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Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Substance use disorder (SUD) among anesthesiologists



During the past decades, organizations that regulate training and practice in anesthesiology worldwide have approached a series of risks associated with occupational activity. The guidelines issued by these organizations are universally acknowledged for making anesthesia safer for patients, and for anesthesiologists.

The literature however has shown epidemiological data that reaffirm previous information published that substance dependence and suicide among anesthesiologists are problems widely not solved. Thus, the currently defined substance use disorder (SUD), which includes opioid abuse, is prevalent among anesthesiologists within the general medical category. The data has been revealed by epidemiological research published by authors associated with the American Society of Anesthesiologists (ASA), among other institutions.

The time has come for all of us to play a leadership role in medical occupation well-being issues, by objectively and actively defining concrete actions to correct the causes of substance abuse, proposing support to those affected by substance abuse disorder. A poignant question emerges: if not now, when?

The use of substances that modify consciousness has pervaded the evolution of mankind.[1] It has always been so, and so will probably continue. A contemporary example is the ''recreational opioid use crisis'' that is occurring in several regions in the world, particularly in the US, and that has not reached Brazil yet.[2,3]

In the opioid use crisis, besides illicit substances for recreational purposes, many medically prescribed opioid analgesics have been used in the SUD scenario.[3] However, other legal substances, such as tobacco and alcohol, in addition to benzodiazepines, also are among the substances playing a significant role in SUD, including in Brazil.

SUD is characterized by the occurrence of negative consequences related to substance use, such as consequences to user's health and social life, and to economic problems. Frequently, individuals with SUD are also involved in criminal activities.

If the general population is exposed to the risks represented by SUD, physicians and other health professionals are particularly susceptible to SUD. In this case, not only the health of professionals is at risk, but also their reputation and, potentially, the safety of the patients under their care,[4] given that anesthesiologists with SUD expose patients to the risk of dying.[5]

Although SUD rates among health professionals have not been totally elucidated, they may be similar to those in the general population, but recently have grown.[5] Unlike the general population, health professionals handle medications, such as benzodiazepines and opioids, more frequently,[4,6] and easier access to these drugs can play an important role in this specific feature.

Anesthesiologists are considered health professionals at a high risk of developing SUD, and the estimated occurrence rate is 1.6%, excluding alcohol dependence.[4] Just as in the general population, men are more affected, as are individuals with other psychiatric comorbidities.[5,7] According to Sousa et al in an innovative Brazilian study published in the present edition of BJAN, 23% of anesthesiologists included in the sample admitted having used psychoactive substances at some point in time, a much higher percentage than the one found in the US. Surprisingly, in the Brazilian study, 82% of anesthesiologists knew a colleague that already abused of a psychoactive substance.[8]

Among the substances used by Brazilian anesthesiologists with SUD, alcohol excluded, opioids stand out, and are used by 67% of professionals.[8] In the US, opioids are also the most used recreational substances among anesthesiologists, although 26% of professionals abuse of more than one substance concomitantly. The most frequent opioids among US anesthesiologists are injectables, chiefly fentanyl and sufentanil.[4]

In the overall Brazilian population, the age-adjusted estimated prevalence of individuals with opioid use disorder is 30 to 40 cases per 100 thousand inhabitants – rather lower than the US prevalence, which is 1,050 to 1,300 cases per

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100 thousand inhabitants.[9] The mortality rate by various causes among recreational opioid users is extremely high. The occurrence of overdose in this population is estimated at 19.8%.[10]

The mortality rate of Brazilian anesthesiologists with SUD is not known, but in the United States, a study found a mortality rate of 19% among 601 anesthesiologists who developed SUD between 1977 and 2013.[4]

The present BJAN issue has another interesting Brazilian study on the subject. Authored by Serebrenic et al, the article is a case series describing deaths of Brazilian anesthesiologists in which a ''psychological autopsy'' was performed.[11] The study, in addition to Sousa et al, sheds some light on this scarcely understood and investigated conundrum in Brazil, and in other countries.

Some intriguing data were revealed by the study of Serebrenic et al. Of the 18 cases identified of Brazilian anesthesiologists who died from intentional or accidental drug overdose, most were men. In the study only eight cases included an in-depth analysis, and for four of them, opioid was implicated in death. Among the included deaths the most frequent personality trait was introspection, and these individuals usually performed their professional activities satisfactorily. Some of them, however, stayed longer periods at the workplace and neglected some of their tasks.[11]

As little is known about SUD among anesthesiologists, developing preventive and therapeutic measures for these professionals is challenging. However, substance abuse, stress in the workplace, burnout, depression and anxiety are known to be closely related to the occurrence of medical errors, with potential risks to patients.[5]

We should all be aware of the problem, which is close to every one of us. By being pro-active in the identification of colleagues with SUD, showing empathy and fighting prejudice, we avoid losing lives of colleagues. Individuals with SUD are ill and deserve adequate treatment, and in the same way that we do not abandon our anesthetized patients, we should never turn our back on our colleagues.

Conflicts of interest

GAMB is a researcher and lecturer for Laboratorio Cristalia. GFDN declares no conflicts of interest.

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CLINICAL RESEARCH

Postmortem qualitative analysis of psychological, occupational, and environmental factors associated with lethal anesthetic and/or opioid abuse among anesthesiologists: case series

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KEYWORDS
Anesthetics;
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Abstract

Background: Anesthetic and/or opioid abuse is more prevalent among anesthesiologists than in other medical specialties and it has been associated with high mortality. The aim of this study was to evaluate factors associated with lethal anesthetic and/or opioid abuse among anesthesiologists.

Methods: We evaluated psychological factors, and occupational history and circumstances of death of anesthesiologists who died from anesthetic abuse. Data were obtained *post-mortem* from colleagues, and relatives. After finding eligible cases, we identified the *key informants*, who were interviewed personally or via email, through the qualitative method known as ''Psychological Autopsy''.

Results: Eighteen cases of death were identified, but we were able to interview 44% of them (n = 8), most of whom were young males. They died at home or at the hospital and were found ''at the scene''. Being an introspective person who did not share personal issues at workplace was the most prevalent personal characteristic. At work, they seemed to perform very well their functions, but some presented subtle changes such as to staying more than usual at the workplace and/or neglecting some of their responsibilities. The main reported factors to explain their substance abuse were emotional problems including psychiatric, excessive hours of work, and other health factors.

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Conclusion: This study identified that emotional disturbances, compulsive work, and general health problems were the more prominent factors involved with those deaths. Further, larger studies are needed to better understand how these factors could be early identified in order to timely prevent anesthetic and/or opioid abuse and several deaths among anesthesiologists.
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Introduction

In the United States of America (USA), at the moment, death from drug overdose, fentanyl in particular, overcomes other causes of death, such as gun homicides or car crashes.[1] Physicians are at high risk for abuse of prescription drugs.[2] Among them, anesthesiologists have 2.79 more chances to die from substance-related causes (RR 2.79, 95% CI 1.87–4.15) compared to other specialties.[3] The first five years after graduation is the period of highest risk for death and suicide related to substance use.[4] The rigorous training, personal sacrifice, easy access to prescribed drugs, and high expectations that physicians experience during and after training put them at increased risk to develop a substance use disorder (SUD). Another explanation for this fact is that young medical students are highly exposed to use more potent anesthetics during residency.[4] Substance abuse, work-related stress, burnout, depression, and anxiety are intertwined and tend to lead to medical errors and patient harm.[2] For these reasons, anesthesiology could be considered a high-risk career, especially when compared to other dangerous professional careers such as freight trucking (29/100,000).[5–7]

The most common substances used by resident anesthesiologists are alcohol, cannabis, cocaine, anesthetics, and opioids.[8] A recent study about emerging worldwide trends in substances diverted for personal non-medical use by anesthetists showed that whilst the use of alcohol and opioid medications remains the most likely reason an anesthetist with SUD would be referred to a facility for treatment, there are emerging trends also involving the use of non-opioid anesthetic agents, particularly propofol.[9]

Self-medication for anxiety and depression is mentioned by up to 65.1% of the subjects, suggesting that drug use could be a kind of ''psychological relief'' associated with heavy workload. Fentanyl, in particular, is used by 1.6% resident anesthesiologists[10] and may become more prevalent given its abuse is increasing also on the general population.[11] Substance abuse among this population could lead to very serious consequences: residents with SUD are 15 times more likely to give up studies, 10 times more likely to fail to obtain the professional Board (American Board of Anesthesiology), 7 times more likely to have adverse medical licensure actions after residency, and 7.9 times more likely to die during residency.[12] Studies have shown a high mortality rate among resident anesthesiologists who have SUD varying from 26% to 37%. When not treated during residency, SUD could result in serious future problems, as loss of medical license or restrictions from the practice of medicine.[9] For professionals with SUD, the mortality rate is also high, reaching 20%.[13] The mortality due to substance use including anesthetic abuse among anesthesiologists is high, varying from 9% to 19%.[14,15]

SUD in anesthesiologists is difficult to detect for various reasons. First, physicians are afraid to disclose their problem as it could lead to negative consequences for their job and career.[6] Second, anesthesia professionals are not well equipped to diagnose and help their colleagues.[16]

Despite the high lethality of the problem, to our knowledge, there are no previous post-mortem studies focusing on specific psychological and occupational factors associated with drug use deaths among anesthesiologists.

To understand more in depth the circumstances of death of these physicians we used a methodology called Psychological Autopsy. It is an investigative method dating back to the 1950s that aims to reconstruct data and situations of the deceased that preceded his death through the interview with people close to the victim. First used in a legal context to confirm the cause of death by the police, it was used in the 1970s and 1980s to explore factors associated with suicide.[17]

The goal of the present study was to evaluate psychological, occupational, and environmental factors associated with lethal substance and/or opioid abuse among anesthesiologists. The main reason of studying individuals who died from substance overdose is to identify predisposed factors and to better understand the circumstances of deaths, thus providing evidence-based information that may guide to early detection and other prevention programs for this serious and emerging problem in the medical practice.

Methods

This was a case series study.

Subjects

We used three main search strategies in order to find the anesthesiologists who died from anesthetic abuse: 1) official contact with 12,000 professionals registered at the Brazilian Society of Anesthesiology (SBA) via email in October 2014, and again in February 2015; 2) contact with leaders of the main anesthetic departments in universities and public hospitals, mainly in São Paulo; and 3) snowball sampling as shown in Figure 1.

During 2 years of search (2013–2015), we identified 18 cases of doctors who died from anesthetic abuse in universities and public hospitals mainly in São Paulo in the previous 15 years. From these 18 cases, 10 were males and 8 were females. We had more detailed information only from 8 cases (Table 1), mainly because we could not have access to

Table 1 Gender distribution of anesthesiologists with lethal anesthetic abuse and information about key-contacts.

nº	Case gender	Contact	Interview, when and if not, why not	How
1	Male	Spouse	we were not able to contact the informant	we could not found her contact
		Colleague	Oct/2013	Personally
		Colleague	Nov/2013	Personally
2	Male	Brother	Dec/2013	Personally
		Colleague	we were not able to contact the informant	we could not found his contact
		Colleague	we were not able to contact the informant	we could not found his contact
		Friend	we were not able to contact the informant	não sei (he did not answer our calls?)
		Friend	Feb/2014	Personally
3	Male	Father	we were not able to contact the informant	we could not found his contact
		Colleague	we were not able to contact the informant	we could not found his contact
		Colleague	we were not able to contact the informant	we could not found his contact
4	Female	Father	we were not able to contact the informant	we could not found his contact
		Colleague	Apr/2015	Personally
		Colleague	we were not able to contact the informant	she did not answer our calls
		Colleague	we were not able to contact the informant	he did not answer our calls
5	Male	Colleague	did not know doctor who died	
6	Male	Colleague	we were not able to contact the informant	we could not found his contact
7	Male	Colleague	Sept/14	Personally
8	Male	Colleague	Oct/14	Email
9	Female	Colleague	Nov/14	Email
10	Female	Husband	we were not able to contact the informant	we could not found his contact
11	Female		we were not able to contact the informant	we could not found anyone who knew her
12	Female	Colleague	we were not able to contact the informant	we could not found his contact
13	Male	Cousin	we were not able to contact the informant	he did not answer our calls
14	Female	Mother	we were not able to contact the informant	she did not answer our calls
15	Male	Daughter	we exchanged mail but did not return call	
16	Male	Colleague	we were not able to contact the informant	he did not answer our calls
17	Female	Colleague	Out/14	Email
18	Female	Colleague/friend	Fev/15	Email

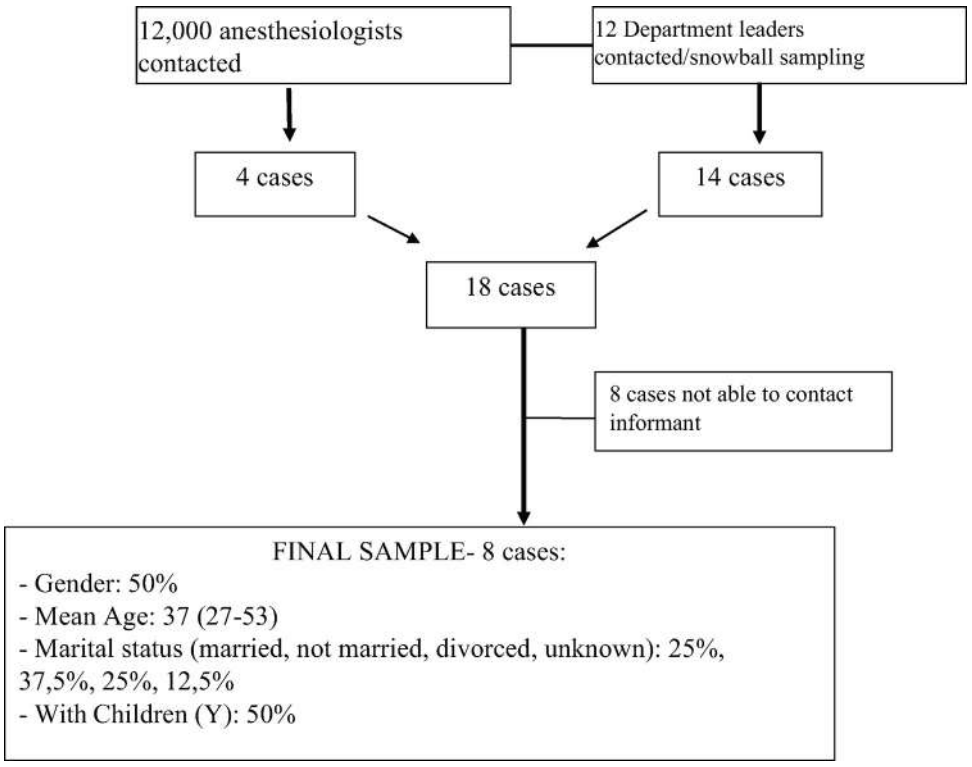

Figure 1 Flowchart showing our search strategies to find the cases and sociodemographic information of anesthesiologists who died from anesthetic abuse.

the other case informants. Half of the sample of the physicians who died were male. The age ranged from 27 to 53 years, being 62.5% (n = 5) aged below 30 years and 33% (n = 3) between 45 and 53 years of age. Although the email from SBA was sent to professionals from all over the country, all the cases were from São Paulo State.

Table 1 presents basic information about how, when, and why we were not able to contact half of the sample, including the details about the 18 initial cases. Although we received a list of possible cases from the leader of the anesthesiology services, and we tried to contact all of them, only 8 were included. The first informant was asked to indicate our key informant, who could be either a relative or an ex-colleague close to the anesthesiologist who died from anesthetic abuse. Of the 10 people interviewed, only one was from the family of the professional who died. The others were close work colleagues who had limited knowledge of the person in question. A close relationship with the professional who died was considered an objective criterion to find key informants who could effectively provide more reliable information for the purpose of this study.

After identifying the eligible cases, an initial contact was made by telephone with the key informants. The key informant was invited to participate after all explanations about the aim of the study. Those who agreed to participate in the study protocol were invited to provide the necessary information. Two interview methods were offered: by email or in person. At the time of the interview, the purpose of the study was explained again and the Informed Consent Form ensuring the confidentiality of the information provided was signed. In the case of an internet interview, the consent form was sent by mail. We interviewed 10 people, of whom 60% (n = 6) were in person. The others answered by email. Of the 10 people interviewed, 4 were through the emails sent via SBA, from where we received 5 email replies, but only 3 people answered the questionnaire (one person answered about 2 different cases). We identified a case in which the family refused to participate, and 2 close colleagues did not want to get involved with. We ended up including this case after another colleague provided adequate information about it.

Interviews

The method used in this study was the Psychological Autopsy mentioned above, which is basically characterized by an interview that sought the detailed and descriptive report of the circumstances of the death.

This method was implemented in our study to understand more in depth the circumstances of death of the physicians. In this regard, occupational and psychological factors of the subject and the characteristics of his/her substance and/or opioid abuse were important topics of the interview.

Data analysis

Data were analyzed according to a quantitative and qualitative method called Discourse of the Collective Subject (DCS), that allows to investigate the meaning of collective opinions. DCS-based research is characterized by individual interviews using basically open questions to stimulate a discursive behavior that allows the idea to be expressed and qualitatively preserved. DCS is a complex process, subdivided

into several moments, carried out through a series of operations based on the verbal material collected. In order to identify the DCSs, four operators/operations are required, which are: a) *Key Expressions* (Ech): selected excerpts from the verbal material of each testimonial that best describe its content; b) *Central Ideas* (Ics): synthetic formulas that describe the meaning(s) presented in the verbal material, and also in the sets of responses of different individuals, which has similar or complementary meaning; c) *Anchors* (Acs): synthetic formulas that no longer describe the senses, but the ideologies, values, beliefs usually presented in the verbal material of individual responses or grouped in the form of generic statements intended to describe particular situations; d) Discourses of the Collective Subject (DCSs) *per se*. The DCS method considered that there are anchorages only when explicit discursive marks of these generic statements are presented in the verbal material.

The Discourses of Collective Subjects are the Key Expressions present in the statements, which have Central Ideas and/or Anchorages of similar or complementary meaning.[18] These Key Expressions of similar meaning form collective statements written in the first person singular, with the primary purpose of expressively marking the presence of collective thinking in the person of a Subject and a Collective Discourse. It is as if everyone spoke as they were (or by means of) one. A typical DCS survey is an opinion poll on a given topic, divided into a few open questions, aimed at being answered by a given population sample. Each of these answers generates a varied number of different placements, i.e., from different DCSs. These DCSs are qualitatively different in that they convey different opinions and positions, and from a quantitative point of view, since each of them is the result of the contribution of a certain number of interviews or testimonies of individuals. In addition, using the software Qualiquantisoft,[19] the results can be quantified by working with well-selected large samples of individuals and, to the register embedded in the program, segment results by the registration variables.

Based on this methodology, after collecting information through the Psychological Autopsy, we organized the material in a way to evaluated responses to 2 questions: 1) ''how was his/her personality?'' 2) ''how was the doctor professionally?''

Ethical procedures

This study was conducted at the Hospital das Clinicas, in São Paulo, and was approved by the Ethical Committee of the Institution.

Results

From the 8 detailed cases, 50% were male, mostly married, with a mean age of 37 (27–53) and 50% had children, as shown in Figure 1.

Table 2 summarizes the information about psychological factors, occupational characteristics, the circumstances of death, and possible factors associated with substance abuse and death. The main substance(s) involved in the episode of lethal use was also registered. In most cases, anesthetic opioid was cited. Alcohol was cited in only one episode. In only one case there was evidence of an addiction. Among others, it seems that the substance was used as an attempt to ''alleviate'' psychological negative emotions, and in a few cases, we found clues to interpret the anesthetic and/or opioid abuse as a suicide rather than an accidental overdose. The death occurred at home or at workplace in the same proportion (50%).

Regarding to the DCS, for the first question regarding personality, the following categories were observed: A) Intelligent and a little impulsive (one answer); B) Pleasant, sociable, vain, handsome, outgoing (3 answers); C) Strong personality, arrogant (2 answers); D) Introspective and arrogant, frank, polite and reserved (2 answers); and E) Agitated and full-mouthed (one answer). For the second question regarding the doctor professionally, we observed the following categories: F) Available (one answer); G) Average (one answer); H) Excellent (2 answers); I) Competent but negligent (2 answers); J) Irresponsible (one answer); K) Competent but arrogant (one answer). In terms of circumstances of death, half of the sample died at the hospital during worktime and half at home. All of them were found alone, mainly in the bathroom and sometimes after the lethal circumstance itself. In most cases, substances involved were anesthetics (meperidine, propofol and sevoflurane) (n = 4), fentanyl (n = 3), midazolam (n = 1), and alcohol (n = 1). Main factors possibly involved in death vary: personality traits such as impulsivity, depression, and difficulties in controlling drug use; relationship problems; and severe clinical illness.

In terms of personality and psychological factors, some of them were described as having personality problems and narcissist/arrogant tendencies, while others were evaluated as more introspective/reserved as well as pleasant, sociable, or even ''outgoing''. At work, they were generally considered excellent and competent while performing their jobs, but closer to the fatal incident, it was reported that some of them started to stay excessively at work and/or became negligent with their responsibilities.

Discussion

This small qualitative study allowed us to observe similar characteristics in this case series analyzed through the Psychological Autopsy.

Being an introspective person who did not share personal issues at workplace was the most prevalent psychological characteristic found among anesthesiologists who accidentally died from substance overdose. At work, most professionals used to perform well their jobs, but right before the lethal incident they started staying excessively at workplace and/or working a lot, but also neglecting their responsibilities. In general, they were found dead alone in the bathroom, at work (hospital), or at home. The main reported reasons to use substances were excess of work, emotional problems, divorce/separation, depression, physical illness, and impulsivity. The reasons regarding professional stress go along with other studies that report work pressure leading to anesthetic abuse[2,4,20] as well as a comorbid psychiatric history. However, other situations described in the present study such as divorce or personality characteristics are not reported elsewhere as risk factors.

Table 2 Personal and professional characteristics of anesthesiologists who died from anesthetic abuse: circumstances of death, substance use and possible other factors involved.

Case	Personality characteristics	How was at work?	Circumstances of death	Substances involved	Main factors possibly involved in death
1[a]	Intelligent and a little impulsive (A) Pleasant, sociable, vain, handsome, outgoing (B)	Available (F)	At the hospital. At the comfort room, in the following day, in the bathroom, 'the door had to be broken and found him dead there, already in deadly rigidity. They found a bulb of dolantine and another of dormonid on the floor. He was tied with a sock on his arm and a syringe injected into his arm, with a needle in his arm.'	Meperidine and midazolam	Impulsivity, relationship issues (being married and maybe liking another man) Stress, doing a lot at the same time, financial problem
2	B	Average (G)	At the hospital	Sevoflurane	A chronic problem with former husband, and a tendency to seek relief from the use of prescribed drugs
3	Strong personality, arrogant (C)	Excellent (H)	At the hospital. Was on duty at the hospital, she left a suicide letter, she made some noise after injecting the drugs, which caught the attention of the staff of the surgical center, she was locked in the duty room, the door was broken open and she was already in a cardiorespiratory arrest, resuscitation was attempted without success	Midazolam, Fentanyl and propofol	Depression that generated opioid dependence, from which she could not get rid of
4	Introspective and arrogant, frank, polite and reserved (D)	Competent but negligent (I)	At home	Fentanyl	He had a severe clinical illness and must have gotten depressed. Because of the illness, he started using the opioids. Too much medication. Doubt about if he had missed the dose of what he was using or had done on purpose.

Table 2 (*Continued*)

Case	Personality characteristics	How was at work?	Circumstances of death	Substances involved	Main factors possibly involved in death
5	B	Irresponsible (J)	At home, found dead with syringe connected to the arm, containing white liquid	Propofol	'Do not believe he committed suicide, think he thought he had control of the situation.' If it was really propofol, think he challenged the danger too much. Always gave a lot of 'duties', maybe he really suffered from severe insomnia.
6	D	I	At home, found by her son on the bathroom in the morning.	Probably Alcohol	Depression, fatality
7	C	H, Competent but arrogant (K)	At home. Alone and did not answer the phone, the bride went home and found him lying on the floor, with a syringe on his side and a glass that seems to be used to applied some substance. It is possible that he had aspirated, that he had a respiratory depression due to the use of the substance, there probably had a respiratory depression, aspired and died. 'He lost his hand, it was not suicide.'	Fentanyl	'Confused relationship with drugs. He used alcohol in a deleterious way and this may have been transfered to another deleterious drug.. . Being an anesthetist so you have access to the drugs, and the fact that he knew what they were used for, facilitate the use.' 'Very ambitious personality, he would never settle down.'
8[b]	Agitated and full-mouthed (E)	No answer (L)	Hospital, was working and was found dead in the duty room.	Not known	Not known

Notes:
[a] Informants: 2 colleagues.
[b] Informants: 1 colleague and 1 family member; the other had one informant (a colleague).

In general, the demographic and behavioral characteristics seemed somewhat diverse, which made impossible to define a unique type of personality among them. Considering the obvious impossibility of having performed a previous semi-structured clinical interview with the subjects who died, we could not classify them in terms of use or abuse diagnosis.

Our results reinforce that psychological and occupational particularities among anesthesiologists in terms of professional daily activities (such as easy access to medication, a lonely and stressful medical activity, and the long working hours) and environmental factors (such as a recent divorce, among others) might have contributed to the abuse of substances and death. Also, details regarding the circumstances of their deaths and psychological characteristics could suggest a possible concomitant psychiatric illness.[21,22] In this regard, the ''self-medication'' hypothesis seems to be a relevant risk factor for substance experimentation and chronic use[23] precisely because of the easy access to large quantities of strongly addictive substances, becoming easier to deviate small quantities of this substance for personal use.[4,15,24,25] The intense professional life with long work hours might lead to chronic emotional stress, and the abuse of those substances could be interpreted as tentative to ''relief'' such psychological burden, leading inadvertently to death.

However, few anesthesiologists have been referred to treatment: Wilson et al.[26] reported that in the USA, 31 of 106 interviewed doctors (29%) were considered addicted, with only 48% of them being referred to rehabilitation. In our sample, none of them was receiving psychological or psychiatric treatment in the period when the lethal use occurred. The physicians' elevated social status brings many rewards, but it may also include an isolating effect when they become addicted, which include a devastating social stigma. The consequence is probably a significant delay in the recognition of their substance abuse as a relevant problem, and consequently another delay in the process of beginning an intervention to prevent substance abuse, thus culminating in a more elevated risk of death by inadvertent overdose or suicide.[27] Additionally, many health professionals sometimes do not have appropriate knowledge about how to deal with this complex problem,[5] leading to what has been called ''conspiracy of silence'' involving families, colleagues and the affected doctors as well.[6] When the substance user is a senior professional, the others tend to fear being punished to bring up the subject. Delay in the diagnosis process includes concern of disclosing an addictive illness and losing not only prestige but also the license to practice medicine and thus livelihood. Families recognize the problem, but also fear talking about it at workplace and must deal with financial and occupational consequences. The false belief that addiction is a personal choice and not a brain disease also significantly limits the medical attention to that matter. Although the literature shows an association between anesthetic/opioid use and suicide among doctors,[4] and that prevalence of suicide ideation among medicine students is high,[20,28,29] it is unclear whether the deaths we searched, in this particular study, were suicides or not. Further studies are needed to disentangle the real motive in other particular lethal cases.

