

When compared to intramuscular and intranasal routes, intravenous sedation is safer, given its predictable effect and duration of action. Combining intravenous with inhalational agents may also be useful to reduce administered

doses and adverse events. Non-depolarizing neuromuscular blockers can be indicated for a patient with a suspected difficult airway, as they facilitate intubation by decreasing airway reactivity and vocal cord movement. Depolarizing neuromuscular blockers have the advantage of a fast onset of action and a relatively short duration of action.[33] Non-depolarizing neuromuscular blockers administered in high doses can create suitable intubation conditions at onset times similar to depolarizing agents, with longer duration of action. If a specific reversal is unavailable, its use is not recommended.[33] Clinicians must ensure that all required drugs, materials, and equipment are available, tested, functioning, and ready for use.

If succinylcholine is administered, the American Heart Association Pediatric Advanced Life Support guideline recommends using atropine (0.02 $mg.kg^{-1}$) for infants under 1 year of age, in children aged 1 to 5 years, and for adolescents receiving a second dose of succinylcholine.[36] However, atropine is not always effective in preventing bradycardia. Table 7 contains the most commonly used drugs during orotracheal intubation in pediatrics.

When to choose between a video laryngoscope and flexible bronchoscope for managing an anticipated difficult airway

First-attempt success rates with flexible bronchoscopy are similar to video laryngoscopy. Most of the literature related to tracheal intubation techniques for children with difficult airways is restricted to experimental simulation studies or studies with small samples or performed in a single center. During the initial approach to difficult airways in neonates, children, and adolescents, the number of intubation attempts should be limited. Oxygenation is critical during the instrumentation of an anticipated difficult airway. The apneic child has a short time to desaturate, less than 6.5 seconds in neonates and infants, and up to 13 seconds in adolescents.[37,38]

Flexible bronchoscopy is not indicated in emergencies, and some factors limit its use:[39,40] hypoxemia due to previous intubation attempts, with already inefficient ventilation or apnea; active bleeding or copious and/or thick secretion, rendering ineffective aspiration through the fiberscope working channel; ineptitude in handling the fiberscope. Table 8 describes the preparation for performing oral or nasal flexible bronchoscopy.

Spontaneous breathing can be attained with a facial mask designed for flexible bronchoscopy, or a regular facial mask attached to a swivel, through which the flexible bronchoscope can be inserted. Using a proper size flexible bronchoscope according to the patient's age enables inserting a tracheal tube with the correct size for the patient. During the entire procedure, assistance from another anesthesiologist is required, while one manages the airway, the other keeps the facial mask attached to the face, allowing spontaneous breathing and adequate oxygenation.

The working channel of the flexible bronchoscope enables the insertion of an 18- or 20-mm epidural catheter to instill local anesthetic, a technique called "spray-as-you-go". Monitoring the volume of local anesthetic used is critical for children, due to the risk of local anesthetic systemic toxicity. After visualization of the vocal cords and, with the airway secured by positioning the flexible bronchoscope, anesthesia can be deepened and the neuromuscular blocker can be administered, averting the reaction to the tracheal tube passage. It is important to be sure the tracheal tube has been inserted beyond the vocal cords.

Flexible bronchoscopy via a supraglottic device is an alternative approach to pediatric difficult airway, using a supraglottic device specifically designed. However, if a dedicated supraglottic device is unavailable, a regular supraglottic device can be used. A supraglottic device allows for continuous oxygenation and ventilation while providing a conduit for intubation. Compared with videolaryngoscopes the technique may be advantageous, as hypoxemia is the most common initial sign of adverse events related to intubation in children with difficult airways, especially in children under 1 year of age. Additionally, supraglottic devices also relieve upper airway obstruction and optimize the bronchoscope view of the larynx.[40]

Nasal flexible bronchoscopy can also be performed and maintenance of spontaneous breathing is also essential. The technique requires administering nasal vasoconstrictors, as nasal bleeding is associated with tracheal intubation failure.[41]

Exceptionally, when a proper-sized flexible bronchoscope is unavailable, the Seldinger technique can be used. Essentially, the airway management steps are the same, except, given its large size, the flexible bronchoscope is not inserted beyond the glottis. Thus, a malleable or J-shape tip hydrophilic guide wire is inserted through the flexible bronchoscope working channel. After visualizing the guide wire passing through the vocal cords, the flexible bronchoscope is removed, and an exchange tube is introduced, followed by the tracheal tube. It should be underscored that the technique is feasible only if it is possible to oxygenate the child using a proper face mask or supraglottic device.

Video laryngoscopy has become an important and frequently used tool in pediatric airway management. In children presenting a difficult airway, it enables superior glottic view and higher tracheal intubation success rates than conventional direct laryngoscopy. It is considered an alternative technique to flexible intubation bronchoscopy. The advantage of being a technique similar to conventional direct laryngoscopy makes the technique easier to learn. Nonetheless, it may be challenging in patients with small or limited mouth opening, situations in which flexible bronchoscopy is indicated. Hyperangulated video laryngoscope blades provide a better view of the rima glottidis and shorten the time to vocal cord visualization.[42-44] There is still no evidence in the pediatric population of the superiority of any device used for video laryngoscopy. Thus, the choice of device depends on the expertise of the clinician and the availability of the equipment.[45,46]

How to manage unanticipated difficult airway after anesthetic induction in children

"The ability to oxygenate and ventilate must be prioritized over tracheal intubation."[47]

The incidence of unpredicted difficult face mask ventilation in children can reach 6% and is not associated with

Table 7 Doses and characteristics of the drugs used during pediatric airway management.

Drug	Dose	Duration of action	Comments
Autonomic nervous system			
Atropine	IV: 0.01—0.02 mg.kg^{-1} (max.: 1 mg)	> 30 min	Inhibits the bradycardia response to hypoxia; can cause tachycardia May cause pupil dilation
Hypnotics sedatives and analgesics			
Diazepam	IV: 0.1—0.2 mg.kg^{-1} (max.: 4 mg)	30—90 min	May trigger respiratory depression or potentiate the depressant effects of narcotics and barbiturates
Midazolam	IV: 0.1—0.3 mg.kg^{-1} (max.: 4 mg)	1—2 h	Minimal cardiac depression Sporadic respiratory depression No analgesic properties
Fentanyl	IV, IM: 2—5 mg.kg^{-1}	IV: 30—60 min IM: 1—2 h	May cause respiratory depression, hypotension, chest wall rigidity with high dose infusions (> 5 mg.kg^{-1})
Anesthetic agents (when administered in the doses indicated)			
Etomidate	IV: 0.2—0.4 mg.kg^{-1}	5—15 min	May cause ventilatory depression Minimal cardiovascular effects Myoclonic activity; can decrease seizure threshold Cortisol suppression; contraindicated in patients dependent on the endogenous cortisol response No analgesic properties
Lidocaine	IV: 1—2 mg.kg^{-1}	~30 min	Myocardial and CNS depression with high doses May decrease ICP Occasionally associated with hypotension
Ketamine	IV: 1—2 mg.kg^{-1} IM: 3—5 mg.kg^{-1}	30—60 min	May increase arterial blood pressure, heart rate, cardiac output May cause increased secretions and laryngospasm Causes mild respiratory depression Bronchodilator May cause hallucinations and awakening hyperactivity
Propofol	IV: 2 mg.kg^{-1} (for small children up to 3 mg.kg^{-1})	3—5 min	May cause hypotension, especially in hypovolemic patients May cause injection pain Highly fat-soluble Causes less airway reactivity than barbiturates
Neuromuscular blocking agents			
Succinylcholine	Infant IV: 2 mg.kg^{-1} Children IV: 1—1.5 mg.kg^{-1} IM: Multiply the IV dose by two	3—5 min	Depolarizing muscle relaxant that causes muscle fasciculation May cause increased ICP, intraocular pressure and intragastric pressure May cause hyperkalemia May cause arterial hypertension Avoid in cases of renal failure, burns, crush injuries or hyperkalemia
Atracurium	IV: 0.5 mg.kg^{-1}	30—40 min	Metabolized by plasma hydrolysis May cause mild histamine release
Cisatracurium	IV: 0.1 mg.kg^{-1}, then 1—5 mg.kg^{-1}.min^{-1}	20—35 min	Metabolized by plasma hydrolysis May cause mild histamine release
Rocuronium	IV: 0.6—1.2 mg.kg^{-1}	30—60 min	Minimal cardiovascular effects
Vecuronium	IV: 0.1—0.2 mg.kg^{-1}	30—60 min	Minimal cardiovascular effects

Table 8 Material required to perform flexible intubation bronchoscopy in pediatric anesthesia.

1. Material preparation
- Nasal cannula
- Mouthpiece
- Fiberoptic intubating airway (e.g.: Berman, Willians, or Ovapassian)
- Facial mask for fibro bronchoscopy and swivel mask
- Supraglottic devices (e.g.: intubating laryngeal mask, LMA Fastrach™, Air-Q™, iGel™, and Ambu-Aura-i™)
- Hydrophilic guide wire
- Suctioning device
- Flexible bronchoscope (with or without working channel) and external diameter of 2.8 to 6.3 mm
- Local anesthetic and atomizer
- Aintree intubation catheter and/or epidural catheter

2. Monitoring
- EKG
- Capnography
- Pulse oximetry
- Noninvasive arterial blood pressure

3. Anesthetic induction
- Inhaled or intravenous
- Keep patient breathing spontaneously

4. Antisialagogue
- Atropine

5. Topical administration of local anesthetic (lidocaine)
- Oral or nasal atomization
- Use an epidural catheter to atomize

difficult intubation.[3] However, previous data have revealed that 13% of difficult intubations in neonates and premature infants under 60 weeks of post-conceptual age also represent challenging face mask ventilation.[3] The Pediatric Difficult Intubation (PeDI) Registry shows that 8% of patients present both difficult tracheal intubation and face mask ventilation, and from these, approximately 7% are impossible to ventilate with a face mask.[22]

What to do during a "no oxygenation" scenario

In daily practice, it is essential to check the anesthesia equipment before connecting the patient. However, equipment failure is not uncommon and can make manual ventilation difficult. In this situation, the most correct approach is to separate the patient from the anesthesia machine and use an external source of oxygen with a self-inflating bag or mask bag.[3]

Airway obstruction is the major cause of anesthesia-related perioperative hypoxemia and requires prompt and appropriate detection and treatment. To manage the situation successfully, it is critical to distinguish anatomical (mechanical) from functional (physiological) causes to implement their distinct treatment strategies.[47]

Anatomical causes are physical and usually relieved with basic and advanced airway maneuvers, while severe functional causes are usually treated with drugs. For example, partial laryngospasm produces anatomical obstruction that can be readily reversed with airway maneuvers, while total laryngospasm often requires drug administration to be treated.

Some examples of mechanical obstruction include inadequate head positioning, adenotonsillar hypertrophy, obesity, foreign body and secretions, and gastric hyperinflation or distension. Functional obstruction occurs both in the upper and lower airway. The major causes are inadequate anesthetic depth, pharyngeal closure, laryngospasm or glottic closure, chest wall rigidity, and bronchial hyperreactivity.[47]

How to restore ventilation and oxygenation in anatomical obstructions

Optimized positioning

Optimal positioning for ventilation and intubation depends on age. In children over 6 years of age, proper positioning is similar to adults, slightly elevating the head, anteriorly displacing the cervical spine, and simultaneously, extending the head at the atlanto-occipital joint.[8]

In newborns and infants, head elevation is not required due to the disproportion of the occiput about the trunk, which maintains the anterior cervical displacement. It is useful to place a cushion below the shoulders or a roller to hold the occiput, preventing head rotation and aligning the oral and pharyngeal axes.[48]

Adjustment of the face mask

A proper face mask size must be selected. The mask is applied on the nose, keeping eyes free and the mask aligned to the nasolabial fold, resting the mask on the jaw and avoiding placing fingers in the region of the mentum. In neonates and infants, it is preferable to pull the jaw at the

temporomandibular joint, close to the tragus, keeping the mouth slightly open and resting the index and middle fingers on the mask and not on the jaw.[48] The combination of the sniffing position, mouth opening, and continuous positive pressure (CPAP) with a maximum inspiratory pressure of 10 cmH_2O set on an adjustable pressure-limiting (APL) valve improves the expiratory tidal volume and peak inspiratory pressure, optimizing face mask ventilation.[49] Another useful alternative for improving face mask ventilation is the bimanual technique.[3]

Devices to relieve airway obstruction

Several supraglottic device designs are available with some advantages over others. Second-generation devices are more effective as they enable lower-pressure ventilation and are easy to insert and secure. However, they are associated with a risk of displacement or poor positioning, incorrect sizing, and local trauma. Therefore, it is important to limit the number of insertion attempts to a maximum of three.[1] Alternatively, a correct size Guedel oropharyngeal cannula or nasopharyngeal cannula will relieve most anatomical upper airway obstructions.[47]

Nasopharyngeal cannulas are not a first-line strategy, but if the mouth opening is insufficient to allow for an oral cannula or a supraglottic device, it is the device of choice. The anesthesia breathing circuit can be connected to any type of nasopharyngeal cannula using the correct orotracheal tube adapter. The technique can facilitate intubation for patients with a difficult airway, allowing the administration of oxygen and anesthetics during airway management.[50]

Orogastric tubes are recommended in cases in which gastric distension results from forced bag-mask ventilation and prolonged ventilation with a face mask or supraglottic device. Gastric distension can obstruct ventilation and oxygenation due to changes in diaphragm mechanics requiring immediate decompression.[47]

How to treat changes in ventilation and oxygenation caused by functional obstruction

Anesthesia depth and neuromuscular blockers

Whenever mask ventilation is challenging and anatomical obstruction has been ruled out, the difficulty is possibly caused by functional obstruction. Therefore, it is recommended to deepen the anesthesia or use neuromuscular blockers.[3] For functional obstruction, prompt use of hypnotics and neuromuscular blockers is a better option than awakening the child, since tolerance to apnea in young children is low and the "no-oxygenation" situation is critical. Propofol is the first option to be used as it promotes airway relaxation. It is noteworthy that careful hemodynamic monitoring is essential, as severe hypotension may occur.[3] Neuromuscular blockers also improve tracheal intubation conditions.[47]

Specific situations of functional obstruction and their pharmacological treatment

Initial management for partial laryngospasm is the administration of 100% oxygen and continuous airway pressure (CPAP), followed by increasing anesthetic depth. In children without intravenous access, anesthesia can be deepened with inhalational agents and, if required, intramuscular succinylcholine at a dose of 4 to 5 $mg.kg^{-1}$ can be used.[3,8] In children with venous access, after initial management the approach is propofol (0.5 to 5 $mg.kg^{-1}$), titrated to the desired effect. If the situation deteriorates, succinylcholine (0.1 to 1 $mg.kg^{-1}$) or rocuronium (0.9 to 1.2 $mg.kg^{-1}$) can be used. Rocuronium has the advantage of neuromuscular blockade reversal if awakening the child is decided.

In the presence of complete laryngospasm, with or without venous access, the management strategies are the same. If a neuromuscular blocker or repeated doses of propofol are administered, face mask ventilation is expected to be easier. If not, tracheal intubation is the next step to be considered.[3] Another example of functional obstruction is bronchospasm, which must be treated with bronchodilator drugs, such as inhaled salbutamol or sevoflurane. Low doses of intravenous epinephrine (1 $mcg.kg^{-1}$) are highly effective for treating severe bronchospasm.

Chest wall rigidity secondary to rapid administration or high doses of opioids is also a cause of functional obstruction, which can be treated using neuromuscular blockers. Attention should be paid to the use of neuromuscular blockers in patients with documented distal airway obstruction (tumors, mediastinal masses), as the drug can precipitate airway collapse, and worsen obstruction.[47]

It is important to underline that arterial oxygen saturation must be monitored in each additional intervention trying to rescue ventilation. Once arterial oxygen saturation has improved, the chosen maneuvers or devices can be resumed. If arterial oxygen saturation deteriorates, inserting a supraglottic device or a tracheal tube should be considered.[3]

What should be done in the "cannot intubate, cannot ventilate" scenario

First failed intubation attempt

When manual ventilation with a face mask is feasible, the clinician should call for help after the first failed attempt of tracheal intubation. This happens rather frequently and there are a limited number of recommended intubation attempts, so it is fundamental to have the best help available fast.[3] In this setting, alternative airway management techniques should be used straight away.[47]

Limit the number of intubation attempts

There is a strong relationship between severe cardiorespiratory events and the number of direct laryngoscopy attempts. Thus, a rapid shift to indirect laryngoscopy is recommended. When required, the initial airway management plan must be reassessed and changed. Intubation attempts should be limited to three to four.[1,22] When the first direct laryngoscopy is challenging, adjusting the head and neck extension is strongly recommended to optimize viewing.[3]

Strategies for optimizing laryngoscopy

The first tracheal intubation attempt must be performed using the best technique. In children up to 2 years of age, a straight blade allows proper tongue positioning in the submandibular space and the creation of a more acute angle between the lip rim and laryngoscope blade, providing a better glottis view.[48]

Larynx external displacement (BURP maneuver: backward, upward, and rightward pressure) is used when the laryngeal view is reduced. In young children, external maneuvers can distort the larynx or trachea anatomy due to excessive external pressure, making tracheal intubation impossible. In this case, prompt cessation or adjustment of cricoid pressure is recommended.[3]

Alternative techniques to assist tracheal intubation

The Gum Elastic Bougie (GEB) is a useful tracheal tube introducer when the epiglottis is visible, but the vocal cords are not, and there is no laryngeal or tracheal injury.[51] Blind insertion of a GEB in a child showing a laryngoscopy laryngeal view classified as Cormack-Lehane grade 4 is not recommended due to the likelihood of injuring the child's fragile airway structures.[3]

Video laryngoscopy is an alternative technique to direct laryngoscopy. It is crucial to provide training focused on the devices available at each facility. It must be underlined that video laryngoscope does not apply to all patients and its use does not assure successful tracheal intubation.[2] Failure in tracheal intubation using these methods should indicate the use of a supraglottic device or, even, canceling the procedure. If local experience and resources are available, tracheal intubation using a flexible bronchoscope (nasal, oral, or supraglottic device-aided) or combined techniques may be useful in the sequence of airway management.[47]

Supraglottic devices

Supraglottic devices are easy to insert confirming their value in pediatric difficult airway algorithms because they secure oxygenation and ventilation. The laryngeal mask airway is the first rescue device to be used in the event of intubation failure, provided that there is no complete obstruction of the upper airway or a condition that could be worsened by the injury resulting from multiple supraglottic device insertion attempts.

There are laryngeal masks dedicated to pediatric patients, particularly for babies and young children, with specific design features that enable better airway sealing and greater protection against lung aspiration and include a working channel for nasogastric tube insertion and stomach decompression. However, the laryngeal mask airway should be avoided in patients with airway obstruction or anatomical distortion.[51]

Once well positioned, supraglottic devices enable oxygenation and ventilation. If inadequate ventilation occurs, the device should be replaced by another with an increased size. For procedures that can safely proceed with a supraglottic device, this approach can become part of the anesthesia technique. Conversely, if the procedure requires tracheal intubation, flexible bronchoscopy aided by a laryngeal mask airway is the most indicated technique for tracheal intubation, providing it is performed by a trained practitioner. After successful insertion of the tracheal tube, the best approach is to maintain the laryngeal mask *in situ*.[3,52]

In case of tracheal intubation failures using the laryngeal mask airway, the first step is to evaluate oxygenation. If oxygenation is adequate, the device is maintained. Then, one should consider if the procedure should be resumed or if it is necessary to wake the patient. However, if after insertion of the supraglottic device inadequate oxygenation (SpO_2 < 90% with FiO_2 1.0) is observed, the device must be removed and ventilation with a face mask resumed.[3,52]

Although there is no consensus, studies suggest that the maximum number of supraglottic device insertion attempts be limited to three, direct laryngoscopy to four, and that only one attempt using a flexible bronchoscope through a well-positioned laryngeal mask airway is acceptable.[3] However, it is worth emphasizing that clinical judgment must be exercised when assessing the need to increase the number of attempts with any technique. Successful intubation allows the procedure to continue. However, if attempts at intubation and oxygenation by alternating devices fail, they result in the severe "cannot intubate, cannot ventilate" scenario.[3]

How to proceed in the "cannot intubate, cannot ventilate" scenario

This is a very rare scenario in children and for this reason, the literature lacks good-quality evidence, and its true incidence is unknown. Even though securing the airway surgically is indicated when it is impossible to intubate and oxygenate, there is no evidence determining the best technique to perform it.[53]

In the event of the condition, it is assumed that safe venous or intraosseous access and complete monitoring are present, that the child has received an adequate dose of neuromuscular blocker, and that all intubation attempts by the most experienced professional available have failed, with manual ventilation remaining inadequate.[3] Temporary oxygenation improvement while other interventions are implemented can save lives.[51]

There is no evidence to guide when to consider waking the child. It is recommended to awaken the patient, maintaining efforts to oxygenate, when oxygen saturation is higher than or equal to 80%, without hemodynamic impairment. In this case, if rocuronium was administered, sugammadex should be used to reverse the neuromuscular blockade. It is crucial to underline that, simultaneously with any attempt to awaken the patient, one must be prepared for surgical airway access, as clinical deterioration can happen at any time.[47]

If awakening the patient does not improve ventilation and oxygenation, airway rescue techniques should be initiated. Yet again, not enough evidence can be found to define exactly when to begin airway rescue techniques. Some researchers define either SpO_2 < 75% and decreasing associated with hemodynamic instability, or SpO_2 < 65% without hemodynamic instability, as thresholds for starting rescue techniques. In both cases, ventilation efforts with 100% FiO_2 should continue.[3] Other researchers argue that absolute values of SpO_2 are not as important as realizing that oxygen saturation is decreasing, despite all efforts.[3]

When and how to perform front-of-neck access in emergencies

The rare, but often discussed front-of-neck access (FONA) in children is considered the last resort during the airway management of cannot intubate, cannot ventilate in pediatric patients. The intervention probably will be ineffective in children in an emergency and, therefore, the priority is to avoid it. It is not possible to practice or gain enough experience to render FONA useful and reliable.[47] If the surgical

airway is deemed the final option after failed intubation attempts and, before airway trauma makes mask ventilation impossible, emergency FONA should be declared on the patient.[47] FONA can be performed with the percutaneous insertion of a cannula over a needle, with wire-guided cricothyroidotomy and transtracheal cannula, and with surgical access for tracheostomy and cricothyroidotomy with a scalpel and gum elastic bougie.[54]

Rigid bronchoscopy is indicated in specific cases if equipment is available, and the team is experienced. It is worth underscoring that not enough evidence and clinical experience support the superiority of any specific device or technique over another.[47]

Performing FONA in infants and young children is challenging. Cricothyroid membrane identification by palpation is difficult when compared to identification by ultrasound, although in emergencies it is not always possible to use ultrasonography.[54] The anatomic relationship between the mandible and trachea makes cricothyroid puncture significantly problematic, even with maximal extension of the neck. The percutaneous technique can lead to compression and perforation of the posterior wall of the trachea, while surgical cricothyroidotomy has a risk of fracturing the laryngeal cartilage. Moreover, the cricothyroid membrane of neonates is very small, about 2.6 to 3 mm, and their larynx is quite cephalad in the neck, making it hard to have enough space to position the needle.[53] The outer diameter of the smallest available tracheal tube exceeds the longitudinal dimensions of the cricothyroid membrane of neonates.[54] The trachea is very mobile and compressible, increasing the likelihood of inadvertent subcutaneous or esophageal puncture and cannulation, especially in techniques requiring blind puncture and force application, such as catheter-on-needle techniques, guided by wire and cannula. Some authors support the technique of using a scalpel in children under 8 years of age or direct exposure of the cricothyroid membrane with a scalpel followed by cannulation under direct vision.[53]

Thus, for children up to 8 years of age, guidelines are unclear. In this population, surgical tracheostomy is preferred and recommended if a trained practitioner is available. However, most airway emergencies leading to "cannot intubate, cannot ventilate" occur in children under one year of age, restricting the usefulness of the technique.[49,51] In children over eight years of age, the size of the cricothyroid membrane allows percutaneous cricothyroidotomy.[54]

It is essential to prevent the need for emergency FONA by identifying high-risk patients and limiting the number of attempts of laryngeal mask airway insertion and tracheal intubation.[44] But if all other measures fail, some form of surgical airway should be attempted.[53] In the presence of specialists (pediatric surgeon, otolaryngologist, general surgeon, or head and neck surgeon), a surgical tracheostomy is recommended.[3,54]

Oxygen jet ventilators are unidirectional flow devices that incorporate a thumb control valve that allows the interruption of gas flow between jets. Transtracheal jet ventilation can be safely performed provided that upper airway patency is maintained. Thus, it is vital to use an oropharyngeal or supraglottic device to facilitate jet ventilation. A time ratio of 1:4 seconds between active jet insufflation and passive exhalation is also recommended, or clinical observation of complete exhalation. The wall-mounted oxygen flow meter connected via oxygen tubing to the cricothyroid cannula and tracheostomy system is a unidirectional system. However, the incorporation of a Y-connector allows for bidirectional flow and pressure release during passive exhalation. An initial gas flow rate of 1 $L.min^{-1}$/year of age is suggested, with increments of 1 L until adequate chest expansion is observed. Using three-way connections to replace the Y-connector is not recommended, given the open side port does not allow sufficient exhaustion of the insufflated gas, resulting in high airway pressures.[3]

The Ventrain™ (Ventinova Medical, Eindhoven, Netherlands) is a new device that allows effective ventilation through a small-caliber cannula, evacuating gas through suction and reducing barotrauma risk.[52]

When to indicate extracorporeal membrane oxygenation (ECMO) for "cannot intubate, cannot ventilate"

The 2022 American Society of Anesthesiologists (ASA) guidelines for the management of difficult airway, suggested using ECMO, when available, as an alternative to invasive airway techniques in the "cannot intubate, cannot ventilate" condition.[4] However, using ECMO in this scenario merits some consideration.

The first relates to the availability of ECMO in Brazil where only a few centers are accredited to perform ECMO (https://elso.org). Moreover, the success of ECMO depends on a setting controlled by precise protocols and qualified staff. For ECMO to be used in emergency scenarios, material and personnel must be readily available for device installation.[55] Due to the time required to assemble and fill the ECMO circuit, many centers keep a standby device ready, pre-primed with crystalloid solution, with the replacement fluid added at the time of ECMO initiation. It is considered safe to keep pre-primed circuits for up to 30 days, and perhaps beyond if the circuit is assembled and primed using standard sterile techniques and the priming is an electrolyte solution. So far, there have been no reports of a cannot intubate, cannot ventilate scenario managed by ECMO in pediatric patients.[56]

How to confirm tracheal intubation

Tracheal intubation confirmation is indicated in all situations, and detection of expired CO_2 or capnography is the gold standard method.[4] Other methods are direct visualization of the tube passing between vocal cords, lung auscultation, flexible bronchoscopy, chest ultrasound, or x-ray. When confirming tracheal intubation is not feasible, tracheal tube removal and face mask or supraglottic device ventilation are recommended.[4]

Undetected esophageal intubation is critical during pediatric difficult airway management. Even when promptly identified, it can be associated with severe hypoxemia, lung aspiration of gastric contents, cardiac arrest due to hypoxemia, and esophageal or gastric rupture. The key points for preventing unrecognized esophageal intubation are:[57] monitoring end-tidal CO_2 and pulse oximetry for all patients; routine use of video laryngoscopy, when available; verbalizing visualization during laryngoscopy in all attempts; always suspecting esophageal intubation at exhaled CO_2 detection failure; when it is impossible to detect exhaled CO_2, the tube

must be removed and face mask or supraglottic device ventilation must be initiated; if the tube was not promptly removed, other methods should be used, such as ultrasound, flexible fiberoptic bronchoscopy, or another laryngoscopy attempt (direct or indirect); physical examination should not be used alone to rule out esophageal intubation.

How to extubate a child with a difficult airway

Children with difficult airways are at high risk of extubation failure; thus, the anesthesiologist must be ready to respond and optimize oxygenation or ventilation.[58] Children presenting a difficult airway should be extubated awake. Observation of at least three of the following signs suggests awake extubation will be safe: contraction of facial muscles (grimacing), spontaneous movement (not to be confused with reflex cough), spontaneous eye opening, spontaneous breathing showing tidal volume > 5 mL.kg^{-1} and conjugate gaze.[59]

Tracheal extubation failure must be anticipated and planning to correct it must be established. The equipment required for extubation and the strategy for reintubation must be prepared, including anesthesia equipment or a bag-valve-mask device, oropharyngeal and nasopharyngeal cannulas, material for epinephrine nebulization for post-extubation stridor treatment and oxygenation equipment for post-extubation support, such as noninvasive ventilation devices or high-flow catheters.[58]

There is little evidence for the use of a tube exchanger for tracheal extubation of children presenting a difficult airway. A series of cases in which the tube exchanger was used led to reintubation success, and the new tracheal tube insertion was easy. Using a tube exchanger enables the detection of exhaled CO_2 and provides oxygen while preparing for reintubation.[60] The size of the tube exchanger is chosen according to the internal diameter of the tracheal tube as depicted in Table 9.[61]

Tracheal reintubation after extubation failure can be even more challenging than initial intubation, especially if anatomical or functional airway changes have happened. A suggestion for safe extubation is to request help from an experienced practitioner and provide all the material used in the difficult airway management that led to the initial tracheal intubation. All tube exchangers come with a 15 mm connector.[61]

Human factors in crisis management

The literature reveals a gradual and constant reflection on how anesthesiologists perform, analyzing the skills required for better performance in a high-risk environment such as the operating room. Some features and limitations of human perception and cognition, in addition to human factors, contribute to adverse events and challenges during crisis management. Cognitive psychology reveals that under stress even well-trained professionals can make common cognitive errors and experience memory retrieval problems. An important component of diagnostic and therapeutic decision errors is cognitive error, which is a thought process failure that happens despite adequate knowledge and skills. Some examples are fixation error (when attention is focused on a particular parameter or condition to the detriment of understanding the situation as a whole) or premature closure (when the first plausible diagnosis is accepted before ruling out others).[62] Cognitive errors cannot be overcome purely by just being aware of them. Cognitive aids such as flowcharts, algorithms, and checklists can help practitioners interrupt a cycle of errors.[52]

In addition to cognitive factors, human factors play an important role in the management of a difficult airway. Understanding human factors and their impact is vital to effectively manage crises. During the management of a difficult airway, human factors cause adverse outcomes in up to 40% of cases.[37] Non-technical skill training (communication, teamwork, and leadership) is believed to result in superior outcomes for patients during crisis management. The concept was included in the 2022 ASA difficult airway management guidelines.[4] Despite the evidence of the importance of human factors in the effectiveness of the anesthesiologist's performance, their inclusion in a guideline does not necessarily translate into changes in clinical practice. Thus, guidelines must be supported by educational planning to ensure that these vital areas are not neglected.

Practice training (including high- and low-fidelity simulation) is critical to ensure that technical skills can be effectively delivered during crises. Discussing technical skills (i.e., skills not imposing additional cognitive load on the operator) in different difficult airway scenarios improves situational awareness and the performance of non-technical skills. The emphasis should also be on training the multidisciplinary team.[63]

New guidelines from the European Society of Anaesthesiology and Intensive Care (ESAIC) and the British Journal of Anaesthesia (BJA)

Recently, the European Society of Anaesthesiology and Intensive Care (ESAIC) and the British Journal of Anaesthesia (BJA) jointly published a new guideline on airway management in neonates and infants.[64] The ESAIC and BJA guideline

Table 9 Characteristics of the tube exchanger.

Tube exchanger size	Tube exchanger internal diameter	Length	Tracheal tube internal diameter
8	1.6	45	3.5 – 4.5
11	2.3	83	5.0 – 6.0
14	3.0	83	6.5 – 7.0

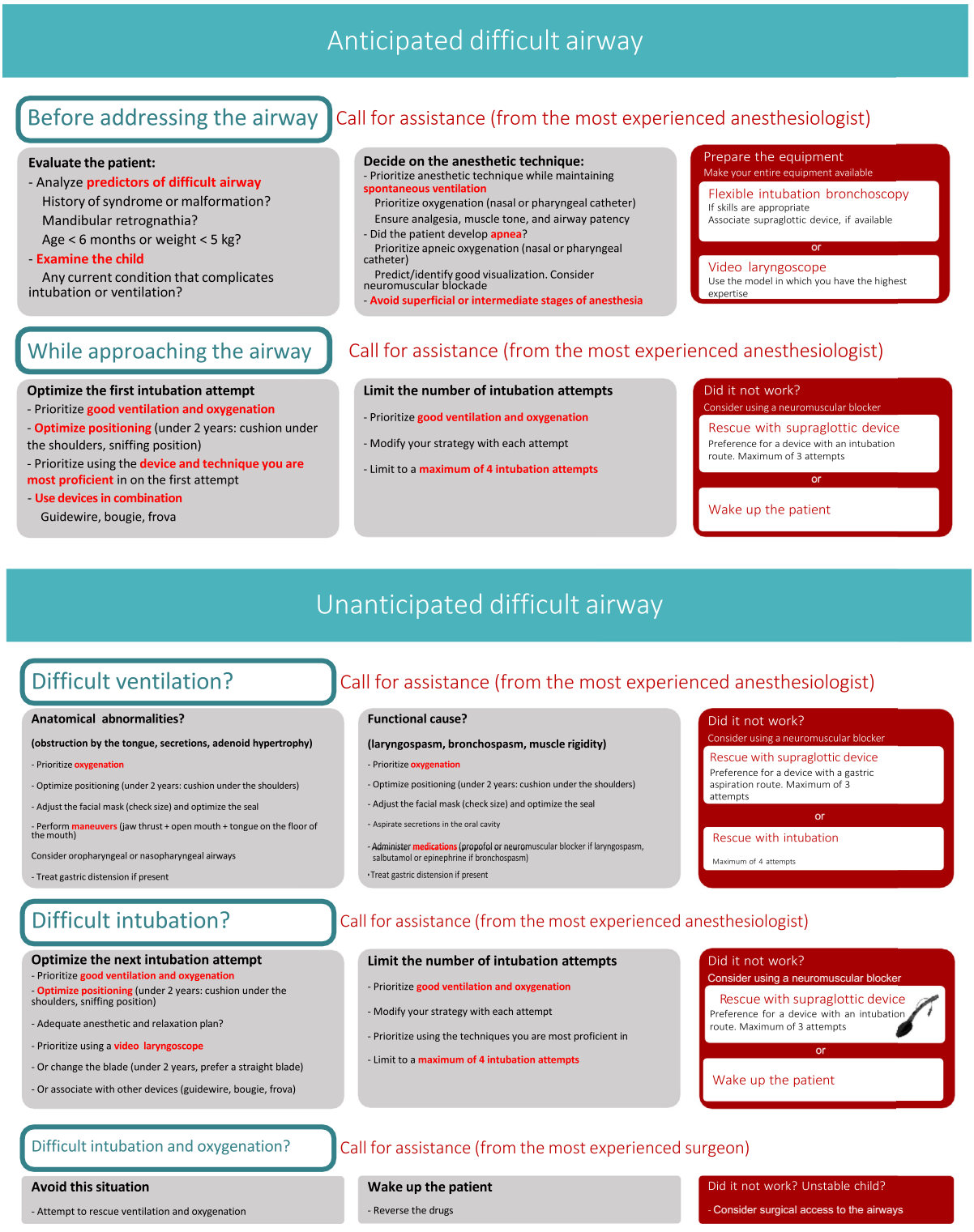

Figure 1 The management of anticipated and unanticipated difficult pediatric airways, as recommended by the task force of the Brazilian Society of Anesthesiology (SBA).

identifies seven key areas of focus for airway management in neonates and infants: preoperative assessment and preparation, medications, techniques and algorithms, identification and treatment of difficult airways, confirmation of tracheal intubation, tracheal extubation, and human factors. The recommendations were formulated using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology, assigning strong '1' or weak '2' recommendations with high 'A', medium 'B', or low 'C' quality of evidence.

In summary, the guidelines recommend the following: utilize medical history and physical examination to predict difficult airway management (1C); ensure an adequate level of sedation or general anesthesia during airway management (1B); administer neuromuscular blockers before tracheal intubation when spontaneous breathing is not necessary (1C); use a video laryngoscope with an age-adapted standard blade as the first choice for tracheal intubation (1B); apply apneic oxygenation during tracheal intubation in neonates (1B); consider a supraglottic airway for rescue oxygenation and ventilation if tracheal intubation fails (1B); limit the number of tracheal intubation attempts (1C); use a stylet to reinforce and pre-shape tracheal tubes when hyperangulated videolaryngoscope blades are used and when the larynx is anatomically anterior (1C); verify successful intubation with clinical assessment and end-tidal CO_2 waveform (1C); and apply high-flow nasal oxygenation, continuous positive airway pressure, or nasal intermittent positive pressure ventilation for post-extubation respiratory support when appropriate (1B).

Finally, considering all the pertinent evidence elucidated in the present document, the task force of the SBA advocates that, in the management of challenging pediatric airways, whether anticipated or unanticipated, practitioners should meticulously adhere to the procedural sequence outlined in Figure 1.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Recommendations from the Brazilian Society of Anesthesiology (SBA) for difficult airway management in adults



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Abstract
Difficult airway management represents a major challenge, requiring a careful approach, advanced technical expertise, and accurate protocols. The task force of the Brazilian Society of Anesthesiology (SBA) presents a report with updated recommendations for the management of difficult airway in adults. These recommendations were developed based on the consensus of a group of expert anesthesiologists, aiming to provide strategies for managing difficulties during tracheal intubation. They are based on evidence published in international guidelines and opinions of experts. The report underlines the essential steps for proper difficult airway management, encompassing assessment, preparation, positioning, pre-oxygenation, minimizing trauma, and maintaining arterial oxygenation. Additional strategies for using advanced tools, such as video laryngoscopy, flexible bronchoscopy, and supraglottic devices, are discussed. The report considers recent advances in understanding crisis management, and the implementation seeks to further patient safety and improve clinical outcomes. The recommendations are outlined to be uncomplicated and easy to implement. The report underscores the importance of ongoing education, training in realistic simulations, and familiarity with the latest technologies available.
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Difficult airway management during anesthesia is a major challenge for the clinician and requires a careful approach and well-designed protocols. Rapid assessment and action are mandatory in this condition, which can occur in a variety of scenarios, from elective procedures to medical emergencies.

It is, therefore, essential to underline the importance of ongoing training, education in realistic simulations and familiarity with the latest technologies available. Multidisciplinary approach and collaboration among healthcare providers, comprising anesthesiologists, surgeons, and nursing staff, play a decisive role in effective difficult airway management.

The present article aims to provide a comprehensive framework of practical recommendations for the management of patients presenting difficult airway, encompassing all steps from initial assessment to intervention strategies. By acknowledging the complexity and variability of these scenarios, the implementation of these recommendations aims to promote patient safety and improve clinical outcomes.

The present document is based on a synthesis and analysis of the current literature, mainly considering the most recent guidelines published by the American Society of Anesthesiologists (ASA),[1] and aims to assist the decision-making process during difficult airway management in anesthesiology. The Brazilian Society of Anesthesiology's (SBA) recommendations are not intended to establish absolute standards and using them cannot assure specific outcomes. The present recommendations may be implemented, adapted, or rejected according to the clinical scenario and the document can be revised as necessary to keep pace with evolving medical evidence.

Airway assessment

How to assess the airway

Before starting anesthetic care or airway management, an assessment should be performed whenever possible. There are two key issues to be observed during the clinical assessment:

- Risk assessment to predict difficult airway and risk of pulmonary aspiration: it includes checking data obtained from the patient's medical history or medical records, comprising personal data (age, sex, body mass index, weight, and height), medical conditions, diagnostic tests and interviews or questionnaires with patient/family. History of difficult tracheal intubation should be considered, as well as distorted airway anatomy, snoring, obstructive sleep apnea-hypopnea syndrome, diabetes mellitus or complementary exam findings (e.g.: plain X-ray, CT-scan).[1]

Several medical conditions can be associated with challenging airway management, such as acromegaly, congenital anomalies, rheumatoid arthritis, cardiopulmonary disease, endocrinopathies, ankylosing spondylitis, temporomandibular disorders, head/neck mass and airway lesions, obesity, pregnancy, burns, and coagulopathies with increased risk of bleeding.[2]

Airway or facial trauma, cervical spine instability, small mouth opening, small mouth, short and muscular neck, burn sequelae, congenital abnormalities, tumors, abscesses, trismus, congenital syndromes, history of difficult tracheal intubation are often associated with challenging tracheal intubation.[2]

Evaluating the risk of pulmonary aspiration is an important part of the pre-anesthesia assessment. For high-risk patients, rapid sequence induction and tracheal intubation or awake tracheal intubation may be necessary. Some factors that increase the risk of pulmonary aspiration are non-fasting, gastrointestinal obstruction, gastroesophageal reflux disease, hiatal hernia, previous gastrointestinal surgery, emergency surgery, delayed gastric emptying caused by conditions such as diabetes mellitus, chronic renal failure, opioid use, pregnancy, and obesity.[2]

- Airway examination (bedside and assisted): aims to detect upper airway disorders or anatomical anomalies by measuring facial and jaw features, anatomical distances and landmarks, obtaining ultrasound imaging, performing virtual laryngoscopy/ bronchoscopy, three-dimensional printing or bedside endoscopy.

Facial and jaw feature measurements comprise assessing mouth opening, voluntary jaw protrusion, head and neck mobility, presence of prominent incisors, presence of beard, and upper lip bite test. Anatomical measurements include modified Mallampati scores, thyromental distance, sternomental distance, interincisor distance, neck circumference, ratio of neck circumference to thyromental distance, ratio of height to thyromental distance, hyomental distance, and hyomental distance ratio.

If a difficult airway is suspected, the patient or guardian must be informed, the patient informed consent form should be carefully documented, and the airway assessment registered in the medical record. If awake tracheal intubation is the chosen management, the procedure should be explained in detail and any questions answered to gain patient collaboration during the procedure.

The assessment must be carried out for every patient even if general anesthesia is not planned. Predictive methods are unable to detect intrathoracic airway issues or hidden conditions.[2] When individually analyzed, the modified Mallampati test has limited accuracy for predicting difficult airways, thus it is not a useful screening tool. No single test reliably predicts how challenging it will be to perform mask ventilation, to accurately insert a supraglottic device, to execute direct laryngoscopy or difficult tracheal intubation. The challenge in airway management grows with the increase in the number of abnormal parameters.

Given most cases of difficult airway are unexpected, a comprehensive airway management strategy should be designed for each patient rather than a one-size-fits-all plan, even when the assessment is normal. Although difficult mask ventilation combined with difficult laryngoscopy is uncommon, it is far from rare.[3]

Predicting problems in airway management is still a defying matter, therefore it is important to always be ready for unexpected difficulties. If in doubt, direct laryngoscopy can be performed under topical anesthesia or very light sedation to assess the possibility of tracheal intubation.[3] Awake tracheal intubation has a high success rate and a favorable

safety profile, but it is underused in cases of anticipated difficult airway.[4]

Federal Council of Medicine (CFM) Resolution # 2,174/2017 provides for the practice of anesthesia and knowledge of its text must be mandatory for every anesthetist working in Brazil.[5] In its Annex II, the Resolution determines that the pre-operative anesthesia documentation must describe, among other aspects, patient risk stratification, and include a specific Informed Consent Form for anesthesia and consultation or pre-anesthetic assessment form. This consent form must contain, among other items, physical examination data, including detailed airway assessment: mouth and jaw opening, Mallampati classification, atlanto-occipital mobility, thyromental distance, dental conditions, dental prosthesis, and neck circumference. The recommended fasting time is 2 hours for clear liquids without residue (water, tea); 4 hours for breast milk; 6 hours for non-human milk or formula; 6 hours for light meals; 8 hours for regular diet.[4]

Ultrasound for difficult airway assessment

Ultrasound for initial assessment of difficult airway

Recent studies suggest that the combination of taking anatomical measurements assisted by ultrasound, performing careful physical examination, and determining facial characteristics, can help identify possible candidates for difficult airway and difficult laryngoscopy.[6,7] As examples, we have the measurement of the distance from skin to the hyoid bone, tongue thickness and distance from skin to the epiglottis.[8]

Prospective observational studies have shown that a difficult airway can be anticipated by measuring both temporomandibular junction mobility and tongue thickness, in association with other predictors, supporting adequate planning and systematization of management.[9]

Preoperative upper airway ultrasound imaging as a predictor of difficult airway in adults without anatomical abnormalities suggestive of difficult laryngoscopy (Cormack-Lehane III and IV)

Despite the availability of several tests as clinical indicators of difficult airway assessment, difficult laryngoscopy can still be a major issue in anesthetic practice. Carsetti et al.[10] published a systematic review aiming to answer this matter. Among the fifteen studies selected, the large majority used distance measurements from skin to epiglottis, skin to hyoid bone, skin to vocal folds and the pre-epiglottic space depth to distance from epiglottis to vocal folds ratio (Pre-E/E-VC). The study found that patients with challenging laryngoscopy had higher scores in the first three measurements, compared to patients with straightforward laryngoscopy, and that the distance from skin to epiglottis was the most frequently studied parameter. Due to the great heterogeneity in the methods of measurements of the distances, such as different head positioning (neutral, extended, or olfactory position) and the execution of external maneuvers during laryngoscopy, we still cannot draw any robust scientific evidence from the findings of Carsetti et al.