More recently, it has been discussed the importance of early detection of afflicted colleagues since the beginning of their training program and the discussion of the issue in medical school.[16]

We consider that the qualitative methodology was consistent in terms of providing a set of possible explanations to a better understanding of the circumstances and personal/professional factors that lead those individuals to die from non-prescribed anesthetic and/or opioid abuse. This was possible through the application of an in-depth qualitative method of analysis, based on a psychological autopsy as a method of data collection, both original in this kind of investigation. At the best of our knowledge, this is possibly the first *post-mortem* qualitative study to show evidence of a set of particular characteristics in terms of psychological issues, occupational factors, circumstances of death, and characteristics of anesthetic and/or opioid abuse among this specific and vulnerable population, derived from reports provided by colleagues and other closer friends, and relatives.

This study has some limitations. First, the retrospective design of this investigation, based on people's memories of a past time could be a limiting factor. Second, in spite of the effort to search for lethal cases (death registration system and search for well-known people, mainly colleagues through snowball sampling, contact with anesthesia service chiefs in our context and mailing – from the local anesthesiology society), there was a great difficulty to identify eligible cases. Moreover, it was not easy to contact the key informants. When available, they had little information due to the socially restricted behavior that we found among the sample. Also, most of the families were not available. After some attempts to contact them, in some cases we gave up after perceiving that it would be extremely sensitive for them to talk about their relative's death. There was only one familiar more available to talk about the subject, perhaps because of his professional background in Psychiatry. Also, it was difficult to find more than one person to talk about the same doctor who died. It seems that they felt very uncomfortable when talking about the person, not wanting to ''commit'' themselves. ''Substance abuse and overdose'' are delicate topics and it seems that people tend to talk only good things about those who are dead, particularly the family of the deceased, in a way to ''preserve their souls''. In general, doctors do not feel comfortable to intervene in what they call ''personal life'' of their colleagues. In the USA, residency program directors did not consistently report SUD to the American Board of Anesthesiology.[8]

This is an exploratory study that, in our opinion, offers precious and original material for designing some initial preventive strategies and should be replicated in a larger scale. First of all, it is clear the need to think about preventive strategies to minimize the significant negative consequences of the illicit anesthetic and/or opioid use, and to avoid a very frustrating/traumatizing end such as an overdose. Knowing better the profile of more ''at risk'' anesthesiologists would facilitate an early detection of more vulnerable individuals in order to approach the physician. Some other possible interventions might help dealing with this problem: 1) basic preventive efforts could focus on providing information about the substances and their effects through psychoeducation; 2) demystifying the topic for users and for colleagues (chiefs and professionals) who could refer them for a proper diagnosis; 3) implementing a systematic

control of substances used in surgical procedures or under sedation or anesthetic diagnosis; and 4) urine and hair analyses that could be systematically implemented for a more precise control, as well as investing in the mental and physical health of professionals who care for people seems to be crucial. It is also relevant to promote an open field for discussion/reflection among professionals about this subject and maximize the support network for health professionals.

In sum, our investigation identified some specific characteristics of this sample, but more studies are needed and strongly encouraged in this area to better understand the factors associated to the abuse of anesthetics among the medical professionals, as well as how preventive strategies may contribute to a more stable and healthy professional life for anesthesiologists.

Conclusion

Our results suggest that a particular anesthetic occupational routine (such as easy access to medication, a lonely and stressful medical activity, and the long working hours), recent emotional problems (i.e., divorce), impulsive personality, and being introspective were relevant factors that might have contributed to the abuse of substances/opioids and consequent overdose/death among anesthesiologists. Possible concomitant psychiatric illness and ''self-medication'' also seem to be significant risk factors for substance abuse and overdose. Larger studies are needed to better understand how these factors could be identified early in order to timely prevent anesthetic and/or opioid abuse and several deaths among anesthesiologists.

Conflicts of interest

The authors declare no conflicts of interest.

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CLINICAL RESEARCH

Drug abuse amongst anesthetists in Brazil: a national survey

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Abstract
Background: The prevalence of Substance Use Disorders (SUD) and acceptance of drug testing among anesthetists in Brazil has not been determined.
Methods: An internet-based survey was performed to investigate the prevalence of SUD among anesthetists in Brazil, to explore the attitudes of anesthetists regarding whether SUD jeopardizes the health of an impaired provider or their patient, and to determine the provider's perspective regarding acceptance and effectiveness of drug testing to reduce SUD. The questionnaire was distributed via social media. REDCap was utilized to capture data. A sample size of 350 to achieve a confidence level of 95% and confidence interval of 5 was estimated. Study report was based on STROBE and CHERRIES statements.
Results: The survey was returned from 1,295 individuals. Most individuals knew an anesthesia provider with a SUD (82.07%), while 23% admitted personal use. The most common identified substances of abuse were opioids (67.05%). Very few respondents worked in a setting that performs drug testing (n = 17, 1.33%). Most individuals believed that drug testing could improve personal safety (82.83%) or the safety of patients (85.41%). Individuals with a personal history of SUD were less likely to believe in the effectiveness of drug testing to reduce one's own risk (74.92% vs. 85.18%, $p < 0.0001$) or improve the safety of patients (76.27% vs. 88.13%, $p < 0.001$).
Conclusions: SUDs are common among anesthetists in Brazil. Drug testing would be accepted as a viable means to reduce the incidence although a larger study should be performed to investigate the logistical feasibility.
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Introduction

Substance Use Disorders (SUD) are a family of diseases that are pandemic throughout society. Healthcare personnel are not immune to these conditions or their impact which commonly includes death.[1] Anesthesiologists are not spared from this illness and may be at higher risk for addiction and substance associated death.[2–4]

This problem extends across countries and anesthesiologists in Brazil are vulnerable.[5–7] Although anesthesiologists only comprise 3% to 5% of the physicians in Brazil, they make up a far higher percentage in recovery programs, similar to the United States.[8–10] Recent data in the United States has demonstrated that this problem may be increasing among trainees in anesthesiology.[2] Education and substance control measures have been the mainstay of preventative efforts, although they have been largely ineffective.[4] Several institutions in the United States have implemented random drug testing in an effort to reduce this problem.[11–13] Results have indicated success.[14]

This survey is aimed to determine the perception of anesthesiologists and anesthesiology residents in Brazil about the prevalence of SUDs, the perceived impact on provider and patient safety, and their attitude towards the use of drug testing to reduce SUD among healthcare providers in anesthesia.

Methods

Ethical approval for this study was provided by the Institutional Review Board of Hospital Sírio-Libanês, in São Paulo, Brazil (CAAE 226224319.0.0000.5461. IBR Chairperson: Dr. Bernardo Garicochea. Date of approval: November 27th, 2019). Study protocol and questionnaire development started mid-2019, guided by the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) for cross-sectional studies and the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guidelines.[15,16] Twenty people from different healthcare areas participated in the survey questionnaire validation process.[17] An English version of the questionnaire was prepared, validated, and transcultural checked to be analyzed by a North American contributor (MGF), an expert on the topic. His comments were incorporated, translated to Brazilian Portuguese, re-validated, and re-checked for transcultural differences.

To build the Electronic Questionnaire (eQ), and to collect and manage data, REDCap, a secure, web-based software platform designed to support data capture for research studies was used.[18] Conditional branching was utilized to make the eQ more intuitive. In questions where drug classes were alternatives (e.g., prescribed stimulants), examples were provided (e.g., methylphenidate). After eQ development, its usability and technical functionality were tested by asking a few anesthetists to use it (their answers were not inputted). Comments were incorporated, and a final version was piloted by the eQ team, after inspection from a third-part reviewer, not a member of the research team.

Social media was used for eQ publishing. Thus, snowball sampling technique was utilized. The eQ link was primarily distributed using instant messages, mobile apps, and through social media channels, including WhatsApp, Telegram, Facebook, and Instagram. The survey link was also emailed to national experts in anesthesia research, and they were asked to share it with their anesthesia groups. There were two main distribution moments, sent on day 1 and on day 10. The eQ was opened for participation from January 16, 2020 to January 30, 2020. No incentives were offered, and participation was voluntary.

Approval of the electronic informed consent was mandatory for survey participation. Neither name, email address, nor other identifying information was collected to maintain anonymity. The questionnaire contained a total of 30 objective questions, plus one last box for comments. An answer time of approximately 3 minutes was estimated. Respondents could review and change their answers before final submission.

Considering a population of approximately 25,000 anesthesiologists in Brazil,[19] confidence level of 95%, and a confidence interval of 5, a sample size of approximately 350 interviewees was estimated. Any anesthesiologist or anesthesiologist's resident living in Brazil were eligible to answer the questionnaire.

Statistics

Categorical data were considered as proportions. Differences between those with and without a personal history of substance use were assessed with a Chi-Square test. In the event of small cell counts, Fisher's Exact Test was employed. For all analyses two-sided p-values < 0.05 were considered statistically significant. SAS 9.4 software (SAS Institute Inc., Cary, NC) was utilized.

Results

Demographic results are included in Table 1. The number of individuals participating in the survey was 1,295. Informed consent was accepted by 1,286 individuals, and 978 affiliated members of the Brazilian Society of Anesthesiology (SBA) completed the survey.

Respondent characteristics

Individuals indicating gender were equally split among male (642) and female (640) physicians. Nearly half of those responding were older than 40 years of age (44.6%) and in practice for more than 11 years (43.3%). Over half of those responding were from southeast Brazil (52.5%).

Knowledge of substance use among colleagues

A high number of individuals knew of at least one colleague who had abused a substance in order to change his/her mental status (n = 1053, 82.07%), and nearly half of those knew of 3–5 colleagues (n = 477, 45.34%). The most commonly identified substance was opioids (67%) followed by marijuana (52.3%). Sleep induction medications (e.g., zolpidem, antidepressants, and antipsychotics, but not propofol), when used in an abusive way, were indi-

Table 1 Respondent characteristics.

	Respondents	No personal history of substance use (n = 988)	Personal history of substance use (n = 295)	*p*-value
Affiliated member of the Brazilian Society of Anesthesiology (SBA)	978 (76.29)	769 (77.83)	209 (71.33)	0.02
Male gender	642 (50.08)	484 (49.04)	157 (53.40)	0.19
Age, years				< 0.0001
≤ 24	5 (0.39)	4 (0.41)	1 (0.34)	
25–29	152 (11.85)	99 (10.03)	53 (17.97)	
30–34	309 (24.08)	218 (22.09)	91 (30.85)	
35–39	245 (19.10)	190 (19.25)	55 (18.64)	
≥ 40	572 (44.58)	476 (48.23)	95 (32.20)	
Years practicing anesthesia after residency				< 0.0001
Current resident/trainee	184 (14.39)	124 (12.60)	60 (20.34)	
≤ 5	338 (26.43)	235 (23.88)	103 (34.92)	
6–10	203 (15.87)	163 (16.57)	40 (13.56)	
≥ 11	554 (43.32)	462 (46.95)	92 (31.19)	
Work region[a]				
South	312 (24.43)	223 (22.73)	88 (29.83)	0.01
Southeast	670 (52.47)	513 (52.29)	157 (53.22)	0.78
Midwest	83 (6.50)	61 (6.22)	22 (7.46)	0.45
Northeast	180 (14.10)	155 (15.80)	25 (8.47)	0.002
North	38 (2.98)	33 (3.36)	5 (1.69)	0.14

Data is presented as n (%).
[a] Respondents could select all that apply. Not all respondents are affiliated to SBA.

cated by 45.6%, whereas benzodiazepines were cited by 40% of responders (Table 2). Anesthetic agents (e.g., inhalational anesthetics, ketamine, and propofol) were reported by 38.3%. The majority of colleagues found to abuse substances were required to withdraw at least temporarily from professional activities (70.3%). Approximately half of those individuals either did not return to practice or returned but ultimately left practice. Nearly all individuals responding to the survey believed that SUD either jeopardized a physician's life (93.1%) or jeopardized patient care (88.2%).

Personal use of substances

Respondents were asked about their own personal use of substances. Two hundred ninety-five individuals acknowledged a personal history of SUD (23%). The most common substance of abuse was illegal recreational use of marijuana (43.2%) followed by sleep induction medications (e.g., zolpidem, antidepressants, and antipsychotics, but not propofol – 42.9%), and prescribed stimulants (e.g., methylphenidate – 36.4%). A high percentage of individuals acknowledged use of illicit substances during and after residency (41.52%) indicating that use during residency is likely to continue into independent practice (Table 3). The number of individuals that acknowledged illicit use of opioids was 4.4% (n = 13). Few individuals who acknowledged the use of substances took time away from practice (n = 8; 2.72%). Less than half of individuals that abused substances believed that they risked their own well-being (36.18%) or patient safety (23.81%) by their personal use.

Attitudes and personal experience regarding occupational drug testing

A very small percentage of anesthesiologists currently work in a practice or institution that performs drug testing (n = 17, 1.33%) but a higher percentage indicated that they had been subject to testing at some point in their career (n = 60, 4.68%). Random drug testing was acknowledged by 7 individuals. The vast majority of individuals responding to the survey indicated that they believed random drug testing could improve personal (82.83%) and patient (85.41%) safeties but individuals that admitted to the use of illicit substances were significantly less likely to believe that random drug testing could improve their own safety or that of their patients (Table 4). Acceptance of pre-placement (pre-employment), random, and reasonable suspicion (''For-cause'') drug test was endorsed by nearly 90%. A total of 244 individuals responded that they did not agree with drug testing. Cited reasons included violation of privacy (68.4%), knowledge that the presence of a substance does not mean a substance is being abused (43.4%), and the fear of false negative results (30.3%).

Discussion

The careers and lives of many anesthesiologists have been lost to SUD since the beginning of the specialty. Education and substance control have been largely ineffective and the incidence among trainees has continued to increase.[2,4]

Table 2 Substance use[a] by colleagues.

	Respondents	No personal history of substance use (n = 988)	Personal history of substance use (n = 295)	*p*-value
Known colleague substance use	1053 (82.07)	791 (80.06)	261 (88.78)	0.001
Number of colleagues known to use				< 0.0001
1–2	325 (30.89)	269 (34.05)	56 (21.46)	
3–5	477 (45.34)	357 (45.19)	119 (45.59)	
6–10	140 (13.31)	102 (12.91)	38 (14.56)	
> 10	110 (10.46)	62 (7.85)	48 (18.39)	
Substances utilized[b]				
Illicit stimulants	339 (32.38)	237 (30.19)	101 (38.70)	0.01
Prescribed stimulants	382 (36.49)	222 (28.28)	160 (61.30)	< 0.0001
Anesthetic agents	401 (38.30)	311 (39.62)	89 (34.10)	0.11
Opioids	702 (67.05)	576 (73.38)	125 (47.89)	< 0.0001
Marijuana	548 (52.34)	364 (46.37)	183 (70.11)	< 0.0001
Benzodiazepines	420 (40.11)	283 (36.05)	137 (52.49)	< 0.0001
Sleep induction/Maintenance medications	478 (45.65)	314 (40.00)	164 (62.84)	< 0.0001
Other[c]	26 (2.48)	19 (2.42)	7 (2.68)	0.81
Time when use observed				0.001
Both during and after residency	571 (54.64)	408 (52.04)	163 (62.45)	
During residency	196 (18.76)	144 (18.37)	52 (19.92)	
After residency	278 (26.60)	232 (29.59)	46 (17.62)	
Colleague withdrawn from professional activities due to substance use	737 (70.26)	595 (75.60)	142 (54.41)	< 0.0001
Colleague returned to original professional activities				0.56
Yes	282 (38.37)	234 (39.39)	48 (34.04)	
Yes, needed to withdraw later	274 (37.28)	221 (37.21)	53 (37.59)	
Did not return	92 (12.52)	71 (11.95)	21 (14.89)	
Unknown	87 (11.84)	68 (11.45)	19 (13.48)	
Respondent believed their colleague might have increased their occupational hazard	979 (93.15)	757 (95.94)	221 (84.67)	< 0.0001
Respondent believed their colleague might have jeopardized patient safety	923 (88.16)	723 (91.87)	199 (76.83)	< 0.0001

Data is presented as n (%).
[a] Note: Substance use is defined as 'ever used or uses any substance with the potential of abuse to change mental status.
[b] Respondents could select all that apply.
[c] Other included alcohol, diethylpropion, crack, ecstasy, gamma-hydroxybutyrate, lysergic acid diethylamide, methamphetamine, fentanyl, toluene inhalation, lisdexamfetamine;

Nearly 20% of anesthesiologists fortunate to survive an initial diagnosis of SUD will die of their disease during their career.[20] Our national survey of anesthesiologists and residents in Brazil revealed several key findings. The first is that most individuals practicing anesthesia or in training know of a colleague who has abused substances (82%) and that a high percentage have recreationally used a substance at least once in their career (23%). A very high percentage of individuals believe that the use of substances with the potential of addiction is a threat to personal and patient safeties although this belief is less common among those that actually abuse drugs. Drug testing is uncommon in Brazil despite the belief that it would enhance provider and patient safeties.

The incidence of SUD among anesthesiologists in Brazil is unclear. Alves' study of resident physicians in Brazil attending outpatient treatment for SUD revealed that anesthesiology and surgery were second only to internal medicine as the most involved specialties.[8] The authors also demonstrated that anesthesiologists make up a far higher incidence of addicted physicians requiring treatment (approximately 20%) when compared to the numbers of practicing physicians (3–5% of physicians). Impaired anesthesiologists in Brazil are predominantly male, in their 30s, abuse opioids, and refer for care early due to pressure from colleagues or governing bodies.[7]

Individuals that have a personal history of SUD know more impaired colleagues than those that do not abuse

Table 3 Personal substance use[a].

	Personal history of substance use (n = 295)
Personal substance use (current or history)	295 (100.00)
Substances utilized[b]	
Illicit stimulants	55 (18.7)
Prescribed stimulants	107 (36.4)
Anesthetic agents	22 (7.5)
Opioids	13 (4.4)
Marijuana	127 (43.2)
Benzodiazepines	89 (30.3)
Sleep induction/maintenance medications	126 (42.96)
Other[c]	7 (2.4)
Time when used	
Both during and after residency	120 (41.52)
During residency	74 (25.61)
After residency	95 (32.87)
Respondent took time away from their professional activities due to substance use	8 (2.72)
Returned to professional activities	
Yes	6 (75.00)
Yes, required time away	1 (12.50)
Did not return	1 (12.50)
Respondent believed they increased their occupational hazard	106 (36.18)
Respondent believed they jeopardized patient safety	70 (23.81)

Data is presented as n (%).
[a] Note: Substance use is defined as 'ever used or uses any substance with the potential of abuse to change mental status.
[b] Respondents could select all that apply.
[c] Other included mushrooms, ecstasy, lysergic acid diethylamide, marijuana, sertraline, and tramadol.

drugs (88.78% vs. 80.06%; $p = 0.001$). This may be due to social networks that contain more individuals that abuse substances. Opioids were the most commonly identified substance abused by a colleague (67.05%) reflecting prior studies in Brazil.[7] The incidence of self-reported SUD was 23% in our study with illegal recreational marijuana being the most commonly abused illicit substance. Opioid use was reported by 1% (n = 13) of those surveyed and 4.4% of individuals that did use drugs.

Over 50% of those reporting a personal history of SUD were either current resident physicians or within the first 5 years after completion of residency similar to data reported by Alexander et al.[21] This study did reveal that 31% of those with a SUD were in practice for over 11 years either indicating that anesthesiologists will develop a SUD years into practice or that many who entered recovery continued to successfully practice in the specialty. Most of the individuals known to abuse substances (70.26%) withdrew from professional practice at least temporarily. Over half of those that were discovered to have a SUD either never returned to the practice of anesthesia or returned and later withdrew. Under the best of conditions recovery rates for addicted anesthesiologists, based upon 5 years of monitoring, is slightly over 70%.[22] Recent data indicated a high projected rate (38%) of relapse within 30 years and a death rate of 19%.[20]

Most, but not all, anesthesiologists in this survey believe that SUD increases risk for both the physicians as well as the patients being treated under their care. Individuals with a personal history of SUD though were statistically less likely to acknowledge the associated risk to care providers (84.7% vs. 95.9%; $p < 0.0001$) or patients (76.8% vs. 91.9%; $p < 0.001$). This apparently indicates that some physicians that abuse substances do not believe that there is the potential for self or patient harm. Physicians often avoid reporting incompetent colleagues due to a lack of confidence in systems, fears of retribution, lack of knowledge of reporting routes, and the notion that someone else is likely addressing the problem.[23]

Physicians in this survey were questioned about their experience and attitude toward drug testing. Only 1.33% (n = 17) of surveyed individuals reported that their institution currently performs drug testing and less than half reported that random testing was a component (n = 7). A far higher number of anesthesiologists (4.68%; n = 60) had been subject to drug testing at some point during their career. This may reflect individuals that trained in international institutions that have drug testing or military facilities. Most anesthesiologists in this survey believed that random drug testing can be used to improve the safety of the individual anesthesiologist and patient, but those individuals with a history of SUD were significantly less likely to hold this view. Such individuals may believe that they can manage the condition themselves. Individuals may also believe that there are means to adulterate tests to avoid detection of a substance.

Anesthesiologists were questioned about reasons why they may disagree with drug testing and the most common notion was that testing was a violation of individual privacy and that the mere presence of a substance did not necessarily define impairment. Lemon et al. surveyed physician attitudes toward drug testing in 1992. Most physicians surveyed at the time believed that physician drug use was either a minor or non-existent problem, but the attitudes were similar to this study.[24] More than half (60%) believed that testing infringed on the physician's right to privacy but 87% would submit to testing if required by a hospital.

There are multiple weaknesses in this study. Individuals could access and open the REDCap link and answer the eQ more than once. Definitions of SUD are open to interpretation. The release of a survey via social media may attract more young physicians that are more media savvy, although almost 45% of those responding to the survey were over 45 years of age.[25] This may be due to the reluctance of early career physicians to complete the survey while more senior anesthesiologists may know of more colleagues that have suffered from SUD. The use of an electronic survey may have created some concerns regarding anonymity, although the platform used has clear-stated strict privacy rules. Finally, drug abuse-related subjects are sensitive topics, which may reflect in the fidelity of some answers.

Table 4 Testing characteristics.

	Respondents	No personal history of substance use* (n = 988)	Personal history of substance use* (n = 295)	*p*-value
Institution currently performs employment drug testing	17 (1.33)	7 (0.71)	10 (3.39)	0.0004
Testing timing[b]				0.16
Random	7 (43.75)	3 (42.86)	4 (44.44)	
Pre-employment	6 (37.50)	4 (57.14)	2 (22.22)	
For cause/ 'reasonable suspicion'	3 (18.75)	0 (0)	3 (33.33)	
Respondent believes that random drug screening can be used to improve safety for anesthesiologists/residents	1061 (82.83)	839 (85.18)	221 (74.92)	< 0.0001
Respondent believes that random drug screening can be used to improve patient safety	1095 (85.41)	869 (88.13)	225 (76.27)	< 0.0001
Respondent would accept pre-employment drug testing	1151 (89.71)	918 (93.01)	232 (78.64)	< 0.0001
Respondent would accept random drug screening	1137 (88.62)	911 (92.30)	225 (76.27)	< 0.0001
Respondent would accept a drug test if their performance was determined to be impaired	1137 (88.83)	884 (89.66)	252 (86.01)	0.08
Drugs respondent believes are important to be tested for[a,b]				
Illicit stimulants	976 (86.52)	772 (88.13)	203 (80.88)	0.003
Prescribed stimulants	415 (36.79)	350 (39.95)	64 (25.50)	< 0.0001
Anesthetic agents	932 (82.62)	713 (81.39)	218 (86.85)	0.04
Opioids	1083 (96.01)	840 (95.89)	242 (96.41)	0.71
Marijuana	636 (56.38)	527 (60.16)	108 (43.03)	< 0.0001
Benzodiazepines	583 (51.68)	473 (54.00)	109 (43.43)	0.003
Sleep induction/maintenance medications	374 (33.16)	308 (35.16)	65 (25.90)	0.01
Other[c]	34 (3.01)	28 (3.20)	6 (2.39)	0.51
Reasons to disagree with drug testing[b,d]				
Not effective	34 (13.93)	22 (14.97)	12 (12.37)	0.57
Risk of false-positive results	74 (30.33)	52 (35.37)	22 (22.68)	0.03
Cost	20 (8.20)	18 (12.24)	2 (2.06)	0.005
Lack of established guidelines	66 (27.05)	44 (29.93)	22 (22.68)	0.21
Presence of a drug does not define impairment	106 (43.44)	41 (27.89)	65 (67.01)	< 0.0001
Violation of privacy	167 (68.44)	99 (67.35)	68 (70.10)	0.65
Other	27 (11.07)	18 (12.24)	9 (9.28)	0.47
Personally, been subject to drug testing	60 (4.68)	43 (4.36)	17 (5.78)	0.31

Data is presented as n (%).

[a] Only assessed among people who indicated they would accept drug testing (pre-employment, random, or performance-based) or believed it would improve safety (of either patients or healthcare workers).

[b] Respondents could select all that apply.

[c] Other included alcohol, anabolic steroids or performance-enhancing drugs, ecstasy, lysergic acid diethylamide, lisdexamfetamine, and zolpidem.

[d] Only assessed among people who indicated they would not accept drug testing or did not think it would improve safety.

[*] Note: Substance use is defined as 'ever used or uses any substance with the potential of abuse to change mental status.

The community of anesthesia providers in Brazil is not spared of the diseases that are SUDs. Brazilian anesthesiologists do recognize that drug may place their health and the safety of the patient in jeopardy, but when acknowledging drug use, they are less likely to admit that they represent a risk to the patient. Drug testing is rarely utilized in Brazil but would be accepted by anesthesiologists despite concerns about testing. We believe that a more widespread survey of SUD in Brazil as well may reveal the scope of the problem of SUD and efforts to reduce the incidence. Drug testing is a potential tool in this fight, but proper research is critical to gain improved understanding.

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Conflicts of interest

Professor Fitzsimons is the Chairperson of the American Society of Anesthesiologists (ASA) Substance Use Disorders Prevention Advisory Panel and leads the drug testing program in the Department of Anesthesia, Critical Care, and Pain Medicine at the Massachusetts General Hospital. De

Sousa, Muller, Quintão, and Simões declare that they have no conflict of interest.

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CLINICAL RESEARCH

Risk factors for postoperative pulmonary complications and prolonged hospital stay in pulmonary resection patients: a retrospective study

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Abstract
Background: Postoperative pulmonary complications are the main cause of morbidity and mortality after pulmonary resection. This study was undertaken to determine the risk factors associated with postoperative pulmonary complications (PPCs) and length of hospital stay (LOS) in pulmonary resection patients in a tertiary teaching hospital in Brazil.
Methods: A retrospective data gathering from 196 patients who underwent pulmonary resection between 2012 and 2016 was conducted. Demographic and hospital admission data were collected from patients with complete medical records. Univariate analysis was performed, followed by Poisson's regression for predicting the prevalence of postoperative pulmonary complications and length of hospital stay.
Results: Thirty-nine patients (20%) displayed pulmonary complications in the postoperative period. The risk factors associated with an increased prevalence of postoperative pulmonary complications in a multivariate analysis were: American Society of Anesthesiologists physical status (ASA) $\geq$ 3 (PR 4.77, p = 0.03, 95% CI: 1.17 to 19.46), predicted diffusion capacity of the lungs for carbon monoxide – corrected single breath (PR 0.98, $p < 0.001$, 95% CI: 0.96 to 0.99) and age of the patient (PR 1.04; p = 0.01; 95% CI: 1.01 to 1.06). Those associated with an increased prevalence of prolonged hospital stay were: duration of surgical procedure longer than five hours (PR 6.94, p = 0.01, 95% CI: 1.66 to 12.23), male sex (PR 5.72, $p < 0.001$, 95% CI: 1.87 to 9.58), and presence of postoperative pulmonary complications (PR 11.92, $p < 0.001$, 95% CI: 7.42 to 16.42).
Conclusions: The rate of postoperative pulmonary complications in the study population is in line with the world average. Recognizing risk factors for the development of PPCs may help optimize allocation resources and preventive efforts.
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Introduction

Despite advances in perioperative care, morbidity and mortality associated with pulmonary resection remain relatively high.[1] A review published in 2009 using the Society of Thoracic Surgeons (STS) database revealed a general rate of postoperative pulmonary complications (PPCs) of 13%.[2] The challenge during the preoperative evaluation is to identify which patients are at increased risk for these complications. The preoperative evaluation in patients submitted to this type of procedure is difficult due to the scarcity of knowledge on the risks related to these complications.[3] The study of PPCs is relatively recent when compared to perioperative cardiovascular complications.

Recommendations of European and North American societies of thoracic surgery are usually taken into account during preoperative evaluation of candidates for pulmonary resection.[1] Few risk scores have been adapted to stratify patients candidates for pulmonary resection,[4,5] other scores have been developed to stratify patients according to risk of complications or in-hospital mortality following pulmonary resection.[3,6–10] To the best of our knowledge, there seem to be only a few models capable of assessing the risk of PPCs in pulmonary resection patients.

This study aims to determine the risk factors related to the presence of PPCs and length of hospital stay (LOS) in a tertiary teaching hospital in Brazil.

Methods

Ethical approval for this study (Ethical Committee N° NAC 2.230.948) was provided by the Ethical Committee NAC of Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil (Chairperson Marcia Mocellin Raymundo) on 21 August 2017. The study was conducted retrospectively from January 2012 to December 2016. Informed consent was waived.

According to a previous prospective observational study,[11] we estimated the incidence of PPC of approximately 14,5%. It would be necessary to recruit at least 168 patients to complete the study analysis, considering an alpha level of 5% and an absolute error of 5%.[12]

This retrospective cross-sectional study was performed in a regional thoracic center on all consecutive patients who underwent thoracotomy and lung resection between January 2012 and December 2016. Data from 200 consecutive patient records were screened from the electronic medical charts database of the Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. One hundred and ninety six patients had complete data for statistical analysis. Patients were identified through a structured search using the Query system and the following keywords: segmentectomy, bullectomy, lobectomy, bilobectomy and pneumonectomy.

Data concerning in-hospital mortality (death within 30 days postoperatively or at the same hospital stay) and unplanned reoperation within the 30-day postoperative period were also collected.

The outcome is composed of eight clinically relevant PPCs (pneumonia, atelectasis requiring fibrobroncoscopic intervention, bronchospasm requiring pharmacological treatment for more than 24 hours, acute respiratory distress syndrome (ARDS), pleural effusion requiring surgical intervention, aspiration of gastric contents, hypoxemia and pneumothorax). Medical records were evaluated by three team members applying diagnostic criteria established in the literature for assessment of complications.[13–19] Diagnosis of hypoxemia was considered if patients presented with pulse oximetry (SpO_2) value less than 90% for more than 24 hours, along with the necessity of oxygen therapy. Patients whose charts did not contained laboratory or imaging data confirming the diagnosis on any of PPCs considered were excluded. All patients were prescribed postoperative physical therapy and were handled according to the local institutional pain management protocol. Patients in whom epidural catheter was used in the intraoperative period, but proved ineffective in controlling postoperative pain due to incorrect positioning were considered to have received general anesthesia alone. All pulmonary resection patients aged 16 years or older were included for analysis. Data were obtained manually with the aid of a structured questionnaire and inserted in an electronic spreadsheet (*Microsoft Excel 2013*). Statistical analysis was performed with Statistical Package for the Social Sciences for Windows, release 23 – 2015 (IBM SPSS Statistics, IBM Corp., Armonk, NY, EUA).

Patients who underwent pulmonary resection due to complications caused by non-bacterial active infection, such as pulmonary tuberculosis or aspergillosis, were considered as having non-pyogenic lung infection. All patients who were discharged from the hospital were followed up in an outpatient setting according to the routine of the thoracic surgery service.

The length of hospital stay was recorded on days, from date of hospitalization (or surgical appointment for patients hospitalized for other reasons) to the date of discharge (or death). Studies point out a great variability in the concept of LOS after pulmonary resection surgeries.[20] Prolonged LOS is dependent on factors related to the surgical procedure, characteristics of patients,[21] institutional protocols and development of perioperative complications.[22] Even in patients undergoing uncomplicated lobectomies, the variability of LOS is considerable. In this study, we considered prolonged hospital stay a period of hospitalization greater than 10 days.

In order to determine the risk factors associated with increased prevalence of PPCs (dependent variable, binary type) a univariate analysis was performed followed by multivariate analysis (Poisson's regression). The logistic regression model was constructed using a backward stepwise selection procedure in which the presence of a PPC and LOS were the dependent variables. Independent predictors were entered into the model on the basis of the bivariate analysis ($p < 0.05$) and correlation coefficients between variables lower than 0.4. Potential predictors were sequentially removed if this exclusion did not result in a significant change in the log-likelihood ratio test. The cutoff for variable removal was set at a significance level of 0.05. We then calculated the adjusted odds ratios and the corresponding 95% CI value. Some variables were reconfigured to meet the purpose of the multivariate analysis as follows: ASA (1–2 vs 3 vs 4), chronic obstructive pulmonary disease (absent vs mild vs moderate–severe), and surgical procedure time (0–2 hours vs 2–3 hours vs 3–4 hours vs. 4–5 hours vs more than 5 hours). Surgical technique was divided according to the procedure performed in: segmentectomy, lobectomy,

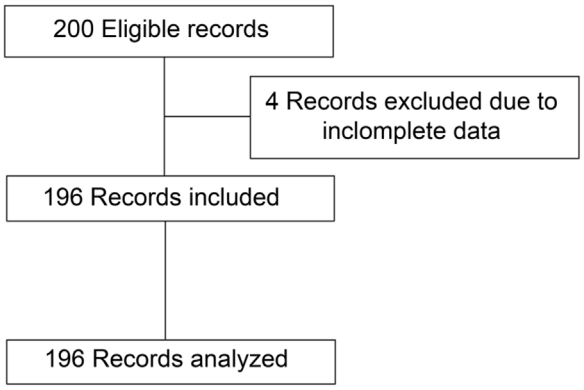

Figure 1 Recruitment flowchart.

bilobectomy and pneumonectomy. The variables postoperative predicted Diffusion Capacity of the Lungs for carbon monoxide – corrected single breath ($ppoDL_{co}$-cSB) and postoperative predicted Forced Expiratory Volume in the first second ($ppoFEV_1$) were calculated as previously published[26] and analyzed as continuous variables. Remaining data were analyzed as binary.

Results

Two hundred and fifty consecutive patients were identified through electronic research. One hundred ninety six different patients showed more than 95% complete data and were included in the statistical analysis, representing 196 elective surgical procedures (Fig. 1). Four patients (1%) had incomplete data and, therefore, were excluded from final analysis. Information on demographic and clinical variables is summarized on Table 1.

Thirty-nine patients displayed PPCs (20%), being pneumonia the most frequent complication (Table 2). Mean time of hospitalization was 10.06 ± 10.60 days; among patients, who developed some type of PPC, mean LOS was 23.5 ± 16.86 days. This study detected a mortality rate of five percent (10 patients). Eight patients (4%) died from postoperative pulmonary complications (six patients had pneumonia in the postoperative period, one patient presented lobar atelectasis, which was followed by pulmonary sepsis, and one presented with ARDS). One patient died from pulmonary thromboembolism and one from sepsis due to pulmonary empyema after lobectomy, followed by multiple organ dysfunction. None of patients presented with immunosuppression and none received chemotherapy in the perioperative period. Lobectomy was the most commonly performed procedure (50%), followed by segmentectomy (43.9%), bilobectomy (4.1%), and pneumonectomy (2%). None of patients underwent emergency surgery.

Factors related to the presence of PPCs in the univariate analysis are depicted on Table 3. The multivariate analysis using Poisson's distribution resulted in a model in which patients classified as ASA score ≥ 3 had almost five fold higher prevalence of pulmonary complications when compared to those with ASA score ≤ 2 (PR = 4.77, p = 0.03, 95% CI: 1.17–19.46). Age was also independently related with PPCs, with a prevalence increase of 4% per year after 16 years of age. (PR = 1.04, p = 0.01, 95% CI: 1.01–1.06). The $ppoDL_{co}$-cSB showed an inverse correlation with the occurrence of PPCs (PR = 0.98, p < 0.001, 95% CI: 0.96–0.99). For each percentage point reduction of $ppoDL_{co}$-cSB from 100%, the prevalence of PPCs increased by 2% Table 4.

Table 1 Demographic and clinical characteristics.

Variable	Patients (%)	Patients with PPC (%)
Age		
< 55 years	61 (31.1)	4 (10.3)
55–65 years	56 (28.6)	8 (20.5)
≥ 65 years	79 (40.3)	27 (69.2)
Gender		
Male	97 (49.5)	22 (65.4)
Female	99 (50.5)	17 (43.6)
ASA		
ASA 1	3 (1.5)	0
ASA 2	70 (35.7)	4 (10.3)
ASA 3 or higher	122 (62.2)	35 (89.7)
COPD		
Absent	75 (38.3)	9 (23.1)
Mild	90 (45.9)	16 (41)
Moderate	21 (10.7)	7 (17.9)
Severe	10 (5.1)	7 (17.9)
Surgical technique		
Segmentectomy	86 (43.9)	10 (25.6)
Lobectomy	98 (50)	25 (64.1)
Bilobectomy	8 (4.1)	3 (7.7)
Pneumonectomy	4 (2.0)	1 (2.6)
FVC[a]	83.16 ± 17.97%	76.74 ± 20.12%
FEV_1[a]	78.71 ± 20.80%	66.79 ± 23.18%
DL_{CO}[a]	60.73 ± 18.91%	51.75 ± 15.10%

PCC, postoperative pulmonary complication; ASA, American Society of Anesthesiologists physical status; COPD, chronic obstructive pulmonary disease; VATS, video assisted thoracoscopic surgery; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; DL_{CO}, diffusion capacity of the lung for carbon monoxide.
[a] Values for FVC, FEV_1 and DL_{CO} are presented as mean ± standard deviation.

Table 2 Frequency of postoperative pulmonary complications.

Postoperative pulmonary complication	Number of patients (%)
Pneumonia	32 (82)
Atelectasis	10 (26)
Bronchospasm	5 (13)
Pneumothorax	1 (3)
Pleural effusion	4 (10)
Acute Respiratory Distress Syndrome	2 (5)
Gastric content aspiration	0 (0)
Hypoxemia	6 (15)
Total Number of Patients with one or more PPC	39 (20)
Death from PPC	8 (4)

PPC, postoperative pulmonary complication.

Table 3 Independent variables for postoperative pulmonary complications in 196 patients identified in the univariate analysis.

Variables entered into the Poisson's regression model	OR	*p*-value	95% CI (Wald)	
Age	1.04	< 0.001	1.02	1.07
Charlson Comorbidity Index	0.12	0.02	0.05	0.20
No. of pulmonary subsegments removed	1.05	0.02	1.01	1.10
ppoDL_{CO}-cSB	0.97	0.001	0.95	0.99
ppoFEV_1	0.89	0.002	0.82	0.96
ASA				
3 or higher	3.81	0.006	1.11	6.51
Smoking history				
> 21 packs-year	1.60	0.032	1.08	6.27
COPD				
Moderate–severe	3.76	< 0.001	1.82	7.77
Duration of surgical procedure				
> 5 hours	6.32	0.003	1.88	21.18
Non-pyogenic lung infection	3.97	< 0.001	2.17	6.94
Functional status (dependent-partially dependent)	4.74	< 0.001	3.00	7.48
Surgical technique*	2.26	0.015	1.17	4.39

ppoDL_{CO}, predicted postoperative diffusing capacity of lung for carbon monoxide; ppoFEV_1, predicted postoperative forced expiratory volume in the first second; ASA, American Society of Anesthesiologists physical status; COPD, chronic obstructive pulmonary disease. Surgical Technique*: for lobectomy. Bilobectomy or pneumonectomy procedures; CI, confidence interval.

Table 4 Independent predictors of risk for postoperative pulmonary complications identified in the multivariate analysis (Poisson's Regression Model).

	Prevalence ratio	*p*-value	95% CI (Wald)	
ASA 3 or higher	4.77	0.03	1.17	19.46
Age	1.04	0.01	1.01	1.06
ppoDL_{CO}-cSB	0.98	< 0.001	0.96	0.99

ASA, American Society of Anesthesiologists physical status; ppoDL_{CO}, predicted postoperative diffusing capacity of lung for carbon monoxide; CI, confidence interval.

Table 5 Independent variables for prolonged LOS in the 196 patients identified in the univariate analysis.

Variable	Odds Ratio	*p*-value	95% CI (Wald)	
BMI (kg m^{-2})	0.41	0.02	0.32	0.611
No. of pulmonary subsegments removed	0.40	< 0.001	0.12	0.67
Male sex	3.72	0.01	1.81	6.64
ASA-PS 3 or higher	3.82	< 0.001	1.12	6.52
COPD moderate-severe	5.9	0.01	1.59	10.21
Duration of surgical procedure > 5 hours	11.97	< 0.001	7.56	16.38
Non-pyogenic lung infection	19.20	< 0.001	11.69	26.71
Functional status (dependent–partially dependent)	14.96	< 0.001	9.77	20.11
Postoperative pulmonary complications	16.22	< 0.001	13.29	19.15
ppoDL_{CO}-cSB	0,88	0.29	0,78	0,98
ppoFEV_1	0.89	0.02	0.82	0.96

LOS, length of hospital stay; BMI, body mass index; ASA, American Society of Anesthesiologists physical status; ppoDL_{CO}, predicted postoperative diffusing capacity of lung for carbon monoxide; COPD, chronic obstructive pulmonary disease; ppoFEV_1, predicted postoperative forced expiratory volume in the first second; CI, confidence interval.

Table 6 Independent predictors of risk for prolonged los identified in the multivariate analysis (Poisson's Regression Model).

	Prevalence Ratio	*p*-value	95% CI (Wald)	
Male sex	5.72	< 0.001	1.87	9.58
Duration of Surgical Procedure > 5 hours	6.94	0.01	1.66	12.23
Postoperative Pulmonary Complications	11.92	< 0.001	7.42	16.42

LOS, Length of Hospital Stay; CI, Confidence Interval.

Factors related to the presence of LOS in the univariate analysis are depicted on Table 5. After multivariate analysis, only three variables showed correlation with an increased prevalence for prolonged LOS (Table 6). The presence of PPCs demonstrated greatest strength of association with prolonged LOS, with an increased prevalence ratio (PR = 11.92, $p < 0.001$, 95% CI: 7.42–16.42) when compared to patients with no PPCs. The variables male sex and surgical procedure time > 5 hours also showed a positive correlation with an increased prevalence ratio for longer LOS: (PR = 5.72, $p < 0.001$, 95% CI: 1.87–9.58) and (PR = 6.94, $p = 0.01$, 95% CI: 1.66–12.23), respectively.

Discussion

In our retrospective cross-sectional study, three variables (ASA, age and ppoDL_{co}-cSB) were shown to be independently related with an increased prevalence of PPCs and three variables with prolonged LOS (male sex, procedure time > 5 hours and the presence of postoperative pulmonary complications). In regard to the occurrence of PPCs, the American Society of Anesthesiologists (ASA) score was the most important predictor, followed by age and ppoDL_{co}-cSB.

When the ppoDL_{co}-cSB and ppoVEF_1 variables were analyzed together, only the former appears as independent predictor for PPCs, similar to the study performed by Amar et al.[24] According to Brunelli et al.,[25] the correlation between FEV_1 and DL_{co} or ppoDL_{co} is weak for predicting patients with or without postoperative complications and, even those patients who present a normal FEV_1 value should include a measurement of DL_{co} in the perioperative evaluation. Although DL_{co} alone is highly associated with PPCs, we chose to use ppoDL_{co}-cSB because it associates a measure of the extension of lung resection and preoperative lung function. None of the patients in our study received chemotherapy in the preoperative period. Therefore, the reduction in pulmonary diffusion capacity seems to be explained by lung disease or by the greater number of resected lung segments in the patients presenting PPCs.

Interestingly, despite its subjectivity, the ASA score in our study appears to be an independent predictor for PPCs. The same result was found by Falcoz et al.[3] in a prospective study involving 15,183 patients on mortality risk factors in pulmonary resection and in a study conducted by Canet et al.[26] involving 2,464 non-cardiac surgery patients.

The Charlson comorbidity index did not appear to be an independent predictor in this sample, as well as other scales, such as functional status and nonintentional preoperative weight loss. In a retrospective study, analyzing a database containing 493 patients undergoing lobectomy for lung cancer, Sanchez et al.[27] concluded that the Charlson comorbidity index, after multivariate analysis, showed to be an important predictor of risk for postoperative complications. A possible explanation for the difference presented between the study by Sanchez et al. and the current study is the fact that, when analyzed in conjunction with other collinear variables (ASA, functional status and preoperative weight loss), the predictability of the Charlson Comorbidity Index is impaired.

When compared to the younger population, elderly patients appear to present higher postoperative morbidity and mortality rates.[28] The current study corroborates this finding, since age appears to be a predictor of PPCs, even when other factors, such as associated comorbidities, are taken into account.[3,29]

We have demonstrated that the presence of postoperative pulmonary complications increased the prevalence for a longer LOS. In our study, 20% of patients presented some type of complication and in-hospital mortality was 4%. None of patients without pulmonary complications died. According to other studies, the percentage of pulmonary complications and mortality may vary depending on the definition used. Even so, some authors agree that pulmonary complications are as common, lethal and costly to the health system as cardiovascular complications.[15,24] The perioperative comorbidities presented by patients in our study did not influence the outcomes. The same happened with the anesthetic and surgical techniques used.

Length of hospital stay in patients undergoing pulmonary resection is quite variable and depends on several factors, such as: surgical factors, comorbidities presented by patients,[26] perioperative complications and different institutional protocols.[29] The study conducted by Freeman et al.[30] deserves to be mentioned. It identified a bimodal distribution in hospital readmissions. Those patients readmitted after an initial hospitalization period of 5 days, pleural effusion, pneumothorax and atelectasis were the main causes of readmission. Although described in several studies as PPCs, these complications may be associated with inadequate duration of postoperative pleural drainage.

Among patients readmitted after an initial hospitalization period of 16 days, several causes were identified, highlighting the development of pneumonia and the functional status. The relationship between prolonged LOS and the presence of PPCs has also been suggested by these authors.

In our study none of patients were readmitted and prolonged LOS (more than 10 days) were related to the presence of PPCs. male sex and duration of surgical procedure more than 5 hours.

It seems important to us to identify risk factors related to prolonged LOS and to adopt care protocols, in order to reduce the time of intention and the rate of readmissions.

Although the sample size was adequate and data were collected with support of a structured questionnaire, containing the *a priori* definitions of outcomes and reducing the chance of subjective evaluations, this study has an exploratory character. Therefore, we believe that a prospective, randomized and larger study, including multiple centers and different populations, is necessary for a better understanding of the risk factors involved in the genesis of PPCs after pulmonary resection. It seems to be adequate to follow the steps of Canet et al.,[26] using a large randomized sample divided into an assembly cohort and a validation cohort, in order to build a more comprehensive risk score.

Conclusions

We believe that data summarized here contributes to further understanding the genesis of postoperative pulmonary complications, especially considering the lack of informa-

tion regarding pulmonary resection in patients outside the oncological scope. The present study findings appear to be in agreement with the results of previous literature. Further studies addressing the incidence of postoperative pulmonary complications following pulmonary resection surgery are warranted and should include a larger sample size, multicentric database, a prospective design, as well as contain information on mechanical ventilation parameters, the amount of fluid and blood products used and consider the intensity of postoperative physiotherapy treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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CLINICAL RESEARCH

Comparison of low dose intravenous fentanyl and morphine infusion for postoperative analgesia in spine fusion surgeries – a randomized control trial

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KEYWORDS
Fentanyl;
Morphine;
Spine surgery;
Postoperative pain

Abstract
Background and aims: Post-operative analgesia for Spine surgeries is difficult without patient control analgesia (PCA) and inadequate monitoring facilities. The objective was to study the effectiveness of analgesia of intravenous administration of low dose fentanyl and morphine for postoperative analgesia following spine fusion surgeries.
Methods: One hundred adult patients undergoing spine instrumentation surgeries were randomly allotted into two groups: Group M (morphine) or Group F (fentanyl). The patients received either 0.02 mg.kg^{-1}.h^{-1} of morphine or 0.3 mcg.kg^{-1}.h^{-1} of fentanyl infusion postoperatively. If the patient had pain, additional bolus dose of 0.04 mg.kg^{-1} and 0.6 mcg. kg^{-1} bolus for morphine and fentanyl respectively were given and noted. The additional analgesic consumption was recorded. The Ramsay sedation score (RSS), visual analogue score (VAS), vital parameters and complications were observed.
Results: The demographic characteristics did not reveal significant difference among the two groups. In morphine group, 32 patients did not require any additional bolus dose, 15 patients needed one bolus dose and one patient each required two and three boluses. In fentanyl group, two, 24, 20 and four patients required 0, 1, 2 and 3 bolus doses respectively. There were no statistically significant variations in hemodynamic features like heart rate, blood pressure and oxygen saturation, RSS and VAS. The complication rate was not significant among the groups.
Conclusion: Low dose continuous infusion of morphine is more effective than fentanyl with fewer requirements of rescue analgesics for postoperative analgesia. Both drugs are safe without any serious complications.
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Introduction

Spine fusion surgeries are major surgeries resulting in varying pain intensity after surgery.[1] The inadequate treatment of pain after surgery can lead to severe emotional disturbance along with autonomic hyperactivity and reduced mobility.[2] An inefficiently managed pain can result in sensitization of central and peripheral nervous system.[3] The pain severity following spine surgery is directly proportional to the invasiveness of the procedure and the number of vertebrae operated.[4] The severity of pain is not different among different levels and remains the same from cervical to lumbar spine surgeries.[5]

The pain following spine instrumentation is usually managed with patient control analgesia (PCA).[6] Morphine remains the gold standard drug of choice to be used in PCA. However, several other agents like fentanyl, tramadol have also been used in PCA.[7] But in developing countries, the PCA pump may not be available in all the hospitals. The continuous opioid infusions are rarely being used in these hospitals because of inadequate monitoring facilities and fear of complications like respiratory depression, nausea, vomiting, and pruritus. The patients are inadequately treated for pain postoperatively which can lead to severe emotional disturbances. Hence, we decided to perform this study to analyze the efficacy and safety of continuous morphine or fentanyl infusion for postoperative analgesia following spine instrumentation surgeries.

The primary objective of our study was to study the efficacy of morphine and fentanyl administration for postoperative analgesia following spine fusion surgeries. The secondary objectives were to assess visual analog scale (VAS), sedation score and complications.

Patients and methods

We registered our study in the Clinical Trial Registry India (CTRI/2017/11/010629). (The study can be accessed in the following link in the study registry: http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=21232&EncHid=&userName=2017/11/01 0629). The first patient was enrolled on December 1st, 2017 and the study was completed on May 31, 2019. After obtaining approval from the institutional ethical committee, this randomized, prospective, double-blinded study was done on 100 patients who underwent lumbar spine fusion surgeries in a tertiary care hospital linked to medical college. Patients of the American Society of Anesthesiologists (ASA) I, II or III posted for lumbar spine instrumentation surgeries for spondylolisthesis were recruited in the study. The patients between 18–60 years and weighing from 50 to 100 kg were included. Patients with cardiac, renal or hepatic disease, allergic to opioids, pregnant patients and with history of obstructive sleep apnea were excluded from the study. The participants were informed about the study and consent was obtained from all patients. They were randomly divided into two groups: Group M (morphine) or Group F (fentanyl) infusion by computer-generated random numbers method. The printout was taken and kept in a sealed envelope.[9] The general anesthesia was standardized in both the groups with propofol as an induction agent, vecuronium as a muscle relaxant and maintained with nitrous oxide, oxygen, and sevoflurane. Fentanyl 2 $mcg.kg^{-1}$ was used as the intraoperative analgesic with further bolus 0.5 $mcg.kg^{-1}$ given hourly. The patient was shifted to the post anesthetic care unit after recovery. The number of spinal segments involved in fusion surgeries and the duration of surgery was noted.

The envelope was opened at this stage and the first anesthesiologist prepared the solution according to the group involved. Morphine was prepared as 1 $mg.ml^{-1}$ and fentanyl as 15 $mcg.ml^{-1}$ solution in an identical looking 50 mL syringes.

The amount of infusion and bolus dose for breakthrough pain was decided by the first anesthesiologist based on body weight in $mL.h^{-1}$ to be infused in a syringe pump. He documented it and handed it to the second anesthesiologist. The first anesthesiologist took no further part in the study. The second anesthesiologist administered the solution as per the dose suggested by the first anesthesiologist. He was not aware of the group involved and did the monitoring and further management of the patient. Group M patients received morphine 0.02 $mg.kg^{-1}.h^{-1}$ continuous infusion with 0.04 $mg.kg^{-1}$ as bolus for breakthrough pain. Group F patients received fentanyl in a dose of 0.3 $mcg.kg^{-1}.h^{-1}$ continuous infusion with a bolus of 0.6 $mcg.kg^{-1}$ bolus for breakthrough pain. If the patient had pain after 15 minutes, the bolus dose was repeated. The total number of additional bolus doses utilized were noted. If the pain was persistent for more than 30 minutes, then the study was stopped, and the pain was treated with morphine in titrated doses. Both groups received infusion for the first 24 hours postoperatively. The patients were followed up for a further 24 hours to observe for complications.