Martinez-Garcia et al.,[11] in a prospective observational study, reported that the distance from skin to epiglottis (DSE) $\geq$ 3 cm could be associated with difficult laryngoscopy, with a positive predictive value (PPV) of 69.23 %. Equally, a difference between skin-epiglottis distance and skin-glottis distance longer than 1.9 cm (DSE $-$ DSG $\geq$ 1.9 cm) had a PPV of 78.57%.[11]

Alessandri et al.[12] and Sotoodehnia et al.[13] described the suitability of ultrasound imaging to identify difficult airways, comprising challenging laryngoscopy and difficult mask ventilation. They revealed that the measurements correlated to difficult airway were distance from skin to epiglottis, distance from skin to hyoid bone; hyomental distance, and hyomental distance ratio.

Ultrasound for identification of the cricothyroid membrane

Anesthesiologists have found it easier to correctly identify the cricothyroid membrane by palpation guided by ultrasound.[14] Siddiqui et al.[15] reported that ultrasound is more accurate than palpation for identifying the cricothyroid membrane in subjects with poorly defined cervical reference points. Transverse laryngeal ultrasonography enables identifying inverted V-shape imaging of the thyroid cartilage with high sensitivity and interindividual agreement but with low specificity (i.e., inverted V-shape images were also viewed at the cricothyroid membrane level, potentially confounding its correct location).[16]

For ultrasound identification of anterior cervical structures, mainly the cricothyroid membrane, we can use the TACA (Thyroid cartilage—Airline—Cricoid cartilage—Airline) method. With a linear transducer placed in the transverse position on the anterior cervical region, we initially identify the triangular-shaped thyroid cartilage (T), then sliding the transducer caudally we visualize the air (A) corresponding to the cricothyroid membrane, moving the transducer further caudally, we identify the cricoid cartilage as a C-shaped structure and, finally, we move the transducer back cephalad until the cricothyroid membrane is visualized and marked. We can also identify the same structures with the transducer placed longitudinally on the anterior cervical region, in a technique called “string of pearls”. With the transducer positioned longitudinally and close to the sternum, we identify hypoechoic images similar to strings or pearls (tracheal rings); sliding the transducer cephalad we visualize a more elongated, wider and more superficial structure (cricoid cartilage), then, immediately more cephalad, the cricothyroid membrane is found. Finally, further cephalad, we identify the thyroid cartilage.[17]

The cricothyroid membrane can be identified by inspection and/or palpation and, if these methods fail, the membrane can be identified by ultrasound. The technique has a quick learning curve with long-lasting retention and has been shown to be more effective than the neck palpation technique.[18] Using ultrasound for pre-anesthetic identification of the cricothyroid membrane in pregnant women is a straightforward and superior choice to computed tomography, as it is devoid of any risk of ionizing radiation to mother and fetus.[19] Additional imaging studies can be used for the correct identification and differentiation of cervical structures.

Inaccurate location of the cricothyroid membrane in “cannot intubate, cannot ventilate” situations can result in cricothyroidotomy failure and a disastrous outcome. It is

sensible to identify the cricothyroid membrane before anesthesia induction as a routine pre-anesthetic assessment, especially for anticipated difficult airway patients, and it is recommended by several practical guidelines.[1,20]

Pre-oxygenation and apneic oxygenation

Pre-oxygenation in patients with difficult airway

The pre-oxygenation goal is to increase patient oxygen reserve to prevent or delay arterial oxygen desaturation during apnea. All difficult airway patients must be pre-oxygenated before general anesthesia induction and denitrogenation can be attained offering a proper 100% oxygen flow to the respiratory system while holding the mask firmly adapted to the patient's face. Pre-oxygenation is effective when the expired fraction of oxygen (EtO2) reaches 0.87 to 0.9.[21] Several pre-oxygenation techniques have been described, two of which are widely used[21]:

- Spontaneous ventilation with 100% O2 for 3 to 5 min using a fresh gas flow rate of 5 $L.min^{-1}$ in the breathing circuit;
- Spontaneous ventilation with 4 to 8 vital capacity maneuvers with 100% oxygen, for 30 and 60 s, respectively.

Nasal apneic oxygenation can be delivered by high-flow oxygen (10 to 15 $L.min^{-1}$) through nasal cannulas and has been shown to significantly delay the onset of desaturation during apnea (safe apnea time) until definitive airway control. The technique has prolonged safe apnea time in the operating room, pre-hospital care and emergency room.[22] An alternative approach for preventing hypoxia during induction and rapid sequence intubation is to avoid apnea altogether. An extensive multicenter study showed that gentle mask ventilation between induction and laryngoscopy reduced the incidence of hypoxia without adversely affecting pulmonary aspiration rates.[23]

Although efficacy data are limited for the non-obese population, pre-oxygenation should be used during the induction of general anesthesia in obese patients, as it enables higher safe apnea time without being harmful to the patient. Desaturation can occur between 19% and 70% of tracheal intubations and it is the most common cause for aborting the first tracheal intubation attempt. Thus, using pre-oxygenation and apneic oxygenation in all patients is a sensible measure. Standard or modified larger caliber nasal cannulas for administration of gas flow rates between 10 and 15 $L.min^{-1}$ are well tolerated, low-risk and a low-cost alternative for patient oxygenation.[22]

Proper patient positioning during pre-oxygenation is important, as a moderate (approximately 25°) head-up position can delay desaturation onset in the general population. In obese patients, controlled studies have also shown the benefit of sitting or the 25-degree head-up position during pre-oxygenation compared to the supine position.[24]

The administration of supplemental oxygen is recommended prior to initiating difficult airway management and, whenever possible, during the difficult airway management process, including tracheal extubation. Opportunities for supplemental oxygen administration include (but are not limited to) delivery of oxygen via nasal cannulas, face mask, or supraglottic insufflation.[1] According to the Difficult Airway Society, administration of supplemental oxygen is also recommended for awake tracheal intubation.[4] Administration of supplemental oxygen should start upon patient arrival in the operating room and continue throughout the preparation for awake tracheal intubation. If available, oxygen administered via a high-flow nasal cannula (HFNO) should be the technique of choice.[4]

Other methods can be considered, especially for critically ill patients. Non-invasive positive pressure ventilation (NIPPV) delivers a high concentration of oxygen, alleviates respiratory muscle fatigue, recruits atelectatic alveoli, and can be used before definitive control of the airway. For patients who do not tolerate the face mask, a supraglottic device can be used to increase oxygenation or to provide a conduit for tracheal intubation.[22]

Awake tracheal intubation

Sedation goals during awake tracheal intubation

Sedation during awake tracheal intubation aims to offer comfort and increase patient cooperation, making the procedure easier, safer, and more tolerable, ensuring optimal conditions for intubation when associated with effective topical anesthesia.[4,25] Sedation should be minimal, promoting anxiolysis, preserving spontaneous breathing and airway patency, keeping the patient responsive to verbal or tactile stimulation and hemodynamically stable. A certain degree of amnesia with a low incidence of recall of the procedure is desirable. The goal is to provide conscious sedation (or moderate sedation) during awake tracheal intubation. Sedation cannot be used as a substitute for ineffective topical anesthesia.[26]

Best candidates for awake tracheal intubation

Awake tracheal intubation should be considered whenever a difficult airway is anticipated.[4] When appropriate, awake intubation should be performed whenever difficult tracheal intubation is suspected and one or more of the following factors are present: difficult ventilation (under face mask or supraglottic device); increased risk of pulmonary aspiration; patient cannot tolerate a brief episode of apnea; difficulty in airway rescue with an invasive emergency approach.

Some examples of patients who may benefit from awake tracheal intubation are: personal history of radiotherapy, head and neck surgery or malignancy, glottic tumors, unstable cervical spine, limited mouth opening or cervical extension, previous anesthesia presenting difficult airway, critical patients (physiological difficult airway), and morbid obesity.[27] Preservation of breathing function is highly recommended for such patient groups, as well as pre-oxygenation in a head-up position, optimizing functional residual capacity, and prolonging safe apnea time.[22]

Methods and devices for topical anesthesia

The success of awake tracheal intubation depends on the effective topical application of local anesthetic to the airways, allowing awake tracheal intubation to be performed with minimal or even no sedation, which is an important step in this

approach to difficult airway. The Difficult Airway Society's practical guidelines[4] for awake tracheal intubation in adults recommend using a cognitive aid, such as a checklist before and during its execution, emphasizing that the main components of awake tracheal intubation are sedation (optional); topical application of local anesthetic; oxygenation; performance of the physician and team. The maximum dose of lidocaine of 9 $mg.kg^{-1}$ of lean body weight must be respected, regardless of the administration technique.[4] Compared to other local anesthetics, lidocaine has advantages due to its lower cardiovascular and systemic toxicity. The lidocaine plasma peak depends on the total dose, rate and site of injection, administration technique and individual patient factors influencing lidocaine distribution, metabolism, and excretion.[28]

Proper topical anesthesia of the larynx and trachea before tracheal intubation prevents increases in heart rate and arterial blood pressure and reduces the likelihood of coughing during anesthesia wake-up. Several techniques are available: atomizers to disperse the local anesthetic, spray-as-you-go technique (local anesthetic instillation through the flexible intubating bronchoscope working channel or a catheter), and nerve blocks. There is no evidence suggesting the superiority of any technique. However, glossopharyngeal and superior laryngeal nerve blocks are associated with high plasma concentrations of local anesthetic, higher systemic toxicity and reduced patient comfort.[27]

Some authors recommend using topical anesthesia in the initial airway management, and if required using glossopharyngeal and superior laryngeal nerve blocks and transtracheal injections as a complement. Atomizers allow drugs to be dispersed in a fine mist of particles measuring between 30 and 100 micrometers consistently and directly onto the nasal mucosa, pharynx, larynx, and trachea, allowing for excellent local anesthesia. Lidocaine can be nebulized, but as its absorption varies, it may require higher doses, increasing the risk of pulmonary absorption and systemic toxicity.[28]

Notwithstanding the administration route used, the anesthesiologist should maintain a high degree of vigilance for the classic symptoms of local anesthetic systemic toxicity. The symptoms generally start with central nervous system (CNS) excitement, such as circumoral numbness, hearing changes, metallic taste, and agitation. Symptoms can progress to seizures, CNS depression, coma, and cardiorespiratory arrest. Classically, CNS toxicity precedes cardiac toxicity.[27] Lidocaine is the local anesthetic most commonly implicated in systemic toxicity and has been used more frequently in tissue infiltration by surgeons and in intravenous infusions for perioperative analgesia. Between 2017 and 2020, 36 published reports of local anesthetic systemic toxicity were identified, one of which occurred in a healthy volunteer during an awake tracheal intubation training course.[29] Large-volume infiltration or topical application of local anesthetic in highly vascularized tissues present risk, especially for cardiac patients; extremes of age with frailty and muscle wasting; poor blood perfusion conditions; compromised liver function and reduced plasma levels of α1- acid glycoprotein. Immediate management begins with discontinuing local anesthetic administration and calling for help. Regarding neurological symptoms, benzodiazepines can attenuate or suppress seizures. Life support measures should be initiated immediately, including immediate airway control, cardiopulmonary resuscitation protocol according to current guidelines, and infusion of 20% lipid emulsion.[29]

Drugs recommended for sedation during awake tracheal intubation

There are several drugs available, and the choice will depend on factors such as availability and familiarity of the anesthesiologist performing the procedure.[27] Safe doses of benzodiazepines, opioids, α-2 agonists, and hypnotics can be administered alone or combined to avoid ventilatory depression and deep sedation.[27] Among benzodiazepines, midazolam is the most used, usually combined with an opioid. The advantage of the benzodiazepine and opioid combination is the straightforward technique, low cost, availability of reversal agents and the vast experience of anesthesiologists with the combination. The disadvantage, however, is that intermittent boluses can be associated with rapid progression to deep sedation.[4] Hypnotics such as propofol have been investigated in several studies, albeit more focused on target-controlled infusion.

Dexmedetomidine and remifentanil are associated with high patient satisfaction, and low risk of deep sedation and airway obstruction. Dexmedetomidine is a superior agent for use in awake tracheal intubation when compared to midazolam, fentanyl, propofol or sufentanil, as it presents the advantage of providing satisfactory conscious sedation without ventilatory depression, an antisialagogue effect, and moderate analgesia.[30] Cabrini et al.,[26] in the first systematic review of randomized clinical trials focused on fiberoptic intubation in awake surgical patients with a difficult airway, suggested that the different methods for performing awake tracheal intubation are equally safe and effective, but were unable to identify a clearly superior protocol. A high degree of efficacy and safety was observed with minimal differences among protocols and a lower incidence of desaturation or apnea episodes when dexmedetomidine or sevoflurane was used for sedation. Thus, dexmedetomidine may offer a superior safety profile compared to other sedatives.[31]

Contraindications for awake tracheal intubation

In general, there are no absolute contraindications other than patient refusal. Relative contraindications are airway bleeding, allergy to local anesthetics, uncooperative patients (change in level of consciousness), pediatric patients, or situations such as fixed obstruction of the larynx, subglottic stenosis or patient scheduled for elective tracheostomy.[1,4]

Video laryngoscopy

Appropriateness of the video laryngoscope as the first option for tracheal intubation

Tracheal intubation involves three distinct components:

1. visualization of laryngeal structures and the glottic cleft;
2. passage of the tracheal tube through the vocal folds;
3. advancing the tube to the tracheal lumen. Improvement in the visualization of glottic structures is evident with video laryngoscopy (components 1 and 2). Video laryngoscopy also lowers the Cormack-Lehane classification grade when compared to difficult direct laryngoscopy and decreases esophageal intubation rates.[32]

Video laryngoscopy has clear advantages over direct laryngoscopy for tracheal intubation, especially when the first attempt is unsuccessful, or when the airway is known to be challenging. Video laryngoscopy is the first rescue option after failed tracheal intubation by direct laryngoscopy and can be elected as the first technique of choice for managing an anticipated difficult airway. For obese patients, using the video laryngoscope instead of the Macintosh-type laryngoscope is associated with more likely successful tracheal intubation on the first attempt, a result more consistent with the use of a tracheal tube introducer guide.[32] To prevent esophageal intubation, the routine use of a video laryngoscope has been recommended whenever possible, as well as monitoring exhaled CO2 (EtCO2) by capnography and pulse oximetry during any airway control situation.[33]

Video laryngoscopy is a crucial tool for teaching and training the laryngoscopy and tracheal intubation techniques.[34] The quality of imaging provided by the device's screen, with adequate brightness and high definition, facilitates the identification of key landmarks, such as the epiglottis or vocal cords, and enables trainees to guide the tracheal tube more quickly and assertively. Another advantage of training with video laryngoscopy is that the instructor follows the maneuver simultaneously by viewing the screen and can make observations or instant corrections to guide the inexperienced laryngoscopist.[34] Nonetheless, there are disadvantages and limitations. The cost of most devices is still high, curbing their wide availability and use. The equipment may present technical issues or failures such as: lens fogging due to temperature gradient, secretions or blood blocking the camera view, and lack of power due to discharged batteries. Adverse outcomes associated with video laryngoscopy include sore throat, laryngospasm, and lip, dental or mucosal lesions.[32]

Video laryngoscopy is not recommended if one of the following factors is present: mouth opening < 2.5 cm; cervical spine fixed in flexion; patient presenting stridor with airway or upper digestive tract tumor.[1] We recommend evaluating if the video laryngoscope can be introduced into the mouth before anesthetic induction. Desaturation at levels below 95% requires interruption of intubation maneuvers in favor of those that allow oxygenation. If there is a proven risk of hypoxemia, video laryngoscopy cannot replace mask ventilation or using a supraglottic device to properly oxygenate the patient.[1,21]

Airway management after anesthetic induction

How to proceed in an unanticipated difficult airway scenario

Unanticipated difficult airway happens even to experienced clinicians. Strategies should preferably be planned before anesthetic induction. Failure in the initial approach may occur and subsequent plans must be well established. The first step is to avoid fixation error (a cognitive error that occurs when the clinician focuses on just one aspect of care and overlooks others more relevant). The number of attempts per device should be limited. We recommend that the maximum number of attempts with the same device should be three, and that, upon a new attempt, the oxygen supply to the patient should be optmized.[21]

Whenever a tracheal intubation attempt fails, one should call for help early and disclose to the team involved that the initial plan could not be executed, in order to improve team awareness of the condition. Be aware of elapsing time, the number of attempts and oxygen saturation.[20] We recommend checking the ventilation with a face mask by connecting a capnograph to the mask and by monitoring arterial oxygen saturation (SpO2) throughout the process.

Confirmation of adequate ventilation by capnography and maintenance of SpO2 in a safe range enables the clinician to consider which device is most suitable for a given patient. There are several alternatives: video laryngoscopes, alternative laryngoscope blades (change of size or shape), flexible intubating bronchoscopes, bougie-type introducer guides, optical stylets, external laryngeal maneuvers, or a combination of techniques (combining video laryngoscopy and a bougie introducer, for example).[1]

Alternative techniques must be chosen according to the knowledge and skills of the clinician handling the case. It is important to avoid multiple attempts with the same device, as they can cause airway trauma, leading to worse face mask ventilation, deterioration of SpO2, and progression to a cannot intubate, cannot ventilate scenario.[20]

It is worth underscoring that there are situations in which a decision must be made to continue the procedure using an alternative device (e.g., maintain ventilation with face mask or supraglottic device) when it is impossible to perform tracheal intubation without harming the patient, provided that the ability to keep an adequate ventilation is preserved. Waking the patient, postponing the case, or delaying intubation and rescheduling the case with more suitable resources should be considered.[1]

What should be done during the "cannot intubate, cannot ventilate" scenario

After anesthetic induction, the inability to intubate and ventilate the patient at the same time may occur. This is rare, but extremely challenging and depends on logical, sequential, and quick thinking to prevent catastrophic complications. We initially recommend that the first laryngoscopy attempt be performed with the dominant eye, with optimized positioning of the patient and operating table, and using the bimanual technique. Equally, face mask ventilation should be optimized using oropharyngeal cannulas (e.g., Guedel cannula) and the four-handed ventilation technique. If ventilation and/or tracheal intubation fails, help must be requested immediately.[1,20]

At this time, immediate ventilation rescue must be obtained using, preferably, a second-generation supraglottic device with a gastric drainage channel and designed to facilitate intubation through the device's internal lumen.[1] If successful, adequate oxygenation has been achieved once again, allowing for alternatives for continuing the case or deciding on equipment for performing the tracheal intubation, or even canceling or postponing the case.

If the chosen supraglottic device fails, the recommendation is to try another one, preferably with a format different from the one previously attempted, provided that oxygen saturation is kept at acceptable levels and the patient does not present severe bradycardia.[1,20] If adequate oxygenation cannot be sustained and when it is impossible to awaken the

patient, an invasive technique will be necessary to manage the airway. Several invasive techniques have been described: surgical tracheostomy, surgical cricothyroidotomy, needle cricothyroidotomy and pressure-regulated ventilation, and large-caliber cannula cricothyroidotomy (including the approaches using the Seldinger technique over a guide wire).[1,20,21]

If the cricothyroid membrane is palpable, the percutaneous technique can be performed. We recommend large-caliber cannulas (with an internal diameter above 4.0 mm), as they can deliver ventilation with low-pressure devices such as bag-valve device or conventional mechanical ventilator. We do not recommend using small-caliber cannulas, as they must be ventilated using high-pressure devices, which are not routinely available in hospitals in countries with limited resources.

Open surgical cricothyroidotomy is the fastest and most reliable method for securing airway control in an emergency scenario.[1] Several surgical techniques have been described, but there is no evidence of superiority of one over another.[1] All techniques have common steps: cervical extension, cricothyroid membrane identification, incision through the skin and cricothyroid membrane, and insertion of the cuffed tracheal tube. The Difficult Airway Society recommends the sequential use of a scalpel, bougie introducer and tracheal tube. This technique must be performed with the patient's head in cervical hyperextension and associated with a neuromuscular blocker. With the cricothyroid membrane palpable, a transverse incision is made in the skin and cricothyroid membrane (sharp edge directed caudally), the bougie introducer is inserted into the trachea towards the patient's chest until resistance to progression is found, usually after approximately 15 cm of the bougie is inserted. Then, using the bougie as a guide, a 6.0 mm cuffed tracheal tube is pushed down the trachea and the bougie is removed. After inflating the tracheal tube cuff and confirming tracheal intubation capnography, the tracheal tube should be properly secured. When the cricothyroid membrane is impalpable, an 8-10 cm vertical midline skin incision is made, caudad to cephalad. Blunt dissection with the fingers of both hands separates tissues to identify and stabilize the larynx in order to incise the cricothyroid membrane, followed by the steps described above.[1,20,21]

When to awaken the patient, cancel or postpone the procedure

Postponing or canceling the case has the following main objectives: wait for or request specialized help, optimize the preparation of the patient, change strategy and perform awake tracheal intubation, or wait for the arrival of suitable equipment unavailable at the time. Therefore, if the case is not an emergency, this strategy should be contemplated before proceeding with alternative airway approaches.[1]

Human factors in airway management

Human factors and how they are related to the management of difficult airway

Human factors constitute the scientific discipline that examines interactions between humans and system components. It aims to improve clinical performance by acknowledging the impact that teamwork, tasks, equipment, workspace, culture, and organization have on human behavior and applying this understanding to clinical situations.[35] By their very nature, humans inevitably make mistakes. The study of human factors tries, first, to estimate the likelihood of an error occurring, and then to establish barriers to prevent the error to progress and harm the patient.[36] Up to 80% of anesthetic adverse events are human error-related.[37] In the UK, the study linked to the 4th National Audit Project (NAP4) concluded that issues related to human factors (poor judgment, ineffective communication and poor teamwork) were present in 40% of major complications in airway management and were considered as factors impacting the outcome in 25% of cases.[38] The most critical points were failure to anticipate risks, incorrect decisions, difficulty in performing tasks, untrained practitioners, time pressure, tiredness, hunger, stress, poor communication and limitations in competence. Overall, the contribution of human factors, related to issues harming the patient during airway management, is at least as important as those arising from technical problems.[39]

Non-technical or soft skills

Currently, the complexity of patient care requires anesthesiologists with a wide range of skills and attributes. Traditional training has placed great emphasis on acquiring technical knowledge and practical skills to ensure competent services. However, some social behaviors, psychological states and cognitive functions relate to superior outcomes and lower rates of adverse events. These attributes have been called non-technical skills or soft skills and have been identified as teamwork, task management, decision making, and situational awareness. They can also be classified as cognitive and mental skills (planning, decision-making under pressure, dealing with stress, situational awareness, appropriate use of technology) and social and interpersonal skills (teamwork coordination, leadership, effective communication).[40,41]

Efficient teamwork depends on the exchange of relevant information in a coordinated and fast way to execute tasks. Skills and abilities of team members must be identified, and roles assigned, seeking to explore the best in each individual, but paying attention to avoid stress and fatigue. The different tasks must be executed in a coordinated and simultaneous manner, with all team members supporting and assisting each other. The responsibility lies with all members and not individuals.

Decision-making is based on the prior identification of possible options in a given scenario. Discussion with the team and the support of algorithms help reach the correct choice. It is necessary to continually reassess the scenario and, if required, change or adjust decisions. Task management is also known as leadership. A good leader plans and gets ready to execute tasks and must be aware of the available resources and their appropriate use to achieve goals. A leader must always be aware of priorities and be focused on patient safety and quality of care. Situational awareness is the perception of environmental elements and events concerning time or space, the understanding of their meaning, and the prediction of their future status. Situation awareness is a critical foundation for successful decision-making in a wide range of situations in medicine, aviation, industry,

and education. Lack of situational awareness has been identified as a major factor in accidents attributed to human error. Self-knowledge to recognize one's abilities and limitations in a given situation is essential. Collecting and analyzing information on the patient's condition and comparing it to expected standards or goals in a systematic way enables the establishment of diagnoses and the planning of the next steps.[42]

Stress is one of the most important factors impacting human behavior. It undermines cognitive status, effective communication, and both technical and non-technical skills, which damage the ability to respond to a crisis. Although stress susceptibility may differ among individuals in terms of impact on performance, it is present in everyone, if pressure exceeds limits. Stress-related cognitive impairment can cause fixation error, distorted perception of time, memory failure, and impaired judgment. These issues can induce even experienced physicians to make mistakes in matters that are considered basic when managing airways in emergency situations. A common event during airway management is the fixation on tracheal intubation, overlooking alternatives for oxygenating the patient using a face mask or a supraglottic device.[43]

How to develop and apply non-technical skills

Training and continuing education are fundamental for attaining practitioners with high technical capacity and non-technical skills. Some teaching tools can be used, such as the mnemonic ARACHNID,[36] which includes the following parameters: Algorithms — use algorithms to direct management; Resilience — when an event occurs, listen and support those involved, and solve it to prevent the event from recurring; Cognitive Aids — cards or warnings with structured and quickly available information to improve clinician cognition and adherence; Checklists; Handover — it is vital to comprehensively transfer patient information and continuity of care; Non-technical skills — they are crucial tools, such as communication, teamwork, situational awareness, avoiding task fixation, leadership and continuity, hierarchy and stress management; Incident investigation; Design of equipment, packaging, drugs, operating rooms, modern and intelligent emergency rooms — create barriers to mistakes and facilitate best practices.

Another fundamental tool is realistic simulation, which has been increasingly used as a training and knowledge retention strategy. By following the concepts of crisis resource control, realistic simulation enables teaching and assessing skills required to effectively overcome crises. Moreover, high-fidelity simulation tools enable reenacting complex clinical situations to analyze individual or team behavior during decision-making processes. Simulation also allows reviewing concepts based on scientific literature to discuss and provide feedback on behavioral aspects of performance, and evaluate and understand the difficulties found.[31]

Initiatives such as The Airway Lead or Rapid Response Teams projects to control the airway proved their extreme importance during the COVID-19 pandemic. Non-technical aspects were highlighted while training the teams responsible for managing the most critical cases, often under great pressure and psychological stress.[44,45]

Confirmation of intubation

Methods available to confirm tracheal intubation

According to the CFM Resolution #2,174/2017,[5] the minimum safety conditions for the practice of anesthesia comprise the availability of continuous monitoring of oxygen saturation of hemoglobin through pulse oximetry and continuous monitoring of ventilation through exhaled carbon dioxide levels by capnography, in the following situations: anesthesia using an airway device (such as tracheal or bronchial intubation or supraglottic device), clinical situations requiring artificial ventilation, or exposure to triggering malignant hyperthermia agents. Thus, all tracheal intubations must be confirmed and monitored using continuous waveform capnography, considered the gold standard for confirming intubation given its sensitivity of 98 to 100% (percentage of tracheal intubations correctly detected by a positive test result) and 100% specificity (percentage of esophageal intubations correctly detected by a negative test result).[46] Capnography generally provides earlier confirmation of effective ventilation than SpO2, which should also be employed continuously during airway management. Continuous monitoring capnography waveform must be used in all intubated patients, in every hospital area, including during patient transportation inside the hospital.[46]

After tracheal intubation, if proper tube positioning is uncertain, the clinician must decide between removing the tracheal tube or optimizing ventilation. Additional techniques to confirm tube positioning can also be used, namely: visualization techniques (any technique), flexible bronchoscopy, ultrasound or radiological examinations.[1] Systematic reviews and meta-analyses have revealed that ultrasound is a valuable and reliable accessory tool for determining correct tracheal tube location, including resuscitation in cardiorespiratory arrest.[47,48] According to Chrimes et al.,[33] the standard reaction when an expected $ETCO_2$ waveform is not shown should be to remove the tracheal tube and attempt ventilation using a face mask or supraglottic device. Clinical examination should not be used to rule out esophageal intubation. The tracheal tube should be removed if any of the following conditions are true: esophageal intubation cannot be ruled out; $ETCO_2$ waveforms are absent; SpO_2 deteriorates before the $ETCO_2$ sustained curve resumes.

Safe tracheal extubation

When to extubate the patient

Careful tracheal extubation planning increases safety and prevents complications. Although the rate of extubation failure or reintubation in the operating room after a surgical procedure is relatively low (0.1% to 0.45% incidence), when it occurs, the event is related to increased mortality.[49] Extubation failure after general anesthesia is defined by the patient's inability to maintain a patent airway and spontaneous ventilation, after intentional tracheal extubation, within a specified time. The NAP4 report revealed a mortality rate of approximately 5% associated with extubation failure after general anesthesia and an incidence of severe complications in 13% of patients presenting extubation

failure.[38] One in every six severe adverse events related to airway management occurred at the end of anesthesia or upon arrival at the post-anesthesia care unit.[38]

After the end of any anesthetic procedure, the anesthesiologist must evaluate whether the patient is fit for extubation. Every extubation must be elective, and it is necessary to select the appropriate moment and place to execute it, for example, in the operating room, post-anesthesia care unit or intensive care unit. Postoperative residual neuromuscular blockade remains a frequent issue, with a reported rate between 20% and 64%.[50] In most elective cases, extubation can be done in the operating room, as long as physiological parameters are stable, recovery from anesthetic effects is complete and reversal of neuromuscular blockade is adequate. At the time of extubation, it is crucial to ensure the immediate availability of supplemental oxygen, reintubation equipment and the presence of an assistant.[21] Monitoring ventilation, airway patency and maintaining continuous oxygenation until complete recovery are essential after tracheal extubation.[21]

How to design a strategy for extubation and subsequent airway management

Algorithms can reduce complication rates related to extubation and the need for reintubation. The detection of the risk factors related to the patient's physical status and comorbidities and the possible clinical repercussions caused by anesthesia and surgery is essential. Thus, several guidelines and cognitive aids have been made available: 1. Proper extubation requires meticulous preparation, comprising reversal of residual neuromuscular blockade, preoxygenation, appropriate positioning, effective team communication, and planning the management of potential complications after extubation. The strategy will depend on the type of surgical procedure and the patient's clinical status at the end of the intervention, but also on the skills and preferences of the attending physician; 2. Assuring that a qualified assistant is present for support for treating potential complications related to extubation; 3. Assessing the indication and feasibility of short-term use of an airway exchange catheter and/or supraglottic devices that can be used as alternatives for oxygenation and fast-track reintubation; 4. Before attempting extubation, assessment of the risks and benefits of elective surgical tracheostomy in specific situations; 5. Assessment of the risks and benefits of awake extubation versus extubation before return to consciousness. Patients who require suppression of hemodynamic responses may benefit from awake extubation associated with drugs attenuating the hemodynamic response, or extubation under deep anesthesia using a supraglottic device, aiming at a smoother transition during awakening; 6. Use of supplemental oxygen throughout the extubation process.[21,49,51]

Most complications related to extubation can be prevented. Before extubation, the clinician must carefully prepare all necessary resources to deal with fairly predictable complications. Practical guidelines are useful in rare and serious situations, and some evidence has suggested superior results when using them.[1,51]

Clinical factors that increase the risk of extubation failure

Obesity, asthma and chronic obstructive pulmonary disease are the most common comorbidities associated with adverse events related to airway management. According to data from the NAP4 report, upper airway obstructions caused by laryngospasm, tracheal tube or supraglottic devices are among the main causes of airway complications during awakening and post-anesthesia recovery.[38] Upper airway obstruction, even when short-lasting, can cause post-obstructive pulmonary edema (or negative pressure pulmonary edema) and severe hypoxia. In most reported events, the time window from upper airway obstruction onset to pulmonary edema symptoms was only a few minutes.[52]

Other frequent causes of airway obstruction are edema and bleeding, especially after head and neck surgeries and Ear-Nose-Throat procedures. Airway bleeding requires careful inspection and thorough suctioning before tracheal extubation. Cervical hematoma can cause airway edema and obstruction due to reduced venous drainage and can render reintubation significantly difficult, even in patients showing easy direct laryngoscopy at the beginning of the procedure. Surgical manipulation can produce glottic and periglottic edema, disrupt airway patency and cause obstruction. Other conditions may also be associated with this mechanism, such as multiple tracheal intubation attempts in difficult airway situations, fluid overload, pre-eclampsia or angioedema.[51]

Robotic surgery has increased the use of the Trendelenburg or steep head-down position, which can cause atelectasis and significant reduction in lung compliance, worsen intraoperative ventilation mechanics, and can contribute to desaturation after tracheal extubation. Airway edema can take place in between 0.7 and 26% of patients.[53] Clinicians should pay special attention to a triad of airway risk factors: head-down position, high peak pressure during mechanical ventilation and fluid overload.[53] In the presence of the triad, it is vital to exclude significant edema, subcutaneous emphysema, barotrauma, and pneumothorax before tracheal extubation.

The main risk factors for postoperative reintubation are residual neuromuscular blockade, preventable human factors (inexperience, lack of standardized procedures), clinical conditions reducing cardiac or pulmonary functional reserve and airway obstruction.[21]

How to manage morbidly obese patients and obstructive sleep apnea-hypopnea syndrome after tracheal extubation

Morbidly obese patients, with or without obstructive sleep apnea-hypopnea syndrome (OSAHS), should prophylactically receive supplemental oxygen in the upright or semi-sitting position.[54] Both groups can be safely monitored in a surgical ward after discharge from the postanesthetic care unit. NIPPV devices, such as CPAP (Continuous Positive Airway Pressure) or BiPAP (Bilevel Positive Airway Pressure), should be considered in the presence of ventilatory discomfort. Patients with OSAHS using CPAP or BiPAP at home preoperatively must use the device during the immediate postoperative period. Patients with obesity hypoventilation syndrome (obese patients presenting chronic daytime hypercapnia)

have an increased risk of developing perioperative ventilatory adverse events. NIPPV should also be considered in the immediate postoperative period in this patient population, mainly in the presence of hypoxemia.[54]

Conflicts of interest

The authors declare no conflicts of interest.

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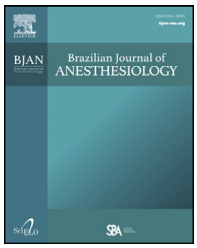

ORIGINAL INVESTIGATION

Palonosetron versus ondansetron for prophylaxis of postoperative nausea and vomiting in laparoscopic cholecystectomy: a non-inferiority randomized controlled trial☆



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KEYWORDS
Pre-exposure prophylaxis;
Risk factors;
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Antiemetics

Abstract

Background: We tested the hypothesis that, within the margin of 15% of risk difference, palonosetron is not inferior to ondansetron in reducing the incidence of postoperative nausea and vomiting (PONV) in laparoscopic cholecystectomy.

Methods: We conducted a double-blind, non-inferiority, randomized, controlled trial of 212 patients aged 18 to 65 years undergoing laparoscopic cholecystectomy under general anesthesia in two secondary care hospitals. Patients were randomly assigned to receive either palonosetron (0.075 mg) or ondansetron (8 mg) intravenously at induction of anesthesia. Ondansetron (8 mg) was also administered 8 and 16 hours postoperatively. All anesthetic and surgical procedures were standardized. Patients were evaluated for 24 hours postoperatively for the occurrence of PONV.

Results: A high incidence of PONV was observed at 2–6 hours postoperatively, with a rate of 36.8% (95% confidence interval [CI] 28.2–46.3) in the palonosetron group, as compared to 43.4% (95% CI 34.4–52.9) in the ondansetron group. The risk difference (95% CI) between palonosetron and ondansetron for PONV was 0 (-10.9 to 10.9) at 0–2 hours, -6.6 (-19.4 to 6.5) at 2–6 hours, -0.9 (-11.0 to 9.2) at 6–12 hours, and -2.8 (-9.6 to 3.6) at 12–24 hours. There was no statistically significant difference between the palonosetron and ondansetron groups in the use of rescue medication (dimenhydrinate). There were no adverse events associated with the medications under study.

☆ This study was presented as a free paper at the 66th Brazilian Congress of Anaesthesiology held in Goiânia, Brazil, 13-16 November 2019.

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Conclusion: Palonosetron is not inferior to ondansetron in patients at risk of PONV undergoing laparoscopic cholecystectomy, providing a good option for PONV prophylaxis, as it can be administered in a single dose.
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Introduction

Nausea and vomiting are undesirable events commonly experienced by patients postoperatively, which are frequently cited as a major cause of patient dissatisfaction with anesthesia.[1] After general anesthesia, the occurrence of nausea and vomiting may lead to prolonged stay of patients in the recovery room and, consequently, to delayed discharge from hospital.[2] These symptoms occur more frequently in the first 24 hours after general anesthesia, with an incidence of up to 80% in patients with associated risk factors and without the use of any prophylactic medication.[3]

Ondansetron was one of the first 5-hydroxytryptamine-3 ($5\text{-}HT_3$) receptor antagonists to be used in the prophylaxis of postoperative nausea and vomiting (PONV) and, currently, it is still widely used. In the same pharmacological class, palonosetron has a receptor binding affinity 100 times that of other antiemetics.[4] Its use has been reported in the control of PONV with a prolonged half-life of 40 hours and therapeutic effect lasting up to 72 hours when administered intravenously. Palonosetron is the only $5\text{-}HT_3$ receptor antagonist not associated with prolonged QT interval.[5]

Several studies have compared palonosetron and ondansetron in laparoscopic surgery,[6–9] but none has evaluated palonosetron versus three intravenous doses of ondansetron, 8 mg, a dose considered to be optimal in the prophylaxis of PONV.[10] Considering this strategy to be fairer than those comparing palonosetron with a single dose or with lower doses of ondansetron, as these two drugs have a very different pharmacokinetic profile, we planned a non-inferiority trial to compare the efficacy of palonosetron versus ondansetron in reducing the incidence of PONV in adults undergoing elective laparoscopic cholecystectomy. The non-inferiority hypothesis is that palonosetron, compared with ondansetron (control), does not have an inferior effect in reducing PONV due to a risk difference less than or equal to the non-inferiority margin of 15%.

Methods

After approval by the institution's research ethics committee, a double-blind, non-inferiority, randomized, controlled trial was conducted in adult patients undergoing elective laparoscopic cholecystectomy in two secondary care hospitals. The trial was designed and reported according to the CONSORT Statement and is registered at the Brazilian Clinical Trials Registry platform (ReBEC, www.ensaiosclinicos.gov.br), number RBR-4mjv6r. We prospectively included patients in the study from February 2017 to October 2018. Eligible participants were aged 18 to 65 years, of both sexes, with physical status classified as American Society of Anesthesiologists (ASA) I and II. Exclusion criteria were allergy to the medications under study, use of antiemetics within 48 hours prior to surgery, and presence of hiatal hernia. During preanesthetic evaluation, patients were informed of the study purpose and procedures, and those interested in participating provided written informed consent for enrolment in the study.

Interventions

After an 8- to 10-hour fast and 30 minutes before surgery, a single dose of midazolam was administered orally as a 15-mg tablet. A peripheral intravenous line was placed in the upper limb and lactated Ringer's solution was infused ($20\ mL.kg^{-1}.h^{-1}$) throughout the surgery.

A staff member with no active involvement in the anesthetic-surgical procedures prepared the syringes with the medications to be administered according to previously sealed envelopes, which had been prepared and sequentially numbered from 1 to 212, as follows: ondansetron group, three identical syringes containing 4 mL of solution, with 8 mg of ondansetron (4 mL), were prepared and numbered 1, 2, and 3; palonosetron group, one syringe containing 0.075 mg of palonosetron (1.5 mL) and 2.5 mL of 0.9% saline was prepared and numbered 1, while two identical syringes containing 4 mL of 0.9% saline were prepared and numbered 2 and 3. The solutions were prepared following the numerical order of the envelopes. Before induction of anesthesia, the anesthesiologist, blinded to group allocation, administered solution number 1 intravenously. Eight hours after intravenous injection of solution number 1, solution number 2 was administered intravenously by a healthcare professional blinded to group allocation; after 16 hours, solution number 3 was also administered intravenously. Patients with recurrent PONV were given an intravenous injection of a solution containing dimenhydrinate, 30 mg, repeated every 6 hours, if necessary.

Induction of anesthesia was standardized for all patients, who received fentanyl ($3\ \mu g.kg^{-1}$), propofol ($2\ mg.kg^{-1}$), and atracurium ($0.4\ mg.kg^{-1}$). Anesthesia was maintained with remifentanil (0.1 to $0.3\ \mu g.kg^{-1}.min^{-1}$) and sevoflurane at an alveolar concentration of 2 to 3%, fresh gas flow of $2\ L.min^{-1}$, and inspired oxygen fraction of 60%. We did not plan to reverse neuromuscular blockade, but, if necessary and according to our clinical judgement, neostigmine ($0.03\ mg.kg^{-1}$), preceded by atropine (1 mg), would be administered. For postoperative analgesia, patients received ketoprofen (100 mg) intravenously every 12 hours, metamizole (2 g) intravenously every 8 hours,

and methadone (0.1 mg.kg^{-1}) intravenously 15 minutes before the end of surgery, repeated every 12 hours if necessary. With return of adequate ventilatory function and after awakening, patients were extubated and taken to the postanesthesia care unit, where they stayed for at least 90 minutes. Patients were discharged to the ward after achieving a score of 9 or 10 on the Aldrete-Kroulik scale.

Outcomes

A dichotomous assessment was performed of whether nausea, vomiting, or nausea and vomiting were present or absent. Patients were evaluated for 24 hours postoperatively, and the outcomes were analyzed according to the period of symptom occurrence: a) first 2 hours after surgery; b) from 2 to 6 hours after surgery; c) from 6 to 12 hours after surgery; and d) from 12 to 24 hours after surgery. An anesthesiologist blinded to group allocation evaluated the patients. The absolute number of doses of dimenhydrinate used in each group was evaluated as a secondary outcome. All adverse effects observed and possibly related to the medications under study were recorded.

Statistical analysis

The non-inferiority margin for this study was defined based on the lowest risk difference calculated between intravenous ondansetron and placebo in the incidence of PONV in patients undergoing laparoscopic surgery.[11–15] The combined analysis of these studies showed a 30% risk reduction for ondansetron, with a minimum effect of 19% (risk difference: -0.3; 95% confidence interval [95% CI] -0.41 to -0.19). Because 19% was the lowest difference, as calculated in these studies, the non-inferiority margin was set at 15%, considering this value to be reasonable from a clinical point of view, in addition to reducing patient exposure to undesirable effects, since the sample size is inversely proportional to the square of the non-inferiority margin. Based on the rate of patients without PONV in these studies (74%) and considering α = 5% and a power of 80%, a sample size of 212 patients was necessary for the upper limit of the 95% CI of the risk difference between palonosetron and ondansetron to exclude the difference favoring the control group (ondansetron) by more than 15%, with this value being used as the non-inferiority margin.

A computer-generated list of random numbers was used for allocation of the participants. The total number of patients was divided into two groups of 106 patients each with a 1:1 allocation ratio by electronic randomization using blocks of eight patients, with an equal distribution of groups in each block. The allocation sequence was concealed by placing the results in opaque envelopes sequentially numbered from 1 to 212, and the study followed the numerical order of the envelopes.

The risk difference used to determine the non-inferiority margin was calculated using Review Manager (RevMan), version 5.2 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2012). The sample size to test the non-inferiority hypothesis was calculated using a virtual platform (Sealed Envelope Ltd. Power calculator for binary outcome non-inferiority trial, https://www.sealedenvelope.com/power/binary-noninferior). Demographic variables and risk factors were compared between groups using Student's *t* test or the chi-square test, as appropriate, on GraphPad Prism, version 7.00.

Results

All 212 patients were evaluated and discharged home 24 hours after the end of anesthesia (Fig. 1). Using the risk score for the incidence of PONV proposed by Apfel et al.,[3] in both groups, most patients had two or three risk factors, accounting for 86 patients (81.2%) in the palonosetron group and 93 patients (87.7%) in the ondansetron group. Demographic characteristics and risk factors for PONV are listed in Table 1. There was no statistically significant difference between groups in duration of anesthesia, surgery, or pneumoperitoneum (Table 2). Only one patient in the palonosetron group had neuromuscular blockade reversed with neostigmine. Only one patient in the ondansetron group received a single dose of methadone 12 hours after surgery.