VAS was explained to the patient and was used to assess the pain.[8] The patients were given an additional bolus dose when VAS > 3. The sedation was assessed using the Ramsay sedation scale (RSS) and was given as follows: 1 – patient is agitated, and anxious or restless, or both, 2 – patient is oriented, cooperative, and tranquil, 3 – patient responding to command only, 4 – a brisk response to a light glabellar tap or a loud auditory stimulus, 5 – a sluggish response to a light glabellar tap or a loud auditory stimulus, 6 – no response to a light glabellar tap or a loud auditory stimulus.[10] The patients were monitored continuously for vital parameters like heart rate, oxygen saturation (SPO_2) and non-invasive blood pressure and values were recorded fourth hourly for 24 hours. The patients were observed for adverse events like pruritus, nausea, bradypnea, vomiting, and respiratory depression characterized by a fall in SPO_2. The total consumption of bolus doses, VAS, RSS, oxygen supplementation and any adverse effects were recorded.

To find out at least 20% difference in additional bolus opioid requirement with the power of 80% and an alpha error of 0.05 a minimum of 44 patients will be required in each group. We included 50 patients in each group to compensate for the possible dropout. Chi-square test and Fischer Exact Test were used for non-parametric data and student t-test was used to analyze parametric data. Statistical significance was considered if p-value is < 0.05 and < 0.001 as highly significant. Statistical Package for Social Science (SPSS) 20.0 was used to perform statistical analysis.

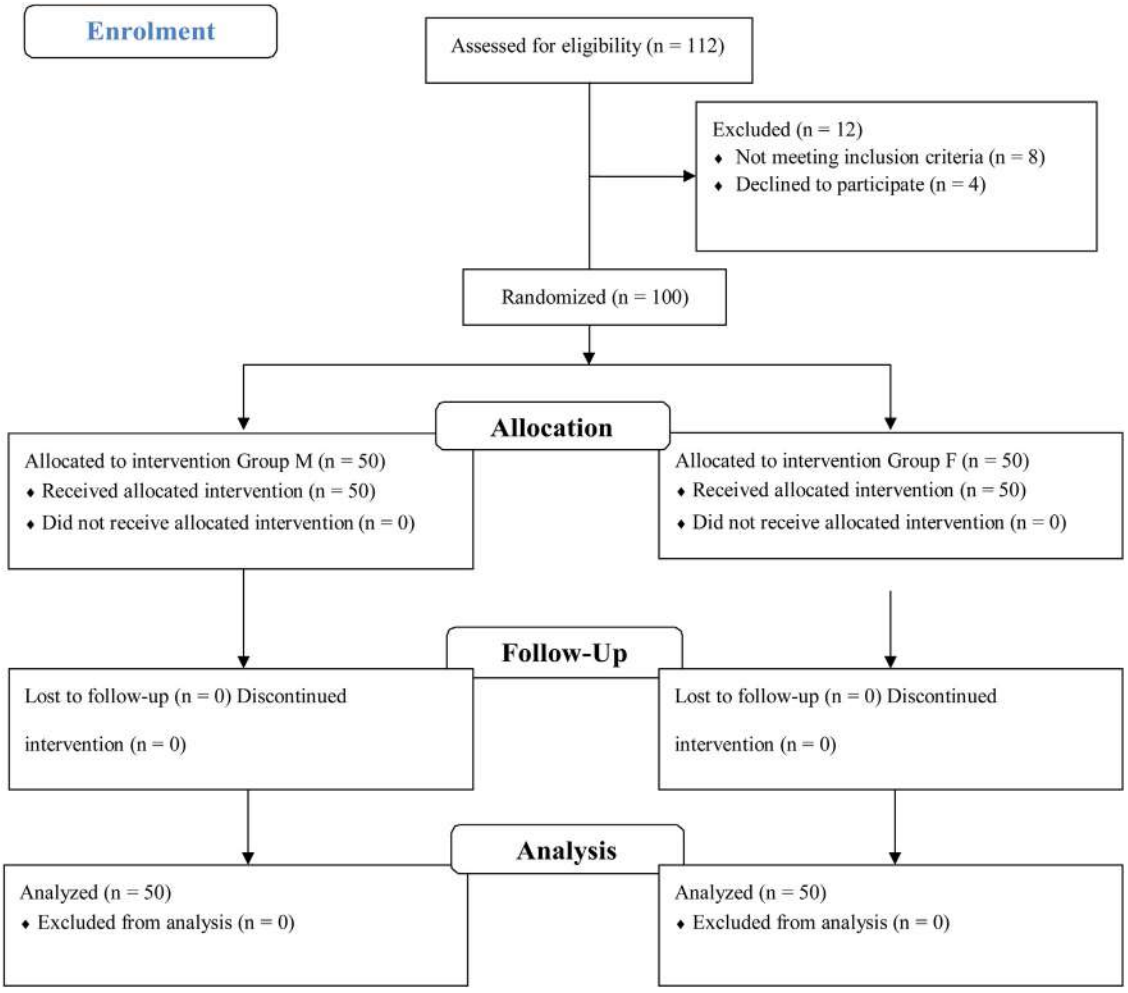

Figure 1 CONSORT Flow chart.

Results

The data analysis was published in online repository Mendeley with the following link Rani, Pushpa (2020), ''Comparison of Low Dose Intravenous Fentanyl and Morphine Infusion for Postoperative Analgesia in Spine Fusion Surgeries – A Randomised Control Trial'', Mendeley Data, v1http://dx.doi.org/10.17632/msw2rg4xgb.1. Of the 112 patients enrolled for the study, 12 were excluded before randomization due to not meeting inclusion criteria (n = 8) and four patients declined to participate. One hundred participants were randomly divided into two groups of 50 each and no patient was lost to follow-up. The Consolidated Standards of Reporting Trials (CONSORT) flow chart was shown in Fig. 1.

The patients who underwent lumbar spine instrumentation surgeries for spondylolisthesis were included in the study. Both the groups were similar in terms of demographic profile, smoking history, duration of surgery and number of spinal segments involved in fusion with no statistical significance. (Table 1) Thirty-three patients in morphine (Group M) did not require any additional bolus dose for postoperative analgesia and VAS was maintained at < 4 throughout the first 24 hours of the postoperative period. Only two patients in the fentanyl group were having VAS < 4 and others required additional bolus doses for adequate pain relief. In the morphine group, 15 patients required one bolus; one patient had two boluses and one patient needed three additional bolus doses. In the fentanyl group, 24 patients required one additional bolus dose; 20 patients needed two doses and four patients had three additional doses to achieve VAS < 4. There was no loss to follow-up as no patient had persistent pain beyond thirty minutes. The results were summarized in Fig. 2. The RSS was similar between the two groups (Table 2). There was no difference in VAS between the two groups and was maintained at less than 4 until 12 hours. After 12 hours, it was significant (Table 3).

There was no significant difference in heart rate, mean arterial pressure and saturation among the two groups (Fig. 3). However, one patient in the morphine group experienced a fall in saturation and required oxygen supplementation through a nasal cannula. Eleven patients in Group M had nausea while three patients in Group F had nausea and it was statistically significant ($p = 0.04$). The vomiting was observed in five patients in morphine and one in fentanyl group and it was statistically not significant ($p = 0.206$). The pruritus was observed in six patients in Group M and one in the Group F ($p = 0.104$). But there was no statistical signif-

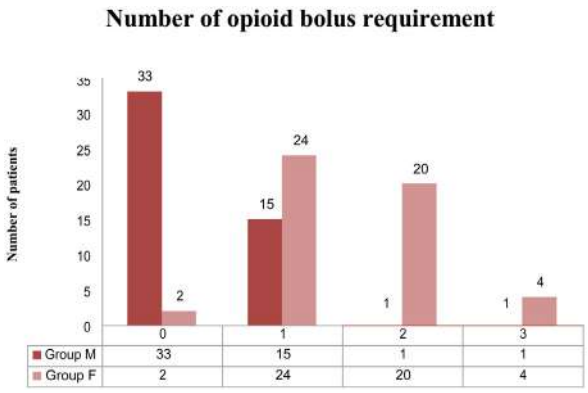

Figure 2 Number of additional bolus doses required.

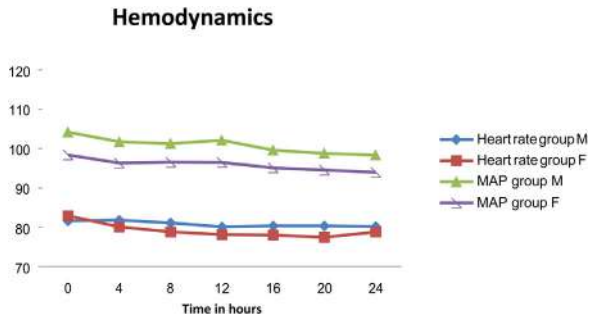

Figure 3 Variations in heart rate (beats/min) and mean arterial pressure (mm Hg).

icance. The reduction in respiratory rate to less than eight and apnea was not reported in any of the patients.

Discussion

The spine fusion surgeries are major surgeries resulting in severe postoperative pain. This pain is often inadequately treated in hospitals where the PCA pump is not available. The patients are frequently managed with paracetamol and non-steroidal anti-inflammatory agents which are not adequate in most of these patients. The opioid-like morphine and fentanyl are hardly used because of inadequate monitoring facilities and the fear of respiratory depression. Hence, we designed this study to test the effectiveness and safety of low dose morphine and fentanyl infusion for postoperative analgesia following lumbar spine fusion surgeries.

Multimodal pain management strategies have been demonstrated to be the most effective treatment modality for spinal fusion surgeries. Several agents like dextromethorphan, ketorolac, or gabapentin have all been tried to reduce pain after surgery and opioid use, with varying results.[11–13] PCA forms the cornerstone for treatment either alone or as part of multimodal treatment. Morphine is usually used in PCA with a bolus dose of 1 mg and a lockout interval of 5-10 minutes. Hence patients may use up to 12 mg in one hour. There is a potential to cause respiratory depression in these doses, hence monitoring by trained staff with a multiparameter monitor including pulse oximeter is mandatory when using a PCA pump. PCA pump and adequate monitoring may not be available in all the hospitals in developing countries.

The narcotics morphine and fentanyl can be used in various routes like intravenously, intramuscular, epidurally, intrathecally, orally (morphine) and transdermally (fentanyl).[14] Guinard et al.[15] studied three different doses of analgesics with fentanyl and demonstrated both intravenous (IV) as well as epidural fentanyl had the same efficacy in pain relief after thoracotomy. Loper et al.[16] proved that epidural infusion continuously was not able to provide any significant clinical advantage over continuous IV infusion of fentanyl.

Table 1 Demography.

	Group M	Group F	*p*-value
Age	47.62 ± 9.477	46 ± 10.6	0.379
Sex (Male/Female)	39/11	37/13	0.64
ASA (I/II/III)	26/22/2	25/21/4	0.701
Duration of surgery (minutes)	128.63 ± 18.92	122.73 ± 16.27	0.097
Number of spinal segments involved (1/2/3)	12/35/3	9/37/4	0.731
Smoking (Yes/No)	28/22	25/25	0.548

Values are in Mean ± Standard deviation (SD) or number of patients.

Table 2 Ramsay sedation score.

Time in hours	Group M	Group F	U value	Z Score	*p*-value
0	1 (2-1)	2 (2-1)	1103.5	0.84682	0.395
4	2 (2-2)	2 (2-2)	1110.5	0.79783	0.423
8	2 (2-2)	2 (2-2)	1203.5	-0.31373	0.756
12	2 (2-2)	2 (2-2)	1200.5	-0.16797	0.865
16	2 (2-2)	2 (2-2)	1200.5	0.3378	0.727
20	2 (2-2)	2 (2-2)	1173	-0.36042	0.718
24	2 (2-2)	2 (2-2)	1200.5	-0.16797	0.865

Values are in median (Inter Quartile Range).

Table 3 Visual analog score.

Time in hours	Group M	Group F	U value	Z Score	*p*-value
0	2 (3-2)	2 (5-1)	1137	-0.61237	0.541
4	2 (3-2)	2 (5-1)	1133	-0.64037	0.522
8	2 (2-2)	2 (5-1)	1046	-1.24924	0.211
12	2 (2.5-2)	2 (5-1)	1105.5	-0.83283	0.406
16	2 (2-2)	1.5 (2-1)	809	-2.90789	0.003[a]
20	2 (2-2)	2 (2-1)	743.5	-3.3663	< 0.001[a]
24	2 (2-2)	2 (2-1)	644	-4.06265	< 0.001[a]

Values are in median (Inter Quartile Range).
[a] *p*-value statistically significant.

Fentanyl is a short-acting opioid that is used for both intraoperative and postoperative analgesia. Fentanyl has a quick onset with the duration of action less than morphine. The number of patients requiring additional rescue bolus dose was more in Group F than the Group M. Russo et al retrospectively compared analgesia after gynecological surgeries with intravenous infusion of morphine with fentanyl continuously. They compared 0.3 $mcg.kg^{-1}.h^{-1}$ fentanyl with 0.02 $mg.kg^{-1}.h^{-1}$ morphine for total intravenous analgesia for gynecologic surgeries. The dosage used is similar to the dose used in our study. The primary endpoint of that study was taken as a requirement for rescue analgesia postoperatively and the time to gastrointestinal bowel recovery was also measured. They found that both fentanyl and morphine infusion was effective in providing adequate pain relief and fentanyl was more effective than morphine in the requirement of rescue analgesic therapy, faster bowel recovery time and shorter hospital stay.[17] But the inference of our study was in contrast to this study and we found that morphine was associated with a lower requirement of rescue analgesia.

RSS remained same between the two groups with no difference statistically. Pain scores as assessed by VAS were also not different between fentanyl and morphine. VAS was kept under four in both the groups and rescue analgesics were used when it was exceeded. Russo et al demonstrated that the fentanyl group achieved significant sedation at first postoperative hour than morphine with no statistically significant variations after one hour between the two groups. The RSS in the fentanyl group gradually decreased over 12 hours and remained stable after that period. However, in the morphine group, it gradually increased from first to the sixth hour and remained relatively stable after six hours. In our study, the maximum sedation score was achieved at four hours for the fentanyl group and at eight hours for the morphine group.

There were no significant variations in heart rate, blood pressure and saturation between groups statistically. Heart rate was lower and mean arterial pressure was higher in the fentanyl (F) group than in Group M, with no statistical significance. The complications like nausea, vomiting, and pruritus were reported more frequently with morphine than the fentanyl group. One patient in the morphine group had a fall in saturation to 88% and required oxygen by nasal cannula. None of the patients developed apnea or required assisted ventilation showing the safety of both fentanyl and morphine when used in low dose continuous intravenous infusion.

The present study has few limitations: first, we were able to demonstrate the requirement of rescue analgesics was less in morphine than the fentanyl group; we did not encounter any serious complications like respiratory depression with this sample size. The sample sizes needed to be larger to confirm the safety profile. Secondly, we did not study urinary retention as all the patients were catheterized. Bowel disturbance was also not studied. There was not much literature evidence available regarding the comparison of intravenous infusion of opioids. Finally, we did not study the risk factors for postoperative nausea and vomiting. Hence, we cannot comment with certainty about the significance of increased incidence of nausea and vomiting in the morphine group.

To conclude, continuous low dose infusion of morphine is more effective than fentanyl with fewer requirements of rescue analgesics for postoperative analgesia following spine fusion surgeries. Both drugs are safe and are devoid of any serious complications.

Conflict of interest

The authors declare no conflict of interest

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CLINICAL RESEARCH

Propofol with or without fentanyl for pain relief after transrectal ultrasound-guided prostate (TRUS-P) biopsy: a randomized controlled study☆

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KEYWORDS
Postoperative pain;
Cancer of prostate;
Deep sedation;
Propofol;
Fentanyl

Abstract
Background: Postoperative pain from transrectal ultrasound-guided prostate (TRUS-P) biopsy under sedation is often mild. Benefit of opioids used during sedation is controversial.
Objective: The objective was to compare numeric rating scale (NRS) score at 30 minutes after TRUS-P biopsy between patients receiving propofol alone or with fentanyl.
Methods: We randomly allocated 124 patients undergoing TRUS-P biopsy to receive either fentanyl 0.5 mcg.kg^{-1} (Group F) or normal saline (Group C). Both groups received titrated propofol sedation via Target-controlled infusion (TCI) with Schneider model until the Observer's Assessment of Alertness/Sedation (OAA/S) scale 0–1 was achieved. Hemodynamic variables, patient movement, postoperative pain score, patient and surgeon satisfaction score were recorded.
Results: Overall, most patients (97.5%) had no to mild pain. Group F had significantly lower median NRS score at 30 minutes compared to Group C (0 [0, 0] vs. 0 [0, 0.25], $p = 0.039$). More patients in Group C experienced pain (90% vs. 75.8%, $p = 0.038$). Perioperative hypotension was higher in group F (81.7%) compared to Group C (61.3%) ($p = 0.013$). Thirty-five (56.5%) patients in Group F and 25 (42.7%) patients in Group C had movement during the procedure ($p = 0.240$). Surgeon's satisfaction score was higher in Group F (10 [9, 10]) than Group C (9 [9, 10]) ($p = 0.037$).
Conclusion: Combining low dose fentanyl with TCI propofol sedation may provide additional benefit on postoperative pain after TRUS-P biopsy, but results in perioperative hypotension. Fentanyl may attenuate patient movement during the procedure, which leads to greater surgeon's satisfaction.
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Introduction

Transrectal ultrasound-guided prostate (TRUS-P) biopsy is a common minor urological procedure which unacceptable pain during this procedure was reported by 22–68% of the patients.[1,2] Pain and discomfort are usually caused by rectal probe insertion and 10–12 core needle biopsies. After the procedure, some of the patients may still feel uncomfortable with the gauze or cotton balls packing inside the rectum.

Various techniques have been used to alleviate pain during TRUS-P biopsy, for instance, intrarectal local anesthetics (IRLA), periprostatic nerve block (PNB), periprostatic infiltration of local anesthetic (PILA), low-dose spinal anesthesia, and intravenous mild to deep sedation.[3] Sedation has been reported to improve pain after the procedure and increase patient's satisfaction.[4,5] Several drug regimens and administration methods have been described, including midazolam and fentanyl (infusion),[5] propofol alone (intravenous bolus),[6] propofol (target-controlled infusion; TCI) and remifentanil,[4] propofol (intravenous bolus) and fentanyl,[6] and propofol and ketamine (ketofol) (intravenous bolus).[7]

Barbosa et al.[6] compared between propofol alone (intravenous bolus) and propofol with low dose fentanyl and reported incidence of moderate to severe postoperative pain were much higher in the group without fentanyl (40% vs. 7%, respectively). On the other hand, Park et al.[8] studied on TCI propofol sedation and reported that patients sedated with TCI propofol alone until either no response to noxious stimuli or mild padding during the procedure was achieved, had low postoperative pain score (mean pain score of 1.4) and high satisfaction score. It is well-demonstrated from these previous studies that deep sedation can reduced pain and discomfort during and after TRUS-P, however, the benefit of adjunct fentanyl to deep propofol sedation is controversial.

The primary objective of this study was to compare the intensity of immediate postoperative pain after TRUS-P biopsy between propofol alone or combined propofol and fentanyl. We also compared the incidence of pain, adverse events, and satisfaction.

Methods

This was a prospective randomized, double-blinded, parallel group, placebo-controlled study. This single-center study was conducted in a 2,500-bed tertiary care university hospital in Bangkok, Thailand. This phase IV study was designed as a superiority study because we hypothesized that adjunct fentanyl could be helpful in alleviate pain after the procedure. The study was approved by the Institutional Review Board (IRB number Si 106/2016) (Appendix 1) and was registered in ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02733705) prior to patient recruitment.

Informed consent was obtained from all patients. Patients aged over 18 years with American Society of Anesthesiologists physical status (ASA) classification I–III and BMI < 30 $kg.m^{-2}$ who were scheduled for TRUS-P biopsy were included in this study. Exclusion criteria were patients with a history of allergy to the study drugs or drugs dependence, abnormal coagulogram or unable to cooperate. Randomization (block of 4) was computer-generated. The allocation assignments were put into sealed envelopes with running numbers 1 to 124. The patients were equally randomized into two groups (1:1); Group F (propofol and fentanyl) and Group C (propofol and normal saline). Both groups received propofol infusion using a target-controlled infusion (TCI) with Schneider model[9] (Fresinius Kabi, Injectomat TIVA Agilia®). In Group F, the patients received 0.1 $mL.kg^{-1}$ of fentanyl (5 mcg. mL^{-1} in 10 mL syringe), while Group C received 0.1 $mL.kg^{-1}$ of placebo (normal saline in 10 mL syringe). The study drugs were prepared by anesthesia personnel who did not involve in the anesthesia care and normal saline was used as placebo. The caregivers and the outcome assessors were blinded to the patient's group.

Upon arrival to the operating theater, routine standard monitoring (noninvasive blood pressure – NIBP, electrocardiogram, pulse oximetry and respiratory rate) was placed and oxygen supplementation was given via nasal cannula 3 $L.min^{-1}$. The study drug was administered 0.1 $mL.kg^{-1}$ bolus prior to propofol infusion. Propofol was administered using target-controlled infusion (Schneider model)[9] started with the target of effect-site concentration (Cet) at 2.5 mcg. mL^{-1} and incrementally increased by 0.1 mcg. mL^{-1} until the observer's assessment of alertness/sedation (OAA/S)[10] scale 0–1 was achieved before incision. The OAS/S was graded as follows: 0, no respond to painful trapezius squeeze; 1, respond only after painful trapezius squeeze; 3, respond only after mild prodding or shaking; 4, respond lethargically to name spoken in normal tone lethargic; and 5, respond readily to name spoken in normal tone. During the procedure, patient movements were evaluated to determine the quality of sedation and were graded as: 1, no movement; 2, minor movement not interfering with the procedure; 3, purposeful movement transiently interfering with the procedure; 4, purposeful movement that made the procedure difficult; and 5, requirement for supplementation with general anesthesia to complete the procedure.

At the end of the procedure, the surgeons were asked to evaluate a 10-point satisfaction score. After the procedure, the patients were transferred to the postanesthesia care unit (PACU) where postoperative NRS score (0 = no pain, 10 = the worst imaginable pain), hemodynamic variables, Aldrete score, nausea and vomiting, urinary catheterization, hematuria, bleeding per rectum, fever, and patient's satisfaction were evaluated. We also calculated the total cost of sedation included propofol, fentanyl ephedrine, atropine, nasopharyngeal airway, TCI machine, and medications given in the postanesthesia care unit. The cost of propofol was calculated per ampule not per milliliter of drug.

Statistical analysis

In this study, it was anticipated that there would be a difference in mean NRS score within 30 minutes after procedure between fentanyl and NSS group. A previous study in the propofol group revealed mean pain score before discharge from postanesthesia care unit was 0.9 (standard deviation [SD] = 1.1).[8] Using the difference of 0.5, SD of 1.1, type I

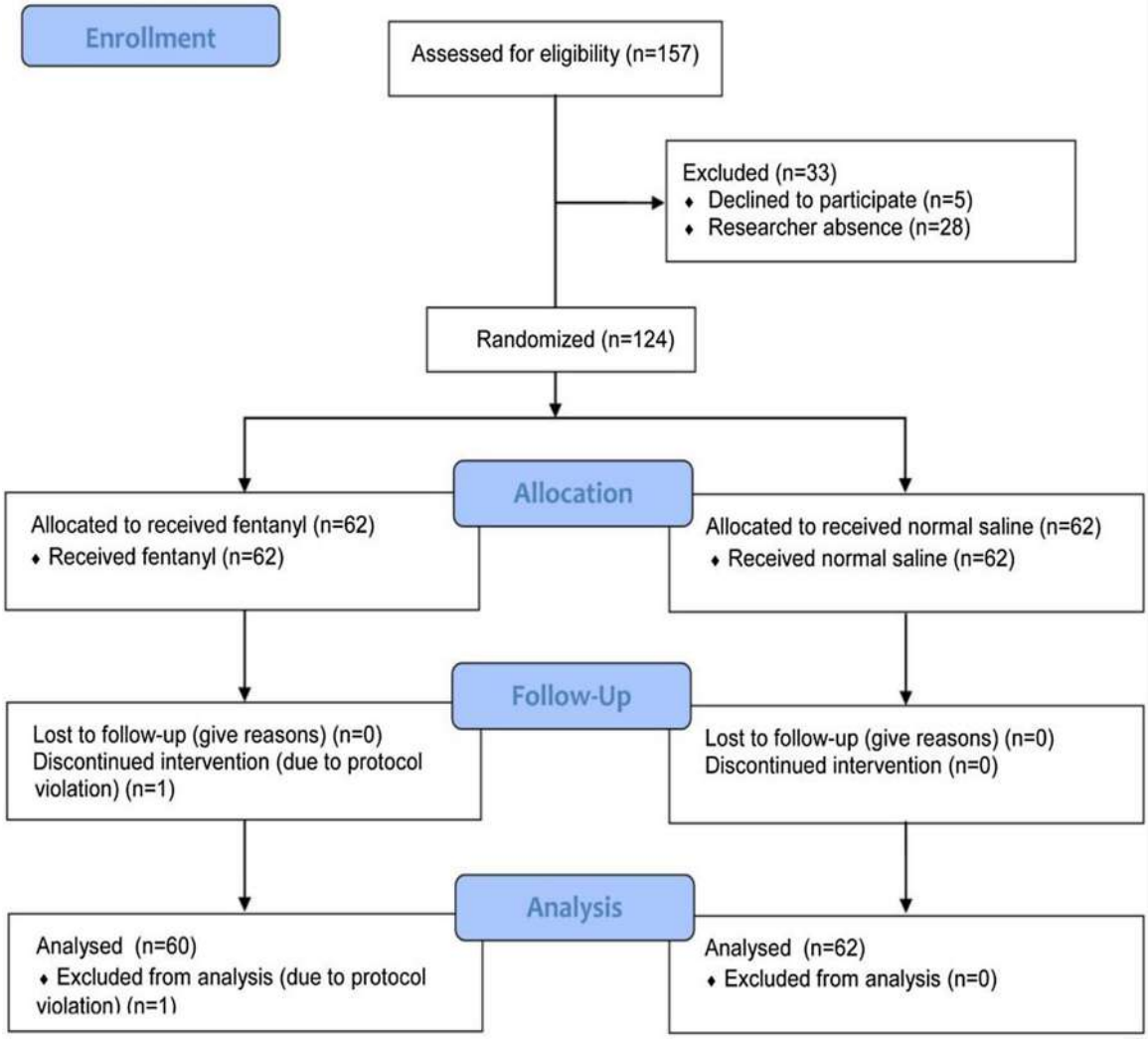

Figure 1 CONSORT flow of the included patients.

error of 0.05 and 80% power, a sample of 61 patients per group was calculated.

Data were analyzed using Predictive Analytics Software Statistics 18.0.0 (Chicago, IL, USA, SPSS Inc.). Continuous data such as age, body mass index (BMI), NRS score, target of effect-site concentration (Cet), and time to achieved (OAA/S) scale 0–1 are presented as mean ± SD or median (P_{25}, P_{75}) and compared using the Student *t*-test or Mann-Whitney U test.

Categorical data such as gender, ASA and incidence of side effects are presented as number (percentage) and were compared using the chi-square test. A *p*-value less than 0.05 was considered statistically significant.

Results

From January 2017 to May 2018, 157 patients scheduled for TRUS-P biopsy were screened for eligibility criteria. Of these, 5 patients refused to participate and the research team was not available in 28 patients. As a result, a total of 124 patients were included in the study. In Group F, one patient had repetitive purposeful movements, so the investigator had to terminate the protocol and one other patient was excluded due to protocol violation (Figure 1). Finally, 60 patients in Group F and 62 patients in Group C were included in the final analyses. Demographic data for both groups are presented in Table 1. There were no significant differences in demographic and perioperative data between the two groups.

The median (P_{25}, P_{75}) NRS pain score at 30 minutes after TRUS-P biopsy in Group F was significantly lower than Group C (0 [0, 0]) vs. 0 [0, 0.25], $p = 0.039$). At 30 minutes, pain was reported by 6 (10.0%) patients in Group F compared to 15 (24.2%) patients in Group C ($p = 0.038$). One patient (1.7%) in Group F reported severe pain (NRS = 8), while two patients (3.2%) in Group C (NRS = 7), in which, all required narcotics for pain treatment (Figure 2).

The mean propofol dosage were significantly lower in Group F (137.5 ± 44.6 mg) compared to Group C (161.4 ± 43.0 mg) ($p = 0.003$). The median [P_{25}, P_{75}] of maximum Cet to achieve OAA/S of 0–1 for the procedure was also lower in Group F (2.8, [2.6, 3.1]) compared to Group C (3.1 [2.9, 3.3]) ($p = 0.0003$) (Figure 3). However, the incidence of hypotension was also higher in Group F

Table 1 Patient characteristics and perioperative data.

	Group F (n = 60)	Group C (n = 62)
Age (yr)	69.1 (7.3)	68.2 (8.5)
BMI (kg.m^{-2})	24.0 (3.4)	24.6 (3.0)
ASA I:II:III	1 (1.7): 43 (71.7): 16 (26.7)	5 (8.1):45 (72.6): 12 (19.4)
Anesthetic time (min)	15.2 (5.9)	16.4 (5.1)
Operation time (min)	8.3 (3.7)	8.6 (3.2)
Time to OAA/S 0–1 (min)	6.3 (4.0)	7.2 (2.7)
Bleeding per rectum	2 (3.3)	2 (3.2)
Packing gauze/cotton ball	57 (95.0)	59 (95.2)
No. of core needle biopsy	12.7 (2.2)	12.5 (2.2)
Urinary catheter		
No	39 (65.0)	44 (71.0)
Yes, intermittent after the procedure	1 (1.7)	2 (3.2)
Yes, retained	20 (33.3)	16 (25.8)

ASA, American Society of Anesthesiologists physical status; OAA/S; Observer's Assessment of Alertness/Sedation Scale.
Data are present as mean (SD) or number of patients (%).

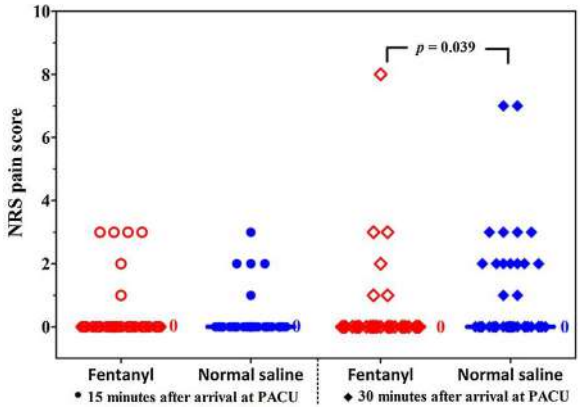

Figure 2 Distribution and median numeric rating scale (NRS) pain score of Group F (red) and Group C (blue) at 15 and 30 minutes after arrival at postanesthesia care unit (PACU).

(81.7%) compared to Group C (61.3%) (p = 0.013) (Table 2). The incidence of movement that interfere with the procedure were slightly higher in Group C (25.8%) in compared to Group F (16.7%), however, no statistical significance was demonstrated (p = 0.240) (Table 2).

There was no significant difference in patient's satisfaction score in groups F (10 [10, 10]) and C (10 [10, 10]) (p = 0.780), whereas surgeon's satisfaction score was significantly higher in Group F (10 [9, 10]) than Group C (9 [9, 10])) (p = 0.037). There was also no difference in hypoxia and bradycardia between the two groups. The average anesthesia cost of per patient in Group C (US$ 11.8) was US$ 1.9 higher than Group F (US$ 9.9).

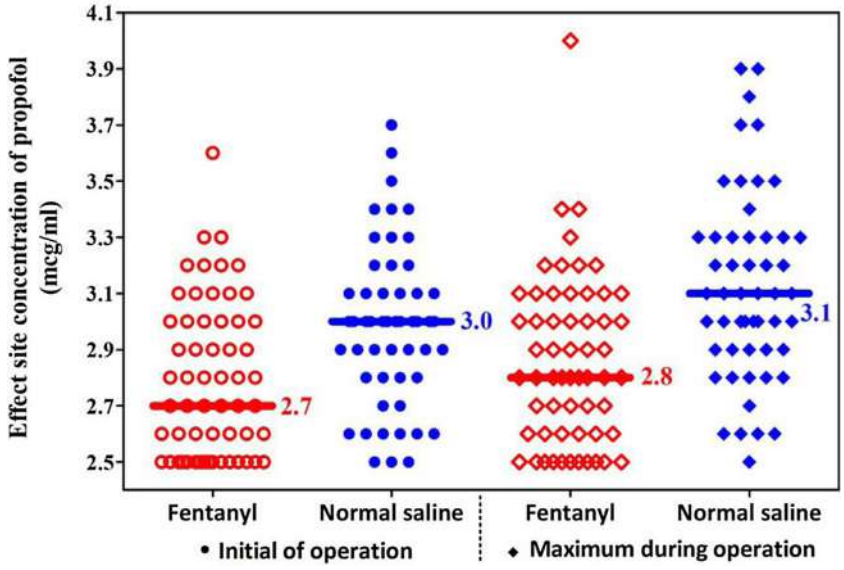

Figure 3 Distribution and median of effect site concentration of propofol (Cet) among Group F (red) and Group C (blue) at start and at maximum concentration.

Table 2 Incidence of perioperative complications.

	Group F (n = 60)	Group C (n = 62)	*p*-value
Hypoxia			0.550
Arouse	0 (0)	1 (1.6)	
Airway management	4 (6.7)	3 (4.8)	
Nasopharyngeal airway	1 (1.7)	3 (4.8)	
Hypotension	49 (81.7)	38 (61.3)	0.013
Bradycardia required intravenous atropine	1 (1.7)	1 (1.6)	0.981
Movement during the procedure			0.240
No movement	35 (58.3)	27 (43.5)	
Not interfere with procedure	15 (25.0)	19 (30.6)	
Interfere with procedure	10 (16.7)	16 (25.8)	

Data are present as number of patients (%).

Discussion

The main findings of this study are that 1) target-controlled infusion of propofol can be used as a sedation technique for TRUS-P biopsy to reduce pain and discomfort, 2) despite no to mild immediate postoperative pain was mostly observed in both groups, adjunct low-dose fentanyl further reduce pain, 3) fentanyl also decreases TCI propofol dosage and patient's movement interfering the procedure but results in a higher incidence of hypotension, and 4) overall high patient's and surgeon's satisfaction can be achieved using TCI propofol sedation, however, surgeon's satisfaction is higher in fentanyl group.

Postoperative pain after TRUS-P biopsy

Although some previous papers had demonstrated high incidence of pain and pain score during TRUS-P biopsy, only no to mild pain was reported in studies using intravenous sedation. The incidence of moderate to severe pain for TRUS-P biopsy using propofol alone were 7–40%,[6,11,12] and only 0–7% when combined with opioids.[4,6,12,13] Overall, average pain score from previous studies were 0–3, with or without opioids.[4,6,11,14] In our study, 17.2% of the patients in both groups had experienced any pain in PACU and among them, only 3 patients reported severe pain. The findings from previous studies and ours demonstrated that intravenous sedation using propofol with or without opioids was an effective method to reduce pain from TRUS-P biopsy and resulted in no to mild pain in most patients.

Our study demonstrated that adding low-dose fentanyl to TCI propofol sedation can reduce both the postoperative pain score and the incidence of postoperative pain 30 minutes after TRUS-P biopsy. These results were consistent with previous studies, which combined the use of opioids with propofol for sedation in TRUS-P biopsy. Seo et al.[12] reported that adding 0.5 $mg.kg^{-1}$ meperidine to propofol sedation resulted in less average postoperative pain compared to control (Mean NRS pain score of 1.5 ± 1.9 vs. 0.4 ± 1.0, $p = 0.012$). Nichikawa et al.[13] compared fentanyl with propofol sedation with spinal anesthesia for TRUS-P biopsy. They reported no to mild pain in all patients during PACU stay in both groups and no significant difference was found in the incidence of mild pain in fentanyl/propofol group (25%) compared to spinal anesthesia (20%). Barbosa et al.[6] also demonstrated that patients receiving propofol with either 0.5 $mcg.kg^{-1}$ fentanyl had significantly lower pain at 15 and 60 minutes and required less pain killer after the procedure compared to those who received propofol alone. Postoperative pain score among patients undergoing TRUS-P biopsy in all studies is already low, however, our data demonstrated that approximately 20% of the patients still experienced pain. Further reduction in pain with low dose fentanyl may provide clinical benefit in some patients.

Hypotension

In this study, the incidence of perioperative hypotension required treatment was higher in patients receiving fentanyl (81.7%) compared to the control group (61.3%), which were higher than previous studies. In contrast to our study, Nishikawa et al.[13] found that 47.5% of the patients receiving fentanyl 1 $mcg.kg^{-1}$ together with propofol infusion experienced hypotension Meanwhile, in other studies, the incidence of hypotension in patients receiving only propofol were 40–48.6%, which was also lower than both groups in our study (61.3%). Propofol was given by bolus and followed either by infusion[15] or incremental bolus,[7,8] unfortunately, the total dose of propofol was not reported. The higher incidence of hypotension in our study compared to others might be due to the fact that we used propofol infusion guided by TCI model, which generally, result in higher amount of propofol dose in a shorter duration than the dose used in other studies.

Park et al.[8] also used TCI infusion of propofol for sedation in TRUS-P biopsy and reported no hypotension in their study. Unlike our study, the authors gradually titrated Cet of propofol until desirable level of sedation was achieved. They reported the mean Cet of 2.1 ± 0.3 $mcg.mL^{-1}$ was used to achieve a similar level of sedation to our study (OAA/S 0–1), which was lower than initial Cet setting of our study (Cet 2.5 $mcg.mL^{-1}$). The greater rate of hypotension in our study was likely due to higher Cet setting. Moreover, we did not include a protocol for Cet reduction when the patients developed hypotension. Thus, the incidence of hypotension may be reduced by starting with a lower Cet setting and then titrating to the target level of sedation.

However, the total sedation time was much longer although the procedural time was even shorter compared to

our study. Interestingly, combining propofol with fentanyl resulted in significantly higher incidence of hypotension despite smaller amount of total propofol given and lower Cet setting at the start of the procedure. On the other hand, previous studies demonstrated no significant difference in blood pressure profile among both patients receiving propofol alone either with 0.5 mcg.kg^{-1} fentanyl[6,7] or 0.5 mg.kg^{-1} meperidine.[12,14] Many studies comparing the use of propofol alone and combined with fentanyl for procedural sedation suggested that adding fentanyl could reduce propofol requirements without significant difference on blood pressure.[16–18] Similar to previous studies, the total dose of propofol was lower in the fentanyl group, however, the dose difference in our study was small and may have only little clinical significance. This may be due to the fact that we did not have a protocol for step down in Cet setting when blood pressure decreased.

Therefore, additional small dose of fentanyl could cause hypotension. The results suggested that TCI of propofol is a comparable option for TRUS-P biopsy sedation either alone or combined with fentanyl. The initial Cet of 2.5 mcg. mL^{-1} may be used for short induction time but should be decreased once blood pressure starts to decline to avoid hypotension. If opioid was given in addition to propofol, start with lower Cet and dose reduction early to prevent adverse hemodynamic effects.

Satisfaction

Patients' satisfaction scores for both groups in our study were high and not different between the two groups. Several studies had also showed similar results.[4,8,13,15,19] Although the overall cost is higher, the results were consistent among studies that patients receiving sedation with propofol had higher satisfaction score than those receiving local or topical analgesia.[4] Pain, even mild degree, is the main influencer on patient's satisfaction score. We did a further analysis and found that patients who had any level of pain demonstrated significantly lower satisfaction score than those without pain (10 [9, 10] vs. 10 [10, 10], $p = 0.029$). As a result, measures to alleviate pain should be considered to improve patient's satisfaction.

Surgeons' satisfaction score was higher in the fentanyl group. This is related to the frequency of patient movement during the procedure. Patient movement not only delays the surgery but may also be harmful to the patient and can disturb quality of tissue biopsy. In the previous study by Abdellatif et al.[7] reported a significantly better surgical condition in patients undergoing TRUS-P biopsy under ketofol (combined ketamine and propofol) compared to propofol alone. Another study by Sundarathiti et al.[15] also reported 100% vs. 57% of no movement during surgery using selective spinal anesthesia and propofol sedation, respectively.

Although we could not demonstrate a significant difference in movement between the two groups, the group receiving fentanyl seemed to have lower incidence of patient movement, especially the movement that interfere with the procedure. The results suggested that pain may be the primary reason for the patient to move during the procedure, therefore, adding low dose fentanyl may facilitate surgical condition.

Further study

Since most of the patients experienced no to mild pain, preoperative slow release oral paracetamol, especially 650 mg, which last 8 hours, may be a cost-effective alternative pain treatment for this procedure.

Limitations

The limitations in this study are no Bispectral index (BIS) monitoring and the protocol in this study did not provide a decrease in Cet during the study. Therefore, this may cause the higher incidence of hypotension.

Conclusion

In summary, combining low dose fentanyl with TCI propofol sedation may provide additional benefit on postoperative pain after TRUS-P biopsy, but results in higher incidence of perioperative hypotension. Fentanyl may attenuate patient movement during the procedure, which leads to greater surgeon's satisfaction.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjane.2021.02.001.

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CLINICAL RESEARCH

Effect of intravenous lidocaine on short-term pain after hysteroscopy: a randomized clinical trial



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KEYWORDS
Anesthesia;
Hysteroscopy;
Lidocaine;
Postoperative pain;
Propofol

Abstract
Background: The role of intravenous lidocaine infusion in endoscopic surgery has been previously evaluated for pain relief and recovery. Recently, it has been shown to reduce postoperative pain and opioid in patients undergoing endoscopic submucosal dissection. Similar to endoscopic submucosal dissection, operative hysteroscopy is also an endoscopic surgical procedure within natural lumens. The present study was a randomized clinical trial in which we evaluated whether intravenous lidocaine infusion would reduce postoperative pain in patients undergoing hysteroscopic surgery.
Objective: To evaluate whether intravenous lidocaine infusion could reduce postoperative pain in patients undergoing operative hysteroscopy.
Methods: Eighty-five patients scheduled to undergo elective hysteroscopy were randomized to receive either an intravenous bolus of lidocaine 1.5 $mg.kg^{-1}$ over 3 minutes, followed by continuous infusion at a rate of 2 $mg.kg^{-1}$. h^{-1} during surgery, or 0.9% normal saline solution at the same rate. The primary outcome was to evaluate postoperative pain by Visual Analog Scale (VAS). Secondary outcomes included remifentanil and propofol consumption.
Results: In the lidocaine group, the VAS was significantly lower at 0.5 hour ($p = 0.008$) and 4 hours ($p = 0.020$). Patients in the lidocaine group required less remifentanil than patients in the control group ($p < 0.001$). However, there was no difference between the two groups in the propofol consumption. The incidence of throat pain was significantly lower in the lidocaine group ($p = 0.019$). No adverse events associated with lidocaine infusion were discovered.
Conclusion: Intravenous lidocaine infusion as an adjuvant reduces short-term postoperative pain in patients undergoing operative hysteroscopy.
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Introduction

Operative hysteroscopy is performed under General Anesthesia (GA), which benefits both physicians and patients. First, GA can reduce potential difficulties of intrauterine access compared with local anesthesia.[1] Second, although a few studies have reported that non-pharmacological approaches to pain control for hysteroscopic procedures (including distension methods and physical stimuli) have contributed to improving patient satisfaction, hysteroscopy continues to be painful for a very high percentage of patients.[2] Obviously, GA has been demonstrated to alleviate patients' experience of pain during hysteroscopy.

Intraoperative lidocaine infusion has been widely accepted as an alternative to GA, as it can achieve opioid sparing, good pain relief, decreased postoperative nausea and vomiting, and excellent recovery.[3,4] Furthermore, recent studies have shown that intravenous lidocaine infusion can reduce postoperative pain and opioid requirements in patients undergoing Endoscopic Submucosal Dissection (ESD).[5] Similar to ESD, operative hysteroscopy is an endoscopic procedure within natural lumens. However, to the best of our knowledge, the efficacy of intravenous lidocaine in operative hysteroscopy has not been fully elucidated. Therefore, our study explored whether the administration of intravenous lidocaine can reduce postoperative pain, and propofol and remifentanil requirements in patients undergoing operative hysteroscopy.

Methods

Study population

The study protocol was conducted in compliance with the Helsinki Declaration and approved by the Hospital Ethics Committee of Renmin Hospital of Wuhan University. Written informed consent was obtained from 85 patients with an American Society of Anesthesiologists (ASA) classification of I–II undergoing operative hysteroscopy. The exclusion criteria were as follows: less than 18 years old; hypersensitivity to lidocaine; only performing diagnostic hysteroscopy; chronic abuse of opioid or nonsteroidal anti-inflammatory drug; chronic pain; mis- or lack of understanding of oral information about the study; other severe systemic diseases; and serious surgical complications. The study was registered under the Clinical Trials Register number ChiCTR1800016857.

Study group

Patients were categorized into two study groups using a random number table method performed by an Independent Anesthetist (IA) not involved in the treatment or follow up. The study drugs were prepared in syringes with an identical appearance by the same IA as follows: a 20 mL syringe contained 1% lidocaine solution or 0.9% normal saline solution (for the bolus), and a 50 mL syringe contained 1% lidocaine solution or 0.9% normal saline solution (for the continuous infusion). The treatment and follow-up anesthetists were all blinded to patient assignment until analysis completion. The IA would cease the blinding if the patient experienced abnormal conditions (such as serious complications) during the trial. All operative procedures were performed by the same surgeon, including the same hysteroscopic instrumentation.

Interventions

All patients received the study drugs prepared by IA with a bolus dose of 0.15 $mL.kg^{-1}$ over 3 minutes prior to anesthesia induction, followed by continuous infusion at a rate of 0.2 $mL.kg^{-1}.\ h^{-1}$ until the end of the surgery. Patients were treated under the same anesthetic protocol without premedication. Standard monitoring included five-lead electrocardiography, oxygen saturation, noninvasive blood pressure, continual end-tidal carbon dioxide and Narcotrend (NT) monitoring (MT Monitor Technik GmbH & Co, KG, D-24576 Bad Bramstedt, Germany). The Narcotrend Index (NTI) determined by the Narcotrend monitoring system is a dimensionless continuous variable ranging from 0 to 100 that reflects the depth of anesthesia. Based on the NTI, the depth of anesthesia ranges from stage A (awake) to stage F (very deep anesthesia), with stage D (37–64) indicating the routine depth of anesthesia for surgery.

Anesthesia was induced with propofol 2.5 $mg.kg^{-1}$ and then with remifentanil 1.5 $\mu g.kg^{-1}$ within one minute followed by the placement of a paraffin oil-lubricated laryngeal mask (ALMA type, HangZhou FuShan Medical Appliances Co, Ltd. China). The specific size of advanced laryngeal mask airway (ALMA) was selected according to the weight of the patient (3# for 30–50 kg; 4# for 50–70 kg; 5# for 70–100 kg), the intracuff pressure of ALMA was the pressure that has been set at the factory (< 2 cm H_2O). We did not deflate before inserting the laryngeal mask, and generally did not inflate after inserting it. If the airway pressure is too high (more than 30 mmHg) or obviously leaking in mechanical ventilation after implantation, adjust the position of the laryngeal mask or proper inflation of air (less than 20 mL), observe the airway pressure, and check the end-breathing carbon dioxide partial pressure to ensure the correct position. 180-degree rotation was used for insertion of laryngeal mask by all anesthesiologists.

Patients were placed on given mechanical ventilation or were converted to assisted ventilation when they resumed spontaneous breathing. Anesthesia was maintained with continuous remifentanil and propofol infusion. Remifentanil was adjusted at a rate of 5–10 $\mu g.kg^{-1}.\ h^{-1}$, and the rate of propofol was adjusted according to the following NTI target values: during maintenance in a range from 37–64; 5 minutes before the end of surgery in a range from 65–79. In the case of intraoperative patient movement, additional remifentanil (1 $\mu g.kg^{-1}$) was injected immediately. Anesthesia was performed by the attending anesthesiologist for more than 5 years.

Outcomes and adverse events observation

Mean Blood Pressure (MAP), Heart Rate (HR), and NTI data were collected at six separate time points: before intravenous the study drugs prepared by IA e (T0); before anesthesia induction (T1); 5 and 10 minutes after surgery (T2 and T3); at the end of surgery (T4); and at the time of

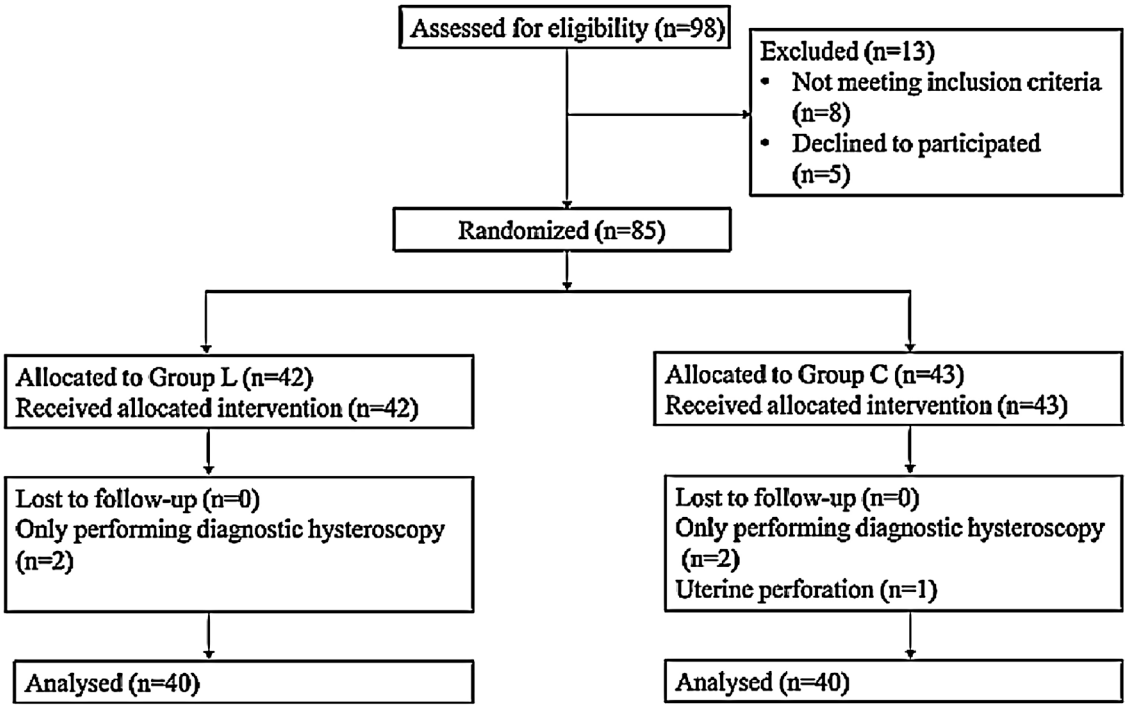

Figure 1 Flow diagram of patient recruitment.

laryngeal mask removal (T5). The total administered doses of remifentanil and propofol were recorded. Postoperative pain at rest was evaluated at 0.5 hour (T6), 4 hours (T7), and 24 hours (T8) after surgery by the visual analogue scale (VAS, 0 = no pain, 10 = unbearable pain). In the case of a VAS score $\geq$ 6, 50 mg of flurbiprofen was given intravenously. The incidence of throat pain was assessed using the VAS within 24 hours after surgery (any VAS score $\geq$ 2 was considered to represent a sore throat). The incidence of postoperative nausea or vomiting was also recorded up to 24-hours after the procedure.

Statistical analysis

The primary outcome variable was postoperative pain. The sample size was calculated based on the 0.5 hour postoperative VAS score of 5 patients (mean = 2.3; Standard Deviation −SD = 1.5) administered saline in a preliminary study. To demonstrate a 35% difference in the mean VAS score at 0.5 hour postoperatively between the two groups with a two-tailed α of 0.05 and a power of 80%, 36 candidates in each group were required. To compensate for the possibility of dropout for various reasons, we initially enrolled 85 patients in total for randomization. Statistical analysis was performed using GraphPad Prism version 6 (GraphPad Software Inc.). The Kolmogorov-Smirnov test was used to test the assumption of normal distribution. Normally distributed data are reported as mean $\pm$ SD and were compared among groups using unpaired *t*-test. Non-normally distributed data are reported as median (minimum−maximum) and were compared between groups using the Mann-Whitney U test. Repeated-measured data within the group, such as VAS, HR, MBP, and NIT were analyzed with two-way analysis of variance. When the interaction was statistically significant, sidak's multiple comparisons test was performed. Categorical data were compared between groups with Chi-Square test. p-values less than 0.05 were considered to represent a statistically significant difference.

Results

The study flowchart is shown in Figure 1. Of 98 patients assessed for eligibility, 85 patients were enrolled and randomly assigned to two groups. Five patients (2 in Group L and 3 in Group C) were excluded from the analysis because only diagnostic hysteroscopy or uterine perforation was performed. Patient characteristics were similar between the groups (Table 1). For MAP, HR and NTI data at the corresponding time points no significant differences were found between the two groups (Figure 2).