The overall incidence of nausea and/or vomiting during the 24-hour postoperative period was 47.1% and 51.8% in palonosetron and ondansetron groups, respectively ($p > 0.05$). The highest incidence of PONV, in both groups, occurred between 2 and 6 hours after surgery, with no significant difference between groups. In all periods of the study, the upper bound of the risk difference was inferior to the non-inferiority margin of 15%, thereby characterizing non-inferiority of palonosetron compared with ondansetron (Table 3).

No patient had adverse events attributable to the medications under study, such as headache, arterial hypotension, and extrapyramidal symptoms.

As for the use of rescue medication, the 2- to 6-hour postoperative period had the highest values of all four periods assessed (Table 4). Nonetheless, for this specific period, the value of the upper limit of the 95% CI of the risk difference was above the non-inferiority margin used in the present study, i.e., 15% (risk difference: 3.8, 95% CI -8.2 to 15.6). According to the non-inferiority method, this yields inconclusive results regarding the non-inferiority hypothesis (for the use of rescue medication at 2 to 6 hours postoperatively). In all other postoperative periods, non-inferiority results were found, as the upper limit of the 95% CI of the risk difference was below the non-inferiority margin of 15%.

The patients' raw data file is available at https://data.mendeley.com/datasets/gn2pzvgj82/1.

Discussion

The present study confirmed the hypothesis that palonosetron is non-inferior to ondansetron in the prophylaxis of PONV in laparoscopic cholecystectomy, within the non-inferiority margin of 15%, since the 95% CIs of the risk difference found in the postoperative periods assessed were below the non-inferiority margin.

Considering that palonosetron has been identified as the only 5-HT$_3$ receptor antagonist that does not promote QT interval prolongation,[16,17] that there are no other significant differences between the side effects of ondansetron and palonosetron,[18] and that palonosetron is administered

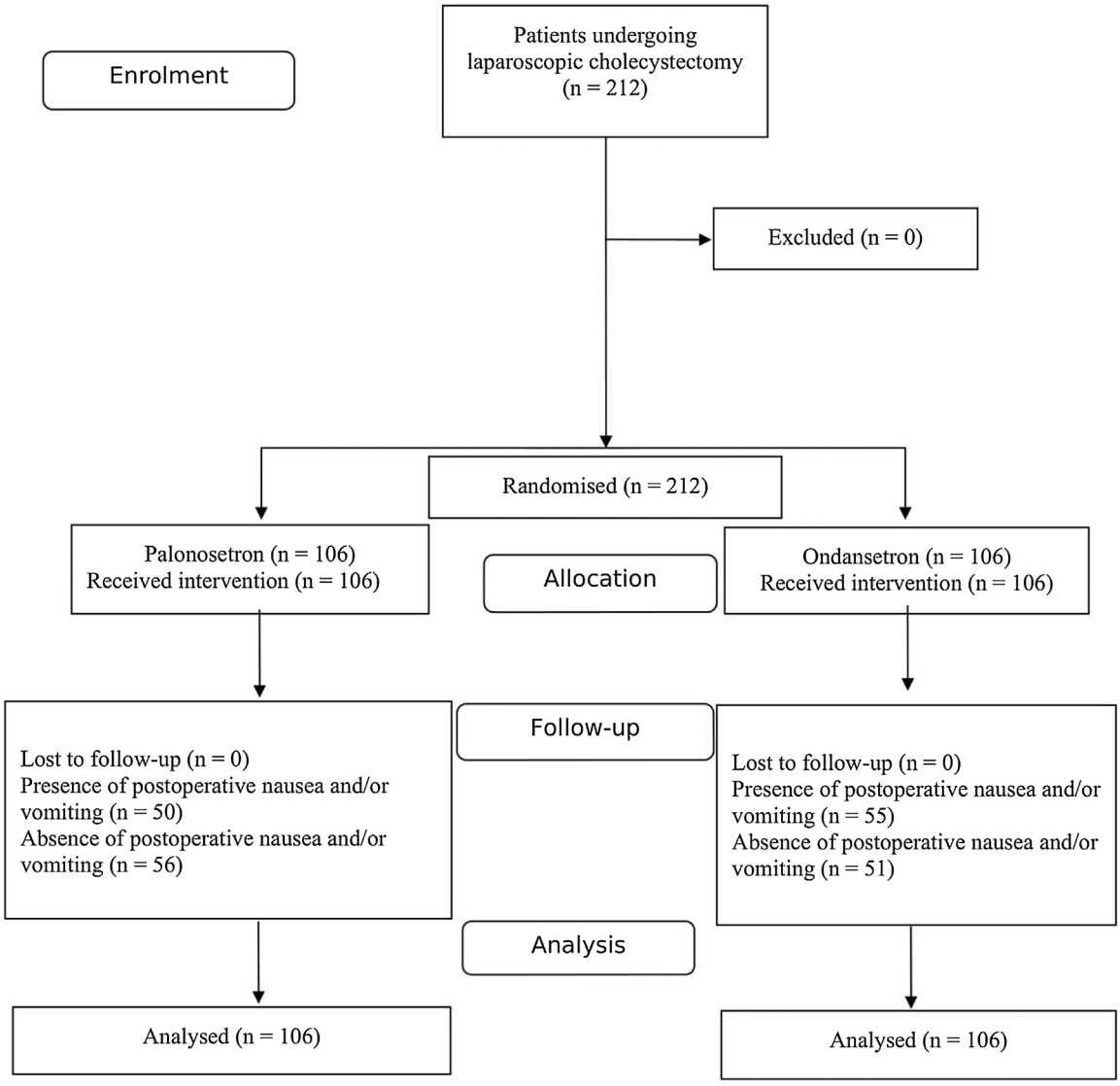

Figure 1 Flow diagram of the study.

Table 1 Demographic data and risk factors in patients receiving palonosetron or ondansetron for the treatment of postoperative nausea and vomiting in laparoscopic cholecystectomy.

Variables	Palonosetron n = 106	Ondansetron n = 106	*p*-value
Female sex	76 (71.7)	87 (82.1)	0.102
Age (years)	45.5 (13.1)	47.1 (13.8)	0.382
Weight (kg)	75.9 (19.0)	75.7 (16.8)	0.924
Body mass index (kg.m-2)	27.5 (5.5)	28.2 (5.7)	0.366
Non-smoker	95 (89.6)	96 (90.6)	0.999
Motion sickness	16 (15.1)	13 (12.3)	0.689
Patients with risk factors			
0	0 (0)	0 (0)	0.416
1	5 (4.7)	2 (1.9)	
2	29 (27.4)	23 (21.7)	
3	57 (53.8)	70 (66.0)	
4	15 (14.2)	11 (10.4)	

Values are presented as absolute number (percentage) or mean (standard deviation).

Table 2 Duration of anesthesia, surgery, and pneumoperitoneum in patients receiving palonosetron or ondansetron for the treatment of postoperative nausea and vomiting in laparoscopic cholecystectomy.

Variables	Palonosetron n = 106	Ondansetron n = 106	*p*-value
Duration of anesthesia (min)	88.7 (23.8)	88.8 (25.8)	0.967
Operative time (min)	60.0 (22.1)	60.0 (20.3)	0.999
Duration of pneumoperitoneum (min)	51.9 (20.0)	51.0 (18.3)	0.747

Values are presented as mean (standard deviation).

Table 3 Incidence of postoperative nausea and vomiting in patients receiving palonosetron or ondansetron for the treatment of postoperative nausea and vomiting in laparoscopic cholecystectomy.

Variables	Palonosetron n = 106	Ondansetron n = 106	Risk difference (Palonosetron - Ondansetron)
0 to 2 h after surgery			
Nausea	17.0 (11.0–25.3)	13.2 (8.0–21.0)	3.8 (-6.0 to 13.5)
Vomiting	3.8 (1.5–9.3)	7.5 (3.9–14.2)	-3.8 (-10.8 to 3.9)
Nausea and/or vomiting	20.8 (14.1–29.4)	20.8 (14.1–29.4)	0 (-10.9 to 10.9)
2 to 6 h after surgery			
Nausea	13.2 (8.0–21.0)	19.8 (13.3–28.4)	-6.6 (-16.6 to 3.5)
Vomiting	23.6 (16.5–32.5)	23.6 (16.5–32.5)	0 (-11.4 to 11.4)
Nausea and/or vomiting	36.8 (28.2–46.3)	43.4 (34.4–52.9)	-6.6 (-19.4 to 6.5)
6 to 12 h after surgery			
Nausea	5.7 (2.6–11.8)	5.7 (2.6–11.8)	0 (-6.9 to 6.9)
Vomiting	10.4 (5.9–17.6)	11.3 (6.6–18.8)	-0.9 (-9.6 to 7.7)
Nausea and/or vomiting	16.0 (10.3–24.2)	17.0 (11.0–25.3)	-0.9 (-11.0 to 9.2)
12 to 24 h after surgery			
Nausea	3.8 (1.5–9.3)	6.6 (3.2–13.0)	-2.8 (-9.6 to 3.6)
Vomiting	0 (0–3.5)	0 (0–3.5)	0 (-3.5 to 3.5)
Nausea and/or vomiting	3.8 (1.5–9.3)	6.6 (3.2–13.0)	-2.8 (-9.6 to 3.6)

Values are presented as percentage (95% confidence interval).

Table 4 Use of rescue medication (dimenhydrinate) in patients receiving palonosetron or ondansetron for the treatment of postoperative nausea and vomiting in laparoscopic cholecystectomy.

Variables	Palonosetron n = 106	Ondansetron n = 106	Risk difference (Palonosetron - Ondansetron)
0 to 2 h after surgery	3.8 (1.5–9.3)	7.5 (3.9–14.2)	-3.8 (-10.8 to 2.9)
2 to 6 h after surgery	29.2 (21.4–38.5)	25.5 (18.1–34.5)	3.8 (-8.2 to 15.6)
6 to 12 h after surgery	9.4 (5.2–16.5)	12.3 (7.3–19.9)	-2.8 (-11.5 to 5.8)
12 to 24 h after surgery	1.9 (0.5–6.6)	2.8 (1.0–8.0)	-0.9 (-6.3 to 4.1)

Values are presented as percentage (95% confidence interval).

in a single dose, we can state, based on the results of the present study, that palonosetron provides a good option for the control of PONV in patients with associated risk factors.

Despite obtaining the necessary values to demonstrate non-inferiority in the pre-specified margin, the present study was not planned to investigate a possible superiority of palonosetron over ondansetron.[19] Nonetheless, according to the risk difference and its 95% CI (always crossing the zero-risk difference), our study, besides showing non-inferiority, also shows equivalence between palonosetron and ondansetron.

Finding the right balance in the prevention or treatment of PONV is critical. In recent years, there has been an increased interest in research that focuses on non-pharmacological or alternative treatments for these symptoms, such as acupuncture, use of ginger, vitamin C, and even chewing gum, among others. However, finding the best setting that might demonstrate the efficacy of each antiemetic drug associated with its side effects, duration of action, patients' level of satisfaction with postoperative recovery, and mainly the best cost-benefit ratio to reduce hospital expenses is not an easy task. As for minimizing hospital expenses, it is worth noting the marked reduction observed in the present study in the incidence of nausea and vomiting between 12 and 24 hours postoperatively, which could allow these patients to be discharged within

12 hours of surgery with respect to PONV, since the presence of these symptoms is one of the most common causes of delayed discharge from hospital.[20] In these cases, patients would receive only a single dose of palonosetron, with post-hospital continuity of care. This should reduce the length of stay in wards and, consequently, health care expenses, in addition to possibly increasing the level of satisfaction of patients and their families.

With the predominance of two or three risk factors for PONV, according to the risk score proposed by Apfel et al.,[3] approximately 85% of patients in the present study had a likelihood of up to 60% of developing these symptoms. Even though around 50% of patients presented PONV, there was a considerable drop after 12 hours that supports the choice of a 24-hour assessment period after surgery, as it would be unnecessary to keep patients in the hospital for more than 1 day in the absence of significant symptoms.

According to the guidelines proposed by Gan et al.,[21] the use of ondansetron combined with dexamethasone should always be considered for PONV prophylaxis or treatment mainly in patients at moderate to high risk for PONV. Dexamethasone, whose mechanism of action seems to be associated with prostaglandin synthesis and endorphin release, has also been shown to be effective in postoperative pain control by significantly reducing the need for analgesics after laparoscopic cholecystectomy.[22]

In a meta-analysis, Tramer et al.[10] suggested 8-mg intravenous ondansetron as the optimal dose to prevent PONV, because increasing the dose from 4 mg to 8 mg led to a decrease of more than 20% in the number of patients who required rescue medication for nausea and vomiting up to 48 hours after surgery, but further increasing the dose to 16 mg led to no clinically relevant improvement. Therefore, 8 mg ondansetron was used in the present study based on evidence that the recommended doses for pediatric patients range from 0.1 $mg.kg^{-1}$ to 0.3 $mg.kg^{-1}$[23] and, according to Paventi et al.,[24] that ondansetron 8 mg is more effective than ondansetron 4 mg when administered intravenously in a single dose to prevent PONV after laparoscopic cholecystectomy. In addition, it has been shown that the use of 8-mg intravenous ondansetron does not increase the risk of cardiac abnormalities.[25]

Similar studies comparing the efficacy or duration of effect of intravenous ondansetron for PONV in laparoscopic surgery have been performed with the administration of a single dose.[6–9] In the present study, we opted for the administration of ondansetron at 8-hour intervals, intravenously, in order to maintain the effect of this antiemetic for the 24 hours during which PONV assessments were performed, because the plasma concentration of ondansetron shows a maximum peak of effect after 2 hours and duration of effect of 6 to 8 hours.[26] Thus, compared with palonosetron, which has a prolonged half-life of 40 hours, when administered intravenously, both groups remained under the effect of antiemetics for the 24 hours during which they were evaluated. Our study is novel in this respect and provides support for the non-inferiority method, since it provides a fair comparison with respect to the periods of action of these drugs. In addition, ondansetron has a high potential to reduce PONV, proven to be superior to placebo[11–15] and, maintaining its effective plasma concentration for 24 hours, we could speculate that its effect could be even greater than that of palonosetron, justifying the non-inferiority study/hypothesis.

In the present study, the use of rescue medication was higher between 2 and 6 hours after surgery than in all other postoperative periods, supporting the need for supplemental antiemetic therapy during this postoperative period. However, in the two treatment arms, we also observed that, in the 2- to 6-hour period, the rates for incidence of PONV (36.8% and 43.4%) were higher than those for use of rescue medication (29.2% and 25.5%). Some patients reported sudden improvement of nausea after a single episode of vomiting. This is in accordance with the pathophysiology of the vomiting mechanism, when patients often report absence of nausea soon after vomiting,[27] and do not require any further rescue medication.

Several aspects have already been discussed here with regard to carrying out a non-inferiority trial, such as practicality of drug administration and occurrence of fewer or less severe adverse effects. However, an advantage of using a drug defined as non-inferior would be a substantially lower cost, which would compensate for the difference in the non-inferiority margin. In this respect, we made a cost comparison analysis [https://consultaremedios.com.br/cloridrato-de-ondansetrona/pa, in US dollars; currency exchange rate, Brazilian Reais (R$) to US dollars (US$): R$ 5.00 US$ 1.00, December 21, 2020] of intravenous palonosetron (0.075 mg) versus intravenous ondansetron (8 mg), which cost, on average, approximately US$ 15.00 and US$ 1.20 per dose, respectively. According to the present study, the in-hospital cost of treatment would be US$ 15.00 with palonosetron and US$ 3.60 with ondansetron. Considering a scenario of discharge from hospital within 12 hours of surgery and home-maintenance of the antiemetic effect for 24 hours, initial prophylaxis with ondansetron (8 mg) would lead to a final antiemetic cost of US$ 14.40 – as two 8-mg ampoules would be used in the hospital within 12 hours (US$ 2.40), and one or two tablets of ondansetron (8 mg, orally) would be used at home within the subsequent 24 hours (at a cost to patients of approximately US$ 12.00 for purchasing a 10-tablet package). Initial prophylaxis with palonosetron, however, would lead to a final antiemetic cost of US$ 15.00, but at no cost to patients – they would be discharged home with no prescription for antiemetics, as they would still be under the action of the drug for 36 hours after surgery.

Also, to be considered is palonosetron patent expiration, which will occur on July 30, 2024.[28] This may result in a decrease in its market value, which would make palonosetron more accessible and a likely option to replace ondansetron for PONV prophylaxis in the coming years, due to its practical administration (single dose) and, at the very least, non-inferior effects.

The use of a dichotomous assessment of nausea can be seen as a limitation of the present study, since it is known that there are different intensities of nausea, which could be rated on a numerical scale or even qualitatively as mild, moderate, and severe. However, we chose this type of assessment for understanding that nausea is a subjective unpleasant sensation, and a single postoperative episode may not be easy to rank. Another possible limitation is that we did not evaluate patient satisfaction; however, this is sometimes complex to evaluate, and also considered a surrogate end point. Nonetheless, we followed Apfel et al.'s

recommendations on the conduction of studies on PONV in all aspects, thus ensuring good external validity.[29]

In conclusion, palonosetron is non-inferior to ondansetron when used in patients at risk of PONV undergoing laparoscopic cholecystectomy. Therefore, palonosetron provides a good option of antiemetic agent for PONV prophylaxis in patients at increased risk for these events when undergoing laparoscopic cholecystectomy, as it can be administered in a single dose.

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Conflicts of interest

The authors declare no conflicts of interest.

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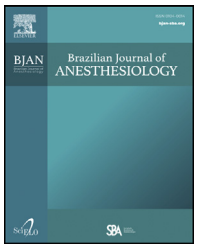

ORIGINAL INVESTIGATION

Hemodynamic impact of increasing time between fentanyl and propofol administration during anesthesia induction: a randomised, clinical trial

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KEYWORDS
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Abstract
Background and objective: Anesthesia induction can produce severe propofol dose-dependent hypotension. Fentanyl coadministration reduces the catecholaminergic response to orotracheal intubation allowing propofol dose reduction. The aim of this study is to determine whether the hemodynamic response is improved by increasing the time between fentanyl and propofol administration and reducing the dose of the latter without increasing the time to achieve optimal hypnosis.
Methods: After approval by the Research Ethics Committee, patients undergoing non-cardiac surgery with endotracheal intubation were randomized by a computer-generated table into six time-dose groups (1 or 2 minutes/1, 1.5, or 2 $mg.kg^{-1}$ of propofol). Patients with high bronchoaspiration risk, a difficult airway, hemodynamic instability, or anesthetic allergies were excluded. After giving intravenous fentanyl (2 $\mu g.kg^{-1}$), each group received different doses of propofol after 1 or 2 minutes. Non-invasive blood pressure (BP) and heart rate (HR) were measured at pre-induction, pre-intubation, and post-intubation. Time to hypnosis (bispectral index < 60) was also recorded.
Results: Of the 192 recruited patients, 186 completed the study (1 min group n = 94; 2 min group n = 92). It was observed that HR and BP decreased after propofol administration and increased after intubation in all groups ($p < 0.0001$). In patients over 55 years, the 2 min – 2 $mg.kg^{-1}$ group showed the greatest systolic BP reduction (36 ± 12%) at pre-intubation, while the 1 min – 1.5 $mg.kg^{-1}$ group showed the least hemodynamic alteration between pre- and post-intubation (-4 ± 13%). No significant differences were found in younger patients or in the time to reach hypnosis between the six groups. While no cases of severe bradycardia were recorded, 5,4% of the sample required vasopressors.
Conclusion: Increasing the time between the administration of fentanyl and propofol by up to two minutes results in greater hypotension in patients over 55 years.
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Introduction

Propofol is the most commonly used hypnotic in non-cardiac surgery due to its pharmacokinetic characteristics, such as short onset time, high metabolism and elimination, and short half-life. However, it leads to a series of unwanted hemodynamic effects (decrease in systemic vascular resistance, negative inotropism, and bradycardia).[1,2]

Older patients are more sensitive to propofol because of a decreased central compartment and a lower concentration of plasma proteins, which result in a reduced distribution volume and cardiac output.[3] These physiological changes led manufacturers to suggest a reduction in the induction dose, to 1 mg.kg^{-1}, in patients over 55 years or those with a high anesthetic risk.

Concomitant administration of fentanyl during anesthesia induction aims to reduce the catecholaminergic response to laryngoscopy, as post-intubation hypertension increases the risk of myocardial infarction, heart failure, pulmonary edema, intracranial hemorrhage, etc.[4] The prior administration of opioids has been proposed in order to decrease the need for propofol, mainly due to pharmacological synergy.[5,6] Taking into account that propofol-associated hypotension is dose-dependent, a dose reduction based on opioid coadministration would result in less hemodynamic instability.[7]

No studies have been found that assess the optimal time between the administration of both drugs to enhance this supra-additive relationship and allow the maximum reduction of propofol doses. The aim of this study is to determine whether increasing the time between fentanyl and propofol administration and reducing the dose of the latter, improves the hemodynamic response in different age groups without increasing the time required to achieve optimal hypnosis.

Methods

This prospective, randomized clinical trial was approved by the Research Ethical Committee of the Hospital Central de la Defensa ''Gómez Ulla'' in October 26th 2017 (approval nº: 09/17), registered at clinicaltrials.gov (NCT04194151) and was conducted after obtaining written consent from all participants.

All adults who were scheduled for general anesthesia with endotracheal intubation for non-cardiac surgery in our hospital between November 2017 and October 2018 were considered eligible. Patients with an increased risk of bronchoaspiration (absence of fasting, stomach retention, intestinal obstruction, etc.), a difficult airway, allergies to anesthetic drugs, or baseline systolic blood pressure (SBP) $\leq$ 90 mmHg were excluded.

Study protocol

Sample size was calculated with a power of 80% (beta risk 20%) to detect an expected minimal significant SBP difference of 5 mmHg between groups, an overall two-sided alpha level of significance of 0.05, assuming a pooled standard deviation of 22 mmHg and maintaining a group ratio of 1:1:1:1:1:1. A minimum of 162 patients were required (27 in each group). We raised this to 192 patients, estimating a possible loss of 15% and keeping the group proportion (32 in each group).

Table 1 Study groups.

Group	Time until propofol (min)	Propofol dose (mg.kg^{-1})
1	2	2
2	2	1.5
3	2	1
4	1	2
5	1	1.5
6	1	1

Two time-groups were established (1 and 2 minutes), and these were each divided into three dose subgroups (1, 1.5, and 2 mg.kg^{-1}), resulting in six time-dose groups (Table 1). Randomization was achieved using a computer-generated randomization table, leading to six groups of 32 patients. Each subject who met the inclusion criteria and accepted participation was assigned to the corresponding group according to his/her order number (1 to 192). Because the grouping was established prior to data collection, age, sex, and American Society of Anesthesiologist (ASA) physical status risk were not randomized. Only the anesthesiologist and the data collector were aware of the allocated group.

In the operating room (OR), monitoring included electrocardiogram, pulse oximetry, non-invasive blood pressure (BP), and bispectral index (BIS – Covidien Complete Monitor System P/N 185-0151, USA). After preoxygenation (expired oxygen fraction $\geq$ 80%), 2 μg.kg^{-1} of intravenous fentanyl were administered. After 1 or 2 minutes (depending on the study group), 1, 1.5, or 2 mg.kg^{-1} of propofol were given. We registered the time until the BIS value dropped below 60. Muscle relaxation was performed with rocuronium 0.6 mg.kg^{-1}, and endotracheal intubation was achieved by the same experienced anaesthesiologist.

The primary outcome was to identify hemodynamic alteration through SBP or heart rate (HR) during the different phases of anesthesia induction. SBP and HR were collected manually and set as follows: baseline (SBPb and HRb) was recorded before fentanyl administration; the pre-intubation value (SBP1 and HR1) was recorded after propofol administration and once the BIS value had reached 60; and the post-intubation value (SBP2 and HR2) was recorded 15 seconds after endotracheal tube placement. In cases where hypotension was observed (SBP < 90 mmHg or SBP reduction > 30%), vasopressors, such as ephedrine or phenylephrine were administered.

Statistical analysis

Values are reported as absolute and relative (percentages) frequencies for categorical variables and mean $\pm$ standard deviation (SD) for quantitative ones. To assess categorical variables, such as presence of hypertension, extra doses of propofol, use of vasopressors, and cardiovascular treatment, chi-square test or Fisher's exact test were used, depending on the sample size. Student's t-test for independent samples was employed to compare parametric data, such as vasopressor use with respect to age, hypertension and antihypertensive treatment with respect to baseline

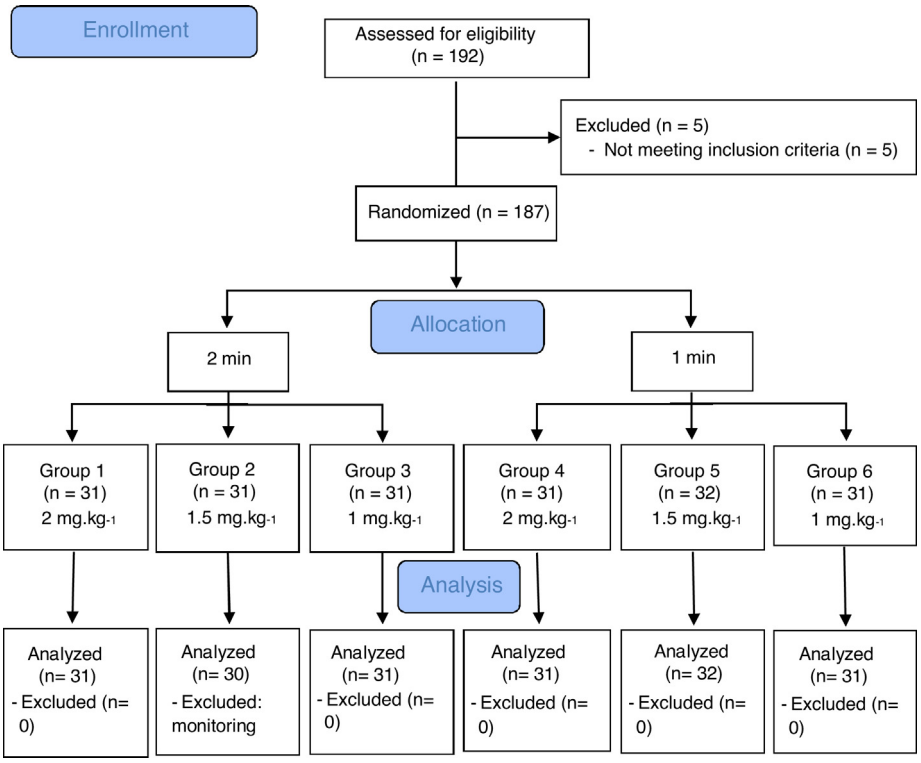

Figure 1 CONSORT flow diagram.

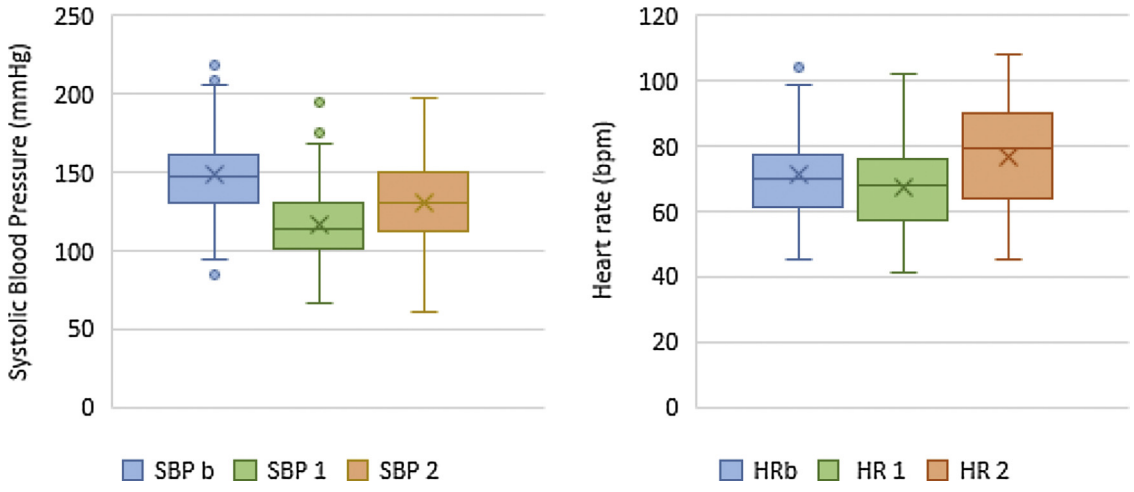

Figure 2 Systolic blood pressure (mmHg) and heart rate (bpm) variation during the study. SBP, systolic blood pressure; HR, heart rate; b, baseline; 1, pre-intubation; 2, post-intubation.

SBP and β blockers treatment with respect to baseline HR, provided a normal distribution could be assumed. ANOVA and Bonferroni correction were used for comparison of hemodynamic values between the groups. Non-parametric statistical tests (Mann-Whitney U-test or Kruskal-Wallis test) were applied when necessary. To analyze data distribution, Shapiro-Wilks or Kolmogorov-Smirnov with Lilliefors correction were conducted for small or large samples, respectively. Boxplots were used to represent quantitative data such as SBP and HR. To compare and represent time to hypnosis between the groups, a Kaplan-Meyers curve was used. A *p*-value of < 0.05 was considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics 22.00 (IBM Corp., Armonk, NY, USA).

Results

From November 2017 to October 2018, we recruited the 192 required patients of whom 6 were removed, generating a sample of 186 subjects in the 6 groups (Fig. 1). No demographic differences were found in age, sex, weight, ASA, or

Table 2 Demographic characteristics of the studied patients.

Group	1 (n = 31)	2 (n = 30)	3 (n = 31)	4 (n = 31)	5 (n = 32)	6 (n = 31)
Age (year)	59 ± 20	61 ± 17	60 ± 19	59 ± 17	64 ± 18	55 ± 16
Female	15 (48,4)	14 (46,7)	17 (54,8)	17 (54,8)	18 (56,3)	14 (45,2)
Weight (kg)	73 ± 16	77 ± 17	70 ± 15	71 ± 15	71 ± 15	73 ± 15
ASA risk,						
I-II	20 (64,5)	19 (63,3)	17 (54,8)	21 (67,7)	13 (40,6)	21 (67,7)
III-IV	11 (35,5)	11 (36,7)	14 (45,2)	10 (32,3)	19 (59,4)	10 (32,3)
Hypertension	15 (48,4)	9 (30)	15 (48,4)	13 (41,9)	16 (50)	13 (41,9)
Hypotensive treat	9 (29)	9 (30)	12 (38,7)	10 (32,3)	12 (37,5)	11 (35,5)
BBlock/Ca Block	11 (35,5)	7 (23,3)	10 (32,3)	9 (29)	11 (34,4)	3 (9,7)

Values are mean ± standard deviation or frequency (percentage). ASA, American Society of Anesthesiologist physical status; Treat, treatment; BBlock, beta blocker; Ca Block, calcium blocker.

in the distribution of hypertensive patients or those undergoing treatment for hypotension or HR control (Table 2).

Thirty-three patients required an extra 0.5 mg.kg^{-1} dose of propofol, 81.8% of whom belonged to the 1 mg.kg^{-1} groups (group 3 – 39.5% and group 6 – 42.3%, $p < 0.0001$). An additional dose was required by 22% of low-risk patients and only 11% of ASA III-IV patients ($p = 0.038$).

There were no cases of severe bradycardia that required anticholinergic treatment. However, 5.4% of the sample showed hypotension that required vasopressors. The mean age of patients requiring its use was 76 ± 13 years, while the mean age of the non-vasopressors group was 59 ± 18 years (p = 0.003). The use of vasopressors was more frequent in those undergoing treatment with HR blockers alone (13.7% vs. 2.2%; $p = 0.006$) or associated with hypotensive drugs (15% vs. 3%; $p = 0.015$), in contrast with the patients with no treatment.

No statistically significant differences were found between baseline BP or HR values between the different groups. However, the mean SBPb was significantly higher in hypertensive patients (156 mmHg, 95% CI 151 – 162 vs. 139 mmHg, 95% CI 138 – 146; $p < 0.0001$) and in those with hypotensive treatment (159 mmHg, 95% CI 152 – 166 vs. 143 mmHg, 95% CI 139 – 147; $p < 0.0001$). On the other hand, the HRb was lower in patients treated with heart rhythm control drugs (71 bpm, 95% CI 67 – 75 vs. 76 bpm, 95% CI 74 – 79; $p = 0.045$). The general tendency was a decrease in BP and HR before intubation and an increase afterwards ($p < 0.0001$), as can be seen in Fig. 2.

No statistically significant differences between the study groups were found with respect to the baseline BIS value or the time required for the BIS to drop below 60, once the patients who required an extra dose were removed from the sample (Fig. 3).

To assess the percentage of BP reduction, the population was divided by patients over the age of 55 and those younger than 55 years, obtaining significant demographic differences between both age groups with respect to ASA ($p < 0.0001$), the incidence of hypertension ($p < 0.0001$) and the use of hypotensive and HR blockers ($p < 0.0001$). In patients under 55 years old, no statistically significant differences were found in the percentages of arterial reduction ($p = 0.99$ for b-1, $p = 0,964$ for b-2 and $p = 0,975$ for 2-1) whereas, in the older population, statistically significant results were obtained (Table 3).

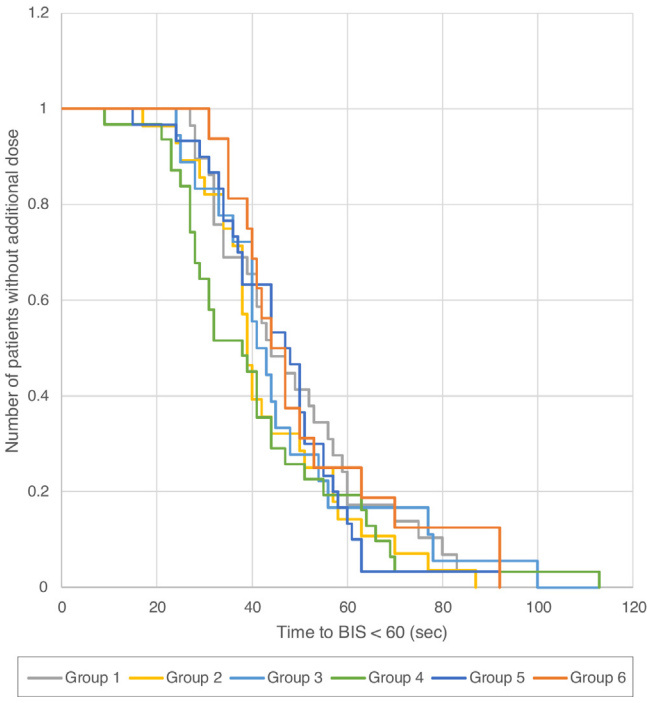

Figure 3 Time (seconds) required for BIS to drop under 60 in the different groups, excluding patients who required an additional propofol dose. BIS, Bispectral Index.

Discussion

This study showed that extending the time between fentanyl and propofol to 2 minutes during anesthesia induction produces more hypotension in adults older than 55 years, even when propofol doses are reduced.

The baseline SBP exceeded the cut-off diagnostic hypertension value established by the latest guidelines of the American College of Cardiology (ACC).[8] However, the OR measurement conditions (decubitus, fasting, and stress) are not those recommended for diagnosis.[9] Despite this, hypertensive patients and those under hypotensive treatment presented higher systolic values than the rest of the sample. When subjected to maintained high tension, the arterial wall suffers pathophysiological changes, such as insensitivity to endogenous vasodilators and a higher response to cate-

Table 3 Percentage of blood pressure reduction in older patients (> 55 years).

Systolic bp	GROUP	BP reduction (%)	group	BP reduction (%)	*p* value
b-1	**1** (n = 18)	36 ± 12	**3** (n = 18)	21 ± 13	0.006
			5 (n = 22)	21 ± 13	0.003
			6 (n = 13)	22 ± 13	0.033
2-1	**5** (n = 22)	- 4 ± 13	**1** (n = 18)	15 ± 25	0.014
			2 (n = 24)	15 ± 17	0.01

Values are mean ± standard deviation. BP, blood pressure; b-1, comparative between baseline and pre-intubation blood pressure; 2-1, comparative between post and pre-intubation blood pressure.

cholamines and stress.[10] On the other hand, the inhibition of β1 receptor activity caused by beta blockers and the voltage and use-dependent blockage of calcium channels generated by calcium antagonists would explain why the HRb was lower in patients under these treatments.[11,12]

Although the propofol manufacturer 's recommendation is that the induction dose could be reduced to 1 mg.kg^{-1} in older patients or those with a high anesthetic risk, in this study the 1 mg.kg^{-1} groups required an extra propofol dose more often, regardless of age. However, we found that ASA I and II patients required an additional hypnotic dose more frequently. The latter is consistent with Schnider et al., who described that those older than 75 years are up to twice as sensitive to propofol as those under 25 years old.[13]

Regarding the use of vasopressors, our incidence is surprisingly lower than that found by Mehandale and Rajasekhar, whose patients reached 24% after administering 2 μg.kg^{-1} of fentanyl and a titrated dose of propofol until loss of consciousness.[14] The main difference was in our propofol administration method (weight-based single bolus). In addition, their study did not specify whether hemodynamically unstable patients or those with an increased risk of hypotension were included.[14] In accordance with a review by Hug et al. which included 25,000 patients of a wide age range, older patients showed a higher incidence of severe hypotension, which supports the greater lability we found in this group.[15] Surprisingly, chronic hypotensive treatment did not present a greater need for vasopressors; however, beta blockers/calcium blockers alone or in association with antihypertensives did. This could be explained by the fact that the latter were suspended 24 hours before surgery, as recommended in the latest perioperative hypertension management guidelines, to reduce cardiovascular complications and, therefore, their half-life was exceeded.[8,16] On the other hand, beta blockers and calcium blockers were administered on the day of the intervention following the same guidelines. As a consequence, these patients have a reduced ability to respond to hypotensive stimulus with tachycardia, peripheral vasoconstriction, and inotropism.

BP variation during induction were as expected, based on the action of propofol on the autonomic nervous system and vascular endothelium, which causes a decrease in preload and peripheral vascular resistance.[14,17] On the other hand, the stress generated by laryngoscopy and orotracheal intubation causes an adrenergic discharge that reverses the hypotensive effects.[18] Multiple studies report a fall after propofol and a rise post-intubation.[14,19,20] Möller Petrun and Kamenik studied cardiovascular changes in 46 ASA III patients who, after a 3 μg.kg^{-1} fentanyl bolus, received propofol or etomidate.[21] Their hypotension peak was 5 minutes after intubation, contrasting with our study where the peak occurred during the pre-intubation period. This could be due to the fact that they initiated sevoflurane straight after intubation, which produces hypotension by itself, adding to the hypotension caused by the other anesthetics administered.[22] HR variations can be understood on the same basis: a slight decrease that was reversed with intubation.[18,23]

Given that the additional hypnotic doses were administered after 120 seconds, when BIS remained above 60, these patients were eliminated when studying the time to hypnosis. We found no significant differences, indicating that waiting 2 minutes between fentanyl and propofol does not increase the risks of prolonging the time to guarantee the airway. Lysakowski et al. found that, in the presence of fentanyl, alfentanil, remifentanil, and sufentanil, the loss of consciousness occurred at a lower concentration of propofol and at a higher BIS compared to the hypnotic as a single drug.[24] These authors used Target Controlled Infusion (TCI) for opioids and propofol, and the loss of consciousness was assessed subjectively based on the response to verbal orders or slight shaking, which can lead to bias. In addition, their objective was to compare propofol with propofol plus different opioids; therefore, they did not study different hypnotic doses as in our study.

We divided the sample into two age groups because propofol manufacturers suggest that the induction dose can be reduced in patients over 55 years and because it has been unequivocally demonstrated that age is a relevant factor in hypnotic needs.[25]

As expected, older patients presented a higher anesthetic risk, higher incidence of hypertension, and higher consumption of hypotensive drugs and HR blockers. This may be due to age-related degenerative processes of the cardiovascular system, which alter inotropic regulatory mechanisms, metabolic alterations, and oxidative stress.[26]

Regarding the decrease in SBP at pre-intubation (b-1), we observed that the hypotensive effect of propofol is greater when the dose is higher, supporting the idea that vasodilation and subsequent hypotension are dose-dependent.[7] Likewise, we found significant differences when adding the time variable (group 1 vs. group 5/6). Our results showed that, when waiting one minute, the maximum peak of the opioid effect has not been reached; therefore, there is less hypotension. A study of 120 patients produced similar findings, whereby fentanyl itself did not cause cardiovascular changes but caused greater hypotension when associated

with propofol.[5] In this study, there was a time period of 5 minutes between the administration of both drugs; therefore, the plasma concentration was higher, obtaining a reduction percentage of 40% for a propofol dose of 2 mg.kg^{-1}.

When comparing SBP variation before and after airway management, group 5 showed better control of post-intubation hypertension, and the 2-minute groups showed the highest percentage of decline. These results confirm a synergistic relationship between fentanyl and propofol. It has been suggested that fentanyl increases the volume of distribution and reduces the clearance of propofol, resulting in an increase in plasma concentration of 25%.[6] When studying the hemodynamic response to intubation, Billard et al. found that the magnitude of post-intubation hypertension is significantly reduced with increasing doses of fentanyl. They also reported that administration should be carried out in close proximity so that the concentration of the biophase and hypotension occur at the same time, avoiding the hypertensive response of the laryngoscopy.[5] In our study, all patients received the same dose of fentanyl (2 μg.kg^{-1}) but, by increasing the time between the administration of both drugs, we allowed a greater blood peak, thus increasing its analgesic capacity. By this, we do not mean that fentanyl generates hypotension per se but that the increase in peripheral vascular resistance caused by the adrenergic response decreases by better controlling the pain produced by the laryngoscopy, and the risk of hypotension caused by the propofol increases.

As this study includes a sample with a wide age range and ASA risk, its results could be easily extrapolated to the general population. However, it has several limitations. First, we did not measure the plasmatic concentrations of both drugs due to lack of means. Further research is needed to specify if, after 2 minutes, the fentanyl plasmatic peak is achieved before intubation allowing a better control of the hypertension associated with intubation. Second, the use of invasive pressure would have decreased measurement bias. We try to reduce them by adjusting the size of the cuff. Third, we did not collect the type of surgical procedure. Although the initial motivation for surgery can influence the baseline state of the patient, this would hardly generate differences during anesthetic induction.[15] Last, type of vasopressors used (ephedrine or phenylephrine) was not recorded. Although this could have altered the HR data obtained, the criteria for its use was based on patients' comorbidities, and both drugs have shown efficiency in the prevention and treatment of hypotension related to anesthetic induction.[19,20,27]

In conclusion, BP falls following administration of the hypnotic and rises after intubation, regardless of the time elapsed between the two drugs or the propofol dose. Despite this, increasing the time between the administration of fentanyl and propofol to two minutes does not generate hemodynamic benefits in patients under 55 years of age. In the older population, increasing this time results in greater BP variation. If greater hemodynamic stability with a decrease in propofol dose in this age group is desired, it is advisable to wait one minute from administration of fentanyl 2 μg.kg^{-1} and to reduce the dose to 1.5 mg.kg^{-1}.

Conflicts of interest

The authors declare no conflicts of interest.

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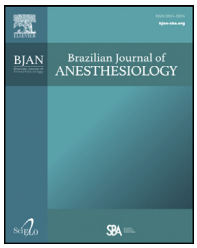

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ORIGINAL INVESTIGATION

Comparison of palonosetron and ondansetron in preventing postoperative nausea and vomiting in renal transplantation recipients: a randomized clinical trial



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KEYWORDS
End-stage renal disease (ESRD);
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Palonosetron;
Ondansetron;
PONV intensity scale;
Renal transplantation recipients

Abstract
Background: End-stage renal diseases patients have a high risk of postoperative nausea and vomiting (PONV), which is multifactorial and need acute attention after renal transplantation for a successful outcome in term of an uneventful postoperative period. The study was done to compare the efficacy of palonosetron and ondansetron in preventing early and late-onset PONV in live donor renal transplantation recipients (LDRT).
Methods: The prospective randomized double-blinded study was done on 112 consecutive patients planned for live donor renal transplantation. Patients of both sexes in the age group of 18–60 years were randomly divided into two groups: Group O (Ondansetron) and Group P (Palonosetron) with 56 patients in each group by computer-generated randomization. The study drug was administered intravenously (IV) slowly over 30 seconds, one hour before extubation. Postoperatively, the patients were accessed for PONV at 6, 24, and 72 hours using the Visual Analogue Scale (VAS) nausea score and PONV intensity scale.
Results: The incidence of PONV in the study was found to be 30.35%. There was significant difference in incidence of PONV between Group P and Group O at 6 hours (12.5% vs. 32.1%, $p = 0.013$) and 72 hours (1.8% vs. 33.9%, $p < 0.001$), but insignificant difference at 24 hours (1.8% vs. 10.7%, $p = 0.113$). VAS-nausea score was significantly lower in Group P as compared to Group O at a time point of 24 hours (45.54 ± 12.64 vs. 51.96 ± 14.70, $p = 0.015$) and 72 hours (39.11 ± 10.32 vs. 45.7 ± 15.12, $p = 0.015$).
Conclusion: Palonosetron is clinically superior to ondansetron in preventing early and delayed onset postoperative nausea and vomiting in live-related renal transplant recipients.
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Introduction

Postoperative nausea and vomiting (PONV) are a significant cause of distress in the postoperative period which spoils the otherwise smooth postoperative experience of the patient, resulting in prolonged hospital stay and postoperative complications. The baseline incidence of PONV in general populations is 20–30% and 75–80% in high-risk groups.[1] Gastrointestinal complications are the most common non-renal complaints known to occur in patients with end-stage renal disease (ESRD).[2] Uremia and dialysis increase the risk of lesions in the gastrointestinal tract leading to dyspepsia characterized by nausea, vomiting, early satiety, delayed gastric emptying, upper abdominal pain, and bloating.[3] The anesthesia technique employed like the use of volatile anesthetics, nitrous oxide perioperative opioids use,[4] the prolonged duration of surgery, and the adverse effects of the immunosuppressive regime predispose the patients undergoing renal transplants to high risk for PONV.

Palonosetron is a newer second-generation 5HT-3 receptor antagonist that has a unique allosteric inhibition property that imparts greater binding affinity and a longer plasma half-life than other drugs of the same class.[5] Recent studies have reported the superiority of palonosetron relative to other 5HT-3 receptor antagonists for the prevention of PONV in patients undergoing general anesthesia.[6–8] Palonosetron has also been shown to be a superior drug compared to ondansetron drug in reducing the incidence of emesis and mitigating the clinical impact of nausea and vomiting on patients functional status during the acute (0–24 h) and delayed (24–120 h) phase after chemotherapy and general anesthesia.[7–9] The pharmacological superiority accompanied by previously studied efficacy of palonosetron in preventing chemotherapy-induced nausea and vomiting and PONV prompted us to explore its effects in preventing PONV in renal transplantation recipients assuming the current practice of routine use of shorter-acting agents like ondansetron for PONV is less effective.

The current study was conducted to evaluate the hypothesis as primary objectives that intravenous Palonosetron provides safe and effective prevention of early and delayed onset PONV as compared to Ondansetron in renal transplantation recipients using the PONV intensity score.[10]

Methods

Trial design

This single-centric study was conducted at government authorized renal transplantation center at SGPGIMS, Lucknow, in North of India. After the approval by the Institutional Ethics Committee (IEC CODE-2019-82-IP-109) the trial was registered with Clinical Trials Registry India Registration No.CTRI/2019/09/021417, accessible online at ctri.nic.in/Clinical trials/pmaindet2.php?trialid=36885). The study was conducted as per the declaration of Helsinki and good clinical practice guidelines for biomedical research in human subjects.

After obtaining written informed consent, 112 ESRD patients planned for live-related donor renal transplantation were recruited for this prospective, randomized, double-blinded study. The study included renal transplantation recipients of either sex between the age of 18–60 years. Exclusion criteria were history of smoking, motion sickness, cognitive impairment, history of allergy to drugs used in the study, usages of medications with known antiemetic effect within 24 hours before surgery, and history of opioid use. Patients who were shifted for postoperative mechanical ventilation were also excluded from the study. After enrollment of patients, they were randomly allotted in a 1:1 ratio to receive either the ondansetron or palonosetron. The group assignment was presented in opaque sealed envelopes to an anesthetist who was not involved in the study. Randomization was performed with a block size of six using a central web-based system by a statistician blinded to the study. Anesthesiologists involved in intraoperative care and investigator collecting data in the postoperative ward were unaware of the group allocation.

All the potential recipients underwent pre-transplantation workup before surgery. Screening and matching of donor and recipient were done before surgery. The immunosuppression induction of the recipient was done as per institutional protocol. Post-hemodialysis hemogram and coagulation profile along with kidney function tests were assessed a day before surgery. Preoperative standard fasting guidelines were followed and no antiemetic was administered before surgery.

After patients arrived in the operating room, standard ASA monitoring was applied (electrocardiography, pulse oximetry, and a noninvasive blood pressure cuff, TOF monitoring). The arteriovenous fistula site was protected and periodically checked for flow. All patients received balanced general anesthesia and a lower thoracic epidural catheter was placed before the induction of anesthesia. Intravenous fentanyl (2 $mcg.kg^{-1}$) was followed by induction with propofol (1.5 $mg.kg^{-1}$) and neuromuscular blockade was achieved by atracurium (0.5 $mg.kg^{-1}$) in all patients. Maintenance of anesthesia was done by desflurane with intermittent boluses of fentanyl (1 $mcg.kg^{-1}$) and neuromuscular blockade was achieved by TOF guided atracurium boluses. An anesthetist who was not involved in the study opened the sealed envelopes and prepared the medications as injectable solutions of either palonosetron 0.075 mg or ondansetron 4 mg. Both of the drugs were diluted in normal saline to make a total volume of 2 mL and loaded in identical-looking syringes. The study drug was administered intravenously (IV) slowly over 30 seconds, 60 minutes before extubation. Tracheal extubation was done at the end of surgery after reversal with neostigmine according to TOF monitoring when appropriate criteria were met and patients were shifted to the postoperative care unit (PACU) for further recovery. All patients received a continuous epidural infusion with 0.1% ropivacaine and 1 $mcg.mL^{-1}$ fentanyl at the rate of 6–8 $mL.h^{-1}$ in the postoperative period.

Sample size calculation and patient randomization

Based on previous studies,[8] there was a reduction of 25% in the incidence of PONV in patients receiving palonosetron (50%) compared to ondansetron (75%). Assuming the same (25%) difference in PONV in our study power of 80%, and a significant level of 5% ($\alpha = 0.05$), the calculated sample size

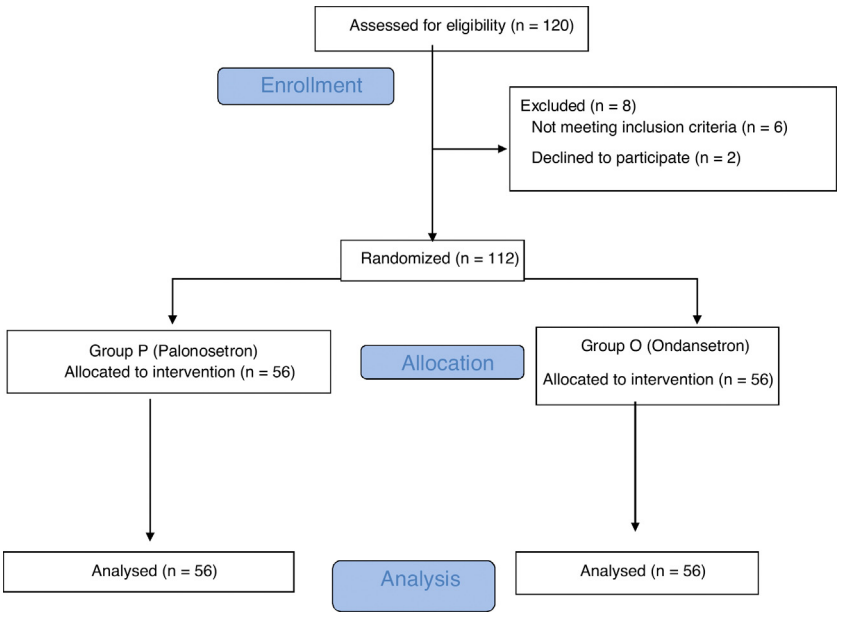

Figure 1 Consort diagram of the study.

was 56 patients in each group (a total of 112 patients). After considering the dropouts, we decided to take 60 patients in each group. The sample size was estimated using the software G Power version – 3.1.9.2 (Düsseldorf University, Germany).

Data collection tool

Patient's demographic data were collected and they were interviewed by one of the investigators at 6, 24, and 72 hours postoperatively about vomiting, antiemetic medication, or complications related to PONV-by-PONV intensity scale and VAS nausea scale (Fig. 1).

PONV intensity scale and VAS nausea score

The PONV intensity Scale (Appendix-1) and VAS scale for nausea were applied at regular intervals. Patients were asked to score postoperative pain on a 10-point verbal numerical rating scale (NRS), and nausea on a 100-mm Visual Analogue Scale (VAS-nausea). The limits of the nausea VAS were ''no nausea'' to ''nausea as bad as it possibly could be''. A score greater than 70 was the cut-off for severe nausea. Vomiting was objectively measured as the total number of patients who had emesis and the number of episodes of vomiting. A score was calculated for each patient and a PONV intensity Scale score of $\geq$ 50 was defined as clinically significant PONV.[10]

Statistical analysis

The normality of the continuous variables was assessed using the Z score of the skewness and a variable was considered normally distributed when the Z score was within the range of 3.29. Normally distributed variables were presented in mean $\pm$ standard deviation and compared by independent samples *t*-test. Ranking data presented in median (interquartile range ''IQR'') and compared by Mann-Whitney U test. Categorical variables were presented in frequency (%) and tests of the association between study groups and categorical variables (including the incidence of nausea, vomiting) were assessed by the Chi-square test/ Fisher exact test as applicable. *P*-value < 0.05 was considered, as statistically significant. Data were analyzed using Statistical Package for social sciences, version-23 (SPSS-23, IBM, Chicago, USA).

Results

A total of 120 renal transplant recipients were included in the study. Two patients did not consent to participate in the study. Three patients did not meet the inclusion criteria and two patients were shifted to PACU on mechanical ventilation and one patient was re-explored 12 hours after surgery and was excluded from the study. Thus, the study included 112 kidney transplant recipients (56 in Group P and 56 in Group O). The mean age of the patients was 34.71 years (median, 35, IQR [19–55]) with a higher proportion of males (84.8%). There was no significant difference in mean age and gender between the two study groups. The mean duration of the surgery was 5.42 hours with no significant difference between the groups (p = 0.268) (Table 1). The incidence of postoperative nausea and vomiting in patients was compared between the two study groups (P and O). There was a significant difference in incidence of PONV between groups P and O at 6 hours (12.5% vs. 32.1%, p = 0.013) and 72 hours (1.8% vs. 33.9%, p < 0.001) but no difference at 24 hours (1.8% vs. 10.7%, p = 0.113). The use of rescue antiemetic (metoclopramide 10 mg slow IV) was compared between the groups. Group P showed decreased requirement of metoclopramide, [7/56 (12.5%) vs. 25/56) (44.6%), p < 0.001] at 72 hours significantly as compared to the Ondansetron, (Group O) in the postoperative period (Table 2, Fig. 2). There

Table 1 Distribution of demographic and clinical values in study groups.

Variables	Total (n = 112)	Group P (n = 56)	Group O (n = 56)
Age (years)	34.71 ± 8.30	34.20 ± 8.92	35.21 ± 7.70
Sex (male)	95 (84.8%)	49 (87.5%)	46 (82.1%)
Duration of Surgery (hours)	5.42 ± 0.60	5.48 ± 0.69	5.36 ± 0.49

Mean ± SD, compared by independent samples *t*-test.
Frequency (%), compared with the Chi-square test used.

Table 2 Association between PONV intensity scale, VAS Nausea score, and effect of rescue antiemetic.

	Total			With rescue			Without rescue		
	P (n = 56)	O (n = 56)	*p*	P (n = 7)	O (n = 25)	*p*	P (n = 49)	O (n = 31)	*p*
PONV: Frequency (%)[a]									
6 h	7 (12.5)	18 (32.1)	0.013	7 (100)	18 (60)	0.069	0 (0)	3 (9.7)	0.055
24 h	1 (1.8)	6 (10.7)	0.113	1 (14.3)	6 (24)	0.099	0 (0)	0 (0)	-
72 h	1 (1.8)	19 (33.9)	0.001	1 (14.3)	19 (76)	0.006	0 (0)	0 (0)	-
VAS: Median (IQR) [Mean][b]									
	P (n = 56)	O (n = 56)	*p*	P (n = 7)	O (n = 25)	*p*	P (n = 49)	O (n = 31)	*p*
6 h	2 (2-3) [2.48]	2.5 (2-3) [2.51]	0.7812	(2-3) [2.29]	2 (2-3) [2.48]	0.442	3 (2-3) [2.51]	3 (2-3) [2.55]	0.741
24 h	3 (2-4) [2.86]	3 (2-3) [2.77]	0.607	4 (2-4) [3.29]	2 (2-3) [2.68]	0.116	3 (2-3) [2.80]	3 (2-3) [2.84]	0.710
72 h	3 (2-3) [2.77]	2.5 (2-3.8) [2.75]	0.792	3 (2-4) [3.00]	2 (2-3.5) [2.72]	0.390	3 (2-3) [2.74]	3 (2-4) [2.77]	0.919
VAS-nausea score: Mean ± SD [Median][c]									
	P (n = 56)	O (n = 56)	*p*	P (n = 7)	O (n = 25)	*p*	P (n = 49)	O (n = 31)	*p*
6 h	41.43 ± 6.99 [40]	43.21 ± 9.93 [50]	0.273	44.29 ± 7.87 [70]	44.80 ± 12.95 [70]	0.922	41.02 ± 6.85 [40]	41.94 ± 6.54 [40]	0.555
24 h	45.54 ± 12.64 [40]	51.96 ± 14.70 [40]	0.015	65.71 ± 16.18 [50]	61.20 ± 17.40 [40]	0.543	42.65 ± 9.08 [40]	44.52 ± 5.06 [40]	0.300
72 h	39.11 ± 10.32 [40]	45.7 ± 15.12 [40]	0.008	51.43 ± 18.64 [50]	56.00 ± 15.81 [50]	0.520	37.35 ± 7.30 [40]	37.42 ± 7.73 [40]	0.966

$p < 0.05$ significant.
[a] Compared by the Chi-square test/Fisher exact test used.
[b] Median (IQR) [Mean], compared by Mann Whitney U test.
[c] Independent samples t-test used.

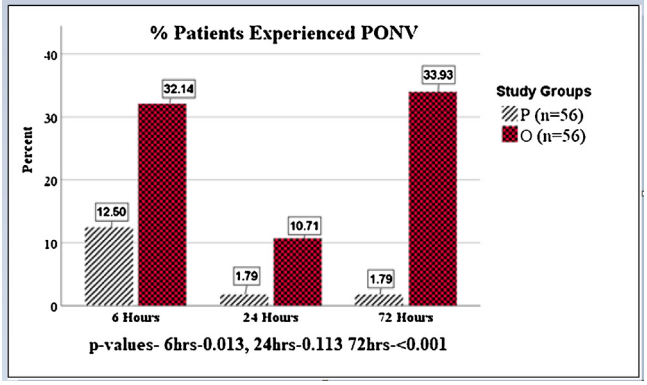

Figure 2 Distribution of PONV incidences in Group P and Group O.

was no difference in the administration of rescue antiemetics at the 6 and 12 hours between the two groups.

NRS used to assess postoperative pain was comparable between the two study groups (Table 2).

Similarly, the VAS-NAUSEA score of patients was compared between the two study groups. VAS-NAUSEA score was significantly lower in Group P as compared to Group O at a time point of 24 hours (45.54 ± 12.64 vs. 51.96 ± 14.70,

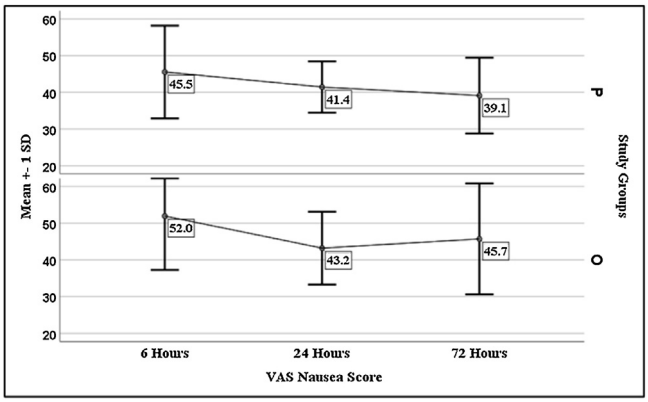

Figure 3 Distribution of VAS-Nausea score in Group P and Group O (p-value 6 h = 0.273, 24 h = 0.015, 72 h = 0.008).

p = 0.015) and 72 hours (39.11 ± 10.32 vs. 45.7 ± 15.12, p = 0.015) but not significant at the time of 6 hours (p > 0.05) (Table 2, Fig. 3).

Discussion

In this prospective randomized trial, we compared a single dose of ondansetron (4 mg) and palonosetron (0.075 mg) to determine the most effective prophylactic antiemetic agent for early and late-onset PONV in renal transplantation recipients.

Patients with ESRD are at high risk for gastrointestinal complications of renal failure like uremic gastropathy, dyspepsia, constipation, diarrhea, and delayed gastric emptying. Dyspepsia is highly prevalent in patients with chronic kidney disease and is characterized by nausea, vomiting, bloating, and early satiety. The prevalence of dyspepsia among HD patients varies between 48% and 70%,[11] predisposing these patients to high risk for perioperative nausea and vomiting. Other factors that increase the risk of PONV include the use of opioids perioperatively, the immunosuppression regime,[12] prolonged duration of surgery, use of volatile anesthetic agents.[13]

PONV can lead to significant morbidity and complication post-transplantation surgery. It can lead to prolonged intensive care stay, increased infections in already immunocompromised patients, and increase the cost of treatment, therefore effective preventive strategies are required to prevent PONV in these high-risk groups.[14] Palonosetron is the new 5-HT_3 (serotonin) receptor, antagonist. Unlike other drugs in this class, it exhibits simple bimolecular binding and positive co-operatively in binding to its receptors this differential interaction triggers a receptor alteration or internalization resulting in a long-lived inhibition of receptor function. Due to the unique interaction palonosetron is substantially longer acting and it has a plasma half-life is 40 hours. Palonosetron also causes prolonged inhibition of serotonin-induced calcium-ion influx that triggers functional effects that persist beyond its immediate binding to 5-HT3 receptors.[5] The molecular interaction leads to increase the effectiveness in preventing and treating both early and delayed onset nausea and vomiting. Previous clinical trials have reported a beneficial role of palonosetron when compared to placebo or other 5-HT3 receptor antagonists for the prevention of PONV.[15,16] Two very recent meta-analyses showed reductions in the incidence of PONV when palonosetron was compared with ondansetron in patients who underwent surgery under general anesthesia.[6,7]

None of the studies have compared palonosetron and ondansetron in ESRD patients undergoing renal transplantation under general anesthesia. In the study, we used the PONV intensity score as developed by Wengritzky et al.[10] It is a validated score to access clinically significant PONV and also helps distinguish early and late PONV. The PONV Intensity scale describes PONV based on its intensity and clinical importance. The key features of the scale include the intensity, pattern, and duration of nausea.[17]

We found the incidence of PONV of 30.35 % in our study in renal transplantation recipients. Patients who received palonosetron (Group P) showed an incidence of 12.5% PONV as compared to 48.21% in patients that received ondansetron. Xiong et al.[7] evaluated 9 randomized control trials including 741 patients undergoing elective surgery under general anesthesia and found that Palonosetron provides more effective prophylaxis against early (RR-0.51) and late postoperative nausea (RR-0.53) and late postoperative vomiting (RR-0.41) compared with ondansetron. In another meta-analysis by Singh et al.[6] included 22 trials comparing palonosetron with first-generation 5-HT3 receptor antagonist or placebo to prevent PONV, the significant statistical difference in favor of palonosetron in the prevention of PONV (acute and delayed) was found, while side effects were comparable between palonosetron and control groups. In this study, palonosetron significantly reduced the incidence of PONV during 0–6 hours and 24–72 hours postoperative period, but not during the 6–24 hours post-transplant surgery, even though palonosetron significantly reduced the overall incidence of PONV during the 0–72 hours postoperative period this was in agreement with Candiotti and colleagues.[16] Thus suggesting a superior prophylactic effect of palonosetron in preventing both early and late-onset PONV in the high-risk group. The use of rescue medication for episodes of vomiting was less in patients who received palonosetron 12.5% as compared to the ondansetron group.

During the 6 to 24 hours and 24 to 72 hours interval, our study showed that significantly fewer patients treated with palonosetron 0.075 mg experienced nausea compared with patients who received ondansetron. The mean at 24 h (45.54 ± 12.64 vs. 51.96 ± 14.70, p = 0.015) and 72 hours (39.11 ± 10.32 vs. 45.7 ± 15.12, p = 0.015) were consistent with the reduction in nausea as reported by Kovac and colleagues[15] in a previous study. No major side effects were encountered in either group of patients. In our experience, palonosetron is effective in preventing both episodes of nausea and postoperative vomiting in the early and late postoperative periods. A single dose of the drug has a prolonged duration of action, thus preventing repeated administration of drugs with minimal side effects. It provides greater patient satisfaction during recovery.

One possible limitation of this study was the modest population size for a dose-response trial, with few patients in each treatment arm for a robust evaluation of the treatment effect on all endpoints and all-time intervals for statisti-

cal analyses. Furthermore, patients' satisfaction was not included in the study. A comparative evaluation with various dosages of the two antiemetics used in the study was not done and a fixed dose of the drug was used in both groups. New multicenter randomized controlled trials with a larger population of renal transplantation recipients are required for further evaluation of these antiemetics on PONV.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

The authors are grateful to P. S. Myles and the team for permission to use the PONV intensity scale for this study. We also thanks Dr. Prabhakar Mishra, Associate Professor, Department of Biostatistics and Health Informatics, SGPGIMS, Lucknow, India for helping in statistical analysis.

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.2021.07.027.

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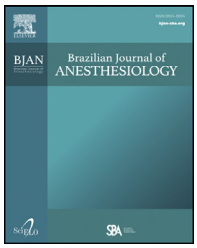

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ORIGINAL INVESTIGATION

Ultrasound-guided pulsed radiofrequency for chronic shoulder pain: a prospective study

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KEYWORDS
Chronic shoulder pain;
Ultrasonography;
Interventional;
Pulsed radiofrequency treatment

Abstract
Background and objectives: Chronic shoulder pain is a frequent cause of suffering and impaired quality of life. Treatment includes non-pharmacological and pharmacological therapies, and interventional procedures such as suprascapular nerve blocks and radiofrequency. This prospective study aims to evaluate the efficacy of ultrasound-guided pulsed radiofrequency of suprascapular nerve for chronic shoulder pain in a clinical setting.
Methods: Therapeutic efficacy was evaluated through pain intensity using numeric pain rating scale at baseline, immediately, 3, and 6 months after, and patient's motor function improvement. The secondary outcome was patient satisfaction.
Results: A total of 34 patients were enrolled and all patients presented a reduction in the numeric pain rating scale immediately after treatment. Pain reduction from baseline to 6 months after the procedure was 34.4% and 36.9% static and dynamic, respectively. The median percentage reduction was statistically significant immediately, 3 and 6 months after. There was also an improvement in range of motion, 39.6% in abduction, 24.1% in flexion, and 29.5% in extension. Ninety percent of patients reported patient's global impression of change superior to six.
Conclusion: This study concludes that ultrasound-guided pulsed radiofrequency of suprascapular nerve reduces pain intensity for at least 6 months, accompanied by improvement of motor function and higher levels of patients' satisfaction. Therefore, this technique represents a valid analgesic approach to chronic shoulder pain.
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Introduction

Shoulder disorders are the third most prevalent type of musculoskeletal complaint in adults. They can significantly impact life quality, entailing considerable health costs, disability, and work absenteeism. Chronic shoulder pain prevalence ranges from 15.5% to 41% in the general population, increasing with age, and is higher for women.[1,2,4,5]

Shoulder pain etiology can be attributable to intrinsic disorders, comprising the rotator cuff, glenohumeral, acromioclavicular, biceps tendonitis, infection, shoulder instability, or as extrinsic shoulder pain such as referred pain, polymyalgia rheumatic, and malignancy.[2,3,5,6]

The nerves supplying the shoulder joint arise from the brachial plexus. The suprascapular nerve supplies 70% of the sensory innervation of the shoulder joint, whereas the remaining 30% is supplied by the subscapular nerve, axillary nerve, and lateral pectoral nerve.[5] The suprascapular nerve is a mixed nerve, both motor and sensitive, originated in the upper trunk of brachial plexus, C5 and C6 roots. It runs inferior, posterior, and laterally to reach the supraspinous fossa in the scapula. The sensitive components innervate the posterior and superior shoulder capsule, glenohumeral, and the acromioclavicular joint. The motor components innervate the supra and infraspinatus muscles.

Shoulder pain treatment involves a multimodal approach, including non-pharmacological (physical therapy, transcutaneous electric nerve stimulation), pharmacological therapies, and interventional procedures such as intra-articular steroid injections, suprascapular nerve blocks, radiofrequency of suprascapular nerve and surgery.[7,9]

Pulsed radiofrequency was first reported in 1998 as a non-neurolytic lesioning method delivering an electrical field and heat bursts (temperature < 42 °C) for pain relief without evidence of neural damage.[8,10] Previous studies demonstrate significant pain relief and functional improvement in patients with chronic shoulder pain of a wide range of etiologies.[11,12] Throughout most studies, authors use fluoroscopy or computed tomography-guided techniques. However, ultrasound-guidance radiofrequency has advantages over other imaging modalities, for instance, portability, real-time assessment and dynamic evaluation, limited trauma, and avoidance of patient and physician radiation exposure.[13–15] Only a few previous studies have evaluated ultrasound efficacy of suprascapular nerve pulsed radiofrequency and patient satisfaction.[15–18]

In this regard, our main objective was to prospectively evaluate the efficacy of ultrasound-guided suprascapular nerve pulsed radiofrequency for chronic shoulder pain treatment in a chronic pain unit. The primary outcome was efficacy using pain intensity and motor function improvement. The secondary outcome was patient satisfaction.

Methods

This prospective study was conducted at our chronic pain unit between May 2016 and December 2019. A total of thirty-six patients were submitted to a diagnostic block, from which thirty-four patients were included in this study as they matched the inclusion criteria.

Ethics statement

The data was collected after receiving approval from the Ethical Committee of our institution. All patients submitted to the suprascapular block and pulsed radiofrequency received oral and written information and signed informed consent before the procedure.

Inclusion criteria

The following inclusion criteria were used: diagnosis of chronic shoulder pain (> 6 months); over 18 years of age; non-pregnancy; non-allergy to local anesthetic or corticosteroids; non-local or systemic infection; reduction of at least 50% in pain intensity after previous ultrasound-guided suprascapular nerve block.

Patient, clinical and outcome variables

Patient demographics

The following information was collected from patients: gender, age, chronic pain duration, dominant upper limb, and shoulder pain etiology.

Numeric pain rate scale

Pain intensity was assessed at baseline, immediately, three and six months after using the Numeric Pain Rate Scale (NPRS). This unidimensional pain instrument consists of a horizontal line with a beginning point marked as zero (''no pain'') and at the opposite end, marked as 10 (''worst pain possible''). Patients report the number which best represents the pain they are/were feeling. Generally, pain in the 1–3 category is ranked as mild pain, 4–6 as moderate pain and 7–10 as severe pain.

Motor function evaluation

Static and dynamic patient motor function was assessed by the same rehabilitation nurse specialist, before and after suprascapular radiofrequency, measuring range of motion (abduction, flexion, and extension) using a goniometer. Muscle strength was also assessed.

SPADI

A validated Portuguese score of Shoulder Pain and Disability Index (SPADI-VP) was used at baseline as a secondary clinical outcome.[19] It contains thirteen issues related to pain and disability associated with shoulder disorders. For each question, there is a scale of 0 to 10. Zero indicates activity without difficulty and ten corresponds to the condition where the individual is not capable of carrying out the proposed activity. The maximum score of the questionnaire is 80 points. The individual obtained score is converted into a percentage, with 100% being the worst condition of shoulder dysfunction. SPADI was designed to measure the impact of shoulder pathology in terms of pain and disability and assess how these metrics evolve.[20]

Patient satisfaction

Patient satisfaction is a good indicator of the quality of health care. This was evaluated using the Patient's Global

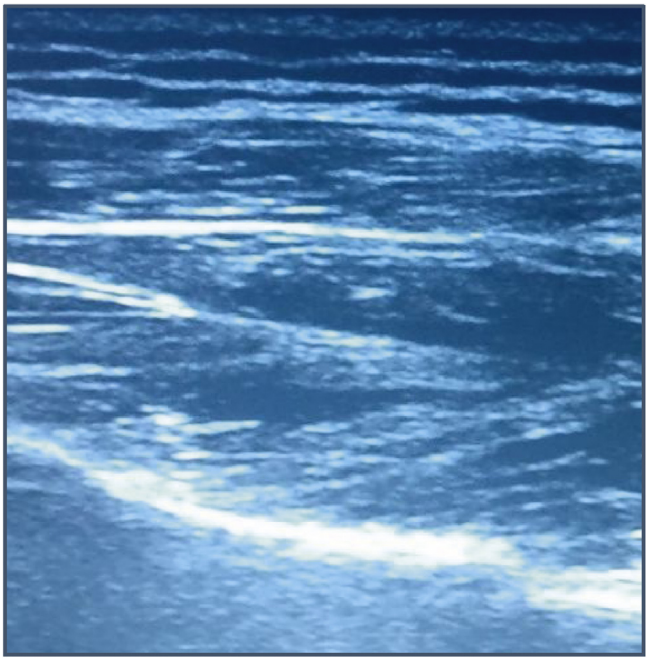

Figure 1 Ultrasound identification of the suprascapular nerve in the suprascapular notch.

Impression of Change Validated Portuguese (PGIC-VP) questionnaire immediately and six months after the procedure. In this unidimensional tool, patients report their treatment improvement on a 7-item scale, with 1 representing ''no change'' and 7 representing ''a great deal better''.[21]

Ultrasound-guided pulsed radiofrequency

All procedures were performed by the same anesthesiologist with expertise in chronic pain management and ultrasound-guided interventions, using Acuson ultrasound from Siemens P300®, linear probe 12 MHz. Patients were placed in a sitting position and standard monitoring was applied. Under aseptic conditions, the linear transducer was positioned just cephalad and parallel to the scapular spine. The suprascapular nerve was identified as a hyperechoic structure below the transverse scapular ligament in the scapular notch. A 22 G 60-mm radiofrequency needle was then advanced under ultrasound guidance toward the scapular notch by using the in-plane approach (Fig. 1). Sensory stimulation was performed with 10–200 Hz, 1 ms pulse width, up to 0.5 volts and the patients reported paraesthesia in the shoulder joint. After motor stimulation (2 Hz, 1 ms pulse width, up to 1 volt), contractions of the infra- and supraspinatus muscles were observed. Pulsed radiofrequency lesioning was then performed for 180 seconds (2 Hz, 30 ms pulse width, temperature < 42 °C). Thirty minutes after the procedure, pain intensity was evaluated using NPRS and patients were discharged home.

A chronic pain appointment was schedule one, three, and six months after the procedure.

Statistical analysis

From the Shapiro-Wilk test, it was assessed that the data does not follow a normal distribution. Thus, the correlation coefficients were calculated using the Spearman test to quantify the association between static and dynamic baseline NPRS and immediate, three and six months NPRS, and among NPRS and dominant arm and between NPRS and PGIC-VP. The accepted level of significance for the correlation was $p < 0.01$ for a strong correlation and $p < 0.05$ for moderate correlation.

Treatment efficacy was quantified by calculating absolute differences and percentage change from baseline. For each patient, a response was considered clinically relevant if the NPRS was reduced by at least 30% relative to baseline, as is standardly accepted.[22]

Table 1 Patient demographics (variables are expressed as mean ± standard deviation and relative frequencies are expressed in percentage).

Demographics		
Gender, n (%)	Male	6 (18%)
	Female	28 (82%)
Age, years		67 ± 9
Age, more than 60 years		24 (70.6%)
Clinical Characteristics		
Duration of chronic shoulder pain (months)		31.57 ± 24.3
Dominant upper limb		22 (65%)
Shoulder pain etiology	Tendinitis/bursitis	23.5 (%)
	Arthrosis	76.5 (%)

Results

Of thirty-six patients, two were excluded from the study because it was not observed a reduction of at least 50% in pain intensity after ultrasound-guided suprascapular nerve block (did not meet the first inclusion criterion).

The demographic characteristics of the thirty-four patients are presented in Table 1.

Changes in NPRS

We started by analyzing the change in static and dynamic NPRS between baseline and immediately after the procedure (Table 2). All patients presented a reduction in NPRS immediately after treatment. Of the patients, 94.1% and 91.2% presented a clinically significant reduction in static and dynamic NPRS, respectively. Complete pain relief (NPRS lower or equal to 1) was obtained in 76.5% and 23.5% of patients, regarding static and dynamic NPRS, respectively. Median percentage reduction in the NPRS immediately after the procedure of 86.8 and 69.6% static and dynamic, respectively.

To characterize treatment efficacy in the long-term, percentage reduction from baseline to 3 months after the procedure was 54.9% and 53.7%, static and dynamic, respectively (Fig. 2). Then it was mandatory to see if a persistent notorious reduction could be observed over time. To this end, we evaluated NPRS reduction after six months (34.4% and 37.0%, static and dynamic). The median percentage reduction was also statistically significant ($p < 0.01$ one-

Table 2 Summary of efficacy evaluation.

NPRS	Mean (99%) p-value < 0.01					
	Static			Dynamic		
Baseline	5.15 [4.21–6.08]			8.38 [7.74–9.03]		
Time	Immediately	3 months	6 months	Immediately	3 months	6 months
Absolute change (mean [ranges])	4.56 [3.48–5.64]	3.15 [2.05–4.25]	2.38 [1.09–3.67]	5.85 [4.83–6.88]	4.56 [3.59–5.53]	3.26 [2.15–4.38]
Percentage change (%) (mean [ranges])	86.81 [75.55–98.08]	54.86 [37.77–71.96]	34.37 [10.41–59.78]	69.63 [59.78–79.49]	53.68 [43.36–64.00]	36.96 [24.76–49.16]
NPRS	Median (99%) p-value < 0.01					
	Static	Dynamic				
Baseline	5.00 [4.06–5.94]			8.00 [7.36–8.64]		
Time	Immediately	3 months	6 months	Immediately	3 months	6 months
Absolute change (median [ranges])	4.50 [3.42–5.58]	3.00 [1.90–4.10]	2.00 [0.71–1.88]	5.50 [4.48–6.52]	4.50 [3.53–5.47]	3.00 [1.88–4.12]
Percentage change (%) (median [ranges])	100.00 [88.74–100.00]	64.58 [47.49–81.68]	45.00 [21.04–68.96]	70.71 [60.86–80.57]	61.25 [50.93–71.57]	37.50 [25.30–49.70]

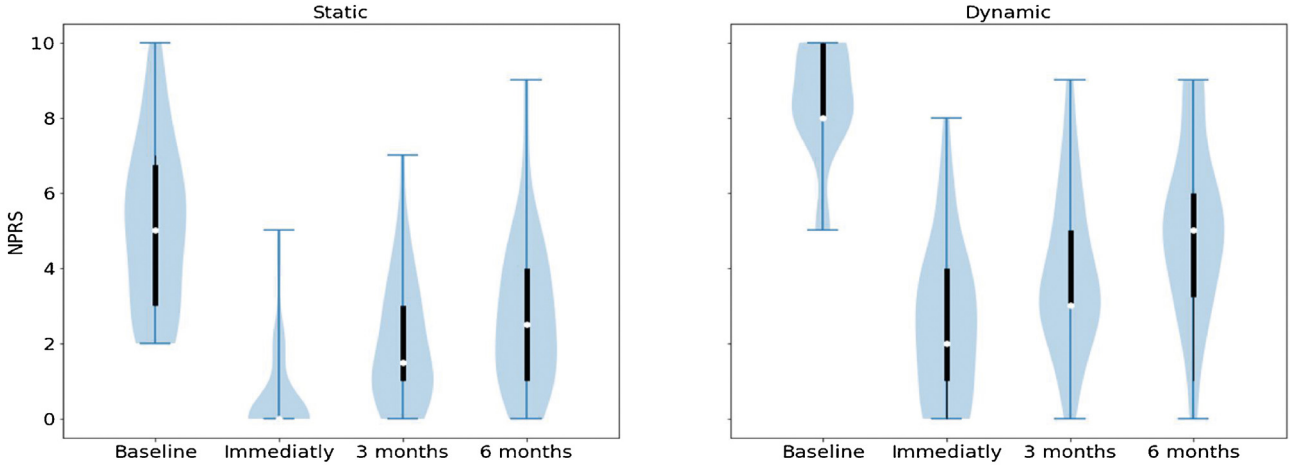

Figure 2 NPRS for each patient before treatment, immediately, 3 and after 6 months for static and dynamic.

sided Wilcoxon signed-rank test); this gauge the treatment effectiveness.

A strong correlation with high statistical significance was found between the reduction of static NPRS immediately, 3 and 6 months, and baseline. A strong correlation with high statistical significance was also found among static and dynamic reduction of NPRS after 6 months. Low correlation and high statistical significance were found among PGIC-VP and higher reduction in NPRS for both static and dynamic. A correlation between the dominant arm and the other variables was not found.

SPADI-VP

SPADI was developed to measure current shoulder pain and disability. In our study median SPADI score was 35.17, with a minimum of 27 and a maximum of 65.7.

Motor function

Treatment efficacy was also analyzed regarding improvement of motor function. Therefore, changes in the range of motion (flexion, abduction, and extension) at baseline and after six months were compared. The median baseline of flexion abduction and extension were 12.5º, 22.5º and 20º, respectively. Increased 39.6% in flexion, 24.1% in abduction, and 29.5% in extension after six months.

Patient satisfaction

Regarding self-report measure PGIC-VP: 50% scored ''7'' representing ''a great deal better''; 40% scored ''6'' indicating ''better''; 10% scored ''5'' representing moderately better. Thus, 90% of our patients had a clinically significant improvement.

Discussion

These results indicate that ultrasound-guided pulsed radiofrequency of suprascapular nerve for chronic shoulder pain provide a statistically significant reduction in static and dynamic pain score and range of motion (flexion, abduction, and extension), and the effect persisted for at least 6 months.

Our study describes an aging population, with 70.6% aged over 60 years. Older individuals have a higher incidence of chronic shoulder pain, mainly due to degenerative rotator cuff pathologies. Recently, a change of the morphology of the suprascapular nerve has been identified in patients with supraspinatus tendon full-thickness tear, resulting in nerve entrapment,[23] rephrasing the importance of suprascapular nerve interventions as a fundamental tool in chronic shoulder pain treatment. However, as the effect of suprascapular nerve block has a limited duration, diagnostic blocks should be performed to identify patients who should proceed to the treatment. A patient with greater than 50% pain relief is considered to have a positive diagnostic block.[14,15] While intra-articular injections have diagnostic value, they have less prognostic value for radiofrequency success.[24,25]

The mechanism pointed for pulsed radiofrequency long-term pain relief is the neuromodulatory effect created via alternating the expression of a gene such as c-fos in pain processing neurons.[26] Pulsed radiofrequency of suprascapular nerve was applied by Rohof in 2002 with a blind technique.[27] Peripheral pulsed radiofrequency has gained acceptance by pain control with the non-destructive mechanism. Both thermal and pulsed radiofrequency ablation of the suprascapular nerve have been described to treat chronic shoulder pain, but there is a theoretical concern of post-ablation weakness in the supraspinatus and in infraspinatus muscles.[28] Research reported that pulsed radiofrequency of suprascapular nerve was effective in treating chronic shoulder pain. Despite the extensive use of fluoroscopy or computed-tomography guidance in literature,[29–31] recent studies start adopting ultrasound guidance.[15,17] Also, some studies did not characterize long-term treatment efficacy.[9]

The etiology of chronic shoulder pain is diverse, as is its treatment. Rotator cuff pathology treatment has been studied with mixed outcomes and little research has been done to evaluate its efficacy in other shoulder etiologies.[15,17] In our work, there was no significant difference in long-term efficacy in both group etiologies (tendinitis/bursitis and arthrosis) for chronic shoulder pain, as such, we cannot pinpoint a specific metric that most prominently factors for the existence of either arthrosis or tendinitis.

Patient satisfaction with chronic shoulder pain treatment has received less attention in previous studies. Satisfaction with treatment of chronic pain is not merely a matter of pain relief. It is important to distinguish satisfaction with care of satisfaction with improvement after treatment. Patient satisfaction is a subjective experience; it can be defined as the emotional feeling resulting from the comparison between the actual perceived performance and quality of the treatment with the original expectations. It is frequently used as an indicator of meaningful change in treatments for chronic pain. The definition of clinically significant change suggests that PGIC-VP values of 6 or more correlate best with actual change. According to PGIC-VP, 90% of our patients had a clinically significant improvement. In our study, patients with higher reduction in NPRS were most closely correlated with PGIC-VP status, regardless of initial pain intensity.

Our study caveat is 2-fold: it was conducted using a small sample size and it lacks a control group. A longer-term follow-up would be desirable.

Future research is needed to assess the best treatment approach for various chronic shoulder pain etiologies.

Conclusions

Ultrasound-guided suprascapular nerve radiofrequency is a safe and effective technique for treating chronic shoulder pain, providing significant improvement in NPRS during at least 6 months, accompanied with improvement of motor function and higher levels of patient satisfaction. Therefore, this technique represents a valid analgesic approach to a multimodal treatment strategy of chronic shoulder pain.

Future randomized control trials are warranted for validating these results.

Conflicts of interest

The authors declare no conflicts of interest.