Details regarding VAS scores, drugs administered, and postoperative events were shown in Table 2. In the lidocaine group, the VAS was significantly lower at 0.5 hour (p = 0.008) and 4 hours (p = 0.020) postoperatively, compared to the control group. The total administered dose of remifentanil was 13% lower in Group L than in Group C, 232 (185−410) vs. 259 (190−420); $p < 0.001$. There was no difference between the two groups in the propofol requirement. No patients were given flurbiprofen after surgery. Regarding to postoperative effects, the lidocaine group had less throat pain (22.5% vs. 47.5%, p = 0.019). The groups did not differ with respect to the incidence of nausea or vomiting. No case of lidocaine-related local anesthetic systemic toxicity was reported.

Table 1 Baseline characteristics of study subjects.

	Group L (n = 40)	Group C (n = 40)	*p*-value
Age (years)	31.38 ± 7.37	32.85 ± 7.73	0.385
Weight (kg)	50 (40–78)	51 (42–82)	0.206
Height (cm)	160.10 ± 7.05	159.20 ± 8.19	0.600
ASA physical status, n (%)			0.485
I	24 (60%)	27 (67.5%)	
II	16 (40%)	13 (32.5%)	
Surgical indication, n (%)			0.819
Polyp	15 (37.5%)	17 (42.5%)	
Intrauterine adhesion	11 (27.5%)	9 (22.5%)	
Submucous myoma	8 (20%)	10 (25%)	
Placenta remnant	3 (7.5%)	1 (2.5%)	
Cesarean scar pregnancy	1 (2.5%)	2 (5%)	
Uterine septum	2 (5%)	1 (2.5%)	
Duration of surgery (min)	25 (18–55)	25 (15–48)	0.357

Values are shown as mean ± SD, median (minimum–maximum) or number of patients (proportion). ASA, American Society of Anesthesiologists.

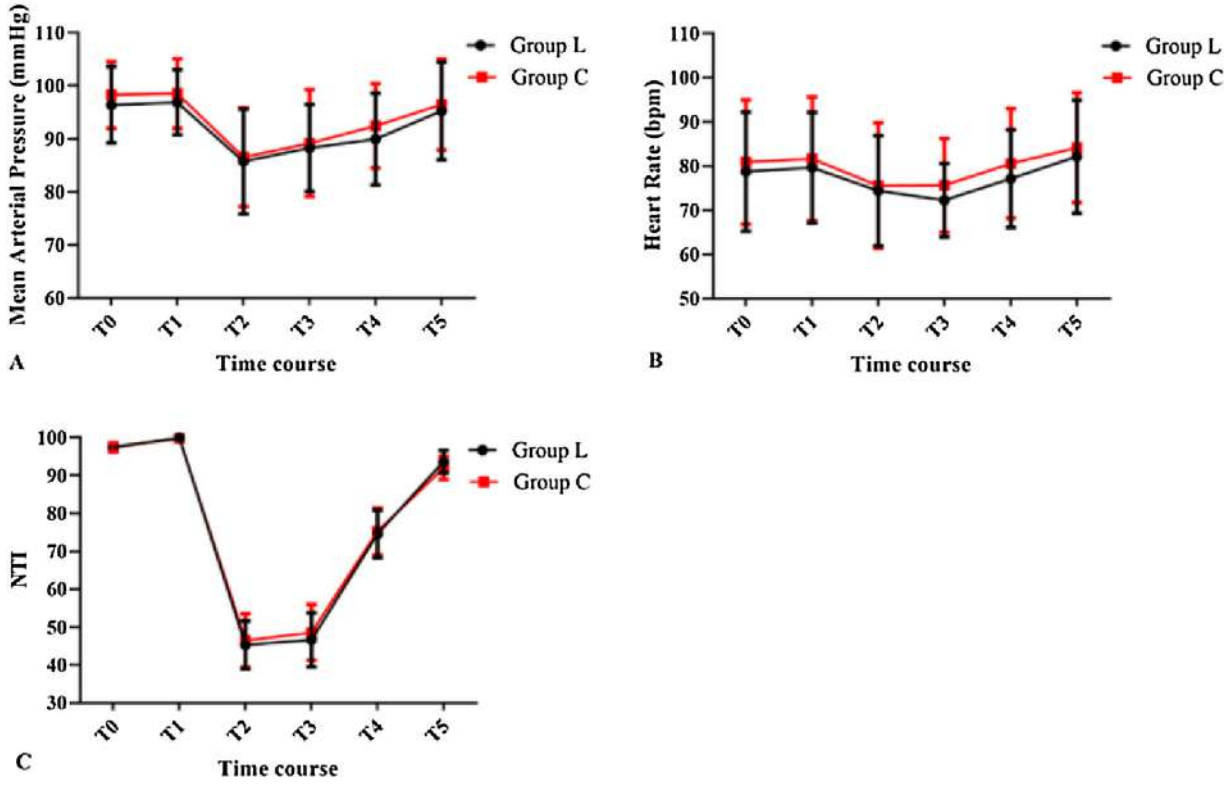

Figure 2 Changes in (A) mean blood pressure, (B) heart rate and (C) NTI. T0, Before intravenous the study drugs; T1, Before anesthesia induction; T2, 5 minutes after the start of the surgery; T3, 10 minutes after the start of the surgery; T4, The end of the surgery; T5, The time to remove the laryngeal mask; NTI, Narcotrend Index. Data are expressed as mean ± SD.

Discussion

Hysteroscopic procedures could be performed under mild sedation, local anesthesia, or GA. In this randomized, double-blinded, placebo-controlled trial, we selected GA for use during operative hysteroscopy, with intravenous lidocaine administered as a bolus of 1.5 $mg.kg^{-1}$ and then a continuous infusion at 2 $mg.kg^{-1}.\ h^{-1}$. We found that this strategy reduces the severity of short-term postoperative pain. Moreover, lidocaine administration also reduces the remifentanil requirement and the incidence of throat pain during operative hysteroscopy.

Intravenous lidocaine infusion has shown efficacy in controlling postoperative pain.[6] The analgesic mechanisms are multifactorial, including sodium channel blockade, reduction in spinal cord sensitivity, synergistic effects with the GA agents and intrinsic systemic anti-inflammatory properties.[7,8] The analgesic efficacy of intravenous lidocaine

Table 2 Perioperative data of study subjects.

	Group L (n = 40)	Group C (n = 40)	*p*-value
VAS			
T6	1.83 ± 1.24	2.43 ± 1.11	0.032
T7	1.98 ± 0.95	2.63 ± 1.23	0.018
T8	0.90 ± 0.81	1.20 ± 0.85	0.490
Total remifentanil (μg)	232 (185–410)	259 (190–420)	< 0.001
Total propofol (mg)	248.5 (175–342)	255 (170–335)	0.229
Throat pain, n (%)	9 (22.5%)	19 (47.5%)	0.019
Nausea or vomiting, n (%)	4 (10%)	9 (22.5%)	0.130

Values are presented as mean ± SD, median (minimum–maximum) or number of patients (proportion). VAS, Visual Analogue Scale (0 = no pain, 10 = unbearable pain). T6, 0.5 hour after surgery; T7, 4 hours after surgery; T8, 24 hours after surgery.

has been observed mainly in abdominal surgeries, including colectomy,[9] gastrectomy,[10] and cholecystectomy.[11] Moreover, Kim et al. confirmed the postoperative analgesic effects of intravenous lidocaine after ESD,[5] an endoscopic surgical procedure with natural lumens similar to operative hysteroscopy. They also estimated that the analgesic effects of lidocaine were mainly on visceral pain.[5] Therefore, we hypothesized that intravenous lidocaine would be beneficial for controlling visceral pain caused by operative hysteroscopy. In our study, administration of intravenous lidocaine resulted in reduced earlier postoperative hypogastric pain intensity and less remifentanil consumption during operative hysteroscopy, which is consistent with a previous study reporting that intravenous lidocaine had a positive impact on pain scores in the early postoperative phase.[4] It has been confirmed that the half-life of lidocaine is only 1.5–2 hours after bolus injection.[8] This may explain why analgesic effects were noted in the earlier postoperative phase rather than at 24 hours postoperatively in our study.

Remifentanil is a preferred drug for endoscopy because of its rapid onset and offset of action, and minimal adverse effects on cardiovascular and respiratory parameters.[12] To observe earlier postoperative analgesic effects of intravenous lidocaine, another advantage of remifentanil is its ability to avoid interference with the use of other opioid drugs. The administration of intravenous lidocaine has been shown to have an opioid sparing effect during GA, including on fentanyl,[13] sufentanil,[14] and morphine.[15] In a recent study, a remifentanil-sparing effect of intravenous lidocaine in the intraoperative period was found,[16] which is consistent with our findings. However, another study reported that perioperative intravenous lidocaine infusion had no significant effect on the remifentanil requirement during hypotensive anesthesia for an elective transsphenoidal endoscopic hypophyseal adenoma excision procedure.[17] Previous studies reported that intravenous lidocaine had a propofol-sparing effect during GA.[18,19] In this study, we ensured that each patient was at a constant anesthetic depth during surgery via Narcotrend monitoring, and we found that there was no difference in the propofol requirement between the two groups. These differences were likely due to the distinct types of surgery performed and different regimes for anesthetic management.

We used a laryngeal mask for mechanical ventilation or assisted ventilation to ensure respiratory safety in this study. In addition, placement of the laryngeal mask could also provide us with another way to observe the analgesic effects of lidocaine. The administration of intravenous lidocaine reduced the incidence of throat pain caused by the laryngeal mask from 47.5% to 22.5% in this study. Our observation is in keeping with the finding of several studies showing that the administration of intravenous lidocaine was effective in reducing throat pain after ESD[5] and postoperative throat soreness caused by tracheal intubation.[20] Last, we did not observe any significant differences in the incidence of postoperative nausea or vomiting, which is consistent with previous reports.[21,22]

There are some limitations to our study. We did not measure the plasma level of lidocaine in our patients. However, the protocol for administering a loading dose followed by the continuous intravenous infusion of lidocaine during GA has been used previously at several centers and reported to result in a level well below the toxic level.[23,24] Another limitation is the small number of patients. A larger-scale trial will provide further details to validate our findings. Finally, our unit did not have the nociception level index or analgesia nociception index monitoring equipment. The use of these devices may provide more accurate results in future studies.

In conclusion, intravenous lidocaine infusion as an adjuvant reduces short-term postoperative pain in patients undergoing operative hysteroscopy.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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CLINICAL RESEARCH

Paravertebral block using levobupivacaine or dexmedetomidine-levobupivacaine for analgesia after cholecystectomy: a randomized double-blind trial

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KEYWORDS
Laparosopic cholecystectomy;
Thoracic paravertebral block;
Levobupivacaine;
Dexmedetomidine;
Postoperative analgesia

Abstract

Background: Thoracic paravertebral block (TPVB) has emerged as an effective and feasible mode of providing analgesia in laparoscopic cholecystectomy. Though a variety of local anaesthetic combinations are used for providing TPVB, literature is sparse on use of dexmedetomidine in TPVB. We aimed to compare levobupivacaine and levobupivacaine-dexmedetomidine combination in ultrasound guided TPVB in patients undergoing laparoscopic cholecystectomy.

Methodology: 70 ASA I/II patients, aged 18–60 years, scheduled to undergo laparoscopic cholecystectomy under general anaesthesia were enrolled and divided into two groups. Before anaesthesia induction, group A patients received unilateral right sided ultrasound guided TPVB with 15 ml 0.25% levobupivacaine plus 2 ml normal saline while group B patients received unilateral right sided ultrasound guided TPVB with 15 ml 0.25% levobupivacaine plus 2 ml solution containing dexmedetomidine 1 $\mu g.kg^{-1}$. Patients were monitored for pain using Numeric Rating Scale (NRS) at rest, on movement, coughing and comfort scores post surgery. Total analgesic consumption in first 48 hour postoperative period, time to first request analgesic and pain scores were recorded.

Results: Total amount of rescue analgesia (injection tramadol plus injection tramadol intravenous equivalent dose) consumed during 48 hours postoperatively in group A was 146.55 mg while in group B was 111.30 mg ($p = 0.026$). Mean time for demanding rescue analgesia was 273 minutes in group A while in group B was 340 minutes ($p = 0.00$).

Conclusion: TPVB using dexmedetomidine 1 $\mu g.kg^{-1}$ added to levobupivacaine 0.25% in patients undergoing laparoscopic cholecystectomy significantly reduced total analgesic consumption in first 48 hours and provided longer duration of analgesia postoperatively compared to levobupivacaine 0.25% alone.

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Introduction

Laparoscopic cholecystectomy is one of the most commonly performed surgeries in gall ball disease patients. A large number of patients undergoing laparoscopic cholecystectomy may suffer from severe postoperative pain if analgesia is not managed appropriately.[1] The presence of acute postoperative pain causes extreme patient discomfort, extended post-anesthesia care unit stays and restricts early recovery that should have been seen in laparoscopic surgeries. Over the past years, paravertebral blocks (PVB) have been increasingly used for providing postoperative analgesia.[2] The use of ultrasound in the administration of thoracic paravertebral block has greatly reduced the incidence of associated complications.[3] There are reports in literature describing the use of TPVB for providing post-laparoscopic cholecystectomy analgesia.[4,5] Though a variety of local anesthetics have been used for administering TPVB, there is scarcity of studies on adjuvants in thoracic paravertebral block in laparoscopic cholecystectomy. Hence the present trial was designed to assess additional analgesic requirement in patients undergoing laparoscopic cholecystectomies after preoperative unilateral thoracic PVB using two different analgesic combinations (levobupivacaine *vs.* levobupivacaine and dexmedetomidine combination). We hypothesized that adding dexmedetomidine to levobupivacaine would reduce the postoperative analgesic consumption and increase the time to first rescue analgesic.

Methodology

Ethics

After obtaining approval from the institutional ethics committee of Post Graduate Institute of Medical Education and Research, Chandigarh (9171/INT/IEC/PG-2Trg/2012/22034), dated November 20, 2013, this prospective, randomized, double-blind trial was carried out by the Department of Anesthesia & Intensive Care and Department of General Surgery of the institute.

Inclusion and exclusion criteria

After obtaining written informed consent, 70 ASA (American Society of Anesthesiologists) I/II patients, aged 18–60 years, scheduled to undergo laparoscopic cholecystectomy under general anesthesia were enrolled in the study. Patients with history of allergy to local anesthetics, coagulopathy, morbid obesity and having decreased pulmonary reserve, cardiac disorders, renal dysfunction, pre-existing neurological deficits, psychiatric illness were excluded from the study.

Randomization

Patients were randomized using coded sealed envelopes computer generated, and subsequently participants were allocated to one of the two groups of 35 patients each. In group A, patients received unilateral right-sided ultrasound guided thoracic paravertebral block with 15 ml 0.25% levobupivacaine plus 2 ml normal saline, while in group B, patients received unilateral right-sided ultrasound guided thoracic paravertebral block with 15 ml 0.25% levobupivacaine plus 2 ml solution containing dexmedetomidine 1 $\mu g.kg^{-1}$.

Blinding

Both the participants and the investigators were blinded to the medications used for the PVB until the completion of study. All the investigators involved in patient's management and data collection, including the patient's anesthesiologist giving general anesthesia, were unaware of the group assignment.

Procedure

In the preoperative room, patients were monitored for heart rate (HR), blood pressure (BP), continuous electrocardiogram (ECG) and arterial oxygen saturation (SpO_2) using standard monitors. Baseline readings were recorded, and an intravenous access was established in all patients. All the patients were premedicated with intravenous midazolam 25 $\mu g.kg^{-1}$, ranitidine 1 $mg.kg^{-1}$ and palanosetron 1 $\mu g.kg^{-1}$. To perform the block, patients were placed in sitting position and spinous process of T8 vertebra was identified and marked. Under aseptic precautions, using a sterile high-frequency (5–10 MHz) ultrasound probe (Sonosite, Inc. Bother. Wa 98021 USA), the thoracic paravertebral space was identified.[6] After infiltrating the skin with 3–5 ml of 1% lignocaine, in-plane needle guidance technique was followed using a 20G epidural needle on unilateral right side. Once the tip of the needle was in a position between the internal intercostal membrane and the pleura, the study drug was administered, after negative aspiration over a period of 30 seconds. During administration of the local anesthetic, downward displacement of the parietal pleura was observed. Patient's hemodynamics were monitored for a period of 20 minutes after giving the block. Following this, patients were shifted to operating room. In the operating room, patients were monitored for heart rate (HR), blood pressure (BP), continuous electrocardiogram (ECG), arterial oxygen saturation (SpO2), end-tidal carbon dioxide ($ETCO_2$) and temperature using multichannel monitors (Datex-Ohmeda S/5 Avance). General anesthesia in all the participants followed a standard anesthetic technique. After preoxygenation with 100% oxygen, anesthesia was induced with injection fentanyl 1.5 $\mu g.kg^{-1}$ and propofol 2–3 $mg.kg^{-1}$. Atracurium 0.5 $mg.kg^{-1}$ was given to facilitate tracheal intubation. The maintenance of anesthesia was provided with oxygen and isoflurane. The patients received top-ups of intravenous atracurium (0.1 $mg.kg^{-1}$) at regular intervals using TOF.[7] Heart rate and mean arterial pressure were maintained within 20% of the baseline values by the administration of additional bolus doses of fentanyl (0.5 $\mu g.kg^{-1}$), if required, and the amount of additional intravenous fentanyl consumed intraoperatively was noted. At the end of surgery, 500 ml normal saline was used for the intraperitoneal irrigation in all the patients, and residual neuromuscular blockade was reversed with injection neostigmine 50 $\mu g.kg^{-1}$ and injection glycopyrrolate 10 $\mu g.kg^{-1}$, and local anesthetics

were not infiltrated in trocar sites. On return of consciousness and adequate recovery of muscle strength, patients were extubated and shifted to the postanesthetic care unit (PACU).

Follow-up

In the postoperative room, patients were monitored for mean arterial pressure (MAP), pulse rate (PR), NRS[8] (0 for no pain and 10 for worst imaginable pain) for parietal pain, visceral pain, and shoulder pain – during rest, on movement and on coughing, nausea or vomiting and sedation at regular intervals (30 minutes, 60 minutes, 1–4 hours, 4–12 hours, 12–24 hours, 24–48 hours) – by an investigator blinded to group allocation. Patients were also assessed for the comfort score,[9] where 0 is the least comfortable and 10 is the most comfortable. If at any time interval patients comfort score was < 6, the intensity of parietal and visceral pain at rest (supine), on movement (sitting up from supine), on coughing and shoulder pain were noted. Rescue analgesia (intravenous injection tramadol 1.5 $mg.kg^{-1}$) was given if comfort score was < 6. If the pain persisted even after 30 minutes of intravenous tramadol administration, then intravenous injection morphine sulphate 0.1 $mg.kg^{-1}$ (second rescue analgesic agent) was given. Time from extubation of the patient to the administration of first dose of rescue analgesic was noted. Total 48 hours intravenous (IV) morphine consumption was converted to IV tramadol equivalent dose and total 48 hours rescue analgesia consumption (IV tramadol plus IV tramadol equivalent dose) during the postoperative period were noted. We also recorded the total number of patients requiring rescue analgesia. Sedation was assessed using sedation score from 0 to 5 (responds readily – 5, lethargic response – 4, responds only after name is called loudly – 3, responds only after mild prodding or shaking – 2, does not respond to mild prodding or shaking – 1, does not respond to noxious stimulation – 0).[10] Nausea and vomiting were assessed in postoperative care unit by PONV score.[11] If the patient complained of severe nausea or an episode of vomiting, rescue antiemetic in the form of injection 10 mg metoclopramide was given intravenously. If it still persisted after giving injection metoclopramide, 4 mg of injection ondansetron was given as second rescue antiemetic. Side effects like shivering, pruritus, nausea/vomiting, dizziness, respiratory depression were noted during the study period. Any patient who failed to understand these scoring systems was excluded from the study design.

Primary and secondary outcomes

The primary outcome was to measure the total analgesic consumption in the first 48 hours postoperative period. The secondary outcome was defined as the time to first request for rescue analgesic, pain scores and side-effects in the postoperative period.

Statistical analysis

The data was analyzed with Statistical Package for Social Studies (SPSS – SPSS for Windows 14, Chicago, IL, USA). The parametric data (age, height, weight) were analyzed using the independent samples *t*-test, while the non-parametric data were analyzed using Mann-Whitney U test. Continuous data like heart rate and blood pressure were analyzed by repeated measure ANOVA after checking the normal distribution. Within group analysis of hemodynamic data was done using post-hoc analysis. The occurrence of postoperative emetic episodes, rescue antiemetic therapy and rescue analgesic therapy was analyzed with Chi-square test or Fisher Exact test where appropriate. Data were stated as mean ± standard deviation (SD), median (25–75%) values or number (n) and percentage (%). A *p*-value of < 0.05 was considered statistically significant.

Sample size calculation

Considering the 20% difference in the consumption of analgesic drug between the two groups with a power of 80% and confidence interval of 95%, 33 patients were required in each group.[11] However, considering the possibility of dropouts, we decided to enroll 35 patients in each group.

Results

A total number of 70 patients scheduled for laparoscopic cholecystectomy were included in this prospective, randomized study. They were divided into two groups (A and B) with 35 patients each (Figure 1). Baseline demographic parameters in both groups were comparable (Table 1). Intraoperative parameters were also comparable in both groups (Table 2). The preoperative, intraoperative and postoperative hemodynamic parameters did not differ significantly between the two groups ($p > 0.05$) (Figure 2).

Primary outcome

The total amount of rescue analgesia (injection tramadol plus injection tramadol intravenous equivalent dose) consumed during the 48 hours postoperatively in group A was 146.55 mg, which was significantly higher than in group B (111.30 mg; $p = 0.026$).

Secondary outcome

The mean time for demanding rescue analgesia was significantly more in group B than in group A (group A was 273 minutes and group B was 340 minutes; $p = 0.00$). The number of patients who required first rescue analgesia (injection tramadol IV) was the same in both the groups, but the number of patients requiring second rescue analgesia (injection morpine IV) differed significantly. In group A, 13 out of 35 patients required a second rescue analgesia, while in group B 5 out of 35 patients required second rescue analgesia ($p = 0.029$). There was no significant difference in the intraoperative fentanyl consumption (group A = 106.98 μg; group B = 92.80 μg; $p = 0.26$)

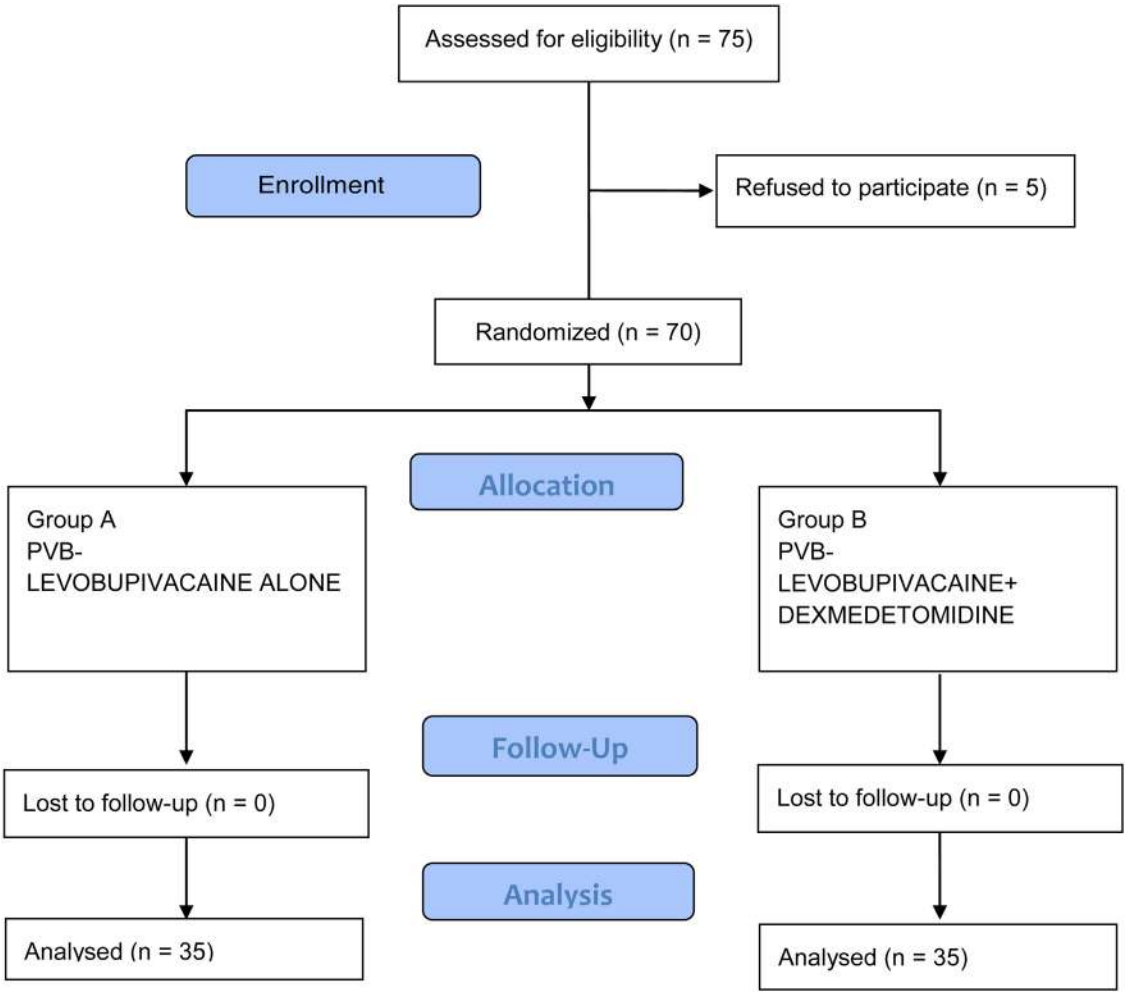

Figure 1 Consort diagram.

Table 1 Demographic features of study population.

Parameters	Group A (Mean ± SD)	Group B (Mean ± SD)	*p*-value
Age (years)	41.23 ± 12.262	40.17 ± 10.001	0.694
Sex (female/male)	27/8	25/10	0.584
Height (cm)	158.17 ± 4.586	157.20 ± 3.932	0.345
Weight (kg)	62.77 ± 10.241	60.71 ± 9.096	0.377
ASA (I / II)	22/13	27/8	0.192
Surgery time	61.07 ± 15.2	58 ± 10.95	0.757
Average fentanyl (μg)	106.98 ± 11.58	92.8 ± 13.03	0.265

Values are expressed as mean ± SD or absolute numbers. ASA, American Society of Anesthesiologists physical status.

Table 2 Intraoperative variables in both the groups were comparable ($p > 0.05$).

Intraoperative variables	Group A (Mean ± SD)	Group B (Mean ± SD)	*p*-value
Duration of surgery (min)	68.67 ± 14.87	70.31 ± 15.16	0.328
Duration of anesthesia (min)	83.56 ± 16.82	86.22 ± 17.99	0.268
Total fentanyl dose (μg)	106.98 ± 11.58	92.80 ± 13.03	0.265
Intra-abdominal pressure	13.47 ± 0.991	13.89 ± 1.385	0.518

Values are expressed as mean ± SD or absolute numbers.