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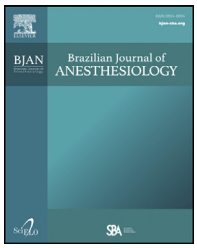

ORIGINAL INVESTIGATION

Influence of exogenous opioids on the acute inflammatory response in the perioperative period of oncological surgery: a clinical study

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KEYWORDS
Opioids;
Cancer;
Cytokines;
Anesthesia

Abstract
Background: Recently, opioids have been related to trigger changes in cytokine release and tumor angiogenesis processes, influencing tumor growth, metastasis, and recurrence.
Methods: This is a prospective randomized clinical study to test whether if exogenous opioids used in the anesthesia during cancer surgery can affect the systemic inflammatory and immunological patterns. Patients were randomly allocated to the OP (opioid-inclusive) or OF (opioid-free) anesthesia group. A total of 45 patients were selected, being carriers of prostate, stomach, pancreas, bile ducts, breast, colon, lung, uterus, kidneys, or retroperitoneum tumors. Plasma levels of IL-4, IL-12, IL-17A, and TNF-α, and their oxidative stress profile before and after surgery were evaluated in both groups. In vitro tests were performed by using healthy donor blood incubated with each isolated drug used in patients' anesthesia for 1 hour, the same cytokines were measured in plasma.
Results: There was a significant reduction in lipid peroxidation in both groups. Patients from OF group had a significant consumption of IL-12 in the perioperative period. The other cytokines evaluated did not vary. It was also observed a significant correlation between IL-12 and TNF-α levels in the OF-post group. Except for atracurium, all tested drugs led to a reduction in IL-12 levels.
Conclusions: This study demonstrated that there is a reduction of IL-12 in the OF-post patients, suggesting acute consumption and that this seems to be a general mechanism of anesthetic drugs, as demonstrated *in vitro*. Also, these findings bring us to reflect if IL-12 changes may influence the disease progression and recurrence.
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Introduction

Cancer is the second main group of diseases responsible for the death of adults in the world.[1] In most solid cancers, surgery represents the greatest chance of cure or increased disease-free survival.[2–5] The surgical procedure causes pain and activates the inflammatory cascade, releasing pro-inflammatory cytokines. It must be considered that the time of surgery increases the patient's vulnerability to local tumor recurrence and maximizes the risk of hematological spread of micrometastasis.[2,3,5–8]

The surgical procedure triggers an increase in pro-inflammatory mediators as interleukin-1β (IL-1β), interleukin-6 (IL-6), and C-reactive protein (CRP). The microenvironment generated by surgical trauma is also rich in reactive oxygen species (ROS), which can induce cellular processes favorable to tumor growth and metastasis. Oxidative stress activates the inflammatory pathways that lead to the transformation of a normal cell into a tumor cell, and changes in its survival, proliferation, chemoresistance, radioresistance, invasion, angiogenesis, and the survival of tumorigenic stem cells.[2,9]

In this context, anesthesia and analgesia are performed in a multimodal way, at different points to block the transmission of pain and inflammatory pathways. Among the therapeutic classes, opioids are often used both as adjuvants in epidural and spinal anesthesia (intrathecal administration), and in general anesthesia. The pharmacodynamics of opioid drugs is related to their binding to opioid receptors, mainly the mu (μ) class, present in the central nervous system (CNS). Tumor cells are thought to express such receptors, and its use in oncological patients seems to favor tumor angiogenesis, tumor growth and spreading of micrometastasis.[10,11] Therefore, the use of opioids in cancer surgery is doubtful because the association with the possibility of disease metastasis and recurrence was observed.[12]

In vitro studies show that opioids as morphine can influence the migration and proliferation of endothelial cells.[12] Also, morphine, methadone, and buprenorphine significantly decrease the cytotoxic activity of NK cells,[13] which is dependent on IL-12. Morphine promotes tumor progression and reduces patient survival due to the increase of tumor angiogenesis, peri-tumor lymphangiogenesis, mast cell activation, and the liberation of higher levels of cytokines and substance P in tumors.[11,14] A study by Khabbazi et al. (2015) shows that morphine prevents the increase in IL-4-induced MMP-9 and IL-4-induced M2 macrophage activation, leading to high tumor aggressiveness.[15]

Considering that the perioperative period for cancer patients is a multifactorial and complex scenario,[16] more studies are necessary to understand the influence of anesthetic drugs on the production of inflammatory mediators that could help to eliminate tumors. In this context, the balance among the pro- and anti-inflammatory cytokine profiles (Th1/Th2/Th17) may be affected by opioids, and its relationship with clinicopathological features of cancer is still poorly understood.

To contribute to the comprehension of the influence of opioid-free anesthesia in the cytokine profile of cancer patients, we investigated its influence on the acute inflammatory response induced using opioids in the immediate pre- and postoperative period of patients with different types of cancer undergoing surgery to remove the tumor. This study aims to quantify the levels of cytokines of the Th1/Th2/Th17 immune profiles (IL-12 and TNF-α for Th1, IL-4 for Th2, and IL-17A for Th17) in the peripheral blood of patients before and after surgery, with and without the use of opioids; establish the profile of blood lipid peroxidation in these patients; and, by *in vitro* investigations, assess if there is any change due to the use of opioids, as well as its putative mechanism of action. Considering that opioids can affect the production of inflammatory mediators under normal conditions, we hypothesized that their use in cancer patients could affect negatively their postoperative levels.

Methods

Design of the study

This is a prospective clinical study, randomized to use or not opioids in the anesthetic technique. It was conducted at the Francisco Beltrão Cancer Hospital (CEONC) from July 2019 to October 2020. Patients were randomly divided into two groups, OP (anesthesia with the use of exogenous opioid) or OF (anesthesia without exogenous opioid, i.e., opioid-free), using the electronic random number table method. They received more epidural general anesthesia with the use of opioids or more epidural general anesthesia free of opioids, respectively. After being processed by the Human Research Ethics Committee (CEP) of the Western Paraná State University (UNIOESTE) – Francisco Beltrão, Brazil, it was approved under CAAE number 15251519.1.0000.0107.

The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is presented in Figure 1.

All adult patients attended at the hospital with an indication for oncological surgery according to the previous evaluation of the surgeons who attend at that institution in the period (July 2019 to October 2020) were included. The sample size was calculated considering the population attended by the 8th State Regional of Health (324,178 people that can be sent to Ceonc if they have cancer), the cancer incidence estimated by the National Cancer Institute, in Paraná, for 2020 (13,990 cases per 11 million people, representing a maximum percentage of 3% of cancer in the studied population), and a confidence level of 95%. By including these data in the general formula to estimate the sample size ($n = N.Z2.p.(1-p)/Z2.p.(1-p) + e2.N-1$), in which n: sample size, N: population, Z: normal variable, *p*: real probability of the event, e: sample error), the minimum number of individuals for the study was 45. In total, 47 adult patients of both sexes were selected for surgery to remove a tumor mass located in the prostate, stomach, pancreas, bile ducts, breast, colon, lung, uterus, kidneys, and retroperitoneum. Of the 47 patients who participated in the research, 2 were excluded due to lack of material on the day of the surgical procedure. Thus, there were 23 patients in the OP group and 22 in the OF group. All the 45 patients were followed up until the end of the study and had their biological samples analyzed.

All patients underwent preanesthetic consultation for the free decision to participate or not in the study, preserving the confidentiality of the information obtained, as well as

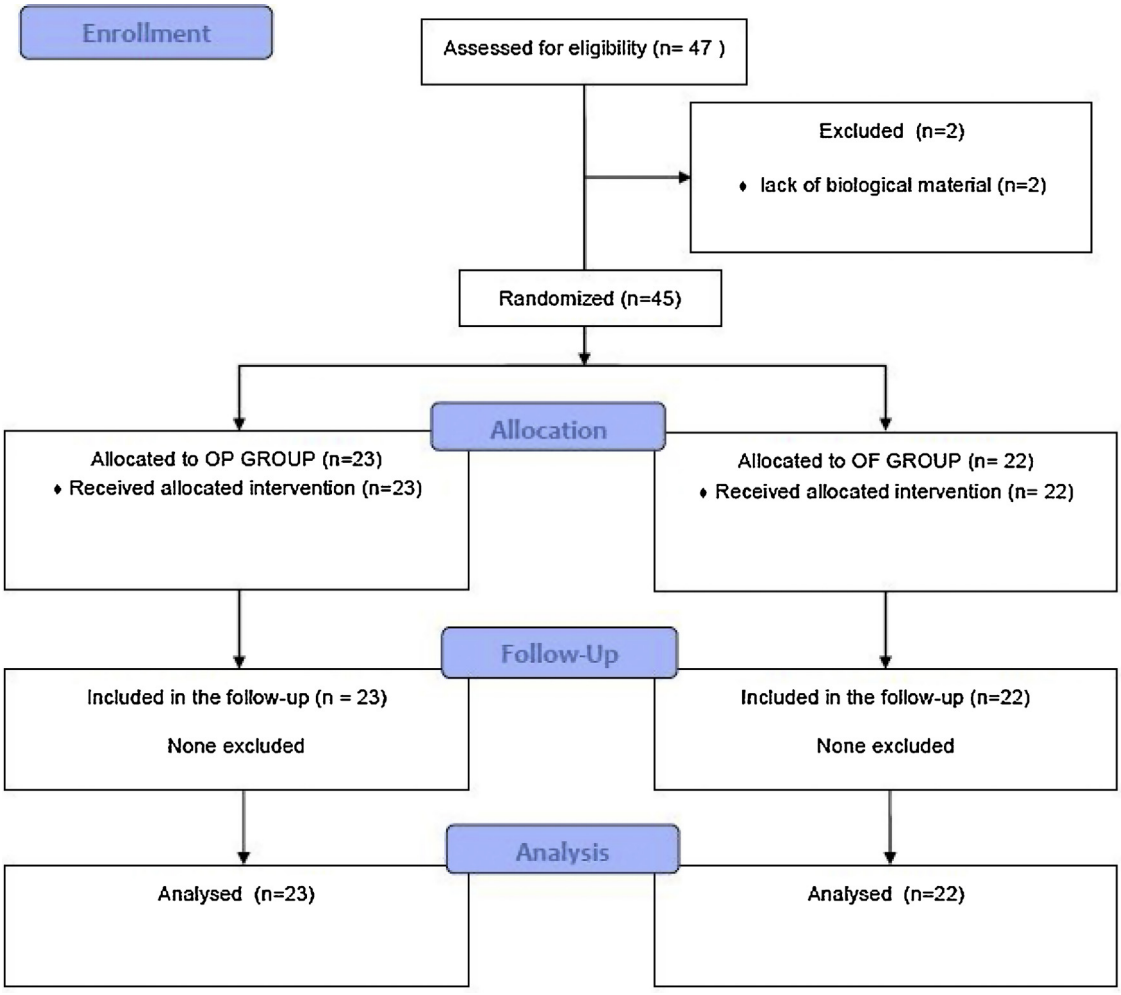

Figure 1 The Consolidated Standards of Reporting Trials (CONSORT) flow diagram for patients selection, allocation, follow-up and analysis.

the identity of the participating patients. After due clarification on the study, everyone who signed the informed consent form regarding anesthesia and the study participated in the research. At the moment of the preanesthetic evaluation, both evaluating physician, patient, and the person responsible for the analysis had no information on whether the sample came from a patient in the OF or OP group. The group to which the patient was allocated was revealed on the day of surgery only to the anesthetist responsible for the anesthetic procedure.

The exclusion criteria were patients under the age of 18, patients with allergies to the medications in the treatment protocols, patients who had previously used opioids or corticosteroids in the last 6 months, patients using immunosuppressive therapy or had autoimmune diseases, patients with chronic or acute pain related or not to cancer, patients with contraindication or refusal to epidural block, and patients who needed transfusion of blood products in the perioperative period. The preanesthetic evaluation was also excluded if patients had severe life-threatening systemic disorders, with or without surgery, and dying patients with little chance of survival. No patient suffered any loss in terms of postoperative pain control due to their allocation in the OF or OP group, with their intensity being routinely assessed and treated, if necessary, through multimodal therapy. All patients were assessed for the Visual Analogue Scale (VAS) for pain, before and after the anesthetic procedure, so the analgesia was effective in both groups.

For laboratory analysis, a sample of peripheral venous blood anticoagulated with heparin was obtained in two moments. The first sample (T1) was collected from the venous system, in the operating room, through the peripheral venous device before installing the line to infuse the solutions and drugs. The caliber of the peripheral venous device was chosen according to the size of the surgery and the patient's anatomy, using 20G, 18G, 16G, or 14G devices. The second collection (T2) of blood was carried out in the operating room, in the immediate postoperative period, as part of the routine postoperative laboratory control of the institution. After T2 collection, patients were transferred to the intensive care unit (ICU) or surgical ward of the hospital unit, according to the anesthesiologist's clinical indication, where they received postoperative care. Samples were immediately sent to the lab, centrifuged (3500 rpm, 5 minutes), and the plasma obtained was frozen until analysis.

Paired comparative analyzes were performed among the peripheral blood samples before and after anesthesia for each group to obtain an overview of the inflammatory profile of the patients. The following names were used for statistical analysis of the results: without preanesthesia opioid (OF-Pre), without postanesthesia opioid (OF-Post), with preanesthesia opioid (OP-Pre), and with postanesthesia opioid (OP-Post).

Data taken from medical records and perioperative records of nursing and anesthesiologists were: number of medical records, age, weight, height, sex, education, marital status, city where the patient live, current and previous illnesses, medications in use, smoking, alcoholism, ASA (|American Society of Anesthesiologists) physical status, duration of surgery (min), volume of estimated blood loss (mL), number of leukocytes. These data were stored in a database for further studies and further analysis.

Anesthetic procedure

In the operating room, standard monitoring was performed with a Dixtal 2010® multiparametric monitor (Dixtal Biomedical, Brazil) and the neuromuscular block was controlled through the sequence of four stimuli with the Watch® SX train-of-four (TOF) monitor (Organon, USA).

Hydration and replacement of losses were performed with an isotonic crystalloid solution (0.9% sodium chloride and/or lactated Ringer) and, when necessary, by blood transfusion.

All patients received dipyrone 30 mg.kg^{-1} intravenously (IV) and antibiotic prophylaxis according to the surgical site and the guidance of the Hospital Infection Control Commission (CCIH) of the institution. The prophylaxis for stress ulcers was by antagonism of the H2 receptor with 50 mg IV of ranitidine hydrochloride.

Conscious sedation for epidural puncture was performed with midazolam 0.05 mg.kg^{-1} IV with oxygen supplementation 3–4 L.min^{-1} in a face mask with reservoir. After installed anxiolysis and immediately before peripheral venipuncture, baseline blood pressure was determined by the average of three successive measurements.

Epidural anesthesia was conducted in the thoracic region with the patient positioned in sitting position. It was performed using aseptic technique. We injected 1% of lidocaine and epinephrine in the skin, throughout the path of the puncture and, if necessary, we inserted a catheter for anesthetic complementation.[17] A syringe was prepared with saline solution for the OF group or with 2 mg morphine for the OP group, with a standard volume of 2 mL.

General anesthesia was combined with epidural block to facilitate airway control and for better perioperative comfort for the patient due to the surgical positioning, surgical time, and standardization of anesthesia.

General anesthesia was administered using the total venous technique, with induction performed with propofol 1.5–2.5 mg.kg^{-1}, lidocaine 1.5 mg.kg^{-1}, magnesium sulfate 25 mg.kg^{-1}, and atracurium 0.3–0.6 mg.kg^{-1}, with tracheal intubation being performed after obtaining no response to the sequence of four stimuli (TOF 0/4). An additional syringe for anesthetic induction was prepared with saline solution for the OF group or with fentanyl 2 μg.kg^{-1} for the OP group, with a standard volume of 5 mL.

Maintenance of the anesthetic plan was performed with lidocaine 1.5 mg.kg^{-1}.h^{-1}, propofol 100–200 μg.kg^{-1}.min^{-1} and, when TOF presented two or more responses to the sequence of four stimuli (TOF $\geq$ 2), a complementary dose of atracurium was administered to maintain adequate muscle relaxation. Older adults with comorbidities need lower doses, therefore their doses were titrated to avoid hypotension during the induction and maintenance of general anesthesia.

At the end of the procedure, the patients were extubated in the operating room and sent to the ICU or surgical ward for immediate postoperative care. During the 24 hours following surgery, the patients were followed up by the anesthesiology service and evaluated for vital signs and anesthetic-surgical complications.

Evaluation of systemic inflammatory status

The circulating levels of interleukin 4 (IL-4), interleukin 12 (IL-12 p70), interleukin 17A (IL-17A), and tumor necrosis factor-alpha (TNF-α), and the lipid peroxidation profile of plasma were evaluated. The levels of cytokines were measured using commercial kits (Invitrogen, USA) using the enzyme immunoassay technique (ELISA), following the analysis protocol recommended by the manufacturer. The kits have a sensitivity of 4 pg.mL^{-1}. The values obtained were used to calculate cytokine ratios (Th1/Th2, Th1/Th17, and Th2/Th17).

We also evaluated the oxidative stress profile of patients, by analyzing their lipid peroxidation status and the antioxidant capacity of plasma. The analysis of lipoperoxidation levels was obtained from the determination of hydroperoxide levels using the chemiluminescence technique induced by t-butyl, after standardization of the test in the laboratory to adjust the analytical technical conditions. For this assessment of plasma lipoperoxidation, 125 μL of the sample was added in 865 μL of 10 mM monobasic phosphate buffer and pH 7.4 in 0.9% NaCl with incubation at 37 °C for 5 minutes. To trigger the reaction, a 10-μl aliquot of the t-butyl solution was added. The reaction reading was performed in a GloMax® 20/20 luminometer (Promega, USA) in the protocol of one reading per second, for 60 minutes, where the qualitative photon emission curve, measured in relative units of light (URL), was evaluated. Concerning the antioxidant capacity of samples, TRAP provides an overview of the antioxidant non-enzymatic defenses of plasma. The compound 2,2'-Azobis (ABAP) reacts with lipids present in the plasma to form lipoperoxides. This reaction emits photons in low quantities, undetectable by spectrophotometry. To amplify this reaction, luminol was added. It is a compound more unstable than lipoperoxides, capable of capturing the unpaired electrons of these lipoperoxides, amplifying the light emission and signal emission to the luminometer. The greater the quantity of antioxidants present in the sample, the greater the delay in the rise of the ABAP curve, which corresponds to the impediment in the formation of lipoperoxides due to the level of low molecular weight antioxidants. The samples were diluted 1:50 in 980 μL of 1 M glycine buffer, pH 8.6, added with 50 μL of

luminol solution (0.0398 mg.mL^{-1}) and 50 μL of ABAP solution (54.24 mg.mL^{-1}) to start the reaction. The results were analyzed using the OriginLab 7.5 software and expressed in nM trolox, based on the ABAP curve inhibition profile of a standard solution of the water-soluble vitamin E analogue (Trolox 0.5 mg.mL^{-1}). Both methods to evaluate oxidative stress were previously published by Herrera et al. 2014.[31]

In vitro study

Aiming to investigate the individual mechanisms triggered by anesthetic drugs that resulted in altered levels of IL-12 and oxidative stress, each drug was tested individually. For this, 1 mL of healthy donor blood (n = 10) was incubated for 1 hour with each of the following drugs and concentrations: propofol (3 μg.mL^{-1}), fentanyl (2.5 ng.mL^{-1}), lidocaine (1.5 μg.mL^{-1}), magnesium sulphate (5 mg.dL^{-1}) and atracurium (0.29 μg.mL^{-1}). The concentrations were estimated based on the therapeutic plasmatic concentration estimated for each drug, as used in the anesthetic protocol of cancer patients. After incubation, samples were centrifuged at 5000 rpm for 5 minutes, and analyzed in the cytokine ELISA kit and oxidative stress protocol, as described above.

Statistical analysis

From the data obtained and properly tabulated in Microsoft Excel® spreadsheets, an analysis of the association of sociodemographic data concerning the different treatments was made: without the use of opioids (OF) and with the use of opioids (OP). This was performed using the Chi-square test of independence, followed by the post-test of adjusted residuals, which allows the identification of which categories the variables have a statistical association.

For each cytokine, to assess their interaction concerning time and treatments, the ANOVA test for repeated measures was applied, followed by the Tukey-HSD test, in case of statistical significance ($p < 0.05$). For this test to be applied, the statistical assumptions of normality (Shapiro-Wilk test) and homoscedasticity of the data (Cochran test) were evaluated. Finally, to assess the existence of an association among the different variables, the PERMANOVA test was applied, followed by the Principal Coordinate Analysis (PCoA) to visualize them. Statistical analyzes were performed using XLStat Version 19.4 (ADDINSOFT, 2018), STATISTICA 7.0 (StatSoft, 2004), and the computer program R (R Development Core Team, 2019), and we assumed a significance level of $p < 0.05$ in all analyzes.

Results

Table 1 shows the clinicopathological profile of the patients. The population showed no difference between the OF and OP groups concerning most sociodemographic data.

As shown in Figure 2, we first investigated by principal component analysis if there was any association among the studied variables. In the analysis of each cytokine separately, in interaction with the different groups (OP/OF) and different times (pre and postoperative), we observed that the cytokines did not show statistical significance. However, when observing the pre- and postoperative periods, in both groups there was a significant reduction in oxidative damage ($F = 20.56$; $p = 0.000$). When analyzing all variables together, we observed an association between them concerning time (pre- or postanesthesia) ($F = 3.11$; $p = 0.022$). However, this association was not seen concerning the groups ($F = 2.40$; $p = 0.101$).

Since the principal component analysis pointed to no association among the variables measured in the plasma, we started to analyze each component individually.

All data concerning the inflammatory profile of patients (oxidative stress profile + cytokines), pre- and postanesthesia, are shown in Table 2 as the minimum and maximum values for each parameter.

Regarding oxidative stress profile, there was a reduction in the generation of lipid peroxidation in the postoperative period, regardless of the use or not of opioids (Fig. 3A, OF PrexPost: $p = 0.0197$; OP Pre × Post, $p = 0.0016$). The antioxidant capacity of plasma was augmented after anesthesia, regardless of the use of opioids (Fig. 3B, OF PrexPost: $p = 0.0033$; OP Pre × Post, $p = 0.0024$).

Concerning cytokines, there was no significant variation in IL-4 (Fig. 4A, $p > 0.05$), IL-17A (Fig. 4B, $p > 0.05$) and TNF-α (Fig. 4C, $p > 0.05$) in the pre- and postoperative periods. Regarding IL-12 (Fig. 4D), there was a significant reduction in the OF group postanesthesia (OF-Pre x Post: $p = 0.0250$).

There was a correlation between the values observed in IL-12 and TNF-α in the OF group. ($R = 0.5089$, $p = 0.051$). There was no correlation between the results of cytokines or lipoperoxidation with the clinicopathological data in Table 1 (Chi-square test, $p > 0.05$).

The in vitro study (Fig. 5) demonstrated that all anesthetic drugs are capable to significantly reduce IL-12 levels in the blood (71.6 ± 20.42 pg.mL^{-1} for propofol, 88.83 ± 9.57 pg.mL^{-1} for fentanyl, 63.3 ± 0.64 pg.mL^{-1} for lidocaine, 76 ± 4 pg.mL^{-1} for magnesium sulfate), excepting for atracurium (173.1 ± 26.17 pg.mL^{-1}), when compared with untreated control blood (123.9 ± 19.15 pg.mL^{-1}, $p < 0.05$). *In vitro* evaluation of oxidative stress parameters shown no difference among groups, and the results were greatly variable (data not shown in graphs).

Discussion

Although anesthesia is a fundamental piece of oncological surgery, the use of opioids is doubtful. Evidence concerning its possible relationship with cancer recurrence and spreading has raised the need of understanding its influence on the inflammatory scenario of operated cancer patients. Considering this, we performed our study aiming to investigate the acute impact of opioids on the inflammatory systemic profile of cancer patients. To reach this goal, we evaluated two groups of cancer patients before and after anesthesia considering the presence or absence of opioids. Our results showed a reduction in the systemic lipid peroxidation profile from both groups, revealing its antioxidant potential against oxidative stress generation. Further, we also demonstrated that opioid-free anesthesia has a significant influence on IL-12 circulating levels, suggesting that this set of drugs may induce its acute consumption, which could be a benefit when

Table 1 Absolute frequency (AF) and relative frequency (FR%) of sociodemographic data and clinical variables data in association with the use or not of opioids.

Variable	Category	On opioids use (OP)		Opioids-free (OF)		*p*-value
		AF	FR%	AF	FR%	
Gender	Male	7	30.43	13	59.09	0.053
	Female	16	69.57	9		40.91
Age (years)	<40	4	17.39	3	13.64	0.380
	50	4	17.39	9		40.91
	60	11	47.83	7		31.82
	≥70	4	17.39	3		13.64
Education	Up to 5 years of study	12	52.17	17	77.27	0,152
	From 6 to 10 years of study	4	17.39	3		13.64
	More than 10 years of study	7	30.43	2		9.09
BMI	Underweight (BMI < 18.5)	2	9.09	1	4.76	0.780
	Normal (18.5 ≥ BMI ≤ 24.9)	12	54.55	12		57.14
	Overweight (25 ≥ BMI ≤ 29.9)	5	22.73	4		19.05
	Obese (30 ≥ BMI ≤ 34.9)	1	4.55	3		14.29
	Extremely obese (BMI ≥ 35)	2	9.09	1		4.76
Marital status	Single	0	0.00	4	18.18	0.007
	Married	14	60.87	12		54.55
	Divorced	1	4.35	5		22.73
	Widowed	8	34.78	1		4.55
SAH	Yes	10	43.48	8	36.36	0.626
	No	13	56.52	14		63.64
Diabetes mellitus	Yes	2	8.70	2	9.09	0.962
	No	21	91.30	20		90.91
CAD	Yes	0	0.00	0	0.00	–
	No	23	100.00	22		100.00
Dyslipidemia	Yes	2	8.70	3	13.64	0.598
	No	21	91.30	19		86.36
Medicines	Yes	18	78.26	16	72.73	0.665
	No	5	21.74	6		27.27
Smoking	Yes	6	26.09	7	31.82	0.671
	No	17	73.91	15		68.18
Alcoholism	Yes	4	17.39	1	4.55	0.170
	No	19	82.61	21		95.45
Tumor location	Prostate	3	13.04	6	28.57	0.125
	Stomach	5	21.74	3		14.29
	Pancreas	0	0.00	1		4.76
	Bile ducts	2	8.70	0		000
	Breast	7	30.43	1		4.76
	Colon	1	4.35	5		23.81
	Lung	1	4.35	1		4.76
	Uterus	1	4.35	2		9.52
	Kidney	3	13.04	1		4.76
	Retroperitoneum	0	0.00	1		4.76
ASA	I	8	34.78	4	18.18	0.449
	II	14	60.87	17		77.27
	III	1	4.35	1		4.55
Surgery duration	Up to 60 min	4	17.39	3	13.64	0.380
	60 to 120 min	14	60.87	10		45.45
	More than 120 min	5	21.74	9		40.91
Blood loss	Up to 100 ml	5	22.73	5	23.81	0.978
	From 100 to 200 ml	8	36.36	7		33.33
	More than 200 ml	9	40.91	9		42.86
Leukocytes/μL	Less than 450	4	21.05	1	5.56	0.151
	Between 4500 and 1100	15	78.95	15		83.33
	More than 1100	0	0.00	2		11.11

BMI, body mass index; SAH, systemic arterial hypertension; ASA, physical status classification system by the American Society of Anesthesiologists; CAD, coronary artery disease (CAD).

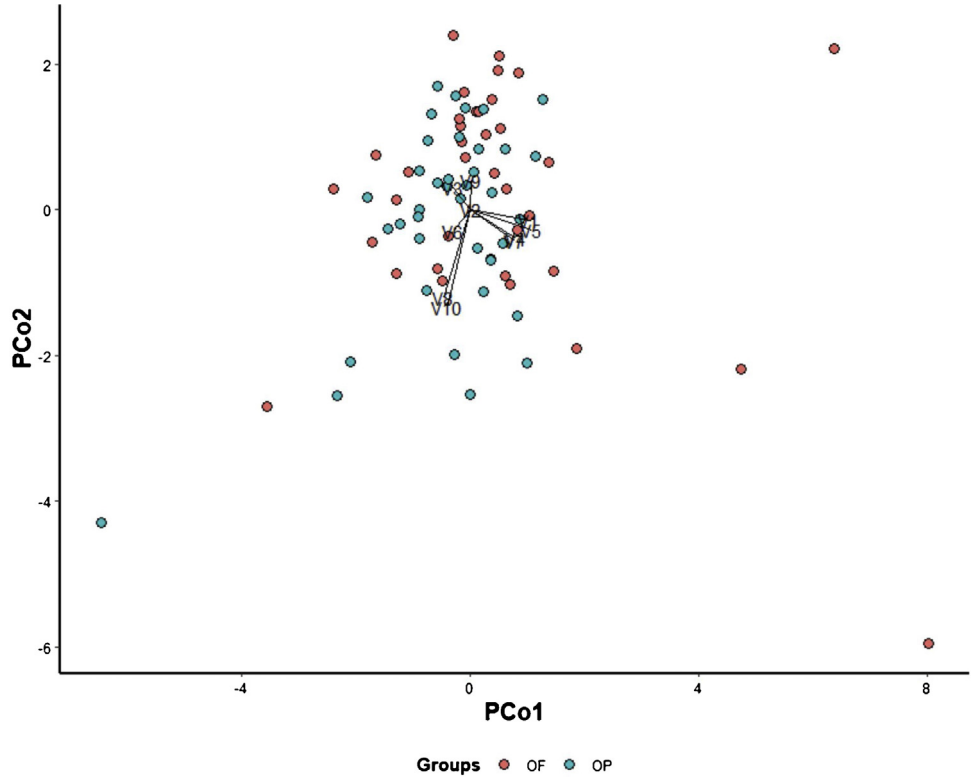

Figure 2 Study of association of the variables investigated in the study through the analysis of main components (PCo). Red dots indicate opioid-free patients and blue dots represent those who received opioids in the anesthetic procedure. V1 = IL-4; V2 = IL-12; V3 = IL-17; V4 = TNF; V5 = RatioTh2/Th17; V6 = RatioTh1/Th2; V7 = RatioTh1/Th17; V8 = Lipidperoxidation; V9 = Antioxidantcapacity; V10 = Stress index.

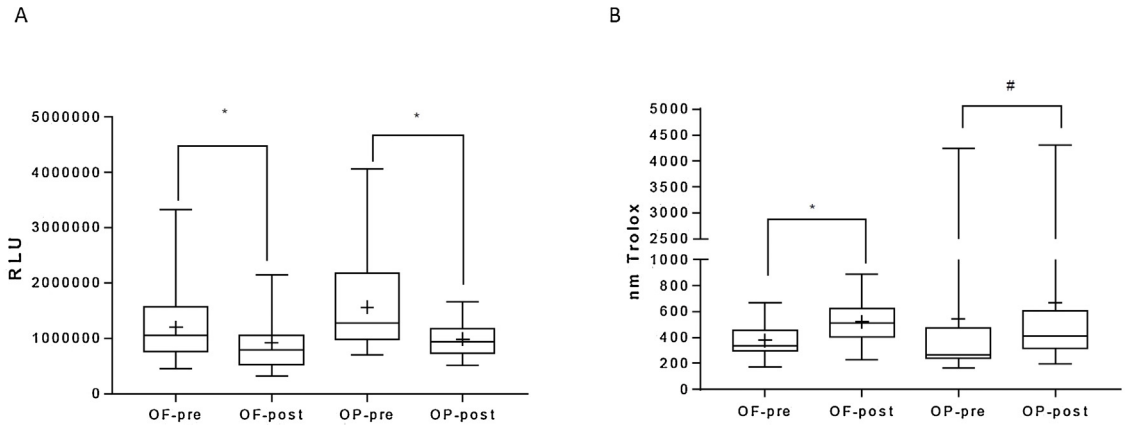

Figure 3 Comparative analysis of the plasma lipoperoxidation profile (A) and antioxidant capacity (B) of cancer patients undergoing anesthesia with (OP) or without (OF) opioid, pre and post anesthesia.
The data are represented in boxplots (min-max). + indicates the average value of each group. * indicates statistical difference ($p < 0.05$), Student' t test or # Wilcoxon test. RLU = relative unities of light.

considering that this cytokine activates the main immune defense against tumors, the natural killer cells (NK cells).

Studies involving opioids and cancer in the perioperative period have mainly reported the relationship between opioids and VEGF production, and their influence on cellular immunity.[15,18–20] Other researchers evaluate the presence of the opioid receptor in cancer, relating it to metastasis, disease aggressiveness, and tumor growth.[10,21–23] Opioids interfere with both cellular and humoral immunity, significantly decreasing the cytotoxic activity of NK cells.[18] They stimulate the apoptosis of macrophages and T cells, as well as the migration and proliferation of tumor cells *in vitro*.[14,24] Opioids inhibit the production of pro-inflammatory cytokines by monocytes and the transcription of interleukin 2 (IL-2) in activated T lymphocytes[25] and increase the production of IL-4.[15] In our study, there was no variation in IL-4 levels,

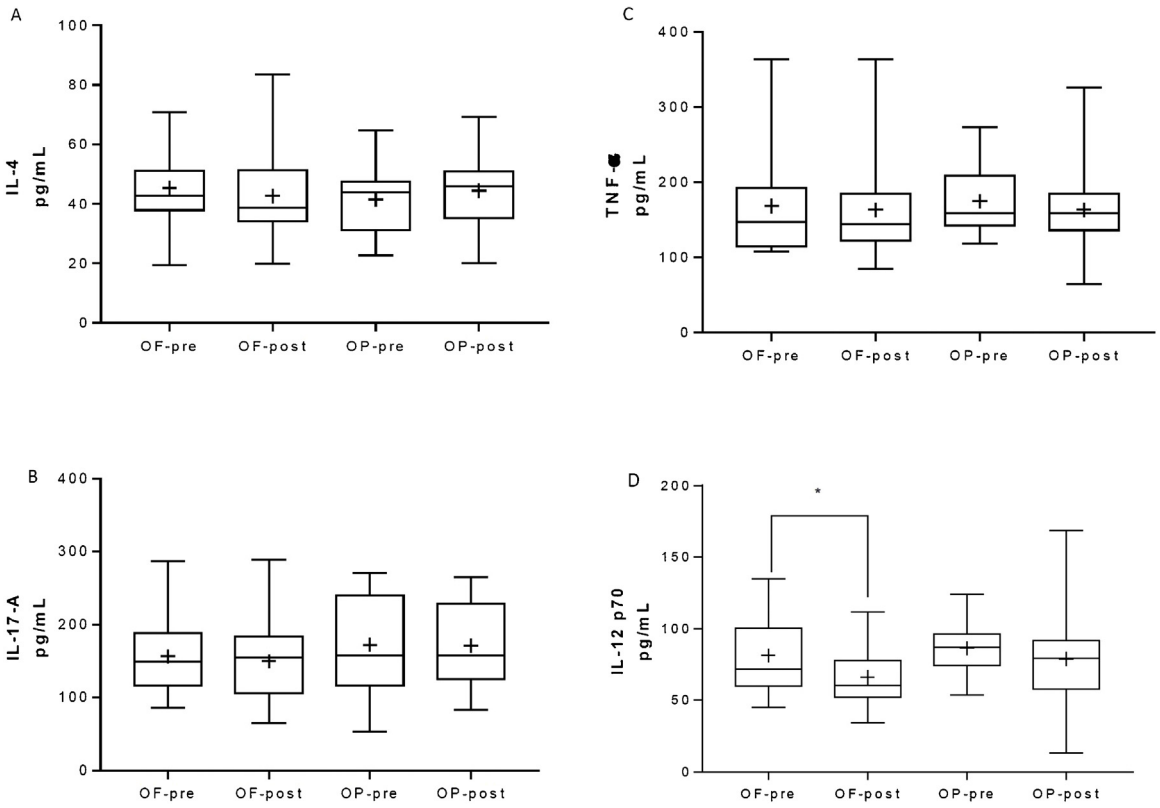

Figure 4 Plasma levels of interleukin4 (IL-4), interleukin17A (IL-17A), tumor necrosis factor alpha (TNF-α) and interleukin12 (IL-12) of cancer patients undergoing anesthesia with (OP) or without (OF) opioid, pre- and postanesthesia.
The data are represented in box plots (min-max). + indicates the average value of each group. * indicates statistical difference ($p < 0.05$), Student's t test or # Wilcoxon test.

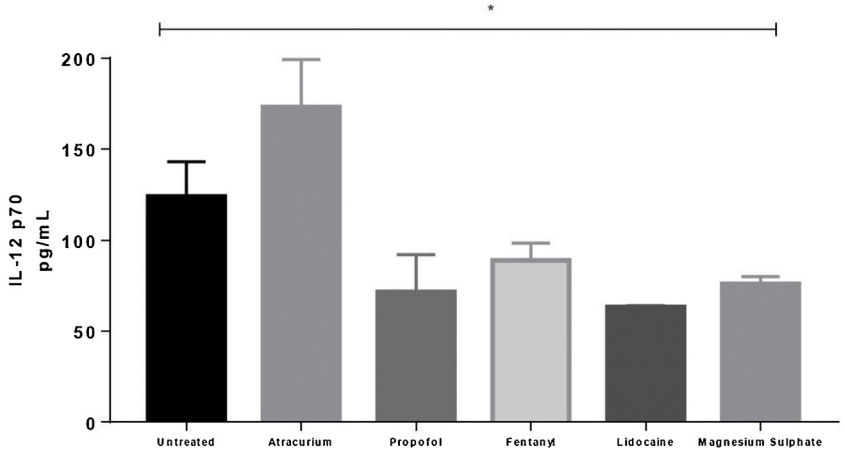

Figure 5 In vitro interleukin12 levels in plasma samples from healthy donnors individually challenged with each of the anesthetic drug employed in cancer patients anesthesic procedure.
Total blood samples were incubated for 1 hour with each individual drug. After this, samples were centrifuged and IL-12 levels measured by ELISA. The data are represented as mean ± standard errors of the means. * indicates statistical difference ($p < 0.05$), ANOVA test with Bonferroni's test as post-hoc.

regardless of the use of opioids, because the assessed time was possibly too short to see any influence of anesthesia on the healing and repair process, of which IL-4 is a pivotal mediator. Also, there was no variation in the levels of IL-17A and TNF-α, regardless of the use of opioids, probably because it does not vary, or it would take more time to allow this cytokine to have its synthesis or consumption altered. In the study conducted by Maher et al. (2019), morphine did not interfere with the concentration of IL-1, IL-2, IL-4, IL-10, IL-17a, TNF-α, IFγ and increased the concentration not

statistically significantly. From IL-6,[18] similarly to our data, in which IL-4, IL-17A, and TNF-α remained stable in both groups after anesthesia.

On the other hand, IL-12 showed a significant reduction in the post-surgical period in the OF group. We hypothesize that this cytokine may be acutely consumed by NK cells, which could become activated, and act in the recognition of tumor antigens that were exposed during the surgical process. Therefore, this process could benefit opioid-free patients in the future, corroborating with literature findings that support less metastasis and disease recurrence when cancer patients do not receive opioids during surgery anesthesia.[10,21–23] We also observed a correlation between IL-12 and TNF-α levels in plasma, suggesting that the production of one cytokine also leads to the production of the other. Likewise, consumption of one leads to consumption of the other.

To better understand this phenomenon, we performed an *in vitro* study, isolating each anesthetic drug applied in cancer patients' surgery, and challenging healthy donor's blood cells with them. We demonstrated that blood cells could acutely consume IL-12 after the anesthetic drug challenge, excepting for atracurium, demonstrating that regardless of being or not an opioid, these drugs can influence this cytokine. Fentanyl has been reported as an anti-inflammatory drug with immediate effects in healthy people,[26] but no information was found concerning its effect on IL-12 levels. The same has been reported to propofol, which acts as an anti-inflammatory by suppressing the cyclooxygenase activity and prostaglandin E production, without impacting IL-12 levels on dendritic cells in an experimental model.[27] Lidocaine seems to be similar since can act as an anti-inflammatory by regulating IL-6 levels operative time and postoperative in healthy people,[28] but no information about its influence on IL-12 was reported. Therefore, our findings of IL-12 seem a novelty, which aligns with the anti-inflammatory effect of anesthesia reported in the literature.

Lipid peroxidation levels, a measurement directly linked to oxidative stress, was also observed as reduced after the anesthetic and surgical procedure, regardless of the use of opioids. Despite data suggesting opioids as ROS inducers in non-cancer individuals,[29] our finding in cancer patients suggests that possibly some of the anesthetic drugs used in the patients may have some antioxidant effect, as demonstrated in our results. Indeed, this information is well known to propofol, which acts as an antioxidant, and has the effect of reducing ROS.[30] Anyway, this information reinforces that some combined anesthetic drugs can influence the immediate inflammatory response of patients in different ways, since oxidative stress constitutes a relevant arm of inflammation.

Concerning the limitations of our study, it is important to consider the time between the collection of blood samples, which lacks a long-term follow-up. It was possible to identify only the changes that immediately occurred after the surgical event, and it was not possible to conclude about the long-term changes or the clinical consequences. However, these patients will be followed up by the research group for further cytokine assessments in addition to the clinical consequences as relapses and metastases. Other limitations include the distinct types of cancer in the evaluated groups, anesthetist unblinding, and patients' emotional distress. It is possible that these factors also affected the cytokine profile, mainly if considering the wide dispersion observed for some cytokines – especially to the not significant ones.

In conclusion, this study demonstrated that in different topographies of cancers, in the perioperative period, the anesthetic schedule may influence the acute inflammatory response by leading to a consumption of IL-12 when opioids are not used. Further, our data showed that oxidative stress production is also affected in such patients and provides information about how anesthetic drugs can regulate IL-12 levels individually and acutely in healthy cells. These findings concerning IL-12 are novelty and may have some association with tumor progression and the appearance of future metastasis in cancer patients undergoing opioids.

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Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Comparison of the effect of adding midazolam versus fentanyl to intrathecal levobupivacaine in patients undergoing cesarean section: double-blind, randomized clinical trial

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KEYWORDS
Cesarean section;
Fentanyl;
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Midazolam;
Postoperative analgesia;
Spinal anesthesia

Abstract

Background: Many adjuvants are added to prolong the effects of spinal analgesia. We investigated the postoperative analgesic efficacy of the addition of midazolam or fentanyl to intrathecal levobupivacaine in women undergoing cesarean delivery.

Methods: Eighty patients were randomly assigned to two groups (n = 40). Group M received 10 mg of 0.5% levobupivacaine plus 2 mg of midazolam. Group F received 10 mg of 0.5% levobupivacaine plus 25 μg of fentanyl. Assessments included motor and sensory block, APGAR score, time to first request for analgesia, postoperative pain score, total consumption of rescue analgesics, and adverse effects.

Results: Sensory blockade was prolonged in Group M compared with Group F (215.58 $\pm$ 27.94 vs. 199.43 $\pm$ 19.77 min; p = 0.004), with no differences in other characteristics of the spinal block in intraoperative hemodynamics or APGAR score. The mean time to first request for rescue analgesia was longer in Group M (351.45 $\pm$ 11.05 min) than in Group F (268.83 $\pm$ 10.35 min; p = 0.000). The median total consumption of rescue analgesics in the first 24 hours postoperatively was 30 mg in Group M vs. 60 mg in Group F (p = 0.003). The median Visual Analog Scale (VAS) scores were lower in Group Ethan in Group F from the 8th to the 12th hour postoperatively, with no differences between the groups at other time points. The incidence of adverse effects was higher in Group F than in Group M.

Conclusion: Intrathecal midazolam (2 mg) was superior to intrathecal fentanyl (25 μg) in increasing the duration of the sensory blockade and postoperative analgesia with lower postoperative pain scores and decreasing the incidence of adverse effects.

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Introduction

Cesarean section is performed with the patient under general anesthesia or regional anesthesia. The subarachnoid blockade is the preferred technique. It avoids the depressant effect of general anesthesia on the neonate and the risk of aspiration with satisfactory postoperative analgesia. [1] Its main disadvantage is that it does not offer prolonged postoperative analgesia if only a local anesthetic is administered.[2]

Levobupivacaine, the S enantiomer of bupivacaine, which has been recently introduced for obstetric spinal and epidural anesthesia, has been found to afford a more selective neuraxial blockade than racemic bupivacaine.[3] Levobupivacaine is a high-potency, long-acting local anesthetic with a moderately slow onset of action. [4] Levobupivacaine has less attraction for cardiac sodium channels and better plasma protein-binding affinity than the dextranomer, which decreases the risk of cardiotoxicity. Plain levobupivacaine is isobaric concerning cerebrospinal fluid, resulting in the more predictable spread of the drug and thus reducing the incidence of hypotension and bradycardia. Levobupivacaine also results in earlier motor recovery linked with racemic bupivacaine. These advantages make levobupivacaine an attractive substitute for racemic bupivacaine for spinal anesthesia.[5]

Various intrathecal additives are added to local anesthetics to increase the speed of onset, improve the quality, and prolong the influence of spinal anesthesia. There are numerous choices of neuraxial additives, such as opioids (morphine, fentanyl, buprenorphine, nalbuphine), N-methyl-d-aspartate antagonists (ketamine), alpha 2 adrenoceptor agonists (clonidine and dexmedetomidine), vasoconstrictors (adrenaline), Gamma-Aminobutyric Acid (GABA) receptor agonists (midazolam), cholinergic agonists (neostigmine), and sodium bicarbonate, but no drug inhibits nociception without its associated side effects. [6]

Opioids such as morphine and fentanyl are extensively used as an adjunct to local anesthetics in neuraxial blockade to enhance the duration of postoperative analgesia.[7] However, worrisome adverse effects, such as pruritus, urinary retention, postoperative vomiting, and respiratory depression, limit the use of opioids in such procedures.[8]

Midazolam has a synergistic effect on postoperative analgesia when administered intrathecally with bupivacaine.[9] Previous studies did not report any major side effects in patients receiving intrathecal midazolam. A large cohort study examining the adverse neurologic effects of intrathecal midazolam also found no association between intrathecal midazolam and neurologic symptoms.[8]

In the current study, we compared the analgesic efficacy of midazolam and fentanyl added to intrathecal levobupivacaine in women undergoing cesarean delivery.

Methods

This prospective, randomized, comparative, controlled, double-blind study was conducted at Assiut University Hospital (Egypt). We enrolled and treated our patients with complete adherence to the most recent declaration of Helsinki. Approval from the local institutional ethics committee was first obtained (17100665). The study was then registered on clinical trials.gov under the number NCT03824314.

This study enrolled eight pregnant women with the American Society of Anesthesiologists (ASA) physical status I or II scheduled for elective cesarean sections. Written informed consent was obtained from all patients. Women with eclampsia or a history of preeclampsia, heart disease, uncontrolled diabetes mellitus, morbid obesity, coagulation abnormalities, vertebral deformities, contraindications to spinal anesthesia, height less than 150 cm or more than 170 cm, or who refused regional anesthesia were excluded from the study.

Randomization and blinding

According to a computer−generated randomized number table, patients were allocated randomly to two groups. Group M received 10 mg of 0.5% isobaric levobupivacaine (2 mL) plus 2 mg of midazolam (0.5 mL), and Group F received 10 mg of 0.5% isobaric levobupivacaine (2 mL) plus 25 μg of fentanyl (0.5 mL) intrathecally. To avoid bias during drug administration, the total drug volume was kept constant at 2.5 mL in both groups.

The syringes of drugs were prepared by well-trained investigators who were not involved in data collection. The surgeon, the patients, the anesthesiologist, and the investigators who collected the data and interpreted the results were unaware of the intervention assignments. The codes of the syringes were stored in opaque envelopes numbered from 1 to 80. Access to the codes was available only to one anesthesiologist who packed the envelopes.

Anesthesia and monitoring

The patients were examined preoperatively, and a full medical history and the examination results were recorded. The patients fasted for 6 h before the scheduled time of surgery. They were premedicated with ranitidine tablets 150 mg the night before surgery, ranitidine tablets 150 mg, and metoclopramide tablets 10 mg orally 2 h before surgery.

Monitoring was established in the operating theater, including Noninvasive Blood Pressure (NIBP), Electrocardiography (ECG), and Pulse Oximetry (SpO_2). Baseline interpretations of vital parameters were noted; intravenous (IV) lines were secured with suitable-sized IV cannulas. Lactated Ringer's 10 $mL.kg^{-1}$ solution was rapidly infused in all patients. Spinal anesthesia was administered under sterile and universal precautions at the L3-L4 interspace with a 25G Quincke spinal needle. At the same time, the patient was

sitting, and the study drug was injected according to the group assignment. Subsequently, the patient was put in a 15° to 20° left lateral supine position. Oxygen 4 L.min^{-1} was administered via a face mask. Heart rate, NIBP, and SpO_2were monitored 0, 3 and 5 min after the block, then every 5 min up to 30 min, and then every 15 min until the end of surgery. Hypotension and bradycardia were recorded when Mean Arterial blood Pressure (MAP) was < 60 mmHg and heart rate was < 60 beats/min and were treated with IV boluses of ephedrine 6 mg and atropine 0.6 mg, respectively. Nausea and vomiting, if occurred, were treated with ondansetron 4 mg IV. When the sensory block reached the level of the T4 dermatome, the surgical procedure was commenced. The block was considered to fail if a complete motor and sensory blockade was not achieved even after 15 minutes. Patients with fallen blocks were transferred to general anesthesia and were excluded from the study.

Assessment parameters

Patients' clinical characteristics included age, weight, ASA physical status, and duration of surgery. The intraoperative data (considering the time of intrathecal drug administration as time 0) were as follows: vital signs including heart rate, NIBP, and SpO_2. Sensory block level was measured by the loss of sharp sensation from a pinprick test and was noted at the midclavicular line bilaterally. Sensory block level was measured every minute for 10 min after administration of the study drug, then at 20 min, and at the end of the operation. The time of onset and the duration of sensory blockade (regression to the S1 dermatome) were recorded. The degree of motor block was evaluated using the Modified Bromage Score (MBS).[10] Motor block was assessed at the same time as a sensory block. The time to the start of the motor block, the time to reach MBS3, and the time of complete disappearance of the motor block were recorded. The duration of the block (the interval from intrathecal administration of the drug to the point at which the MBS was back to zero) was also recorded, and the APGAR scores of the newborn babies were also compared between the two groups at 1 and 5 min after delivery.[3]

During the postoperative period, the patients in both groups were monitored for hemodynamic parameters and pain using the Visual Analog Scale (VAS) scores (ranging from 0 = no pain to 10 = the worst pain imaginable) on arrival at the PostAnesthesia Care Unit (PACU) (time 0) and then every 30 min for 120 min, then hourly for 8 h postoperatively, then every 4 h up to 24 h postoperatively. Rescue analgesia in ketorolac 30 mg IV was administered at the patient's request or when VAS ≥ 4. The time until the first dose of rescue analgesia was requested was recorded. The patients were observed for side effects, such as pruritus, nausea, vomiting, hypotension, bradycardia, headache, and neurologic changes for 24 postoperatively. At the end of the study, a patient satisfaction score was obtained by asking the patients about their experience of anesthesia and analgesia during the intraoperative and postoperative periods. The answers were recorded as 1 (very dissatisfied), 2 (dissatisfied), 3 (neutral), 4 (satisfied), and 5 (very satisfied). Another anesthesiologist in the PACU who did a postoperative assessment was not aware of the drug administered, and a nurse in the ward was also blinded to the drug administered. The patients were discharged home when pain-free with no residual motor or sensory block, and were followed up for 7 days. They were called every day by telephone and examined after 7 days for any neurologic complications.

Outcomes

The primary outcome was the first postoperative request for analgesia after surgery, i.e., the period from intrathecal injection to the administration of the first rescue analgesia. The secondary outcomes were the time taken to achieve adequate motor and sensory block, the total duration of motor and sensory blockade, the incidence of intraoperative hemodynamic changes, the period of effective analgesia, the total amount of analgesia required, and side effects such as pruritus, hypotension, nausea, and vomiting.

Statistical analysis

Using the G-Power calculator 3.1.9.7 for sample size determination, a total sample size of 34 patients in each group would be sufficient for statistical testing based on a priori analysis with *t*-tests. Means: difference between two independent means (two groups) with a two-tailed type I error of 0.05, a power of 0.8, and an effect size of 0.7. Forty patients were enrolled in each group to account for patient dropout. The Shapiro-Wilk test assessed the distribution of baseline variables. Continuous variables were described as mean ± SD) and analyzed by Student's *t*-test and one-way analysis of variance with post hoc multiple comparisons. Nonparametric data were presented as median (range) and analyzed by the Mann-Whitney U−test. Categorical data were reported as numbers and percentages and were analyzed by the Chi-Square test or Fisher's exact test. A *p*-value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed with IBM SPSS statistics version 20 (SPSS Inc, Chicago, IL, USA).

Results

Among the 90 patients who were screened for eligibility, 80 were recruited for the study; each group contained 40 patients (Fig. 1). The two groups were similar in age, height, weight, and duration of surgery; there were no significant differences between the groups regarding demographic data (Table 1).

Hemodynamic vitals

No significant differences were recorded between the groups in MAP, mean heart rate, or SpO_2 at any studied time point (data not presented). NIBP and HR were stable during the whole procedure.

Sensory and motor block

The onset of sensory block was comparable in the two groups ($p = 0.710$). The time to reach the motor block and the duration of the motor block were comparable, with no significant differences between the two groups ($p > 0.05$) (Table 2).

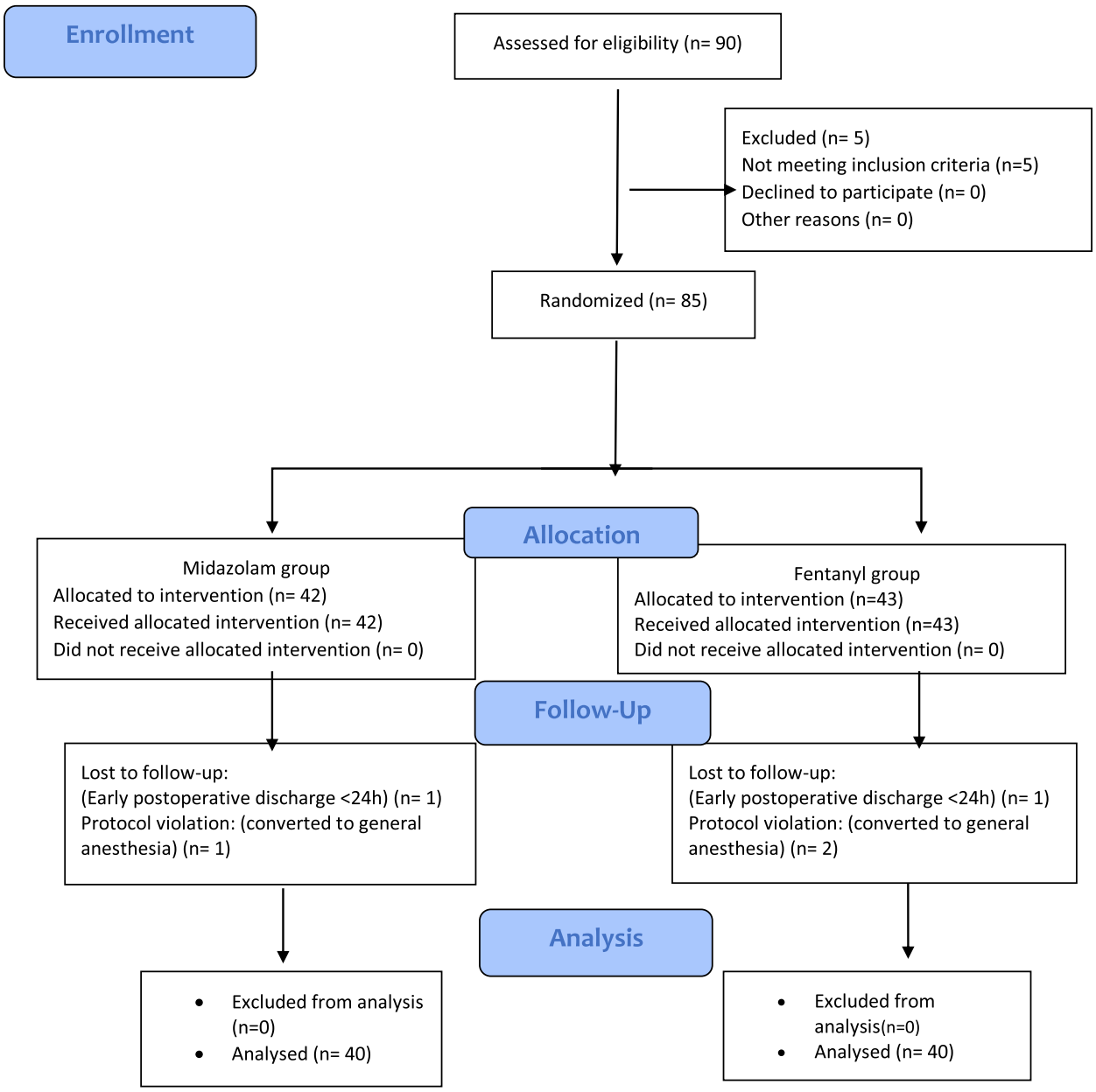

Figure 1 Participants flow diagram.

Table 1 Demographic data, neonatal APGAR score, and duration of surgery.

Variable	Group M (n = 40)	Group F (n = 40)	*p*-value
Age (y)	28.05 ± 6.18	28.82 ± 6.00	0.571
Height (cm)	162.75 ± 5.64	161.18 ± 5.86	0.224
Weight (kg)	75.00 ± 8.58	76.85 ± 8.11	0.325
ASA I/II	40/0	40/0	
Duration of surgery (min)	45.38 ± 2.86	44.38 ± 2.58	0.105
Neonatal APGAR score			
At 1 min: 8/9/10	9/24/7	10/22/8	0.902
At 5 min: 8/9/10	0/20/20	0/18/22	0.654

Data are presented as means ± SD or numbers. Group M, Levobupivacaine Plus Midazolam; Group F, Levobupivacaine Plus Fentanyl; ASA, American Society of Anesthesiologists physical status.

Table 2 Characteristics of the motor and sensory blocks.

Characteristic	Group M (n = 40)	Group F (n = 40)	*p*-value
Time to maximum motor block (min)	3.70 ± 1.11	3.87 ± 1.04	0.470
The total duration of motor block (time to motor recovery) (min)	189.48 ± 22.48	182.68 ± 16.27	0.125
The onset of sensory block (min)	2.65 ± 0.83	2.72 ± 0.96	0.710
The total duration of sensory block (regression to S1 dermatome) (time to sensory recovery) (min)	215.58 ± 27.94	199.43 ± 19.77	0.004[a]

Data are presented as means ± SD. Group M, Levobupivacaine Plus Midazolam; Group F, Levobupivacaine Plus Fentanyl.
[a] $p < 0.05$.

The time to regression to S1 dermatome was significantly shorter in Group F than in Group M ($p = 0.004$).

APGAR score

The neonatal APGAR scores were comparable between the two groups. All neonates scored 9 or 10 at 5 min after delivery (Table 1).

Postoperative pain profile

The mean time to first request for IV ketorolac rescue analgesia was significantly longer in Group M (351.45 ± 11.05 min) than in Group F (268.83 ± 10.35 min; $p = 0.000$). The median total consumption of rescue analgesia in the first 24 h postoperatively was 30 mg in Group M and 60 mg in Group F ($p = 0.003$) (Table 3). The median VAS scores were significantly lower in Group A than in Group F from the 8th to the 12th hour postoperatively, with no significant differences between the groups at other studied timepoints (Fig. 2).

Side effects

In Group M, 31 patients did not experience any side effects, compared with 12 patients in Group F ($p = 0.000$). Nausea, vomiting, and pruritus were significantly more frequent in Group F than in Group M. However, no significant differences were detected between the two groups in other side effects (hypotension, bradycardia, and headache). None of the patients complained of any neurologic deficits.

Patient satisfaction

Assessed by the Likert scale was adequate (very satisfied, satisfied, or neutral) in 90% of the patients in Group M and 82.5% in Group F, with no significant difference between the groups ($p = 0.106$).

Discussion

This study showed that 2 mg of midazolam added to 10 mg of 0.5% levobupivacaine increased the duration of sensory blockade, provided adequate postoperative analgesia, and had fewer side effects than that obtained from 25 μg of fentanyl added to 10 mg of 0.5% levobupivacaine intrathecally for cesarean section, without any major complications.

Bremerich et al. found that, compared with 7.5 mg of levobupivacaine, 10 and 12.5 mg of levobupivacaine prolonged the duration of effective analgesia postoperatively (45 vs. 81 and 96 min, respectively).[11] These authors recommended 10 mg of levobupivacaine for patients undergoing elective cesarean delivery with spinal anesthesia.

In agreement with the present study, Shadangi et al. showed that the addition of preservative-free midazolam to bupivacaine in spinal anesthesia resulted in prolonged postoperative analgesia without an increase in the duration of motor block.[12] In another study, Isazadehfar et al. showed that intrathecal midazolam (2 mg), when used as an additive to bupivacaine, could provide an adequate prolongation of postoperative analgesia with reduced incidence of postoperative nausea and vomiting,[13] a result that was comparable to our study. Other investigators observed that intrathecal midazolam produced significant postoperative analgesia in patients undergoing lower abdominal and perineal operations.[14]

Valentine et al. examined the influence of intrathecal midazolam and hyperbaric bupivacaine for cesarean section under spinal anesthesia and found that no side effects attributable to midazolam were recognized. Intrathecal midazolam appears to be safe and has clinically obvious analgesic properties.[15] In the same year, Borg and Krijnendescribed long-term intrathecal administration of midazolam and clonidine in patients with refractory musculoskeletal pain continuing for more than 2.5 years. They found promising results using intrathecal midazolam up to 6 mg/day. They concluded that

Table 3 Time to the first request and total consumption of postoperative intravenous ketorolac rescue analgesia.

Variable	Group M (n = 40)	Group F (n = 40)	*p*-value
Total analgesic consumption (mg) median (range)	30 (60)	60 (60)	0.003[a]
Number of doses			
1	23	10	
2	15	23	
3	2	7	
Time to first rescue analgesia (min) (mean ± SD)	351.45 ± 11.05	268.83 ± 10.35	0.000[a]

Data are presented as means ± SD. Group M, Levobupivacaine Plus Midazolam; Group F, Levobupivacaine Plus Fentanyl.
[a] $p < 0.05$.

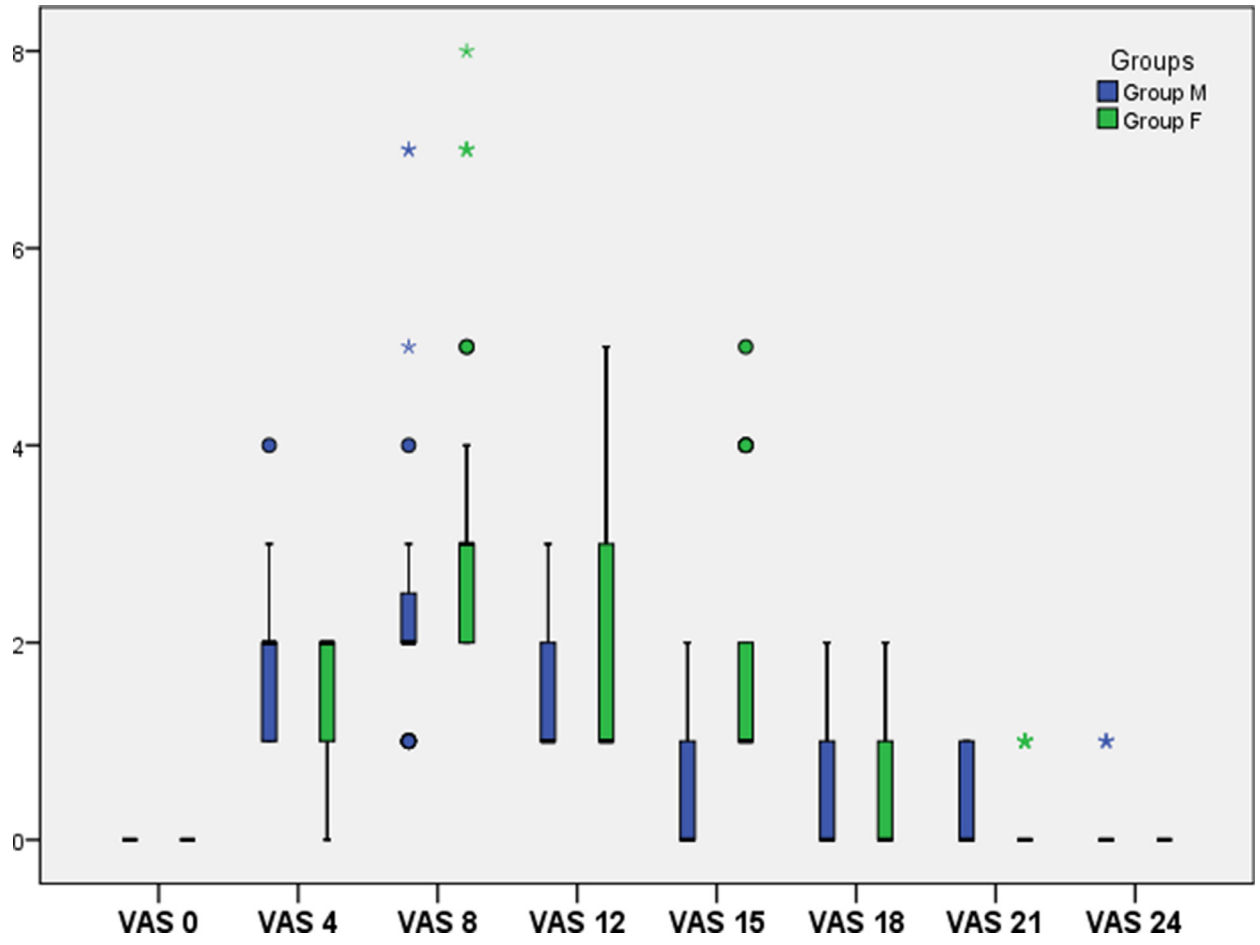

Figure 2 Postoperative Visual Analog Scale (VAS) scores in the two study groups.

this high dose did not cause any adverse neurologic effects in patients suffering from chronic refractory musculoskeletal pain.[16]

Contrary to our findings, Francis et al. reported no significant difference in the duration of effective analgesia between 2 mg of adjuvant intrathecal midazolam and 20 μg of intrathecal fentanyl in patients undergoing lower limb orthopedic surgery.[17]

Midazolam provides spinal analgesia through GABA receptors densely present in lamina 2 of the dorsal horn ganglia. This region plays a prominent role in nociceptive and thermoceptive stimulation processing. Midazolam also acts by activation of spinal opioid receptors.[18]

A study on the influence of 1 mg of adjuvant midazolam compared with 25 μg of fentanyl on the duration of spinal anesthesia with 0.5% bupivacaine in opium addicts established that midazolam is more effective than fentanyl in such cases.[19] Our study corroborates these findings.

In the present study, nausea and vomiting occurred intraoperatively and postoperatively and were less frequent in the Group M. These results were comparable to those of Ho et al. Their meta-analysis of the use of intrathecal midazolam to increase postoperative analgesia reported that midazolam increased perioperative analgesia and decreased nausea and vomiting in patients undergoing cesarean delivery.[20]

In concordance with the results of this study, Gupta et al. measured the start times of motor block and sensory nerve block in patients. They observed a very slight difference between the groups, which was not statistically significant.[21]

Contrary to our findings, Sawhney et al. reported that adding fentanyl to intrathecal bupivacaine in spinal anesthesia for lower limb surgical procedures led to a better quality of postoperative analgesia than in patients receiving midazolam.[22]

Bogra et al.[23] reported that the administration of adjuvant intrathecal midazolam or fentanyl did not cause any additional adverse effects in neonates, as demonstrated by the APGAR score.

Limitations

The limitations of this study include the small number of patients, the absence of the use of intrathecal morphine as an adjuvant in both groups, and the absence of an adequate protocol for postoperative analgesia. Further studies should be done with longer postoperative follow-

up periods, testing other doses of midazolam, and comparison with other drugs.

Conclusion

Intrathecal midazolam (2 mg) was superior to intrathecal fentanyl (25 μg) in enhancing the duration of sensory block by levobupivacaine, improving postoperative analgesia and the time of postoperative pain relief, and decreasing the incidence of adverse effects. The neonatal outcomes were comparable with the use of midazolam and fentanyl.

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Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Association between intraoperative ketamine and the incidence of emergence delirium in laparoscopic surgeries: an observational study



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KEYWORDS
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Abstract
Background: Emergence *Delirium* (ED) is an essential condition in the immediate postoperative period. Systematic review and meta-analysis of randomized controlled trials have concluded that the effect of ketamine on postoperative delirium remains unclear. The present study sought to evaluate if the intraoperative use of ketamine for postoperative analgesia is associated with postoperative ED in laparoscopic surgeries.
Methods: A prospective observational study was performed in the PostAnesthetic Care Unit (PACU) to evaluate patients who had undergone laparoscopic surgery under a rigid intraoperative anesthesia protocol from July 2018 to January 2019. Patients submitted to laparoscopic surgery for cholecystectomy, oophorectomy, or salpingectomy with a score ≥1 on the Richmond Assessment Sedation Scale (RASS) or ≥2 on the Nursing Delirium Screening Scale (Nu-DESC) were considered to have ED. *t*-test, Chi-Square test or Fisher's exact tests were used for comparison.
Results: One hundred and fifteen patients were studied after laparoscopic surgery. Seventeen patients (14.8%) developed ED, and the incidence of ED in patients who received ketamine was not different from that of other patients (18.3% vs. 10.6%, $p = 0.262$). Patients with ED had more postoperative pain and morphine requirement at the PACU ($p = 0.005$ and $p = 0.025$, respectively). Type of surgery (general surgery, OR = 6.4, 95% CI 1.2–35.2) and postoperative pain (OR = 3.7, 95% CI 1.2–11.4) were risk factors for ED.
Conclusion: In this study, no association was found between ED and intraoperative administration of ketamine in laparoscopic surgeries. Type of surgery and postoperative pain were risk factors for ED.
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Introduction

Delirium is described as a common and multifactorial syndrome manifested by decreased attention and perception of the surrounding environment. It can also be accompanied by hallucinations, disorientation, and temporary memory loss.[1] Emergence *Delirium* (ED) is an abnormal mental state that develops after the administration of anesthesia (during the transition from unconsciousness to complete wakefulness), usually limited in time. It is characterized by agitation, irritability, hypervigilance, and hyperactivity.[2,3] It is a condition that occurs in the first 30 minutes of anesthetic recovery, with symptomatic fluctuation or lucid intervals, which often reverses in one hour. Therefore, it is crucial to distinguish ED from postoperative delirium (occurring for days) and from postoperative cognitive dysfunction (which consists of a prolonged post-surgical state of mental disorder and cognitive deterioration).[3,4]

The incidence of ED varies between 5% and 10%, reaching 20% in specific subgroups, such as pediatric age and the elderly, being more prevalent when associated with major surgery, general anesthesia, and in the presence of postoperative pain.[5] Among the variables related to anesthesia, risk factors identified for developing ED are type of anesthesia, orotracheal intubation and volatile anesthetics. Other risk factors are the type of surgery, male gender, cerebral disease, and drug addiction.[4] In adults, ED is difficult to predict, thus anesthesiologists should remain alert to this possibility by appropriately monitoring the state of consciousness of the patients using valid and reproducible scales, such as the Richmond Agitation Sedation Scale (RASS) and the Nursing Delirium Screening Scale (Nu-DESC).[6-8]

Some anesthetic agents, such as ketamine, have an unclear effect on postoperative ED. Ketamine is a potent inhibitor of the NMDA [N-methyl-D-aspartate], and also an effective analgesic due to its affinity for μ opioid receptors.[9,10] It is widely applied in perioperative clinical practice to induce general anesthesia, sedation or reduce pain and the consumption of more potent opioids or in patients with opioid tolerance.[9,11,12] In lower doses (< 1 mg.kg^{-1}), its psychoactive effects, such as visual and auditory hallucinations, depersonalization, changes in body perception and deficits in proprioception, are less evident. There is controversial information related to the implications of ketamine use during anesthesia: some studies suggest a protective effect of ketamine regarding ED, but other studies state that ketamine does not prevent ED or is associated with ED.[13-16] A recent systematic review and meta-analysis of 6 randomized controlled trials concluded that the effect of ketamine on postoperative delirium remains unclear.[17]

Regarding laparoscopic surgeries, the present study aimed to assess whether the occurrence of postoperative ED is associated with the intraoperative use of ketamine for postoperative analgesia.

Methods

Study design

A prospective observational study was performed at the Anesthesiology Department of Centro Hospitalar e Universitário São João (Porto, Portugal) between July 2018 and January 2019 in patients undergoing laparoscopic surgery. The study was conducted following the Declaration of Helsinki and obtained approval from the local ethics committee. All collected data were saved anonymously, and informed consent was requested from all patients. This observational study was performed according to STROBE guidelines.

Sample

Two days a week (Tuesday and Wednesday), during the period of the study, every patient aged between 18 and 65 years with American Society of Anesthesiology (ASA) physical status I or II who underwent laparoscopic surgery for cholecystectomy, oophorectomy, or salpingectomy, and admitted to the PostAnesthesia Care Unity (PACU) at Centro Hospitalar e Universitário São João, were eligible for the study. Exclusion criteria were patient refusal, incapacity to provide informed consent, history of drug addiction or alcohol abuse, pregnancy, urgent surgery, psychiatric pathology, the existence of adverse anesthetic events in the intraoperative or anesthetic recovery, and patients with a Revised Cardiac Risk Index (RCRI) > 1.[18]

Obtaining data and definitions

Anesthesia was provided and monitored according to the criteria of the anesthesiologist in charge, but this conduct followed minimum departmental standards. These standards include administering drugs adjusted to the patient's ideal body weight, namely propofol, fentanyl, rocuronium and dexamethasone, and using inhalational anesthetic sevoflurane for maintenance. All patients had Bispectral® index (BIS) or state entropy monitored, and a deep neuromuscular block guided by Post-Tetanic Count (PTC). Analgesia was provided with fentanyl 3–5 g.kg^{-1} (up to 30 minutes to the end of surgery) and maintenance of normothermia (guided by esophageal temperature). Administration of maintenance fluids with 0.9% saline solution according to the Holliday-Segar formula. Before the end of the surgery, paracetamol 1000 mg, ketorolac 30 mg, tramadol 2 mg.kg^{-1}, morphine 0.5 mg.kg^{-1}, and ondansetron 4 mg are usually administrated. Sugammadex (TOF-guided ratio) was used to obtain reversal of muscle relaxation. Patients were usually extubated in the operating room and transferred to the PACU. Criteria for extubation included sustained head lift or hand grip for more than 5 seconds, the ability to follow simple commands, a stable ventilatory pattern with acceptable arterial oxygen saturation ($SpO_2 > 95\%$), and a TOF ratio greater than 0.9. A face mask was used to administer all subjects 100% oxygen after tracheal extubation. The anesthesiologist was free to decide whether to administer oxygen during the transfer from the operating room to the PACU. Upon arrival at the PACU, all subjects were given oxygen by nasal cannula or face mask. The decision to administer ketamine during anesthesia induction was the responsibility of the anesthesiologist in charge. In these cases, a total of 0.5 mg.kg^{-1} of ketamine (considering the patient's ideal body weight) was administrated during anesthesia induction (after propofol administration). Ketamine

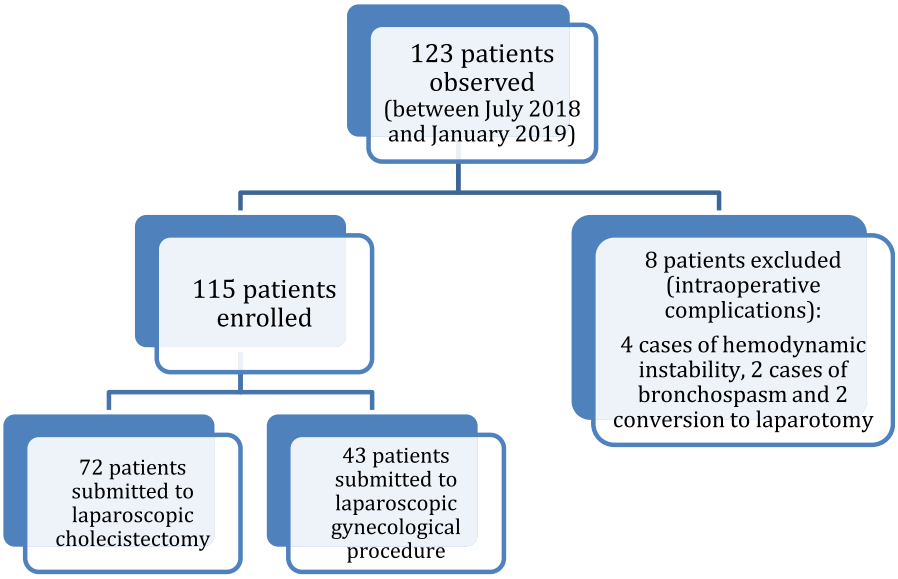

Figure 1 Flow chart of recruitable and included patients.

administration was only considered when used at the above dosage (0.5 mg.kg^{-1}).

A standardized data collection sheet was completed for each patient that included age, Body Mass Index (BMI — kg.m^{-2}), ASA, RCRI, and usual medication, provided analgesia, immediate postoperative vital signs, including the evaluation of pain (using the NRS — Numerical Rating Scale), and discharge data from PACU, postoperative nausea and vomiting, and antiemetic medication during PACU stay. In addition, the presence of hypertension, type 2 diabetes mellitus, obesity, dyslipidemia, respiratory pathology, depression, hypothyroidism, and benzodiazepines at home were also collected from the patient's medical records.

Adapting a classification scheme developed by Lee et al.,[18] we calculated an RCRI score for each patient. At admission to the PACU, the patients were screened for ED using the Nursing delirium Screening Scale (Nu-DESC)[8] (Supplementary Material S1) and the RASS[19] (Supplementary Material S2). Diagnostic values of ED are defined as a total RASS $\geq$ 1 or a total Nu-DESC $\geq$ 2.[8] During the evaluation, patients with a Nu-DESC score of 2 or more points or a score of $\geq$ 1 on the RASS scale (RASS $\geq$ 1) were considered ED-positive. This evaluation was performed by the anesthesiologist in charge of the PACU at the patient's arrival.

Statistical analysis

Considering open-source statistics for public health (www.openepi.com/SampleSize/SSPropor.htm), a minimum sample of 107 patients was calculated, using a 95% Confidence Interval, an 80% power, and a frequency of ED in the population of 7.5%.[5] A descriptive analysis of variables was performed to summarize data. Data following nonparametric distribution based on the Kolmogorov-Smirnov test for normality are presented as median and interquartile ranges. Dichotomous categorical variables are presented as relative or absolute frequencies. ED was evaluated as a dichotomous variable (presence or absence of ED). Univariate analyses were performed to identify differences between patients with and without ED using the *t*-test to compare continuous variables and Chi-Square or Fisher's exact test to compare categorical variables. Differences were considered statistically significant when $p < 0.05$. Binary logistic regression was performed with variables considered to be determinants for ED, and an Odds Ratio (OR) and 95% Confidence Interval (95% CI) were calculated. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 26.0.

Table 1 Patient baseline characteristics.

Variable	Total (n = 115)
Sex, n (%)	
Male	39 (33.9)
Female	76 (66.1)
Age, μ (SD)	46.6 (10.1)
Surgery, n (%)	
General	72 (62.6)
Gynecology	43 (37.4)
BMI (kg.m^{-2}), μ (SD)	28.2 (7.5)
ASA physical status, n (%)	
I	33 (28.7)
II	82 (71.3)
Associated pathology, n (%)	
Obesity	47 (40.9)
Hypertension	33 (28.7)
Dyslipidemia	20 (17.4)
Type 2 diabetes mellitus	14 (12.2)
Respiratory pathology	9 (7.8)
Depression	8 (7)
Hypothyroidism	7 (6.1)
Benzodiazepines at home, n (%)	21 (18.3)
Emergence *Delirium*, n (%)	17 (14.8)
Intraoperative use of ketamine, n (%)	60 (52.2)
Without intraoperative ketamine, n (%)	55 (47.8)

μ, mean; SD, Standard Deviation; BMI, Body Mass Index; ASA, American Society of Anesthesiologists physical status.

Results

Of the 123 patients observed, only 115 were enrolled in this study (Fig. 1). The remaining eight patients were excluded due to intraoperative events, namely 4 cases of hemodynamic instability, 2 of bronchospasm, and two due to conversion to laparotomy. Sixty-six per cent were female, the mean (SD) age was 46 (10) years, 72 patients (62.6%) underwent a general surgery procedure, and 43 patients (37.4%) underwent gynecological surgery (Table 1).

Regarding ketamine administration, 60 patients (52.2%) received the drug. When comparing the two groups (ketamine and no ketamine administration) (Table 2), there appeared to be no differences in sex, age, type of surgery, BMI, ASA physical status, hypertension, type 2 diabetes mellitus, obesity, dyslipidemia, respiratory pathology, depression and hypothyroidism, benzodiazepines at home, postoperative pain, and morphine requirement at PACU. Seventeen patients developed ED (14.8%) in the postoperative period, and no differences in ED were observed between groups of ketamine administration ($p = 0.262$).

Analyzing patients' ED characteristics (Table 3), no differences were found regarding sex, age, BMI, ASA, hypertension, type 2 diabetes mellitus, obesity, dyslipidemia, respiratory pathology, depression, hypothyroidism, and use of benzodiazepines at home. Finally, patients with ED more frequently underwent general surgery ($p = 0.018$), had more NRS scores > 3, (64.7% vs. 29.6% for NRS > 3, $p = 0.005$), and higher morphine requirement at the PACU (76.5% vs. 46.9%, $p = 0.025$).

Logistic regression (Table 4) shows that type of surgery (general surgery, $p = 0.033$) and postoperative pain (as NRS > 3, $p = 0.022$) are independent risk factors for ED.

Discussion

ED is a frequent complication in the postoperative period. Literature is controversial concerning the incidence of ED associated with using some anesthetic agents, mainly intraoperative ketamine, for postoperative analgesia.[17,20] Dissociative characteristics of ketamine could be considered an inducer of ED, being one of the main limitations to its use.[21] However, according to Riddell et al.,[13] using ketamine as adjuvant of anesthesia reduces the risk of ED. Moreover, ketamine can contribute to the symptomatic control of ED. In our study, the incidence of ED (14.8%) was higher than the incidence reported in the literature (5%–10%).[2,4,22] No differences were observed in the incidence of ED when ketamine was administered. These results corroborate several studies,[14,15,23] in which the incidence of ED is not associated with intraoperative administration of ketamine.

Table 2 Ketamine comparison between patients (n = 115).

Variable	Ketamine (n = 60)	No Ketamine (n = 55)	*p*-value
Sex, n (%)			0.515[a]
Male	22 (36.7)	17 (30.9)	
Female	38 (63.3)	38 (69.1)	
Age, μ (SD)	46.2 (9)	47 (11.1)	0.665[b]
Surgery, n (%)			0.580[a]
General	39 (65)	33 (60)	
Gynecology	21 (35)	22 (40)	
BMI ($kg.m^{-2}$), μ (SD)	29.2 (8.9)	27.2 (5.5)	0.151[b]
Physical status ASA, n (%)			0.615[a]
I	16 (26.7)	17 (30.9)	
II	44 (73.3)	38 (69.1)	
Associated pathology, n (%)			
Hypertension	19 (31.7)	14 (25.5)	0.462[a]
Type 2 diabetes mellitus	9 (15)	5 (9.1)	0.333[a]
Obesity	27 (45)	20 (36.4)	0.347[a]
Dyslipidemia	11 (18.3)	9 (16.4)	0.781[a]
Respiratory pathology	4 (6.7)	5 (9.1)	0.735[c]
Depression	4 (6.7)	4 (7.3)	1.000[c]
Hypothyroidism	2 (3.3)	5 (9.1)	0.257[c]
Benzodiazepines at home, n (%)	14 (23.3)	7 (12.7)	0.141[a]
Emergence *Delirium*, n (%)	11 (18.3)	6 (10.9)	0,262[a]
Pain after surgery, n (%)			0.959[a]
NRS $\leq$ 3	39 (65)	36 (65.5)	
NRS > 3	21 (35)	19 (34.5)	
Morphine requirement at PACU	27 (45)	32 (58.2)	0.158[a]

[a] Chi-square test.
[b] *t*-Test.
[c] Fisher's exact test.
μ, mean; SD, Standard Deviation; BMI, Body Mass Index; ASA, American Society of Anesthesiologists physical status; NRS, Numerical Rating Scale; PACU, PostAnesthetic Care Unit.

Table 3 Emergence delirium comparison between patients (n = 115).

Variable	Emergence *delirium* (n = 17)	Without Emergence, *delirium* (n = 98)	*p*-value
Sex, n (%)			0.493[a]
Male	7 (41.2)	32 (32.7)	
Female	10 (58.8)	66 (67.3)	
Age, μ (SD)	45.6 (11)	46.8 (10)	0.672[b]
Surgery, n (%)			0.018[a]
General	15 (88.2)	57 (58.2)	
Gynecology	2 (11.8)	41 (41.8)	
BMI (kg.m^{-2}), μ (SD)	27.5 (5.8)	28.3 (7.8)	0.686[b]
Physical status ASA, n (%)			0.388[c]
I	3 (17.6)	30 (30.6)	
II	14 (82.4)	68 (69.4)	
Associated pathology, n (%)			
Hypertension	5 (29.4)	28 (28.6)	1.000[c]
Type 2 diabetes mellitus	4 (23.5)	10 (10.2)	0.219[c]
Obesity	4 (23.5)	43 (43.9)	0.115[a]
Dyslipidemia	3 (17.6)	17 (17.3)	1.000[c]
Respiratory pathology	3 (17.6)	6 (6.1)	0.128[c]
Depression	1 (5.9)	7 (7.1)	1.000[c]
Hypothyroidism	2 (11.8)	5 (5.1)	0.276[c]
Benzodiazepines at home, n (%)	4 (23.5)	17 (17.3)	0.511[c]
With Ketamine, n (%)	11 (64.7)	49 (50)	0.262[a]
Without Ketamine, n (%)	6 (35.3)	49 (50)	
Pain after surgery, n (%)			
NRS $\leq$ 3	6 (35.3)	69 (70.4)	
NRS > 3	11 (64.7)	29 (29.6)	0.005[a]
Morphine requirement at PACU	13 (76.5)	46 (46.9)	0.025[a]

[a] Chi-square test.
[b] *t*-Test.
[c] Fisher's exact test.
μ, mean; SD, Standard Deviation; BMI, Body Mass Index; ASA, American Society of Anesthesiologists physical status; NRS, Numerical Rating Scale; PACU, PostAnesthetic Care Unit.

Despite these findings, the possible association between ketamine and ED remains not fully understood. Nevertheless, there is evidence that ketamine can be used in the treatment of ED in PACU[14,17] and can also be used intraoperatively to reduce postoperative pain (which is an independent risk factor for ED).[24] According to Hudetz et al.,[15] ketamine prevents ED after cardiac surgery because NDMA receptor antagonism reduces post-ischemic neuronal loss in the cortex. Ketamine-induced neuroprotection can occur through inflammatory suppression. On the other hand, the Podcast trial[20] suggests that administering a subanesthetic dose of ketamine does not help prevent ED or reduce postoperative pain. The net effect of ketamine may be deleterious at the cardiovascular level, by the stimulation of the sympathetic nervous system, and at the psychiatric level with hallucinations and postoperative nocturnal nightmares.[20,25] These controversial results in the literature are probably due to the different intraoperative anesthetic protocols and the different analyses and interpretations of postoperative outcomes. In this study, the adoption of a rigid anesthetic protocol aimed to limit the presence of confounding factors.

Table 4 Logistic Regression analysis for predictors of ED.

Variable	OR	OR (95% CI)	*p*-value[a]
Type of Surgery (general)	6.40	(1.2–35.2)	0.033
Sex (male)	1.41	(0.43–4.65)	-
Age	0.99	–	-
Benzodiazepines at home	0.76	–	-
Pain after surgery, (NRS > 3)	3.70	(1.2–11.3)	0.022

[a] Logistic regression analysis, with variables considered to be determinants for ED.
OR, Odds Ratio; CI, Confidence Interval; NRS, Numerical Rating Scale.

Regarding the association between ED and age, we did not find an association, which is most likely because the study protocol excluded patients under 18 or above 65, and the incidence of ED is higher in extreme age groups.[3-5] We also did not find an association between ED and ASA physical status, possibly because we excluded patients with ASA greater than 2.

Regarding the analgesic effect of ketamine, no difference was found between groups. In some studies, using ketamine in laparoscopic cholecystectomy decreased postoperative pain, but these studies compared ketamine with other analgesic drugs.[26] In the present study, the analgesic protocol is largely multimodal (with paracetamol, ketorolac, tramadol, and morphine) and the scope for improving postoperative analgesia when adding ketamine is narrow. Scientific literature reports an association between ED and the following

risk factors: sex, age, type of surgery ASA and postoperative pain.[4,5] In our study, patients who developed ED more frequently underwent general surgery (cholecystectomy), had more postoperative pain (NRS higher than 3), and needed more morphine for analgesia at PACU.

The present results must be analyzed and interpreted recognizing the study's limitations, namely the fact that it encompasses different types of laparoscopic surgeries (cholecystectomy, oophorectomy, or salpingectomy). Another limitation is that the study excluded patients older than 65 years of age, who are more susceptible to developing ED. Furthermore, the study only considered a standard dose of ketamine (0.5 $mg.kg^{-1}$ of the patient's ideal body weight). Ketamine also has a wide therapeutic interval (from 0.25 $mg.kg^{-1}$ to 4 $mg.kg^{-1}$ intravenously), and it is reasonable to expect that different doses may lead to different results. The lack of association in this study with certain ED risk factors already described in the literature may result from a rigid intraoperative anesthetic protocol and exclusion criteria. The exclusion of patients with an ASA physical status higher than II (patients with more comorbidities and more susceptible to developing ED) probably affects the external validity of this study. The rigid protocol used in this study (exclusion of patients over 65 and with an ASA higher than II) was a methodological strategy to minimize risk factors for ED other than ketamine administration.

Conclusion

Recognition and, if possible, avoidance of ED risk factors is essential to minimize the incidence of ED. Regarding the intraoperative administration of ketamine for postoperative analgesia in laparoscopic surgery, no association was found with ED. Type of surgery and postoperative pain were found as risk factors for developing ED. Despite the controversial literature, this study may help identify subtypes of surgery (in this case, laparoscopic surgeries) where ketamine administration does not result in the development of ED.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2022.10.002.