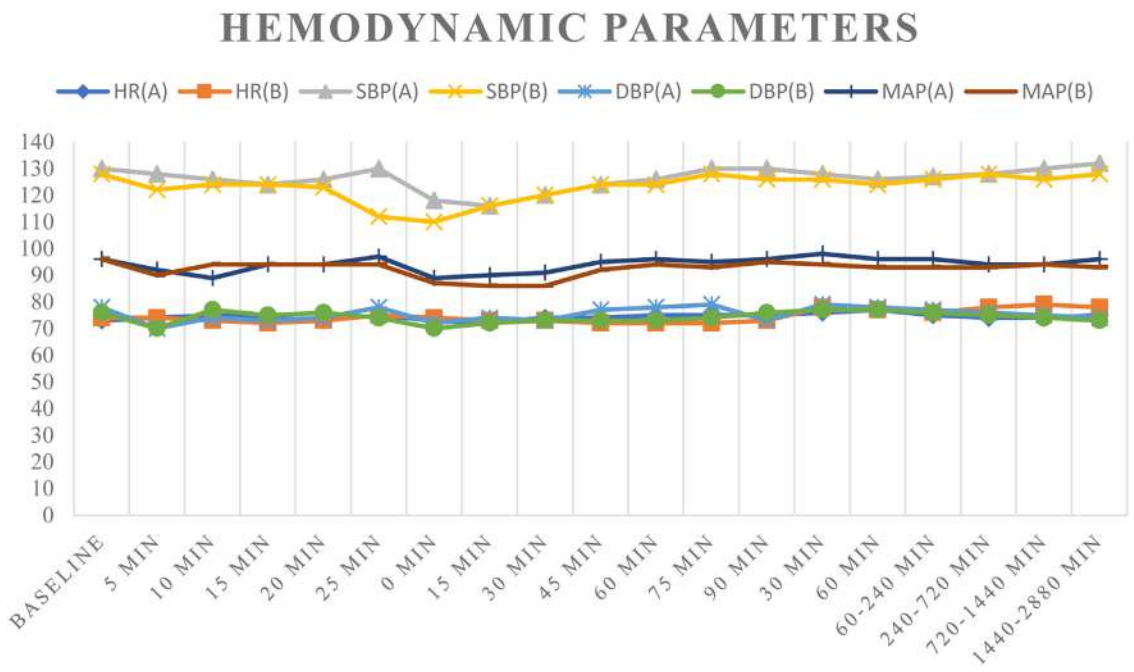

Figure 2 Hemodynamic parameters in the preoperative (0–25 min), intraoperative period (0–90 min) and postoperative period (30–2880 min).
HR(A), Heart Rate group A; HR(B), Heart Rate group B; SBP(A), Systolic Blood Pressure group A; SBP(B), Systolic Blood Pressure group B; DBP(A), Diastolic Blood Pressure group A; DBP(B), Diastolic Blood Pressure group B; MAP(A), Mean Arterial Pressure group A; MAP(B), Mean Arterial Pressure group B.

Comfort score

There was no difference in comfort score between the groups during 30 minutes, 60 minutes, 720–1440 minutes, 1440–2880 minutes time interval (comfort score > 6 in both groups). During 60–240 minutes interval, the number of patients whose comfort score was < 6 in group A was 11, and in group B was 5. But during the 240–720 minutes time interval, all the patients in both groups had comfort score < 6. However this difference was not statistically significant (p = 0.08) (Figure 3).

NRS for parietal and visceral pain

At 60–240 minutes, NRS scores for parietal pain, as well as visceral pain – at rest, on movement and on coughing – were less in group B compared to group A; however this difference was statistically insignificant (Table 3, Figure 4). But during the 240–720 minutes interval, the NRS scores for parietal pain at rest, on movement and on coughing was significantly less in group B compared to group A (Figure 5). During this time, visceral pain scores were almost the same in both groups. We did not assess NRS during 30, 60, 720–1440, 1440–2880 minutes, as the comfort score during this period was > 6 in all the patients.

Shoulder pain

In both groups there was no difference in the number of patients complaining of shoulder pain. Three patients in each group complained of shoulder pain in the postoperative period.

Sedation score

In the postoperative period, the sedation score was significantly low in patients belonging to group B, as compared to those in group A at 30 minutes (p = 0.000) and at 60 minutes (p = 0.001) (Figure 6).

PONV

There was no significant difference between the two groups in the incidence of PONV and usage of rescue antiemetic. Out of 35 patients in each group, 8 patients in group A and 3 patients in group B complained of nausea in immediate postoperative period, and one patient in group A had an episode of vomiting.

Adverse effects

Postoperatively in group A, one patient had an episode of hypotension and one patient had an episode of bradycardia, which was resolved later with IV crystalloids. While in group B two patients had an episode of hypotension which was resolved with IV crystalloids and one patient had an episode of severe episode of bradycardia for which required intervention (injection of atropine 0.6 mg was given). None of the patients in our study reported chest pain or breathlessness, indicative of pneumothorax.

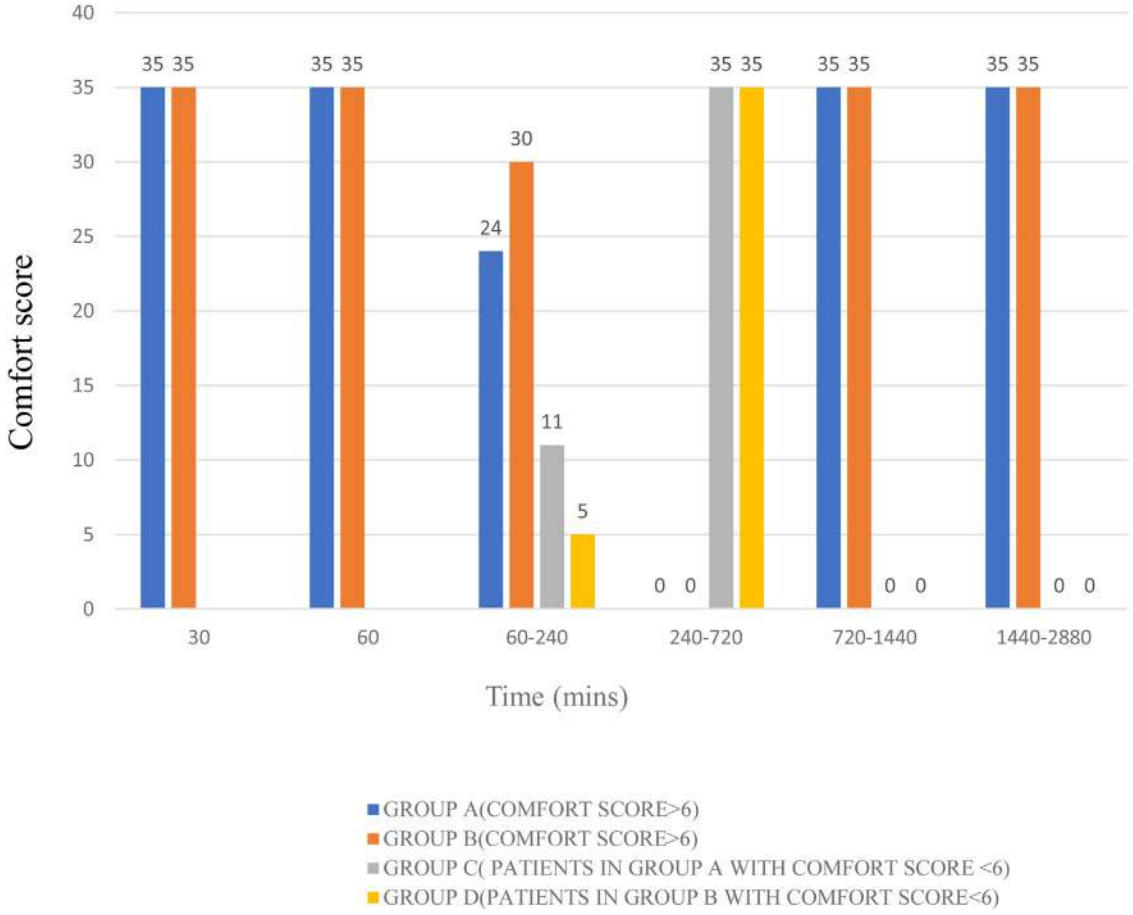

Figure 3 Comfort score (30–2880 min).

Table 3 NRS during 60–240 min interval.

NRS	Group A (n = 35) (Mean ± SD)	Group B (n = 35) (Mean ± SD)	*p*-value
PP NRS R	3.91 ± 0.831	3.40 ± 0.548	0.235
PP NRS M	4.64 ± 0.924	4.20 ± 0.837	0.384
PP NRS C	5.45 ± 0.688	4.80 ± 0.837	0.120
VP NRS R	3.36 ± 0.505	3.00 ± 0.000	0.136
VP NRS M	4.18 ± 0.751	3.80 ± 0.447	0.314
VP NRS C	5.00 ± 0.632	4.60 ± 0.548	0.244

PP NRS R, Parietal pain Numeric Rating Scale at Rest; PP NRS M, Parietal Pain Numeric Rating Scale at Movement; PP NRS C, Parietal Pain Numeric Rating Scale while coughing; VP NRS R, Visceral Pain Numeric Rating Scale at Rest; VP NRS M, Visceral Pain Numeric Rating Scale at Movement; VP NRS C, Visceral Pain Numeric Rating Scale while coughing.
Values are expressed as mean ± SD or absolute numbers.

Discussion

The main finding of this prospective, randomized double-blind trial was the significant improvement in analgesic efficacy of dexmedetomidine and levobupivacaine combination as compared to levobupivacaine alone in PVB in patients undergoing laparoscopic cholecystectomy. Postoperative analgesic consumption was reduced during the entire 48 hours postoperative observation period in patients who received a combination of levobupivacaine and dexmedetomidine in PVB. Furthermore, the pain scores both at rest and in movement were less in these patients, and the time to first rescue analgesic was also significantly more. In addition, patients receiving combination of levobupivacaine and dexmedetomidine had lower incidence of PONV, less sedation scores and better patient comfort score.

Laparoscopic cholecystectomy is now being increasingly performed on an outpatient basis, and hence effective analgesia with opioid-sparing attributes is being preferred to hasten postoperative recovery. Laparoscopic cholecystectomy is associated with a substantial component of visceral pain, and the incidence of shoulder pain probably reflects a component of diaphragmatic referred pain.[12] The risk of chronic postoperative pain has been reported to be 10–40%

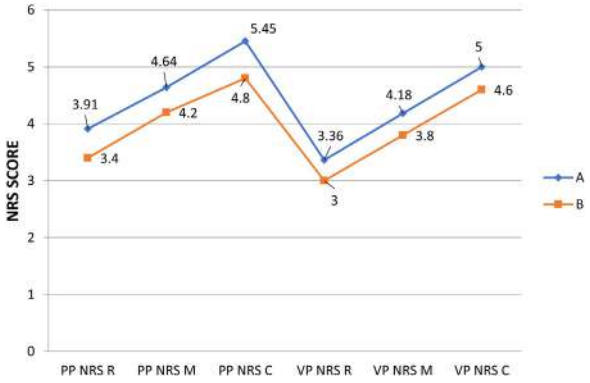

Figure 4 NRS during 60–240 min interval. A, group A; B, group B.
PP NRS R, parietal pain numeric rating scale at rest; PP NRS M, parietal pain numeric rating scale on movement; PP NRS C, parietal pain numeric rating scale on coughing; VP NRS R, visceral pain numeric rating scale at rest; VP NRS M, visceral pain numeric rating scale on movement; VP NRS C, visceral pain numeric rating scale on coughing.

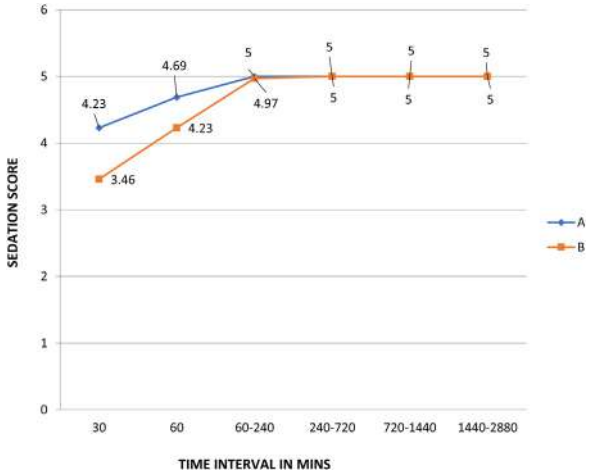

Figure 6 Sedation score was significantly low in patients belonging to Group B, as compared to those in Group A at 30 min ($p = 0.000$) and at 60 min ($p = 0.001$).

after laparoscopic or traditional open cholecystectomy.[13] Thus, in order to provide adequate pain relief, both high quality afferent somatic and visceral pain blockade are most likely necessary in order to successfully treat cholecystectomy pain. Paravertebral blockade has been reported to provide high quality afferent blockade with abolishment of somatosensory evoked potentials,[14] and it has also been found capable of attenuating the postoperative stress response associated with traditional cholecystectomy. Naja et al. assessed the efficiency of nerve stimulator guided bilateral paravertebral blockade (with a combination of lignocaine, bupivacaine, fentanyl and clonidine) combined with general anesthesia *vs.* general anesthesia alone in reducing postoperative pain following laparoscopic cholecystectomy.[4] They found that when used as a complement to general anesthesia, paravertebral blockade with lidocaine, bupivacaine, fentanyl and clonidine improved postoperative pain relief. Aggarwal et al., in their study demonstrating the efficacy of paravertebral block using bupivacaine in laparoscopic cholecystectomy, showed that patients receiving PVB required 38% less PCA morphine compared to those in the control group. Intraoperative supplemental fentanyl requirement in their study group was 54% less than the control group.[11] Junior et al., in their meta-analysis, have compared thoracic epidural with paravertebral block for postoperative pain in patients undergoing thoracotomy and found no statistically significant difference in pain relief between thoracic epidural and paravertebral block, though paravertebral block was associated

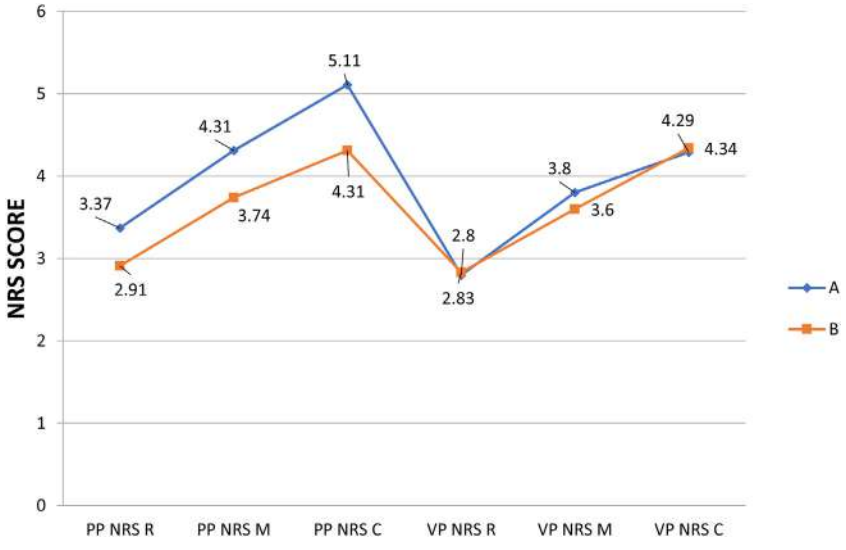

Figure 5 NRS during 240–720 min interval. A, group A; B, group B.
PP NRS R, parietal pain numeric rating scale at rest; PP NRS M, parietal pain numeric rating scale on movement; PP NRS C, parietal pain numeric rating scale on coughing; VP NRS R, visceral pain numeric rating scale at rest; VP NRS M, visceral pain numeric rating scale on movement; VP NRS C, visceral pain numeric rating scale on coughing.

with significantly less incidence of hypotension and urinary retention.[15]

Dexmedetomidine has emerged as a potential adjuvant exhibiting a facilitatory effect with LA.[16] Numerous studies have been reported in literature where dexmedetomidine has been used as adjuvant to local anesthetics for peripheral nerve blockade.[17–24] In most of them, it has shown improved efficacy of the block with no reports of neurological side-effects. The efficacy of paravertebral block using local anesthetics with or without opioids has also been shown in previous studies.[25] However, none of the studies reported so far has evaluated the role of dexmedetomidine along with local anesthetics for giving thoracic PVB in laparoscopic cholecystectomy. In the present study, PVB was given to both groups, but used different combinations of drugs (levobupivacaine – dexmedetomidine/levobupivacaine) for administering the block, and found that the combination of levobupivacaine and dexmedetomidine when used for giving paravertebral block in laparoscopic cholecystectomy resulted in significant decrease in postoperative pain, as compared to using levobupivacaine alone.

PONV is one of the most unpleasant symptoms perceived by the patients following laparoscopic cholecystectomy. Kehlet et al.[26] have extensively reviewed opioid-sparing effects of different regimens and remarked that approximately 30% reduction in opioid requirement was clinically significant. An opioid-sparing analgesic technique should also result in decreased incidence of opioid-related side effects. Hence, we compared the occurrence of opioid-related adverse effects,[27] like dizziness, nausea, vomiting, constipation, and respiratory depression between the two groups. In our study, patients in group B reported less PONV than those in the group A in the postoperative period. The number of patients who complained of PONV and who required rescue antiemetic was 3 out of 35 patients in group B postoperatively, as compared to 8 out of 35 patients in the study group A. This difference reflects significant opioid-sparing benefit of PVB in terms of reduced PONV, but did not attain statistical significance, presumably due to the small sample size.

In the postoperative period, sedation score was significantly low in patients belonging to group B, as compared to those in group A at 30 minutes (p = 0.000) and at 60 minutes (p = 0.001). This could have been due to the addition of dexmedetomidine to levobupivacaine for giving PVB in patients of group B. In a study by Jung HS et al.,[28] who compared the effect of intraoperative infusion of dexmedetomidine with remifentanil on perioperative hemodynamics, hypnosis, sedation, and postoperative pain control, the authors found that sedation score was significantly lower in the dexmedetomidine group than in the remifentanil group after arrival in the PACU. This is because dexmedetomidine has sedative and analgesia-sparing effects via central actions in the locus coeruleus and in the dorsal horn of the spinal cord. It inhibits noradrenaline release, causing an attenuation of excitation in the central nervous system, especially in the locus coeruleus.[29]

Although this is first study comparing analgesic efficacies of levobupivacaine and levobupivacaine-dexmedetomidine combination for PVB block in laparoscopic cholecystectomy, our study has some limitations. We have not evaluated sensory block distribution and drug concentrations in the blood. Another limitation is the lack of pneumoperitoneal insufflation pressure recordings. There is some evidence that maintaining low inflation pressures during laparoscopic surgery may reduce postoperative pain.[30]

Conclusion

The present study concluded that the administration of ultrasound guided TPVB using dexmedetomidine 1 $\mu g.kg^{-1}$ added to levobupivacaine 0.25% in patients undergoing laparoscopic cholecystectomy significantly reduced the total analgesic consumption in the first 48 hours and provided longer duration of analgesia postoperatively, as compared to levobupivacaine 0.25% alone.

Conflicts of interest

The authors declare no conflicts of interest.

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CLINICAL RESEARCH

Quadratus lumborum block (transmuscular approach) versus transversus abdominis plane block (unilateral subcostal approach) for perioperative analgesia in patients undergoing open nephrectomy: a randomized, double-blinded, controlled trial☆

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KEYWORDS
Open nephrectomy;
Regional anesthesia;
Visual Analogue Scale;
Postoperative analgesia

Abstract
Study objective: Patients undergoing open nephrectomy surgery experience severe perioperative pain, which is primarily due to incision of several muscles. Abdominal wall blocks are known to reduce pain without causing epidural-associated hypotension. We conducted this study to compare unilateral ultrasound-guided transmuscular quadratus lumborum block and posterior transversus abdominis block in combination with general anesthesia alone in terms of intraoperative and postoperative analgesics and hemodynamics and postoperative complications.
Methods: This was a randomized, double-blinded, controlled trial conducted in the operating room. This study included 48 patients aged 20–60 years, with ASA I and II, and a body mass index $\leq$ 30 kg.m^{-2} who were scheduled for open nephrectomy procedure.The 48 patients scheduled for nephrectomy were randomly allocated into one of the following three groups after induction of general anesthesia: Group A (n = 16) received USG transmuscular QLB; Group B (n = 16) received unilateral USG posterior transversus abdominis plane (TAP) block; and Group C (n = 16; control group) did not receive any blocks. Introperative fentanyl consumption, and hemodynamics (heart rate and mean arterial pressure (MAP)) were recorded after anesthesia induction, at surgical incision, and every 15 min till the end of surgery. Visual Analogue Scale (VAS) was evaluated immediately at 30 min and 1,2,4,6, and 12 hours postoperatively. The time of first analgesic request was also recorded.
Results: Intraoperative fentanyl consumption (μg) was significantly lower in Groups A and B (164.69 ± 27.35 and 190.31 ± 44.48, respectively) than in Group C (347.50 ± 63.64) ($p < 0.001$). Postoperatively, total pethidine consumption was significantly lower in Groups A and B than

☆ This work was carried out at the Urology Theatre of Kasr Al Aini Hospital, Faculty of Medicine, Cairo University, Cairo, Egypt.

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in Group C (85.31 ± 6.68, 84.06 ± 4.17 mg, and 152.19 ± 43.43 mg, respectively) ($p < 0.001$. Time to rescue analgesia was longer in Groups A and B than in Group C (138.75 ± 52.39 min, 202.50 ± 72.25 min, and 37.50 ± 13.42 min, respectively) ($p < 0.001$). VAS score was significantly lower in Groups A and B than in Group C at 30 min and 1, 2, 4, and 6 hours postoperatively.
Conclusion: Transmuscular quadratus lumborum block and posterior transversus abdominis blocks were effective in providing perioperative analgesia in patients undergoing open nephrectomy. However, quadratus lumborum block provided superior analgesia.
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Introduction

Severe perioperative pain experienced during and after surgical procedures performed by flank incision is primarily due to the incision of several muscles. Postoperative pain affects patients' comfort and satisfaction and prolongs the duration of hospital stay and increases post-procedural complications.[1] Although abdominal wall blocks are known to decrease opioid requirements without causing epidural-associated hypotension, their role in flank surgeries has been less well-established. The dermatomes that need to be covered in flank incision are T9 to T11.[2]

Studies have confirmed that ultrasound-guided (USG) transversus abdominis plane (TAP) block is an effective method of analgesia for upper abdominal surgeries,[3] lower abdominal surgeries,[4] and kidney transplantation,[5] with minimal side effects.

A novel USG QL block is the transmuscular approach that depends on clearly identifiable sonographic bony landmarks. It can provide safe, easy, and effective analgesia covering from thoracic 7 to thoracic 12, lumbar 1. It is considered that the transmuscular QL block is effective for abdominal surgeries such as laparoscopy, inguinal hernia surgery, and femoral–femoral bypass.[6]

This study was designed to compare the success rate of unilateral ultrasound-guided transmuscular quadratus lumborum block with that of unilateral posterior ultrasound-guided TAP block in providing perioperative analgesia in patients undergoing open nephrectomy.

Methods

This study was approved by the ethical committee of Cairo University (N-36-2018), and written informed consent was obtained from all patients. The study was registered as a randomized, double-blinded clinical trial at clinicaltrials.gov (NCT03744923, principal investigator: Amany Hassan, date of registration: November 2018) before patient enrollment. This manuscript adhered to the applicable CONSORT guidelines (Fig. 1). A total of 48 patients aged 20–60 years scheduled for open nephrectomy procedure, with ASA (American Society of Anesthesiologists) physical status I and II, and a body mass index $\leq 30\,kg.m^{-2}$, were included. Patients refusing the use of regional blocks and having ASA III–VI, bleeding disorders, skin lesions or infection at the site of proposed needle insertion, allergy to amide local anesthetics, neurological disorders, and BMI > $30\,kg.m^{-2}$ were excluded from the study.

Patients were allocated to the study groups using a computer-generated random list, and the group assignments were sealed in sequentially numbered opaque envelopes that were opened after the induction of anesthesia. The data collector was blinded to the group assignment and to the monitoring anesthetist, and the person who performed the block was not the data collector (double-blinded).

The anesthesiologist met the guardians and informed consent was obtained, after which the patients were examined, followed by all routine investigations. On arrival to the operating room, an intravenous (IV) cannula 20G was inserted, and Ringer's acetate solution was infused. A five-lead electrocardiogram, a pulse oximeter, and a noninvasive blood pressure cuff were applied. Then, midazolam $0.025\,mg.kg^{-1}$ was administered.

Patients were randomly allocated into one of the following three groups: Group A (n = 16): patients received USG transmuscular quadratus lumborum block (QLB) after induction of general anesthesia; Group B (n = 16): patients received unilateral USG posterior TAP block after induction of general anesthesia. Group C (n = 16) (control group) did not receive any blocks.

Next, general anesthesia was induced using propofol $2\,mg.kg^{-1}$ over 20–30 s, fentanyl $2\,\mu g.kg^{-1}$, and atracurium $0.5\,mg.kg^{-1}$ to facilitate endotracheal intubation. Anesthesia was maintained using isoflurane 1.5% and atracurium infusion at a dose of $0.3\,mg.kg^{-1}.h^{-1}$. For all patients, strict fluid management was followed according to body weight, and blood loss was adequately estimated and replaced.

Group A (transmuscular QLB)

The patient was positioned in the lateral position, with the side to be anesthetized being located upward. Complete aseptic precautions were taken by wearing sterile gown and sterile gloves and sterilizing the site of the block.