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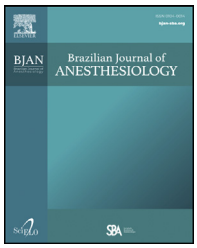

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CASE REPORTS

Platypnea-orthodeoxia syndrome: an intriguing perioperative hypoxemia case report

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KEYWORDS
Dyspnea;
Hypoxia;
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Perioperative period;
Patent Foramen Ovale;
Case report

Abstract Platypnea-orthodeoxia syndrome (POS) is a rare condition of positional hypoxemia and dyspnea. The following is a case of hypoxemia for no obvious reason in the perioperative scenario. A 70-year-old male patient was submitted to a radical prostatectomy. On several occasions after anesthetic induction, peripheral oxygen saturation decreased without any understandable cause. In the postanesthesia care unit, severe hypoxemia occurred in the upright position, oddly correcting with recumbency. An echocardiography showed a right-to-left intracardiac shunt through a patent *foramen ovale* with no pulmonary hypertension, establishing POS. Achieving this diagnosis required a broad workup with a high degree of suspicion.
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Introduction

Hypoxemia is frequent in anesthesiology practice, and can be hypoxemic, anemic, circulatory, or histiocytic in nature. Although rare, a reversible cause like Platypnea-orthodeoxia syndrome (POS) must be thought of.[1] It presents with positional hypoxemia and dyspnea in the upright position, but may have near-normal oxygen saturation levels when lying down.[2–4]

POS is due to three types of causes: intracardiac shunts, arteriovenous shunts, or ventilation/perfusion mismatch in the lungs.[3,4] Cardiac conditions are among the most described causes, in particular related to patent *foramen ovale* (PFO).[4] The mechanism of position-dependent changes in shunting remains elusive, but requires a functional and anatomical defect, and the common pathway seems to be a position-dependent opening of the PFO with right-to-left shunting.[2]

There are no case reports in the anesthesiology field describing the diagnosis of POS in the perioperative scenario. Our goal is to describe a case of hypoxemia without a more obvious reason in this setting. Informed consent

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from the patient and the Institutional Ethical Committee's approval were duly obtained.

Case report

A 70-year-old male patient with prostatic carcinoma was proposed for a radical retropubic prostatectomy. His background included human immunodeficiency virus infection, a one-year prior ischemic cerebellar stroke, discrete bronchiectasis, arterial hypertension, and initial signs of dementia. The patient denied dyspnea or any other cardiovascular symptoms. No previous surgical nor anesthetic interventions. The preanesthetic physical examination was innocent. His laboratory results and electrocardiogram revealed no significant changes.

The patient was submitted to the procedure under general balanced anesthesia and standard monitoring of American Society of Anesthesiologists. Preoperative peripheral oxygen saturation (SpO_2) was 95%. On several occasions after anesthetic induction, SpO_2 decreased from 100% to 86–90% without any feasible causes apart from the fall of mean arterial pressure (MAP) to 60 mmHg. The desaturation did not improve with increased fraction of inspired oxygen nor with recruitment maneuvers, only recovering after phenylephrine 0.1 mg boluses and MAP elevation to 90 mmHg. The operation lasted 60 minutes, the estimated blood loss was 700 ml, and a total of 0,5 mg of phenylephrine was administered. Anesthesia recovery and transfer to the postanesthesia care unit (PACU) was uneventful. In the PACU, even though the patient had almost no complaints of dyspnea, severe hypoxemia occurred (paO_2 5.48 kPa, SpO_2 73.4%), despite oxygen therapy with Venturi mask at 15 $L.min^{-1}$ oxygen flow. The patient empirically received intravenous hydrocortisone, intravenous aminophylline, and nebulization of ipratropium/salbutamol in standard doses. The clinical benefit was minimal.

Analytical control was carried out, showing no significant alterations. A computed tomographic angiography showed peripheral subsegmental pulmonary embolism (PE) that did not fully explain the clinical picture. Oddly, we have noticed significant hypoxemia correction with recumbency (SpO_2 raised to 94–96%) and aggravation with lifting the headboard and sitting position. A transthoracic echocardiography at the bedside was requested, and it revealed findings suggestive of a right-to-left intracardiac shunt through a PFO with no pulmonary hypertension. All intracardiac cavities showed no signs of disfunction nor dilation, with good global systolic function. No valvular or pericardial structural changes were identified. A bubble test was performed, allowing to visualize microbubbles in the left heart cavities, clearly establishing a right-to-left shunt, and assuming the diagnosis of POS.

After the diagnosis, he maintained high flow oxygen therapy, associated with avoidance of upright position. The POS manifestations remained in the postoperative period, with a progressive reduction in oxygen requirements (SpO2 95% lying in bed, and SpO_2 91–92% in the sitting position, without significant dyspnea). He was ultimately discharged to a long-term care unit, with long-term nocturnal oxygen therapy, and awaiting a cardiology consultation to guide the therapeutic approach to the POS.

Discussion

Although it likely remains underdiagnosed, the recognition of POS is increasing.[2] In the preanesthetic evaluation, we should look for an association between breathlessness and upright position. POS mostly occurs in older people, although, in most cases, it is linked to a congenital heart defect, especially PFO.[3] SpO_2 also needs to be analyzed in the lying and the upright position. A drop in the SpO_2 of > 5% in the upright position with improvement on recumbency, should elicit the diagnosis of POS.[4]

In the perioperative period, hypoxia is most likely caused by an inadequate oxygen supply; hypoventilation; alveolar ventilation/perfusion mismatch; right-to-left shunting; and reduction in oxygen carrying and using capacity (decreased cardiac output; anemia and histiocytic hypoxia).[1] The clinical presentation of POS can be subtle and difficult to attain under general anesthesia, so it must be reminded in the differential diagnosis of refractory hypoxemia, after exclusion of classic etiologies in the perioperative setting. As we verified, these patients have a minimal or no response at all to oxygen supply in the upright position,[2,4] nor to traditional therapies for lung and heart dysfunction.[4]

PFO has a prevalence of 25% in general adult population.[2,3] Most people with an isolated PFO are asymptomatic because they do not have right-to-left shunt, since the left atrial pressure is higher than the right atrial pressure, leading to a functional closure.[3,4] Right-to-left atrial shunting despite normal intracardiac pressures and normal pulmonary function through a PFO has still not been completely elucidated, but requires both an anatomical and functional flaw in order to occur.[2,4] Functional defects act through transient reversal of the left-to-right pressure gradient, because they are capable of elevating right atrial pressure to the point that the gradient reverses for certain parts of the cardiac cycle, particularly when the patient is standing.[2] Such phenomenon can be physiologic (posture, inspiration, cough, or Valsalva maneuver)[3] or pathological, producing an increased pulmonary vascular resistance or leading to decreased right-sided compliance, frequently age-related (PE, ascending aortic dilatation, diaphragmatic paralysis, obstructive sleep apnea, chronic obstructive pulmonary disease, right ventricular infarction, constrictive pericarditis, pericardial effusion, right atrial myxoma, eosinophilic myocardial disease, etc.).[2] At the same time, interatrial septum and PFO may acquire a conformational transformation during adulthood that causes blood flow to preferentially route from the right atrium to the left, especially when seated upright, via repositioning of the atrial septum, putting it directly in line with the blood flow from the inferior vena cava.[4]

Our patient had never exhibited symptoms of POS until this intervention. We have seen important desaturation during hypotensive periods in the intraoperative phase. A drop in systemic vascular resistance and significant blood loss probably raised intracardiac shunt fraction, as it has been demonstrated that hypovolemia can change ventilation-perfusion matching and the right-to-left shunt seems to be more likely to develop when in the dehydrated state.[3] Also, desaturation was promptly resolved after phenylephrine boluses, a potent direct-acting alpha-1 adrenergic agonist.

Intravenous α agonists were already used to establish a rapid diagnosis of shunting, upon rapid correction of hypoxemia. Also, it is not uncommon to use adrenergic agonists in cardiac surgery to reduce right-to-left shunting in children with congenital heart defects. In this case, we believe to have temporarily reversed the intracardiac right-to-left shunt by causing a sharp rise in left ventricular end-diastolic and left atrial pressures.[3]

In our patient's case, we confirmed the harmful influence that PFO exerts, as it can be associated with stroke, paradoxical embolism and POS.[3,4] In the perioperative period, patients with PFO are exposed to various physiological threats, such as hemorrhage, mechanical ventilation, patient positioning, and the fall in systemic vascular resistance. This increases the vulnerability to stroke due to hemodynamic changes that favors right-to-left shunting, hypercoagulability, and formation of venous thromboemboli.[5] We have detected a PE that could have led us to stop our investigation, assuming it as the single reason for hypoxemia. However, PE is frequently coexisting with POS.[1] The anesthesiologist must be aware that an otherwise clinically silent PFO, can manifest with POS during a PE. On the other hand, the presence of POS should compel us to seek, not only the presence of an intracardiac communication, but also a possible concomitant disorder.

Transesophageal echocardiography is the gold standard for diagnosing this syndrome. It allows the direct visualization of any cardiac defects or aneurysms that may be present in the atrial septum. However, a transthoracic echocardiography can be useful too. Associating a bubble study with intravenous agitated saline can help us to assess the presence of right-to-left shunting, suggesting an intracardiac shunt if those bubbles appear within three cardiac cycles, and should be the first test in the diagnostic algorithm. These examinations should ideally be executed with the patient in lying and upright positions. Rarely, the shunt can only be seen during a Valsalva maneuver.[2]

Closure of the atrial septal defect is the best treatment for POS, with a fast relief of symptoms. Still, caution is needed when deciding for definitive treatment, considering the benefit-risk profile for each patient.[2–4]

In conclusion, our patient had POS secondary to a PFO without elevated right atrial pressures, making it highly unusual. After excluding more common conditions, especially in elderly patients, where symptoms may otherwise be attributed to ventilation impairment, it is essential to have a high index of suspicion to consider POS, because desaturation and dyspnea are common events in our practice. An echocardiography can suggest the diagnosis and the treatment can signify a great improvement in the patient's quality of life.

Conflicts of interest

The authors declare no conflicts of interest.

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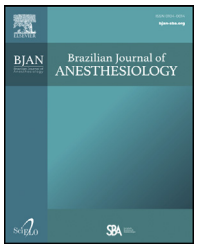

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CASE REPORT

Continuous erector spinae plane block for analgesia and better pulmonary functions in patients with multiple rib fractures: a prospective descriptive study

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KEYWORDS
Rib Fractures;
Erector Spinae Plane Block;
Pulmonary functions;
Analgesia;
Visual Analogous Scale (VAS)

Abstract
Background: The present study explored the role of continuous erector spinae plane (ESP) block for analgesia as well as its impact on pulmonary functions in patients with multiple rib fractures.
Methods: Ten patients with multiple rib fractures were enrolled after getting informed and written consent. Ultrasound-guided ESP block was performed at the level midway between the fractured ribs followed by the insertion of the catheter. Pre- and post-block VAS score, hemodynamics, respiratory rate (RR), peripheral oxygen saturation (SpO_2), inspiratory capacity (IC), blood gases (PaO_2 and PCO_2), and complications were compared.
Results: Pain scores at rest as well as on movement showed a significant reduction from 5.9 and 7.5 pre block to 1.6 and 2.5 respectively at 96 hours ($p < 0.0001$). Similarly, RR, SpO_2, IC, and PaO_2 were significantly better after the block placement ($p < 0.001$).
Conclusion: Continuous ESP block provide adequate analgesia with better respiratory functions in patients with multiple rib fractures.
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Introduction

Rib fractures contribute to the significant morbidity in trauma victims which include pain, hemothorax/pneumothorax, pneumonia, etc. Moderate to severe pain that follows multiple fractured ribs limit the patient's ability to take a deep breath, cough-out secretions, and decrease their mobility. In contrast to the fractures of other bones, rib fractures usually do not require surgical intervention; the conservative management includes adequate analgesia thereby preventing respiratory complications.

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Regional anesthetic techniques including thoracic epidural analgesia (TEA) and thoracic paravertebral block (TPVB) have been performed to provide analgesia in patients with multiple rib fractures. Although both techniques provide adequate pain control, their associated complications are a limiting factor. Recently introduced ultrasound (US) guided erector spinae plane (ESP) block has been used for thoracic neuropathic pain, acute post-surgical pain in breast and cardiac surgeries and multiple rib fractures.[1–3] In this case series, we evaluated the analgesic efficacy of ESP block as well as its impact on pulmonary functions in patients with multiple rib fractures.

Methods

After getting approval from the institute's ethical committee (AIIMS/IEC/2019/845) and written informed consent, a total of 10 patients with American Society of Anesthesiologists (ASA) physical status I to IV, aged between 18 to 70 years, having multiple rib fractures (2 or more ribs) with visual analogous scale (VAS) more than 4 were included in this study. Patient refusal, requirement of mechanical ventilator support, bilateral rib fractures, and infection at the block site were the exclusion criteria. Patients were explained about reporting pain on the VAS scale and were trained regarding the use of Coach 2 incentive spirometer (Smiths Medical) to assess the bedside inspiratory capacity (IC). Baseline hemodynamic parameters [heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP)], peripheral oxygen saturation (SpO_2), respiratory rate (RR), VAS score, IC, and arterial blood gas (ABG) values were recorded before the placement of the block. Under all aseptic precautions, with the help of an ultrasound machine (LOGIQe, GE Healthcare, Chicago, United States) and a high frequency (8–15 MHz) linear probe, the ESP block was performed on the affected side at the level midway between the fractured ribs. After skin infiltration with 2% xylocaine, the hyperechoic shadow of the transverse process was appreciated in the paramedian sagittal view. An 18G 90-mm insulated echogenic needle (Contiplex, B Braun, Bethlehem, PA, USA) was advanced using the in-plane technique until the tip crosses the erector spinae muscle which was confirmed by hydro-dissection with 1–2 mL of normal saline. All patients received 0.3 $mL.kg^{-1}$ of 0.2% ropivacaine as a bolus followed by catheter (20G) insertion 3 cm distal to the needle tip. Subcutaneous tunnelling of the catheter at the insertion site was done and a transparent adhesive dressing was applied to secure the catheter and the catheter insertion site was inspected daily to find out any complication. Infusion of 0.2% ropivacaine (0.1 $mL.kg^{-1}.h^{-1}$) was continued throughout the study period. Rescue analgesia in the form of tramadol 2 $mg.kg^{-1}$ was given on recording of VAS $\geq$ 4 or patient demand. Post-block hemodynamics (at every10 minutes till 60 min, at 6 hours and then at every 12 hours till 96 hours), VAS (at 60 min, at 6 hours, 12 hours and then at every 12 hours till 96 hours), IC and ABG (at every 24 hours) and occurrence of side effects/complications were recorded. The primary outcome of our study was to assess analgesia using the VAS score. The secondary outcomes were to assess IC, ABG, amount of rescue analgesia required, and incidence of any procedure-related complications. For statistical analysis, categorical measurements were presented in numbers or ratio and quantitative variables were presented as median (range) or mean (SD). Repeated measure ANOVA and Friedman's test was used to compare pre and post quantitative and qualitative data.

Table 1 Demographic profile (age, weight, and ASA status), number of fractured ribs, and level at which the block was performed.

Parameters	Mean ± SD/ Median (IQR)
Age (years)	53.4 ± 12.7
Weight (kg)	63.2 ± 10.11
ASA physical status (I/II/III)	10/0/0
Number of fractured ribs	5 (3, 7)
Thoracic level at which block was performed	5.5 (4, 7)

Results

Out of sixteen patients screened, six were excluded (4 not meeting the inclusion criteria and 2 refused to participate). Table 1 represents the demographic profile (age, weight, and ASA status), number of fractured ribs, and level at which block was performed. The mean pain scores at rest as well as on movement showed a significant reduction from 5.9 ± 1.19 and 7.5 ± 1.26 pre block to 1.3 ± 0.67 and 2.5 ± 0.91 respectively at 96 hours ($p < 0.0001$) (Fig. 1). Similarly, RR, SpO_2, IC, and PaO_2 were significantly better after the block placement ($p < 0.001$) (Table 2). The hemodynamic variables (Fig. 2) and PCO_2 (Table 2) did not show any significant change ($p > 0.05$). Four patients required a total of five doses of rescue analgesia (two on day 1, two on day 2, and one on day 3). No complications were reported during block placement and observation period.

Discussion

In the present study, we found that ESP block could provide significant improvement in pain score and the continuous catheter technique ensured adequate analgesia for a prolonged period. Also, adequate analgesia translated into better pulmonary rehabilitation and therefore improved respiratory function.

Mortality from rib fractures has been reported to be as high as 33% and contributing factors are disruption of respiratory mechanics and pain.[4] For patients with pre-existing respiratory comorbidities or opioid sensitivity, regional anesthesia is often lifesaving. Thoracic epidural analgesia (TEA) & paravertebral block (PVB) have been used extensively in patients with multiple rib fractures. However, the associated injuries such as spinal cord injuries, vertebral fractures, unstable pelvis, severe head injury, coagulopathies, and hemodynamic instability limit the use of these blocks. Also, few studies suggest that TEA increases the length of hospital stay in these patients.[5]

ESP block is an interfacial block, simple to perform, and is relatively safer as the target plane is superficial to the transverse process and the needle tip remains distant from pleura, major vessels and discrete nerves.[1,6] Local anes-

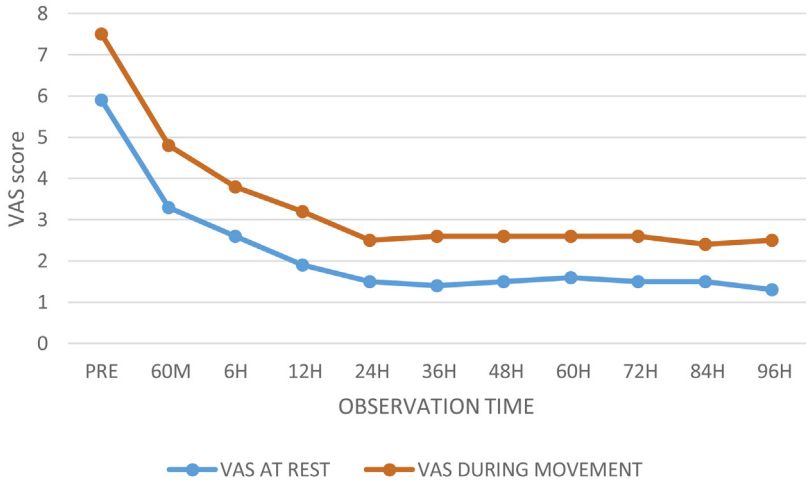

Figure 1 Baseline VAS score and VAS recorded at the various time point of observation at rest and during movement.

Table 2 Respiratory rate, peripheral oxygen saturation, inspiratory capacity, and blood gas values recorded at baseline and at the various time points of observation. Values are presented as [mean ± SD].

Parameters	Pre-block	At 60 min	At Day 2	At Day 3	At Day 4	*p*-value
Respiratory Rate (per min)	23 ± 8.80	18.2 ± 5.16	17.9 ± 3.54	16.5 ± 2.65	16.9 ± 2.132	0.0001
Peripheral Oxygen Saturation (%)	94	96	96	96	98	< 0.0001
Inspiratory Capacity (mL)	437.5 ± 164.68	565 ± 213.5	710 ± 246.98	875 ± 411.8	917.5 ± 427.86	< 0.0001
PaO2 (mm Hg)	64.25 ± 8.452	67.81 ± 8.165	68.86 ± 10.038	70.96 ± 8.951	72.9 ± 9.129	< 0.0001
PCO2 (mm Hg)	32.6 ± 8.45	33.07 ± 6.46	33.18 ± 2.99	33.52 ± 1.33	33.96 ± 2.708	0.9648

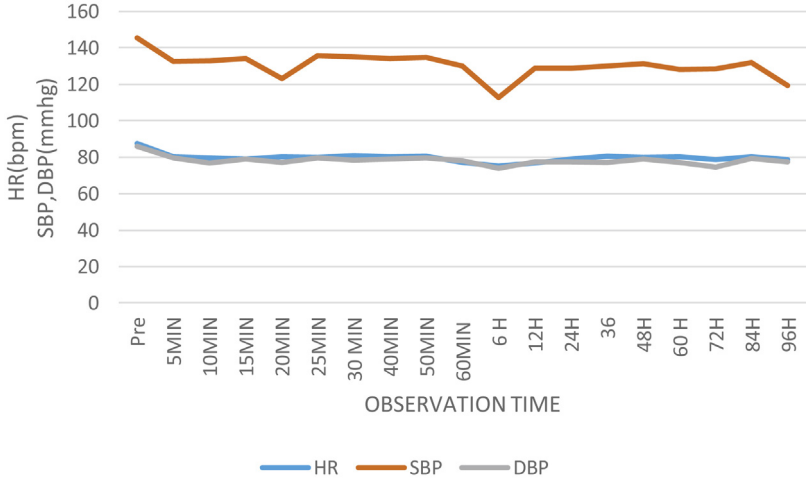

Figure 2 Baseline hemodynamic parameters (HR, SBP, and DBP) and hemodynamic parameters recorded at various time points of observation.

thetic (LA) administered diffuses to the ventral and dorsal rami of spinal nerves, as well as to the paravertebral and the epidural space to provide sensory blockade of multiple dermatomes.[6] Based on earlier studies[2,3] and case reports of erector spinae block, we assumed that the dose and concentration that was used for analgesia in most of the thoracic paravertebral blocks[7] (bolus of 0.3 mL.kg^{-1} of 0.2% ropivacaine) followed by infusion of 0.1 mL.kg$^{-1.h^{--1}}$.h^{-1} is sufficient for analgesia in most of the patients posted for ESP block and this will also help in easy dose calculation.

In a similar retrospective cohort study, authors found that IC was nearly doubled from baseline and this effect was maintained over 72 hours. Maximum pain scores were statistically significantly reduced however, the reduction in 12-h opioid consumption did not reach the significance limit.[2] This difference might be explained by the fact that in their study only 77% of patients received continuous block while the remaining received a single-injection technique. Furthermore, the range of duration for which the catheter remained sited was 0.6–9.3 days.

The extent of dermatomal spread with erector spinae block is variable. Results of a cadaveric study showed that the injected dye spread in erector spinae fascial plane was found to be two to four spinal nerve levels in the majority of specimen,[6] while as per one cadaveric study, drug given at T5 level could spread between C7 and T8.[1] This variable cephalo-caudal extent may be one possible reason for the dermatomal sparing and need of rescue analgesia in three of our patients with multiple fractures and extensive injuries. In these patients, two level blocks can be more effective, although this has yet to be proven.[8] In one of our patients, catheter got blocked on day 2, due to which 1 dose of rescue analgesia was needed and then catheter was reinserted after taking all aseptic precautions.

Few case reports have also showed the role of continuous ESP block for pain relief in trauma patients with multiple rib fractures needing ICU care.[9,10]

Conclusion

To conclude, ESP block provided an improvement in pain scores and respiratory parameters in patients suffering from traumatic rib fractures. It may represent an attractive and viable alternative for such patients. Because of the inherent biases of prospective single arm descriptive study, further studies with adequate sample size and design are required to reciprocate the findings of our study.

Conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORT

Ultrasound evaluation of diaphragm function in patients with cervical spinal cord injury: case report



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KEYWORDS
Lung ultrasound;
Spinal cord trauma;
Diaphragmatic paralysis;
Tracheostomy, case report

Abstract Ultrasound evaluation of diaphragm function allows the detection of diaphragm dysfunction and the adaptation of ventilatory support in patients admitted to intensive care units. The studied patient had a C3 spinal cord injury. Ultrasound evaluation of diaphragm mobility showed that the patient suffered diaphragm dysfunction. A tracheotomy was indicated, and early ventilatory support was initiated. Ultrasound evaluation of diaphragm function in patients with cervical spinal cord injury is a useful and simple technique. It provides fast and reliable data for the diagnosis of respiratory insufficiency of neuromuscular origin.
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Introduction

Traumatic spinal cord injury requires the collaboration of a multidisciplinary team, both for the specialized treatment of the acute phase and for secondary complications. In respiratory management in the acute phase, an evaluation of respiratory function is a priority to anticipate the need for ventilatory support.

Ultrasound evaluation of diaphragm function allows the detection of diaphragm dysfunction in patients with cervical spinal cord injury and provides ventilatory support in anticipation of respiratory complications.[1]

We described the case of a polytraumatized patient with cervical spinal cord injury and the early ventilatory support provided in the intensive care unit, with the aim of analyzing the main evaluation key points and early ventilatory management.

Case report

Polytraumatized 65-year-old man with no medical history of interest, who was admitted to the intensive care unit after an accidental fall from three meters high. The patient presented a mild head trauma of 15 on the Glasgow Coma Scale (GCS) upon the arrival of the emergency service personnel to the scene of the accident. He also presented facial trauma with soft tissue edema in the facial region and active bleeding from the nasal and oral cavities.

A total body Computed Tomography (CT) scan was performed, showing subdural hematoma, subarachnoid hemorrhage, multiple complex facial fractures and complex C4 to C7 vertebral fractures. The injuries caused significant soft

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tissue oedema at the cervical level that displaced the airway to the right.

The patient presented neurological deficits consisting of paresis of the lower limbs with right lower limb hypoesthesia and paresis of the upper limbs with greater involvement of the right arm associated with ipsilateral hypoesthesia. The medullary reflexes were preserved. Given the findings of this clinical examination, an urgent cervical Magnetic Resonance Imaging (MRI) scan was performed. The MRI showed the presence of C6—C7 subluxation with disc protrusion and epidural hematoma anterior to the vertebral body of C6, along with a small rupture of the yellow and interspinous ligaments. The images showed minimal spinal deformity with small patchy areas of myelopathy and showed another area with strong myelopathy at the C3 vertebra (Fig. 1). Upon the radiological findings and the diagnosis of incomplete spinal cord injury (American Spinal Injury Association — ASIA C), the patient was intervened urgently by performing a discectomy and anterior cervical fixation of vertebral bodies C6—C7 using a plate.

After the intervention, the patient presented an adequate neurological state, showing good respiratory dynamics with ventilatory support in Continuous Positive Airway Pressure (CPAP) mode + 6 cmH_2O. The patient was extubated, remaining under clinical supervision. After ten minutes, the intercostal and abdominal musculature appeared to be used in all the respiratory cycles and the patient reported dyspnea. No decrease in Peripheral Oxygen Saturation (SpO^2) was observed on the pulse oximetry monitor. At this time, a diaphragm M-mode ultrasound was performed. It showed bilateral diaphragmatic thinning (Fig. 2).

To perform the ultrasound examination, a high-frequency linear ultrasound probe (10—12 Hz) was used, placing it perpendicular over de 9th—10th intercostal space in the anterior axillary line, to observe part of the area of apposition of the diaphragm with the rib cage (apposition zone). In this area, the diaphragm is seen as 3 layers of different densities arranged in parallel (pleura, diaphragm, and peritoneum).[2,3]

Provided these clinical signs and considering the ultrasound findings and spinal cord injuries shown in the MRI, it was decided to perform a surgical tracheotomy in anticipation of respiratory failure in the patient. Subsequently, the patient remained with ventilatory support as needed.

Discussion

The location and degree of cervical spinal cord injury affects both the onset of mechanical ventilation and the successful weaning of the respirator. Injuries above C5 and ASIA A are among the factors with the highest risk for developing respiratory failure. After the ultrasound examination, it was found a diaphragmatic thickness below 1.5 mm.

One of the ways to measure the diaphragmatic function is the diaphragmatic thickness, using the M mode. This depends on muscle mass and is correlated with forced vital capacity. The decrease in diaphragmatic thickness is associated with a decrease in amplitude assessed by electromyography and may indicate the presence of atrophy or disfunction. The normal diaphragmatic thickness in ventilated patients is 2.4 $\pm$ 0.8 mm, indicating atrophy values below 2 mm. Ratios of 1.8 are considered normal values, accepting ratios of 1.2 as the lower limit.[3]

The presence of respiratory complications are also good predictors. The duration of mechanical ventilation is also determined by age (over 45 years), concomitant lung diseases, smoking, low level of consciousness (GCS less than 9), comorbidities and an injury Severity Score less than or equal to 16.[4]

In C1—C2 injuries, there is no effective respiratory musculature. The diaphragm is innervated by the phrenic nerve, which is composed of the C3, C4, and C5 cervical nerves. Therefore, patients with complete motor injury above C5 will almost invariably need ventilatory support.[1] Injuries below C5 result in paralysis of the intercostal and abdominal musculature; therefore, some patients will require respiratory support.

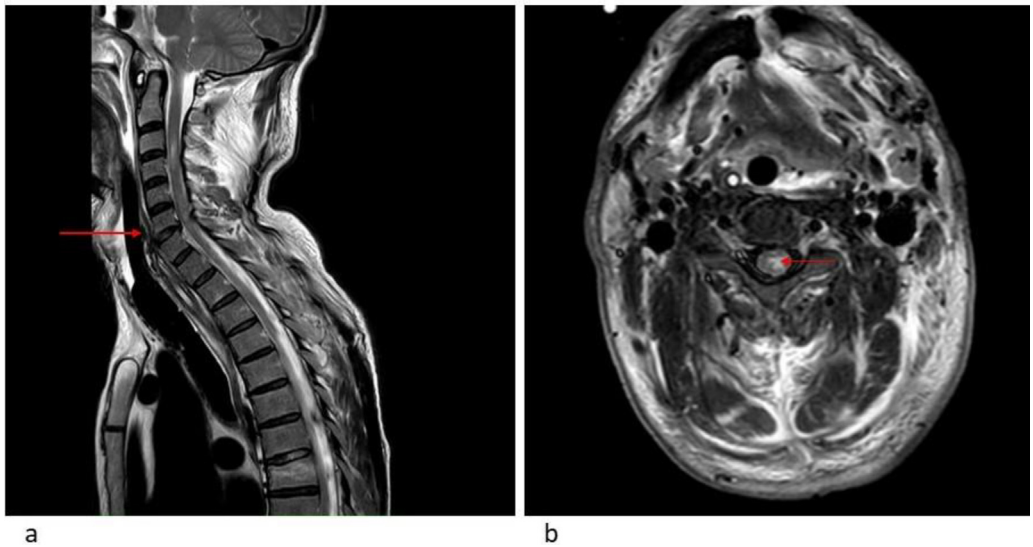

Figure 1 Cervical nuclear magnetic resonance. (a) Sagittal section with anterior ligament injury image at the level of C5 to C7 vertebral bodies. (b) Cross section at the level of the C3 vertebral body showing alteration of the signal suggestive of myelopathy.

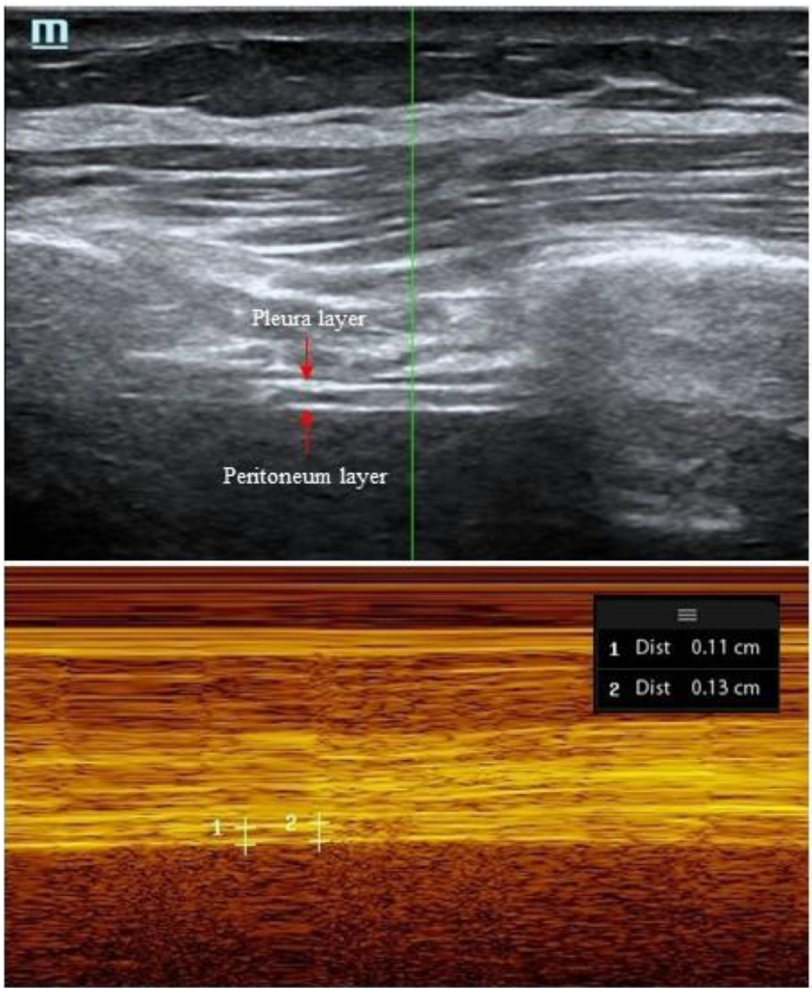

Figure 2 Ultrasound images. Right diaphragm exploration. (a) 2D mode. (b) M-mode ultrasound of the diaphragm. Measurement of diaphragm thickness using M-mode at the level of the right hemidiaphragm. Is visualized as 3 parallel lines. Number 1 represents the inspiratory thickness and number 2, the expiratory thickness.

It is unknown whether invasive mechanical ventilation should be performed preventatively in all patients or selectively based on signs of acute respiratory failure, but there is evidence to support that in patients with injuries above C5 and complete quadriplegia, intubation should be performed routinely and early because delays can cause preventable morbidity.[5]

In this case, the ligament injuries that caused instability of the vertebral bodies were located in C5 to C7, but the nuclear magnetic resonance showed that the extension of the spinal cord injury was from C3 to C7. These lesions are consistent with the injury incident, a fall that caused severe facial trauma and could have caused spinal distraction due to hyperextension of the neck.

Although radiological tests support the diagnosis, only a comprehensive clinical and neurological assessment can confirm the severity of acute spinal cord injuries. The loss of respiratory capacity in patients with cervical spinal cord injury occurs due to exhaustion of the musculature involved in the ventilatory process, hemorrhage or ascending spinal oedema, accumulation of secretions, atelectasis, other associated traumas, or other conditions of the patient.

Tracheotomy is required in 11—35% of patients with cervical spinal cord injury for the treatment of pulmonary complications and pulmonary hygiene.[1] Tracheotomy reduces the duration of respiratory cycles, improves lung capacity to mobilize secretions and reduces resistance of the respiratory tract. As a result, the weaning of the ventilator becomes easier and reduces the mechanical ventilation duration.[4] There is evidence that early tracheotomy reduces the incidence of pneumonia, shortens the duration of mechanical ventilation, reduces the stay in the ICU and reduces the rates of serious complications associated with orotracheal intubation, such as tracheal stenosis. Tracheotomy does not appear to have deleterious effects when performed shortly after cervical fixation surgery and does not promote cross infection despite the proximity of the incisions.[1]

For the patient presented in this article, tracheotomy was indicated to anticipate any signs of exhaustion as an immediate respiratory complication. If this technique was not available, the patient would have required ventilatory support in the short term. In that case, the option of noninvasive mechanical ventilation would have been considered, which, upon presenting multiple facial fractures, could have been difficult.

Ventilatory failure in patients with cervical spinal cord injury occurs more frequently after the fourth day of the injury, which is relevant for the monitoring and consideration of maintaining the intubation after early surgical intervention, especially those from cervical surgical procedures. If it is not necessary to initially secure the airway or ventilatory support, the need for intubation through PCO_2 (capnography and arterial blood gas) and spirometry with monitoring of the vital capacity (which has an excellent correlation with other pulmonary function tests) and Maximum Inspiratory Pressure (PImax) should be considered. This supposes a simple, global evaluation of the strength of the inspiratory musculature, which is a good indicator available at the bedside. In general terms, the PImax estimates the strength of the inspiratory muscles (diaphragm) and is achieved at residual volume and with the greatest inspiratory effort. The evaluation of diaphragm function is carried out through medical history, physical examination, nerve conduction studies and Electromyography (EMG). Nerve conduction and EMG studies are uncomfortable and can sometimes cause complications such as pneumothorax.[6]

Imaging techniques can be used as an approach for the evaluation of diaphragm dysfunction. Paresis or diaphragm paralysis is usually presented as an elevation on simple chest radiography.

Functional imaging with fluoroscopy is a simple and effective method to diagnose diaphragm dysfunction, being classified as paralysis, weakness or eventration. Diaphragm paralysis can be observed as an absence of orthographic excursion of the diaphragm in the respiratory cycles, usually presenting a paradoxical movement with inspiration.[7]

There is no consensus on the best ultrasound assessment method. The measurement of diaphragm shortening, which is the variation of thickness during inspiration/expiration, measured in the apposition zone, provides a simple way to diagnose paralysis or diaphragm dysfunction both unilaterally and bilaterally. Current recommendations on diaphragmatic evaluation by ultrasound is the use of diaphragmatic shortening, over other parameters, such as excursion.[7,8]

Diaphragmatic ultrasound in critically ill patients is a technique that can be performed at the patient's bedside (point of care ultrasound), easily reproductible and is event of adverse effects derived from ionizing radiation.

However, one of the limitations of this clinical case presents are the technical skills and ultrasound management that each one present, as well as the interobserver variability that exists when it is a dynamic test. Furthermore, due to the anatomy of the patient (such as subcutaneous emphysema, rib injuries at the place where the technique was performed, the presence of chest tubes, etc.) may lead to difficulty or impossibility of its performance.

Conclusions

Respiratory failure and pulmonary complications are the main factors that contribute to the morbidity and mortality of patients with cervical or high thoracic spinal cord injury.

This study considers that ultrasound evaluation of diaphragm function as an indicator of respiratory failure in patients with cervical spinal cord injury is a useful, simple, minimally invasive, and inexpensive technique. This technique provides reliable data to establish a prognosis regarding the initial needs for ventilatory support. This evaluation of respiratory function on observing adequate diaphragm mobility can also be applied to patients in the weaning phase of mechanical ventilation.

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.2021.12.005.

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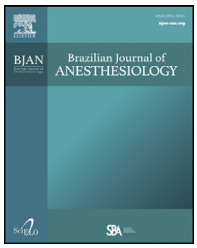

CASE REPORTS

Awake craniotomy for eloquent pial arteriovenous fistula: anesthetic and surgical consideration of a rare case

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KEYWORDS
Arteriovenous fistula;
Awake craniotomy;
Anesthesiology;
Vascular disorders

Abstract Intracranial pial Arteriovenous Fistulas (AVFs) are rare cerebral vascular lesions composed of one or more arterial connections to a single venous channel. We report a 50-year-old patient with a ruptured pial AVF located in an eloquent area. Microsurgery for pial AVF occlusion was proposed with awake craniotomy for motor function and neurological evaluation. Awake craniotomy is a technique that is especially useful for cerebral vascular lesions in eloquent areas, where an occlusion often compromises or suppresses the blood supply, culminating in ischemia with consequent transient or definitive deficits in neurological function.
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Introduction

Cerebral vascular lesions are associated with high morbidity and mortality rates, especially when they rupture.[1] Subarachnoid hemorrhage after aneurysm rupture is the most catastrophic vascular manifestation. However, there are other lesions that may be associated with severe neurological impairment, such as intracranial Arteriovenous Fistulas (AVFs). Pial AVFs are rare vascular lesions, and approximately 150 cases have been described.[1] They are high-flow vascular malformations that present with a high rupture risk, especially after an initial hemorrhage, and poor neurological outcomes.

Brain hemorrhage at an atypical site in young patients may be a presentation of this disease. Treatment usually involves a neurosurgical approach. Comprehensive knowledge of the brain anatomy before and during the procedure is essential to achieve good results. Neurological monitor-

Abbreviations: AVF, Arteriovenous fistula; CT, Computed tomography; ICG, Indocyanine green.

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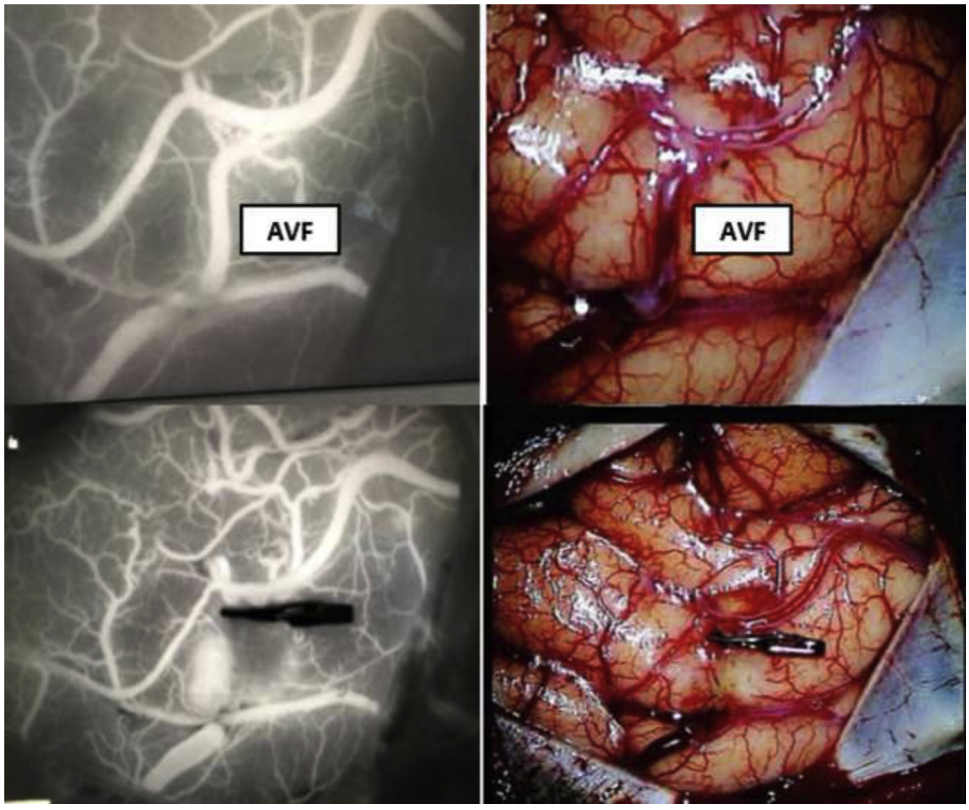

Figure 1 A, Left/superior: intraoperative videoangiography. B, Right/superior: microsurgical view under magnification of the AVF. C, Left/inferior: intraoperative videoangiography with ICG after AVF clipping. D, Right/inferior: microsurgical view after AVF clipping (use of the images authorized by the patient through informed consent). AVF, Arteriovenous Fistula; ICG, Indocyanine Green.

ing may be performed using electrophysiology methods, and awake craniotomy improves the results. Collaborations between neurosurgeons and anesthesiologists are crucial for performing an effective procedure. In the present report, we describe a unique case of a pial AVF that was successfully treated through awake craniotomy.

Case report

A 50-year-old woman presented to the emergency department with the sudden onset of a holocranial headache and mild left hemiparesis (grade 4) associated with a change in superficial sensitivity in the left dimidium with spontaneous regression 5 days after the event. She received analgesic drugs and underwent brain Computed Tomography (CT) and cerebral angiography, which revealed a small-volume intracranial hemorrhage that did not require drainage. During the investigation, complementary examinations were performed (brain resonance imaging, angioresonance, and digital angiography), and the presence of a right frontal pial AVF was confirmed.

Thus, we opted to perform elective surgery while the patient remained awake to continuously assess motricity and sensitivity, since after the occlusion of an AVF, ischemia and acute neurological deficits may occur. There is evidence reported in the literature that during the temporary occlusion of vascular lesions, deterioration in neurological function may occur without concomitant changes in neurophysiological parameters. This information corroborates the indication for awake surgery in cases like the one described.[2]

After occlusion of the AVF using a titanium clip (Fig. 1), we performed motor and sensitive tests on the left dimidium for 15 minutes through active mobilization of the limbs by the patient. In addition, verbal fluency and attention were continuously assessed during the procedure. Vessel patency was evaluated based on the visualization of normal flow after intravenous Indocyanine Green (ICG) administration.

This strategy allowed for the definitive occlusion of the fistula with safety, ensuring the preservation of motor and sensitive functions, and the patient did not develop any neurological sequelae. The duration of the awake procedure was approximately 50 minutes, with a total operative time of approximately 150 minutes. There were no changes in the motor and sensitive evoked potentials. The patient was monitored using electrocardiography, blood oxygen saturation measurements, bispectral index assessments, capnography, and non-invasive blood pressure measurements every 5 minutes during the asleep phases and every 30 minutes during the awake phase. The anesthesiologist placed a venous line (20G catheter) in the forearm of the patient. The patient was comfortably positioned.

The first phase of the procedure (asleep phase 1) was performed with previous oxygenation for 5 minutes, followed by an intravenous dose of 1% lidocaine (0.5 $mg.kg^{-1}$) to reduce or prevent pain at the injection site. Anesthetic induction with propofol (6–8 $\mu g.mL^{-1}$) and remifentanil (4 $ng.mL^{-1}$) was performed, followed by the introduction of a



Figure 2 Awake phase: verbalization (use of the image authorized by the patient through informed consent).

laryngeal mask tailored to the patient. The ventilator was set in a pressure-controlled mode, and the patient received mechanical ventilation. Subsequently, the doses of propofol and remifentanil were immediately reduced to 4 $\mu g.mL^{-1}$ and 1.5 $ng.mL^{-1}$, respectively. A new venous site of injection was set using an 18G catheter.

The patient received a urinary catheter, prophylactic antibiotics (cefuroxim), and drugs to control her symptoms (ondansetron, dexamethasone, dipyrone, pantoprazole) according to her body weight.

Subsequently, the anesthesiologist performed a scalp block with 1% lidocaine with no epinephrine and 0.5% bupivacaine with epinephrine of the supraorbital, supratrochlear, major occipital, zygomaticotemporal, and auriculotemporal nerves bilaterally. A total dose of 150 mg of lidocaine plus 75 mg of bupivacaine was used in 50:50 dilutions. After all the surgical preparation, the procedure surgery was initiated.

After craniotomy and duramater exposure, duramater was soaked with a gauze containing 1% lidocaine (100 mg) for 15 minutes, and the venous anesthesia was disrupted.

Once the patient exhibited an increase in the BIS index (up to 70), or to the awake level, the laryngeal mask was removed, and we initiated the second phase of the procedure: awake (Fig. 2).

The neurophysiologist then continuously monitored the neurological function, helping the surgeon to clip the fistula safely. The patient was awake, with good cognition, without pain, and very collaborative.

After complete clipping of the fistula and neurological evaluations, the patient was submitted to the third phase of anesthesia, asleep phase 2. New induction was performed with propofol and remifentanil, the laryngeal mask was easily reintroduced with the patient positioned with cranial pins, and the patient received mechanical ventilation until completion of the procedure. The patient had an estimated bleeding volume of less than 100 mL. Once completed, the patient was awakened again, not reporting pain or other symptoms. She was admitted to the intensive care unit for 12 hours and then to a hospital bed for 24 hours, being discharged after 36 hours with excellent recovery and the absence of neurological deficits.

This case report describes for the very first-time surgical treatment for a pial AVF while the patient was awake.

Discussion

Pial AVF are rare vascular lesions, and approximately 150 cases have been described[1] that required prompt treatment aiming to minimize neurological sequelae. Based on a review of the current literature, the use of awake surgery for the treatment of AVF has not previously been reported.[2] AVFs may be acquired traumatically, iatrogenically, or congenitally. They are typically classified as a subtype of pial arteriovenous malformations; however, they are differentiated by their lack of an intervening nidus between the arterial feeder and venous drainage.[1] Due to their unfavorable natural course, conservative management is associated with a mortality rate of up to 63%.[3] One of the most common presentations is intracranial hemorrhage,[4] such as in this case.

Owing to their high mortality rate, despite being rare lesions, pial AVFs must be considered as a differential diagnosis in young patients with intracranial hemorrhage in atypical topography. Intraoperative resources such as intraoperative videoangiography using ICG and intraoperative monitoring should be used to increase therapeutic success, preventing neurological complications and the need for further surgeries.

Awake craniotomy for lesions in eloquent area is a well-established procedure in the field of neuro-oncology[5]; however, this method is not widely used for vascular lesions.[3] Intraoperative monitoring of motor evoked potentials is a valuable resource that guides neurosurgeons; however, in some cases, it may be insufficient to prevent neurological motor deficits because electrical conduction may be imprecise. When a patient is awake, a neurological examination may be performed in real time to improve the success of the procedure. Neurosurgeons, neuroanesthesiologists, and neurophysiologists must be in perfect synchronism during awake surgical procedures.

In vascular malformations, the anatomy might be distorted, and a neurosurgeon may not know if a manipulated vessel contributes to the supply of eloquent regions, and every method that aim to minimize sequelae is valuable and should be performed by a trained multidisciplinary team, such as awake craniotomy. Good relationships among the team are mandatory for such delicate procedures because collaboration during the awake phase is essential to the success of the surgery.

However, patients who undergo appropriate neuropsychological and motor evaluations and have good relationships with the team may undergo this procedure without encountering complications.

Conclusion

Advanced resources for surgery for tumors in eloquent areas through awake craniotomy are well described in many papers. Appropriate evaluations of patients before these procedures and collaborations among neurosurgeons and anesthesiologists are mandatory. Nevertheless, awake craniotomy remains less used for vascular lesions. Pial fistulas in

eloquent areas are rare and may evolve with severe and disabling neurological impairments, especially concerning speech and motricity. This is the first report of successful awake craniotomy for a peri-rolandic fistula wherein advanced neuroimaging methods such as with ICG administration were implemented with excellent results. The use of these resources should be encouraged for brain vascular lesions.

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Statement

All data of the patient in this report case was used just after application of the informed consent form and approval from ethical committee.

Conflicts of interest

The authors declare no conflicts of interest.

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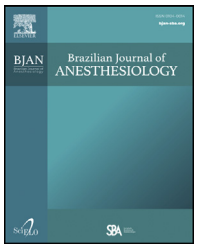

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CASE REPORT

Successful perioperative management of a primary pulmonary arterial angiosarcoma: case report



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KEYWORDS
Pulmonary angiosarcoma;
Pulmonary embolism;
Cardiopulmonary bypass;
Pulmonary hypertension;
Case report

Abstract
Introduction: Primary pleomorphic pulmonary angiosarcomas are extremely rare tumors which could be easily mistaken for pulmonary emboli.
Background and findings: We describe the successful perioperative management of a patient with a pulmonary arterial mass which turned out to be a primary pulmonary angiosarcoma. The severe pulmonary hypertension was a particular challenge compounded with the site and adhesions of the tumor, and pulmonary hemorrhage. The procedure was successfully performed with strict hemodynamic control ensuring stable systemic and pulmonary arterial pressures using perioperative transesophageal echocardiography to continuously monitor cardiac function, along with other standard cardiac surgical monitors including depth of anesthesia monitoring.
Conclusion: Tight hemodynamic control, ensuring stable pulmonary arterial pressures using perioperative echocardiography, and thorough preparation with measures to reduce and prevent increase in pulmonary arterial pressure along with close communication within the multidisciplinary team are essential for successful management of patients with this pathology.
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Introduction

Primary angiosarcomas are rare malignant tumors accounting for only 2% of all sarcomas.[1] Primary malignant cardiac and great vessel tumors are rarer with an incidence of only 0.001% to 0.03%, and a majority of them being rhabdomyosarcomas. Pleomorphic pulmonary arterial intimal angiosarcomas are much rarer and only about a few hundred cases have been reported since first described by Moritz Mandelstamm in 1923, with most of them diagnosed postmortem. It could easily be mistaken for chronic pulmonary emboli.[2] The site and the adhesion of the tumor to the

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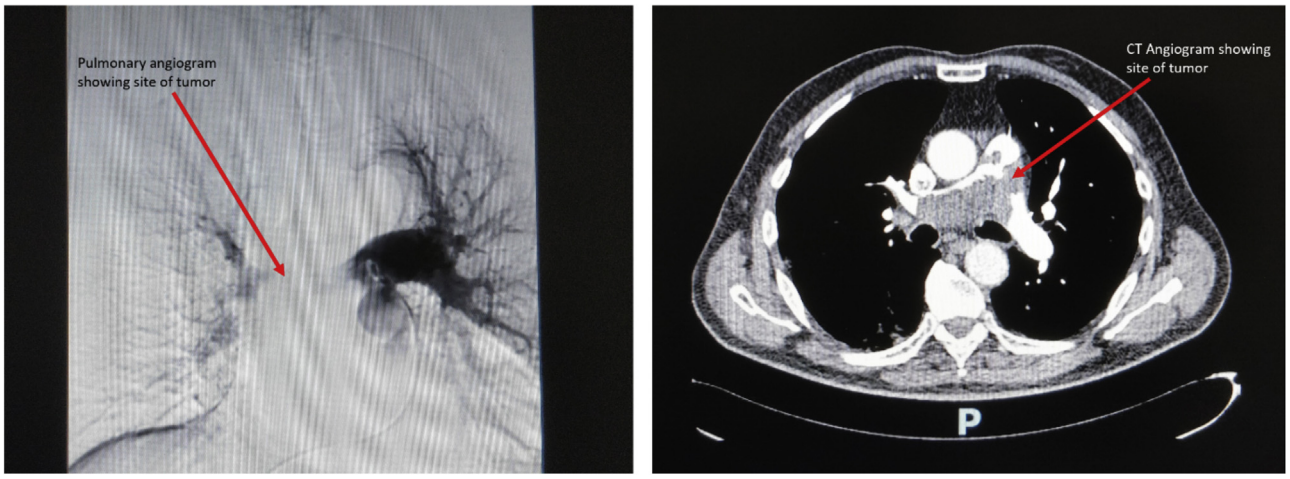

Figure 1 Preoperative pulmonary angiogram and CT angiogram showing pulmonary artery mass.

pulmonary artery and surrounding structures presents a particular challenge in its perioperative management.[3]

Report

Preoperative period

A 72-year-old chronic smoker (weight 71 kg, height 1.68 m), with known hypertension, and dyslipidemia presented with worsening shortness of breath over the last month consisting of intermittent episodes of moderate shortness of breath with no other cardiac symptoms. There was no history of prolonged immobilization or long-distance travel nor any recent weight loss.

On admission, the patient had a clear airway, respiratory rate of 20/minute, oxygen saturation of 94% on room air, heart rate of 75 beats per minute, and blood pressure 150/100 mmHg. He was well hydrated, warm with good peripheral perfusion, conscious and oriented, and normothermic. The hemogram was within normal limits with elevated D-dimer. The biochemistry profile was within normal limits, and the blood gas analysis demonstrated mild hypoxemia with compensated respiratory acidosis.

A transthoracic echocardiogram (TTE) performed on admission showed impaired right ventricular function with TAPSE 1.3 cm, mildly dilated right ventricle with thickened wall, severe tricuspid regurgitation with gradient 85 mmHg and estimated pulmonary arterial systolic pressure (PASP) of 100 mmHg, peak gradient across pulmonary trunk of 50 mmHg, and severely dilated right atrium. The left ventricle showed good systolic function with ejection fraction 60% and a cardiac output of 5.4 Litres/min and no diastolic dysfunction. The patient underwent unsuccessful local thrombolysis with rTPA based on pulmonary angiogram (Fig. 1), and the subsequent echocardiogram performed demonstrated no improvement. A CT angiogram (Fig. 1) subsequently performed showed hemopericardium and pulmonary hemorrhage in the posterior segments of right middle and apical lobes. A decision to perform a pulmonary thromboendarterectomy was made by the multidisciplinary team involving cardiac surgeon, cardiac anesthesiologist, and critical care team after 48 hours of stabilisation.

Intraoperative period

Defibrillator pads were placed on each side of chest and a cardiac arrest trolley was kept ready as a precaution before beginning of anaesthesia as per the European Resuscitation Council (ERC) Advanced Life Support (ALS) guidelines.[4] Prostacyclin and nitric oxide were kept available to reduce pulmonary hypertension as necessary. Monitoring was established as per national standards with addition of Bispectral Index (BIS; Aspect Medical Systems Inc., Newton, MA) monitoring. After placement of a 16G peripheral intravenous cannula and a 20G left radial arterial cannula, 100% oxygen was administered with a face mask. Induction of anesthesia was performed using 0.1 $mg.kg^{-1}$ of midazolam and 6 $mcg.kg^{-1}$ of fentanyl titrated to clinical response and BIS response (target BIS 40–50), and 80 mg rocuronium administered to facilitate intubation. A double lumen 37 Fr left sided tube couldn't be sited despite multiple attempts and hence, the patient was intubated with 8.0-mm tracheal tube with a plan to use a bronchial blocker to control the potential spillage of right pulmonary haemorrhage. The patient remained hemodynamically stable throughout induction of anesthesia. The left subclavian vein was cannulated with a 3-lumen central venous catheter and a second 14G intravenous peripheral cannula was sited. Anesthesia was maintained with sevoflurane targeting a mean alveolar concentration (MAC) of 1.0 for age maintaining 100% oxygen delivery ventilating both lungs with ventilation settings of tidal volumes 490 mL (7 $mL.kg^{-1}$) on pressure-controlled ventilation volume guaranteed mode, at a rate of 12 breaths/minute, I:E ratio 1:2, peak pressure 18 cmH_2O and PEEP 5 cmH_2O. Further fentanyl boluses (up to 2.0 mg) and rocuronium were administered as required. Perioperative antibiotic prophylaxis was administered as per protocol. Perioperative transesophageal echocardiography (TEE) was performed confirming the findings of the TTE performed earlier.

A midline sternotomy and pericardiotomy were performed. After full heparinization with 220 mg (3 $mg.kg^{-1}$)

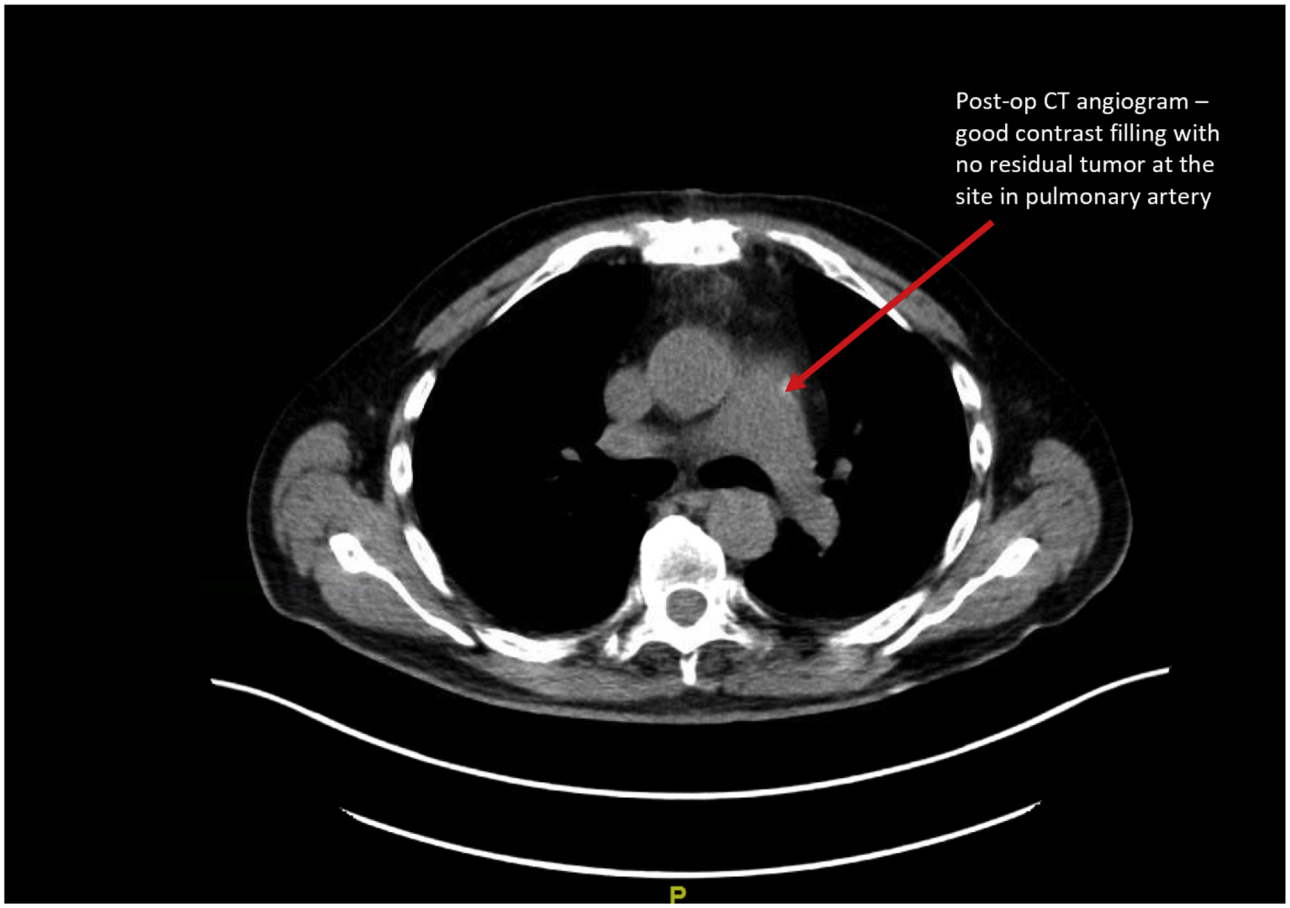

Figure 2 Postoperative CT angiogram demonstrating absence of residual tumor.

of unfractionated heparin to achieve an activated clotting time of 452 seconds, aortic cannulation and right atrial 2-stage cannulation were performed, and a cardioplegia cannula was placed in the aortic root. Cardiopulmonary bypass (CPB) was rapidly initiated and the entire procedure was performed without inducing cardiac standstill and aortic cross clamping, with the patient cooled to 24 degrees Celsius. The tumor principally extended in the right pulmonary artery which was clamped to prevent tumor migration. Anesthesia was maintained during CPB using Propofol infusion at 4 $mg.kg^{-1}.h^{-1}$ (300 $mg.h^{-1}$) and Sevoflurane 1–2% administered by the Perfusionist guided by BIS (target 40–50) and mean arterial pressure (MAP) (target 40–50 mmHg). The tumor was excised piece-meal to avoid damage to the pulmonary artery and valve leaflet to which it was adherent, and sent for histopathological evaluation. Teflon patch was applied to the posterior wall and right branch of the pulmonary artery. Dobutamine 3 $mcg.kg^{-1}.min^{-1}$ infusion was commenced as the patient was being rewarmed to 36.5 °C-degree Celsius. The patient was, subsequently, successfully weaned off cardiopulmonary bypass and decannulated. Noradrenaline infusion was started at 0.04 $micrograms.kg^{-1}.min^{-1}$ to maintain a MAP of 70–75 mmHg.

The total cardiopulmonary bypass time was 210 minutes. Protamine 270 mg was administered via peripheral cannula as a slow infusion over 20 minutes monitoring the right ventricle in mid-esophageal 4 chamber view on transesophageal echocardiography with final activated clotting time of 124 seconds (baseline 128 seconds). A pool of platelets and 4 units (approximately 1,000 mL) of fresh frozen plasma were administered. Perioperatively, a total of 1,500 mL of crystalloids was administered with a 600 mL blood loss and 1,050 mL urine output. A post CPB echocardiogram demonstrated a reduction in the tricuspid regurgitation from severe to moderate with PASP reduced to 50 mmHg from 100 mmHg and peak gradient across pulmonary trunk from 50 mmHg to 24 mmHg. The patient was transferred with tracheal tube in situ, with lungs ventilated with portable ventilator with 100% oxygen, and full portable monitoring according to international standards to the critical care unit with infusions of Noradrenaline titrated to optimal hemodynamic parameters, and Propofol at 150 $mg.h^{-1}$.

Postoperative ICU management

The patient was successfully weaned off mechanical ventilation and extubated around 12 hours postoperatively, and noradrenaline weaned off over the next 48 hours. Pain was managed on the ICU with regular paracetamol and morphine PCA (patient-controlled analgesia) with adequate pain control. The patient was then discharged to the ward after further 12 hours without any significant multiorgan consequences and discharged home after further 5 days. A

postoperative CT angiogram (Fig. 2) was performed which was negative for any residual lesion. A further echocardiogram performed just prior to discharge demonstrated an improvement in right ventricular function (TAPSE 1.5 cm) and further reduction in PASP to 44.5 mmHg. The patient underwent six cycles of chemotherapy with paclitaxel following the diagnosis of intimal fusiform/pleomorphic grade 3 pulmonary artery angiosarcoma. A PET scan performed did not show any metabolically active lesion. At the 3-months follow up, the patient had symptomatically improved and leading a moderately active life. However, the patient had a recurrence at the next follow up at 4 months and, unfortunately, died of a cardiac arrest following an acute pulmonary thrombosis on the recurrent tumour.

Discussion

Primary pulmonary artery angiosarcomas are very rare tumors with very poor prognosis even in the absence of metastasis. Less than half of the patients diagnosed survive the first year despite treatment.[3] Pulmonary artery sarcomas usually originate from the intimal cells and histologically consist of poorly differentiated mesenchymal cells, with fibroblastic and myofibroblastic components. Thus, according to the French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading they are high grade tumors, which was the case with our patient. Due to the extremely rare occurrence of the tumour the literature on the medical and perioperative including anaesthetic management is very limited.

Given the severe pulmonary hypertension (PASP 100 mmHg) and a physical partial obstruction in the pulmonary artery, along with hemopericardium and right pulmonary hemorrhage, it is prudent to take precautions to reduce the risk of cardiac arrest and also put measures in place to readily treat such an occurrence as per international and ERC ALS guidelines.[4] Lung isolation strategy should be planned to reduce the possibility of spilling over of hemorrhage from the right to the left lung and for the possibility of performing a pneumonectomy. However, the evidence for pneumonectomy for a complete eradication is inconclusive and could result in worsening of pulmonary hypertension.[5]

Induction of anesthesia should be closely titrated to avoid haemodynamic instability and 100% oxygen administered throughout the procedure before initiation of CPB to avoid worsening of pulmonary hypertension. Measures to control acute fluctuations in pulmonary arterial pressures should be in place. The use of BIS or cerebral oximetry is recommended to titrate the depth and ensure cerebral perfusion, respectively. The maintenance of hypothermia and infusion of propofol provides cerebral protection during the procedure thus helping to reduce adverse postoperative cerebral consequences. Early support with inotropes and/or vasoconstrictors helps to ensure hemodynamic stability thus maintaining good tissue and organ flow as well as perfusion in the post CPB period. The use of perioperative TEE is paramount in such cases as a perioperative monitor in detecting acute chamber and valve failures due to tumor embolism, the status of the repair, and damage to the surrounding tissues.

Conflicts of interest

The authors declare no conflicts of interest.

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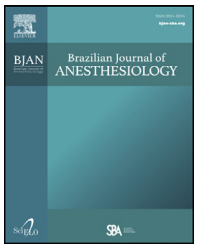

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CASE REPORTS

Ultrasound-guided pericapsular nerve group and obturator nerve phenol neurolysis for refractory inpatient hip cancer metastasis pain: a case report

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KEYWORDS
Regional anesthesia;
Pain management;
Chemical neurolysis;
Hip;
Metastasis

Abstract
Introduction: Bone cancer metastasis may produce severe and refractory pain. It is often difficult to manage with systemic analgesics. Chemical neurolysis may be an effective alternative in terminally ill patients.
Case report: Female terminally ill patient with hip metastasis of gastric cancer in severe pain. Neurolytic ultrasound-guided blocks of the pericapsular nerve group and obturator nerve were performed with 5% phenol. This led to satisfactory pain relief for 10 days, until the patient's death.
Discussion: This approach may be effective and safe as an analgesic option for refractory hip pain due to metastasis or pathologic fracture in terminally ill patients.
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Introduction

Hip pain is a common and disabling condition in adults. Its incidence is 12–15% among adults over 60 years of age.[1] The most frequent causes are osteoarthritis, labral tears, synovitis, osteonecrosis, and greater trochanteric pain syndrome. Other conditions, such as septic arthritis, aortoiliac insufficiency, and bone tumors (primary or metastasis), are less common but raise concern. Bones are the third most frequent site of cancer metastasis, following the lungs and liver. Bone metastasis usually indicate advanced stage disease and poor prognosis. They are major causes of morbidity causing severe and refractory pain, pathologic fractures, impaired mobility, and spinal cord injuries. The treatment of bone cancer pain involves multiple approaches, including pharmacotherapy, radiotherapy, chemotherapy, bisphosphonates, calcitonin, and neural blockades.[2] Interventional

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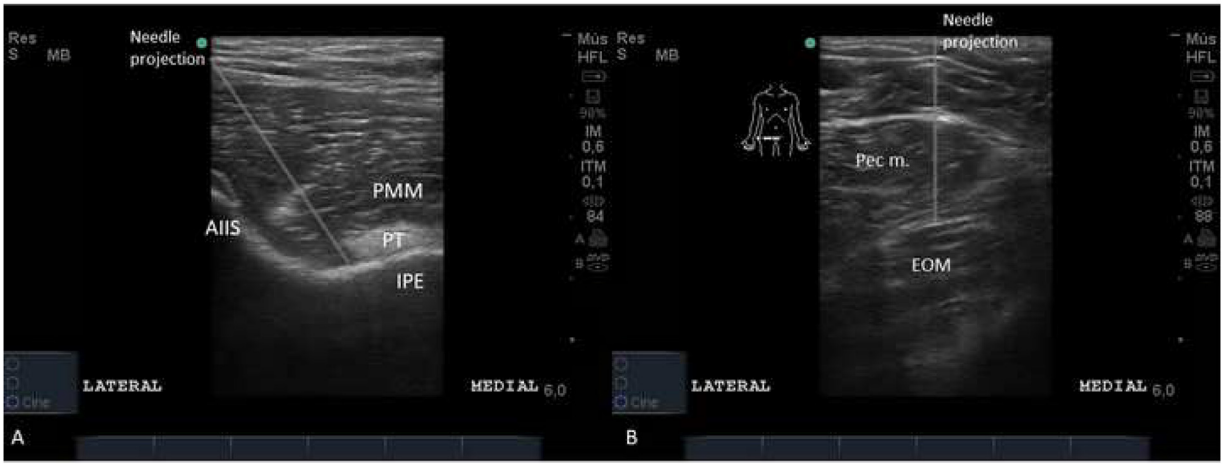

Figure 1 A, Pericapsular nerve group neurolytic block; B, Obturator nerve neurolytic block. AIIS, anterior inferior iliac spine; EOM, external obturator muscle; IPE, iliopubic eminence; Pec m., pectineus muscle; PMM, psoas major muscle; PT, psoas tendon.

procedures may be an alternative in refractory cases. Neurolytic block may be a potential option.

We present a case report of a gastric cancer patient who presented bone metastasis in the right femoral head, leading to severe refractory pain, with serious functionality and quality of life impairment. The patient was treated using a neurolytic block of the right pericapsular nerve group and the obturator nerve, resulting in satisfactory analgesia until her death 10 days later. Written informed consent to publication was obtained from the patient.

Case report

This article adheres to the applicable Enhancing the Quality and Transparency of Health Research checklist (Case Report Guidelines, CARE). The patient was female, 49 years of age, weighed 68 kg, and had a height of 159 cm. She had recently been diagnosed with a signet ring cell carcinoma of the stomach with bone metastasis, one of which was situated in the right femoral head. She had no other comorbidities, but her tumor was already untreatable and she was on palliative care. At the time, her symptoms were related to uncontrolled pain due to the osteolytic lesions, mainly in the right hip.

The patient had severe pain with a Numeric Verbal Scale (NVS) score of 10 (the NVS varies from 0 to 10, in which 0 indicates the absence of pain and 10 means unbearable pain) in the first evaluation. She was unable to sit or stand up because of the pain. She felt a slight relief with morphine rescue analgesia. Her prescription included the following medications: intravenous (IV) dipyrone 2 g 6/6 h, transdermal (TD) fentanyl patch 50 mcg.h^{-1}, IV morphine 4 mg 4/4 h when necessary (*pro re nata*, PRN) (mean daily dose of 8 mg.day^{-1}), IV ketamine 0.15 mg.kg^{-1}.h^{-1} in continuous infusion, and *per os* (PO) cyclobenzaprine 5 mg 8/8 h. After explaining the therapy options, possible adverse effects, and possible benefits to the patient, and after receiving her informed consent, a neurolytic block with 5% phenol was performed on the articular branches of the right femoral nerve and of the right obturator nerve in an attempt to control the pain.

The procedure was performed in the operating room with the patient in the supine position. The right hip region was cleaned with antiseptic solution and covered with sterile drapes. A high-frequency linear ultrasound probe was placed over the anterior superior iliac spine (ASIS), then slid caudally until the anterior inferior iliac spine (AIIS) was visualized. Then, the probe was positioned aligning the AIIS to iliopubic eminence.[3] A 20G 90-mm Quincke needle was inserted in-plane lateral to medial until the tip made contact with the bone, right beneath the iliopsoas muscle tendon. After negative aspiration, 4 mL of 5% phenol was injected (Fig. 1A). Then, the probe was slid medially over the superior pubic ramus towards the pubic tubercle. At that point, the transducer was slid caudally until an image of the pectineus and external obturator muscles formed.[4] The needle was introduced in an out-of-plane approach until its tip was located in the plane between the pectineus and external obturator muscles. Then, 3 mL of the 5% phenol was injected after negative aspiration.

Before the procedure, the patient noted a NVS pain score of 5 at rest and a NVS pain score of 10 during movement. Immediately after the procedure, a NVS score of 1 and 90% pain relief was reported by the patient. The day after the procedure, the patient had no pain at all. On subsequent days, the patient had no pain and reduced her opioid consumption, as summarized in Table 1. The patient died on the 10th post-neurolysis day. Until her death, she had no complaints of any decrease in muscle strength of the right lower limb.

Discussion

Pericapsular nerve group and obturator nerve phenol neurolysis in this patient led to a remarkable decrease in her pain scores. The intensity of the hip pain was drastically reduced, with no apparent side effects (motor weakness). As she was under palliative care, pain control was a priority, and the procedure gave her comfort until her death 10 days later.

Hip pain is frequent among adults above the age of 65 years due to a variety of causes and has been shown to be a relevant area in which improved pain treatment is needed.

Table 1 Summary of post-procedure pain management evolution of the patient.

	Opioid consumption in oral morphine equivalent (mg)	NVS at rest	NVS at movement
Pre-procedure	144	5	10
1st post-procedure day	132	0	1
2nd post-procedure day	132	0	0
3rd post-procedure day	120	0	0
4th post-procedure day	132	0	0
5th post-procedure day	120	0	0
6th post-procedure day	120	0	0
7th post-procedure day	41	0	0
8th post-procedure day	138	0	0
9th post-procedure day	78	0	0

Bone metastasis can cause chronic and disabling pain. Its management can be challenging due to a patient's critical condition and the adverse effects of opioids and other analgesic medications. Once comfort is imperative in patients under palliative care, pain control is usually a high priority.

Hip denervation can be used as an alternative for refractory pain. It can be performed by percutaneous radiofrequency denervation or chemical neurolysis.[5,6] These procedures may provide satisfactory analgesia, but information about the long-term effects or possible complications is still lacking. Although articular branches are sensory nerves, it is important to bear in mind that obturator and femoral nerves are mixed nerves, and great care to avoid motor injury has to be taken while performing both blocks. Considering the terminal conditions of the patient in our case, it was decided that 5% phenol neurolysis of the articular branches of femoral and obturator nerves could benefit her and reduce her disabilities. To our knowledge, this approach is relatively innovative, and it had successful individual results in this case, allowing the patient to sit or stand, leading to improved quality of life during the patient's final days. Phenol was the agent of choice because its injection is less painful than 99% ethanol, and larger volumes were not necessary for the proposed procedure. The concentration of 5% was used because it is the highest phenol formulation available in our institution.

This case report, although describes a relatively good result, has several limitations. First of all, one single case description cannot be taken as a general and appliable method to other patients. This patient was in a severe condition, with very low status performance, and limited to bed most of the time. As she was not considerably mobilizing, it was not [1–6] possible to adequately evaluate any motor blocks to her lower limb. The follow-up time can also put some limitation on the long-term assessment. As the patient passed away after 10 days, it was not possible to check for how long the chemical neurolysis kept the analgesic effect.

This case report may suggest that the articular branches of the femoral and obturator nerves may be good targets for chemical neurolysis (with phenol or ethanol injection) for hip pain management when intending long-term analgesic effect. Chemical neurolysis may be an easier and low-cost modality of hip pain treatment compared to hip denervation by radiofrequency ablation. Of course, this is a case report about a patient under palliative care. Larger studies with long-term follow-up, including randomized controlled trials assessing this technique in end-of-life patients, or even in non-cancer patients (hip osteoarthritis, for example), may be of interest to certify chemical neurolysis of the hip articular branches as a therapeutic option in hip pain treatment.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

We thank the colleagues of the Oncology and Palliative Care teams, who trusted and accepted the Pain Management Team suggestions and treatment options.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bjane.2021.02.037.

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LETTER TO THE EDITOR

Exploring the analgesic effects of pregabalin for post-chikungunya arthralgia: a comparative double-blind study

Dear Editor,

Chikungunya represents a debilitating syndrome triggered by a homonymous virus. Its predominant clinical manifestation involves arthralgia coupled with physical limitations, mirroring rheumatoid arthritis.[1] Despite the absence of disease-specific therapies, the joint pain accompanying chikungunya is inflammatory in nature and exhibits neuropathic characteristics. Pregabalin has displayed beneficial effects, even among patients not meeting neuropathic pain criteria.[2] Notably, preceding research underscores the role of cytokines in the development of chikungunya-associated joint disease, akin to that seen in rheumatoid arthritis. This suggests potential benefits from immunomodulatory therapies such as hydroxychloroquine.[3] Given the disease's prevalence and the consequent morbidity, the necessity for more efficacious treatment options for chronic chikungunya-related arthralgia remains unmet.

This double-blind study compares a combined regimen of pregabalin and hydroxychloroquine (PH group) against a placebo and hydroxychloroquine regimen (H group) for managing chronic chikungunya. The primary focus is on pain intensity, with supplementary analgesic requirements, Quality of Life (QoL), and adverse events as secondary outcomes. The study received ethical approval from the institutional Research Ethics Committee (CAAE 34247020.6.0000.5505) and was registered with the Brazilian Registry of Clinical Trials (REBEC RBR-6mkndk). All participants provided informed consent, and allocation occurred via the Randomizer® program. Pregabalin capsules were indistinguishable from placebos. Both researchers and patients were blinded to the allocated treatment. Sample size determination was based on a two-tailed hypothesis test with 80% power, significance level of 5%, and a minimum mean difference of one point on the visual analog scale for pain. This resulted in a calculated sample size of 16 individuals per group. Inclusion criteria encompassed chronic chikungunya-related arthralgia of at least 3 months duration, confirmed diagnosis by serology (ELISA IgM-/IgG+), age 18 or older, any gender, and a referred pain intensity score of ≥4. Exclusion criteria included a history of rheumatoid arthritis, cognitive impairment, psychiatric disorders, drug hypersensitivity, illicit drug use, or pregnancy.

The PH group received a daily dose of 75 mg pregabalin for the initial 5 days, followed by 75 mg twice daily, alongside hydroxychloroquine at 400 mg/day for a total of 3 months. Conversely, the H group received placebo alongside hydroxychloroquine at the same dosage. Supplementary analgesia involved dipyrone (1 g) as needed, with a maximum recommended dose of 6 g/day. Patients experiencing inadequate pain relief were permitted to use tramadol (50 mg) up to a maximum of 400 mg/day.

Conducted at an outpatient medical center in Açailândia, Brazil, the study assessed pain intensity and QoL at baseline, 2 weeks, and months 1, 2, and 3. The study also tracked supplementary analgesia use and adverse effects. Pain intensity evaluations used a verbal numerical scale ranging from 0 to 10. Quality of life was evaluated using the WHOQOL-100 questionnaire. For statistical analysis, the Mann-Whitney test and Fisher's exact test were employed, with a significance level of ≤0.05.

Initial randomization allocated 18 participants to the PH group and 17 to the H group. However, one participant from the H group was lost to follow-up, yielding 18 and 16 evaluable participants in the PH and H groups, respectively. Statistical analysis revealed no significant inter-group differences in pain intensity, supplementary analgesia use, QoL, or the incidence of adverse events during the specified time points (Table 1).

Analgesic medication to manage chronic chikungunya-related arthralgia hinges on existing treatment approaches for other chronic joint conditions.[4] The pathogenesis of chikungunya arthralgia bears resemblance to that of rheumatoid arthritis, making hydroxychloroquine's efficacy in reducing inflammation pertinent.[3] While drugs targeting neuropathic pain have been proposed for refractory chikungunya-related arthritis, these recommendations largely stem from extrapolations and limited prior investigations.[5] Despite the potential merits of pregabalin, its use did not yield observable benefits in the current study. This could be attributed to the effectiveness of conventional analgesic

Study conducted at the Universidade Federal de São Paulo; Rua Botucatu 740; Vila Clementino, São Paulo, SP, Brazil; Postal code: 04023-900.

Link to the study registry: https://ensaiosclinicos.gov.br/observador/submissao/sumario/10097

https://doi.org/10.1016/j.bjane.2023.09.002

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Table 1 Comparation between groups.

Variables	Group PH	Group H	*p*-value
Participant data – median (range)			
Duration of pain (years)	5 (3–7)	5 (2–8)	0.763[a]
Weight (kg)	73 (55–104)	73 (48–124)	0.276[a]
Height (cm)	1.6 (1.5–1.7)	1.6 (1.5–1.7)	0.245[a']
Number of joints	5.5 (2–12)	7 (2–14)	0.211[a]
Edema, n (%)	11 (68.8)	14 (77.8)	0.703[b]
Pain intensity at rest by numerical scale – median (range)			
T0	8 (4–10)	8 (7–10)	0.281[a]
2 weeks	5 (1–8)	6.5 (0–9)	0.515[a]
4 weeks	2 (0–7)	5 (0–9)	0.378[a]
8 weeks	0 (0–6)	0.5 (0–8)	0.101[a]
12 weeks	0 (0–8)	0 (0–9)	0.477[a]
Number of individuals who used supplemental analgesics – number (%)			
Dipyrone			
2 weeks	7 (38.9)	6 (37.5)	0.934[b]
4 weeks	9 (50.0)	7 (43.8)	0.716[b]
8 weeks	6 (33.3)	7 (43.8)	0.533[b]
12 weeks	4 (22.2)	6 (37.5)	0.329[b]
Tramadol			
2 weeks	6 (33.3)	8 (50.0)	0.324[b]
4 weeks	5 (27.8)	6 (37.5)	0.545[b]
8 weeks	7 (38.9)	7 (43.8)	0.774[b]
12 weeks	5 (27.8)	4 (25.0)	0.855[b]
Quality of life – median (range)			
Overall			
T0	62.5 (12.5–87.5)	46.9 (25.0–100.0)	0.175[a]
12 weeks	71.9 (25.0–100.0)	62.5 (25.0–100.0)	0.151[a]
Number of individuals who had adverse effects – number (%)			
Dizziness	5 (27.8)	2 (12.5)	0.405[b]
Drowsiness	3 (16.7)	4 (25.0)	0.681[b]
Abdominal pain	2 (11.1)	0 (0.0)	0.487[b]
Nausea	0 (0.0)	2 (12.5)	0.214[b]
Diarrhea	1 (5.6)	1 (6.3)	1.000[b]

[a] Mann-Whitney test.
[b] Fisher exact test.
Group PH, Pregabalin + hydroxychloroquine; Group H, Placebo + hydroxychloroquine; Quality of life, Evaluated by the WHOQOL-100 Questionnaire; NC, Not Calculated.

approaches, rendering pregabalin unnecessary. Moreover, the addition of pregabalin did not result in a heightened occurrence of adverse events. Concerning the dose of pregabalin, variability exists, with therapeutic utilization ranging from 25 to 600 mg/day, thus aligning with the dose implemented in this study. Future research should consider evaluating patients pre-screened for neuropathic pain to elucidate any potential role for pregabalin in managing chikungunya-related arthralgia.

In conclusion, the combination of 75 mg twice-daily pregabalin and 400 mg/day hydroxychloroquine over a 3-month period did not enhance pain control, quality of life, or decrease the need for supplementary analgesics in individuals with chronic chikungunya-related arthralgia.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval statement

Institutional Research Ethics Committee (CAAE 34247020.6.0000.5505) and registered in the Brazilian Registry of Clinical Trials (REBEC RBR-6mkndk). All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent statement

Informed consent was obtained from all individual participants included in the study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2023.09.002.

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LETTER TO THE EDITOR

How would a completely homogeneous malignant hyperthermia susceptible sample be?

Dear Editor,

We read with interest the letter to the editor by Finsterer et al.[1] We appreciated the interest in our article[2] and the comments, which gave us the opportunity to include additional data from our research and deepen the discussion on how would a completely homogeneous malignant hyperthermia (MH) susceptible sample be.

First, specifically regarding the additional data of our sample, all patients selected for MH investigation in our service are initially submitted to clinical investigation, with detailed standardized general clinical history and specific questionnaire for anesthetic MH.[3] A complete general physical and neurological examination is then performed. Next, an extensive laboratory evaluation is ordered, with an electrocardiogram, chest X-Ray, complete blood count, and serum biochemistry including electrolytes, kidney and liver function, and research for endocrine diseases. This evaluation allowed, as already stated in our article,[2] to "exclude patients with other chronic morbidities and/or neurological disorders, or those under chronic use of medications". The MH non-susceptible (MHN) patients underwent the In Vitro Contracture Test (IVCT) because they were relatives of malignant hyperthermia susceptible (MHS) patients. Regarding group sizes, the sample size calculation has been already detailed in the article.

All patients filled out the forms in person, by themselves, in the presence of the researchers. The scales (fatigue severity scale, Baecke habitual physical exercise scale) and the Beck depression inventory are based on self-assessment and widely employed for clinical studies in many diseases, such as the neuromuscular disorders.[4] The clinical studies of our group are preliminary and are being followed by additional available studies with objective methods such as cycle ergometry, where the physical activity and environmental conditions can be fully controlled. The great advantage of scales over the objective methods is their accessibility and low cost for fast detection by the health professional in the clinical setting.

The molecular study already disclosed ryanodine receptor type 1 (*RYR1*) gene variants related to 18 of the 22 MHS individuals included in our article;[2] four are still under study. The contracture test is still a gold standard for MH, due to the genetic heterogeneity of MH.[5] The finding of a variant in genes related to MH, such as the *RYR1* gene, is usually not diagnostic until its validation is performed by means of strict criteria that consider associated data on positive contracture tests and calcium release studies, showing channel gain-of-function (i.e., increased calcium release).[5-7] Moreover, there are hundreds of variants reported in the principal gene related to MH, the *RYR1* (https://databases.lovd.nl/shared/genes/RYR1). That is the reason why only 66 *RYR1* gene variants are accepted as pathogenic by the European Malignant Hyperthermia Group (https://www.emhg.org/diagnostic-mutations) and there is a variant curation expert panel specifically working on MH variants.[7] Due to the rarity of the MH crisis and to the genetic variability of MH, with a candidate gene still absent in many families, a significant and completely homogenous MHS sample with the same causal variant in the same gene would be a challenging task. Alternatively, in the current state of knowledge, a significant sample with the commonest characteristic of channel gain-of-function would be more feasible.

With the exception of metabolic diseases such as glycogen and lipid storage diseases,[8] there are no extensive clinical studies dealing with the possible effects of diet on clinical complaints like fatigue in neuromuscular disorders in general and MH in particular. This possibility could be a theme of future research in the field. About the relationship between fatigue and exercise intolerance, our article[2] does not imply that fatigue and effort intolerance are equal, but rather that, when fatigue and effort intolerance are found in the same patient, they can arrive from the same disease, thus being, as suggested by Grassi et al., 2015, "two sides of the same coin".[9]

Finally, we would like to comment on why MH susceptibility is generally considered an autosomal dominant disorder[5-7] and core myopathy autosomal dominant or recessive,[10] despite both being associated with *RYR1* gene variants in many families. Patients with core myopathy can harbor one variant in the *RYR1* gene (heterozygous), two identical variants in the *RYR1* gene (homozygous), or two different variants in the *RYR1* gene (compound heterozygous).[11] If any of

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these variants are associated with gain-of-function and increased calcium release, their relatives with even only one of these variants, despite not presenting core myopathy, are at risk of MH crisis if exposed to halogenated anesthetics and/or succinylcholine. The STAC3 gene was associated with a recessive clinical myopathy and episodes of MH, but results of IVCT in heterozygous relatives with the described variants remain to be published.

Conflicts of interest

The authors declare no conflicts of interest.

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