An ultrasound device was used, in which a convex probe with broadband (5–8 MHz) covered with sterile plastic sheath was placed in the mid-axillary line cranially to the iliac crest to identify the three muscles of the anterior abdominal wall (transversus abdominis, internal oblique, and external oblique). Then, scan dorsally to keep the transverse orientation until seeing the aponeurosis of the transverses abdominus muscle and by following this aponeurosis, QL muscle was visualized with its attachment to the

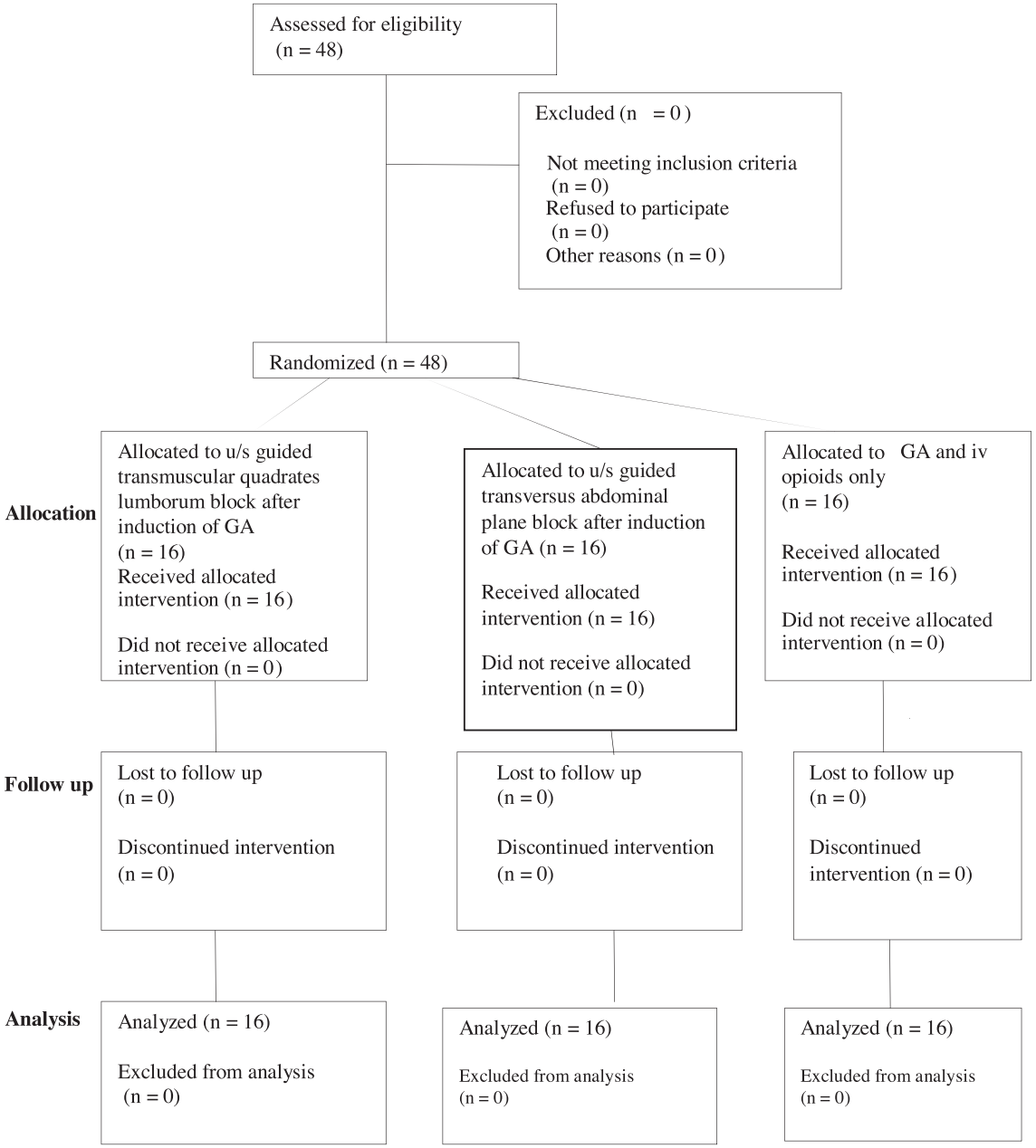

Figure 1 CONSORT chart.

lateral edge of the transverse process of the L2 vertebral body and visualize the thoracolumbar fascia at the lateral edge of the QL muscle. The view of the psoas major muscle anteriorly, the erector spinae muscle posteriorly, and the QL muscle adherent to the apex of the transverse process result in a well-known view of a Shamrock with three leaves (trifoliate).

A spinal needle (20G) was inserted in-plane from the posterior to anterior direction, and the tip of the needle was advanced through the QL muscle, penetrating the ventral proper fascia of the QL muscle. The target site for injection was the plane between the quadratus lumborum and psoas major muscles. A test dose of 1 mL of 2% lidocaine was injected for hydrovisualization of the needle-tip position and for confirming its correct positioning. This was followed by injection of 0.5% bupivacaine (0.25 mL.kg^{-1}) and 2% lidocaine (0.15 mL.kg^{-1}) together. The dose of both agents did not exceed the safe limits (2 mg.kg^{-1} for bupivacaine and 3 mg.kg^{-1} for lidocaine).

Group B (TAP block group)

The patient was positioned in the supine position. The probe was positioned transversely midway between the iliac crest and the costal margin at the level of the mid-axillary line. Once the external oblique muscle (EOM), internal oblique muscle (IOM), and transversus abdominis muscle (TAM) were visualized at the level of the posterior axillary line between

the 12th rib and the iliac crest with visualization of the anterior pole of the QL muscle, the puncture area and the ultrasound probe were prepared in a sterile manner. A 20G spinal needle was directed to approach the TAP using the ''in-plane'' USG-guided technique. Once the tip of the needle was placed in the space between the IOM and TAM at the closest point to the QL muscle, a 1 mL test dose of 2% lidocaine was injected for hydrovisualization of the needle-tip position and for confirming its correct positioning. This was followed by injection of 0.5% bupivacaine (0.25 mL.kg^{-1}) and 2% lidocaine (0.15 mL.kg^{-1}) together. The dose of both agents did not exceed the safe limits (2 mg.kg^{-1} for bupivacaine and 3 mg.kg^{-1} for lidocaine). The drug was observed as a dark oval shape spreading in the TAP.

In the three groups, skin incision was delayed for 10 minutes after performing the block to ensure its spread and efficacy. The observing anesthetist was advised to inject fentanyl increment doses (0.5 μg.kg^{-1}) when the mean blood pressure, heart rate, or both increased by > 20% from the baseline.

At the end of surgery, inhalational anesthetics were discontinued, the muscle relaxant was reversed with atropine (0.01 mg.kg^{-1}) and neostigmine (0.05 mg.kg^{-1}), spontaneous breathing was allowed, the endotracheal tube (ETT) was removed, and then the patient was transferred to postanesthesia care unit.

Postoperatively, all patients received IV paracetamol 1 g every 8 hours. As a rescue analgesic, meperidine (0.5 mg.kg^{-1}) was used when the Visual Analogue Scale (VAS) was > 4.

Primary outcome

The primary outcome of our study was measurement of the total amount of fentanyl consumption during the intraoperative period in the three allocated groups as an indicator of hemodynamic stability and efficacy of both types of blocks.

Secondary outcomes

The secondary outcomes were as follows: hemodynamic stability (mean blood pressure and heart rate not exceeding 20% of baseline levels), meperidine consumption over 12 hours in all groups, estimation of the time to rescue analgesia in all groups, patient satisfaction (measured using pain scores at rest and during movement according to the VAS score; a VAS score < 4 will be considered as satisfactory), ease of performing the respective blocks (assessed using the time required to perform the blocks in minutes and number of attempts required to reach the plane of block), comparison of both types of blocks in providing adequate analgesia perioperatively (assessed using fentanyl consumption intraoperatively and meperidine consumption and VAS score postoperatively in the groups of both blocks). Postoperative complications were also recorded in both groups (bowel injury, injury of the kidney, hematoma formation, intravascular injection, pruritus, nausea, vomiting).

Statistical analysis

Data were coded and entered using the statistical package SPSS version 25. Data were summarized using mean and standard deviation or median and interquartile range for quantitative variables and frequencies (number of cases), and relative frequencies (percentages) for categorical variables. Between-group comparisons were conducted using unpaired *t*-test or analysis of variance with multiple comparison post hoc test for normally distributed quantitative variables, whereas nonparametric Kruskal–Wallis test and Mann–Whitney test were used for non-normally distributed quantitative variables.[7] Chi-square (χ^2) test was performed for assessing categorical data. Exact test was used instead when the expected frequency is less than 5.[8] The Kaplan–Meier analysis was performed to assess the duration of analgesia. Significance values were adjusted by the Benferroni correction for multiple tests. *P*-values < 0.05 were considered statistically significant.

Sample size calculation

Our primary outcome was intraoperative fentanyl consumption. A previous study reported an intraoperative fentanyl consumption amount of 580 (91) μgin this operation.[3] Sample size was calculated using the MedCalc software to detect a mean difference of 15% (58 μg) between study groups. A minimum number of 45 patients (15 patients per group) was required to reach a study power of 90% and an alpha error of 0.05. The number was increased to 48 patients (16 patients per group) to compensate for possible dropouts.

Results

A total of 48 patients who were scheduled for open nephrectomy surgeries were enrolled in our study. These patients were randomly allocated into three equal groups using the closed envelope method. After the induction of general anesthesia, Group A received ultrasound-guided transmuscular QL block, Group B received ultrasound-guided posterior TAP block, and Group C received only general anesthesia.

There were no statistically significant differences in the demographic data of the patients (Table 1). The time to perform TAP block was less than that required for quadratus lumborum block, with a statistically significant difference (Table 2). The mean arterial pressure (MAP) (Fig. 2) measured intraoperatively revealed significant differences between the three groups. Statistically significant differences were also observed in the intraoperative heart rate between the groups (Fig. 3). The average heart rate and MAP measurements over the 12-hours postoperative period exhibited significant differences between the three groups (Table 2).

The number of times of fentanyl administration and the amount of fentanyl consumption during the intraoperative period are shown in Table 2. Statistically significant between-group and within-group differences were observed in these parameters, with the lowest finding being observed in the QL3 group. The number of times of fentanyl administration and the total amount of fentanyl consumption were

Table 1 Patients characteristics and duration of operation.

		Control group Mean (SD)	Mean (SD)	TAP group Mean (SD)	QL3 group *p*-value
Sex	Female	5 (31.2%)	10 (62.5%)	6 (37.5%)	0.169
	Male	11 (68.8%)	6 (37.5%)	10 (62.5%)	
Age	40.31 (7.22)	40.19 (5.65)	42.69 (9.97)	0.598	
Weight	82.50 (14.26)	78.44 (13.87)	77.88(14.09)	0.601	
Duration of operation (min)	151.88 (26.20)	143.44 (25.67)	150.94 (29.22)	0.630	

TAP, transversus abdominis plane.
For sex, data was represented as count and percentage. For others, Data was expressed as mean and standard deviation. *P*-value < 0.05 is considered significant.

Table 2 Intraoperative fentanyl consumption and times of administration of fentanyl between, mean postoperative MAP and HR over 12 hours in and time to perform the block.

	Control group Mean (SD)	TAP group Mean (SD)	QL3 group Mean (SD)	*p*-value
Number of fentanyl times administration (induction dose excluded)	4.56 (0.96)	0.87 (0.96)	0.25 (0.45)	< 0.001
Total fentanyl consumption (mic)	347.50 (63.64)	190.31 (44.48)	164.69 (27.35)	< 0.001
Postoperative HR	97.62 (8.41)	78.38 (8.06)	75.50 (8.37)	< 0.001
Postoperative MABP	97.00 (10.77)	85.38 (7.54)	87.69 (3.72)	< 0.001
Time to perform block(min)	-	3.56 (1.03)	4.44 (0.81)	0.012

TAP, transversus abdominis plane.
Data expressed as mean and standard deviation. *P*-value < 0.05 is considered significant.

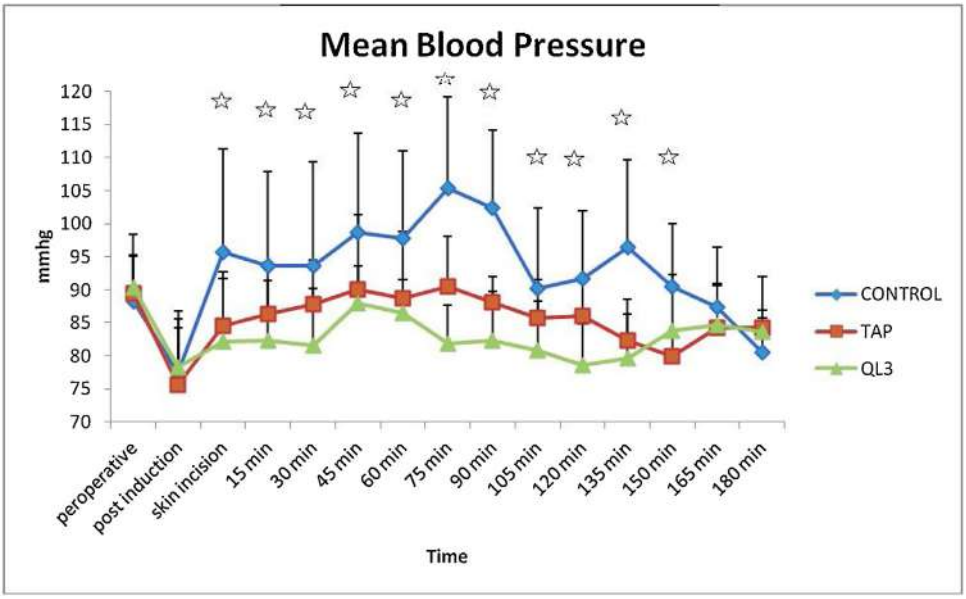

Figure 2 Comparison of intraoperative mean blood pressure between the three groups. TAP, transversus abdominis plane. *P*-value < 0.05 is considered significant.

less in the QL3 group than in the TAP group, but there were no statistically significant differences (Table 3).

The time to first request of rescue analgesia was statistically significantly longer in both QL3 and TAP groups than in the control group, as shown in the Kaplan–Meier graph (Fig. 4). The total amount of pethidine consumption and the number of times of pethidine administration were statistically significantly lower in the QL3 and TAP groups than in the control group.

Regarding the time to rescue analgesia, number of times of pethidine administration, and total amount of pethidine consumption between the QL3 and TAP groups, it was observed that the time to rescue analgesia was statistically significantly prolonged in the QL3 group. However, the

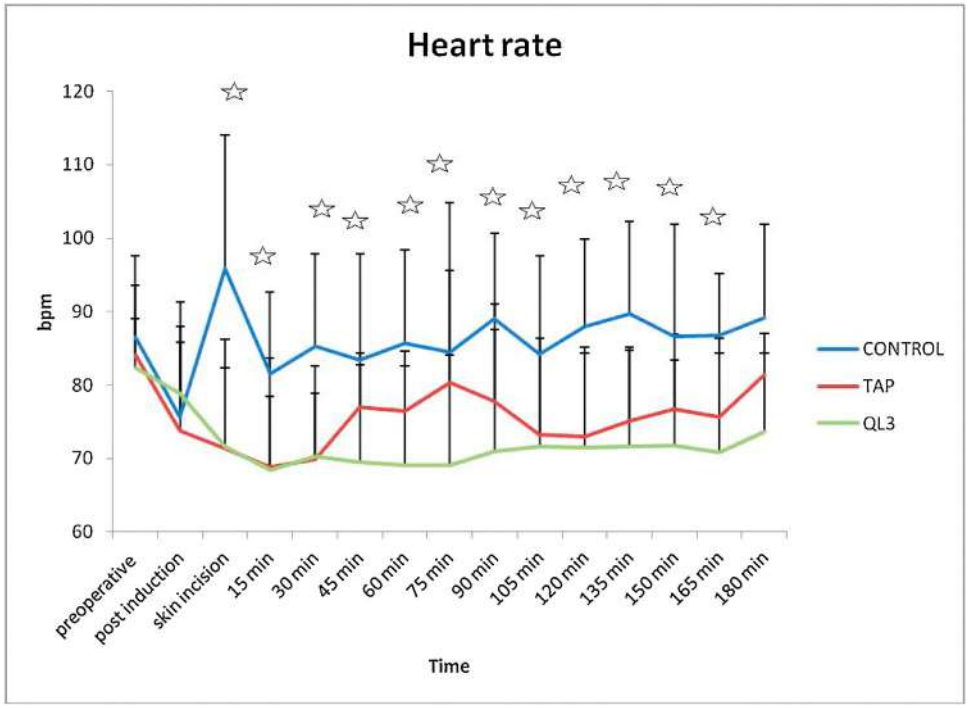

Figure 3 Comparison of intraoperative heart rate between the 3 groups. TAP, transversus abdominis plane. *P*-value < 0.05 is considered significant.

Table 3 Comparison between three groups with regarding nausea and vomiting.

		Control group		TAP group		QL3 group		*p*-value
		Count	%	Count	%	Count	%	
PONV	Yes	**12**	75.0%	**3**	**18.8%**	**2**	12.5%	< 0.001
	No	**4**	25.0%	**13**	**81.2%**	**14**	87.5%	

TAP, transversus abdominis plane.
Data is expressed in terms of count and percentage. *P*-value < 0.05 is considered significant.

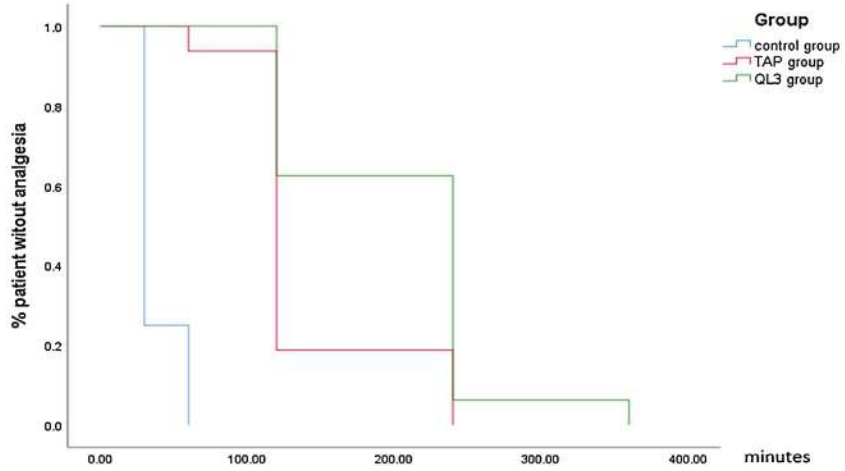

Figure 4 Kaplan–Meier curve representing comparison of time of rescue analgesia between the three groups. TAP, transversus abdominis plane.

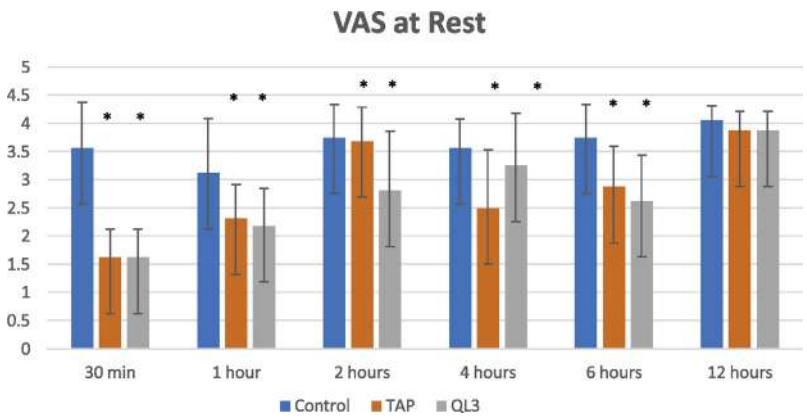

Figure 5 VAS score at rest between three groups at different study times. Data expressed as mean and Standard deviation. VAS, visual analogue scale; TAP, transversus abdominis plane.

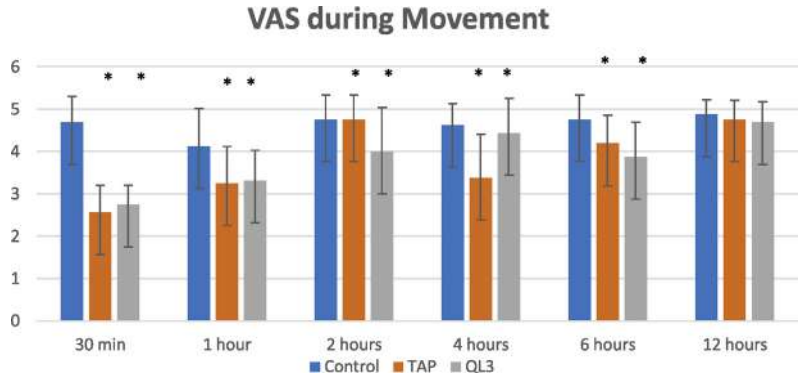

Figure 6 VAS scores during movement between the three groups at different study time points. Data are expressed as mean and standard deviation. VAS, visual analogue scale; TAP, transversus abdominis plane.

number of times of pethidine administration and the total amount of pethidine consumption were not significant.

Regarding the VAS pain scores at rest and during movement, there were statistically significant differences between the three groups at all study time points, except at 12 hours postoperatively (Figs. 5 and 6). VAS score was statistically significantly lower in the QL3 group than in the TAP group at 2 hours postoperatively. It was also statistically significantly lower in the TAP group than in the QL3 group at 4 hours postoperatively.

Postoperative nausea and vomiting (PONV) were observed in 12 patients in the control group, whereas only 3 and 2 patients in TAP and QL3 groups experienced PONV, respectively ($p < 0.001$). None of our study patients experienced any other complications such as bowel injury, injury of the kidney, hematoma formation, intravascular injection, and pruritus.

Discussion

This study compared the efficacy of unilateral ultrasound-guided transmuscular quadratus lumborum block (Group A) and unilateral posterior ultrasound-guided TAP block (Group B) in combination with general anesthesia with that of general anesthesia alone (control; Group C) to evaluate the success rate of providing perioperative analgesia in patients undergoing open nephrectomy.

To our knowledge, this is the first study to compare the efficacy of quadratus lumborum block and TAP block in providing intraoperative and postoperative analgesia in patients undergoing open nephrectomy surgeries.

The results of this study were divided into intraoperative and postoperative findings. The time to perform the block was significantly lower in Group B (3.56 ± 1.03 min) than in Group A (4.44 ± 0.81 min). Intraoperatively, both groups (A and B) exhibited lower recordings in heart rate (HR) and MAP intraoperatively than the control group, with statistically significant differences. Moreover, both groups (A and B) showed high analgesic efficacy with significant reduction in fentanyl consumption (164.69 ± 27.35 and 190.31 ± 44.48 μg, respectively) compared with group C (347.50 ± 63.64 μg). Group A exhibited lower fentanyl consumption than Group B; however, this was not statistically significant. The number of times of fentanyl administration was also significantly lower in Groups A and B than in Group C.

Our results were consistent with those reported by Shafeek et al. who conducted a study comparing the analgesic efficacy of ultrasound-guided transmuscular quadratus lumborum block (QL3) with that of TAP block and general anesthesia with intravenous opioid drugs during laparoscopic

bariatric surgery and in the early postoperative period. Their results revealed statistically significant differences between the two block groups and the control group in terms of intraoperative hemodynamic changes (mean blood pressure and heart rate). Moreover, the GA group had the highest pain scores, shorter time of first request of rescue analgesia, and more consumption of morphine than the groups treated with quadratus lumborum block and TAP block.[9]

In addition, Elsharkawy et al. investigated the subcostal approach to anterior quadratus lumborum block in providing analgesia in patients undergoing open urological surgeries. Their findings revealed that the subcostal approach to anterior QL block provided adequate analgesia between T6–7 and L1–2, which was required for analgesia following open urological surgical procedures. This is consistent with the findings of our study indicating the efficacy of transmuscular quadratus lumborum block in providing analgesia in patients undergoing flank incision surgeries.[10]

Our study findings are also consistent with those reported by Yousef NK who compared bilateral TAP block versus QLB in 60 patients undergoing total abdominal hysterectomy under GA. They demonstrated that the QLB group consumed less intraoperative fentanyl than the TAP group (43.16 ± 19.5 μg in QLB vs. 110.6 ± 22.4 μg in TAP). Despite showing significance that was not obviously evident in our study, their study result supported the final finding of our study that QL block is more effective than TAP block.[11]

Postoperatively, with respect to VAS score, our study demonstrated that the time to first request of rescue analgesia was the longest in Group A (202.50 ± 72.25 min) compared to that in Group B (138.75 ± 52.39 min) and Group C (37.50 ± 13.42 min). The total amount of pethidine consumption during the total 12 hours postoperatively was similar in Groups A and B (84.06 ± 14.17 and 85.31 ± 16.68 mg, respectively), which was significantly lower than that in Group C (152.19 ± 43.43 mg). The number of times of pethidine administration in the 12-h period showed the same relationship. The VAS score was significantly lower in Groups A and B over the 12-h period than that in Group C during rest and movement. VAS score was high in Group B compared with Group A at 2 hours, which necessitated rescue analgesia. At 4 hours, Group A showed a higher VAS score than group B, which could be attributed to the early administration of pethidine to Group B.

Regarding complications, more patients experienced PONV in Group C (12 patients) than in Group B (3 patients) and Group A (2 patients).

Our study findings are consistent with those of Yousef NK who reported shorter time of analgesia and more morphine consumption in the TAP group than in the QLB group.[11]

In the above-mentioned study of Shafeek et al., their results were consistent with our results regarding the time to first call for rescue analgesia (quadratus lumborum group 187.66 ± 23.84 vs. 202.50 ± 72.25 min in our study, and TAP group 128.07 ± 15.25 vs.138.75 ± 52.39 min in our study). Furthermore, VAS pain score and PONV comparison were significant in the early postoperative period until 6 hours postoperatively in the comparison between the three groups. Total morphine consumption amount was significantly less in the QL3 group than in the TAP group in their study, which contrasts with our study finding. However, they finally concluded that TAP block was more effective than intravenous opioid drug analgesia, and quadratus lumborum block was more effective than TAP block.[9]

Another double-blinded, randomized, controlled study whose findings were consistent with our study findings was performed by Blanco et al. in 50 patients undergoing elective cesarean section under spinal anesthesia. In this study, the first group received a QLB with bupivacaine, and the second group received a QLB with normal saline. Patients in the local anesthetic group showed lower consumption of morphine than the control group ($p < 0.001$) at 6 and 12 hours after the cesarean section. The VAS score was lower in the local anesthetic group than the control group at rest and during movement at all time points, except at 24 hours after the cesarean section.[12]

A case series study was performed by Warusawitharana et al. to investigate ultrasound-guided continuous transmuscular quadratus lumborum analgesia for open renal surgery (mean morphine consumption 50 mg over 48 hours) compared with wound infusion analgesia (93 mg morphine over 48 hours). Their study findings added further support to our study regarding the effectiveness of transmuscular quadratus lumborum block in flank incision procedures.[13]

In another study, Baidya et al. examined the effect of transmuscular quadratus lumborum block for perioperative analgesia in children undergoing pyeloplasty. They reported that transmuscular QL block provided satisfying postoperative analgesia in children undergoing lumbotomy and pyeloplasty surgeries.[14]

Our study findings are also consistent with those reported by Öksüz et al., who performed a randomized controlled trial to compare quadratus lumborum block and TAP block in 50 pediatric patients undergoing lower abdominal surgeries after general anesthesia induction. They reported a lower number of patients requiring analgesia in the first 24 hours postoperatively.[15]

In contrast to our study, a prospective, randomized, double-blinded study was reported by Kumar et al. in 70 adult patients undergoing lower abdominal surgeries. The patients were allocated into 2 groups –quadratus lumborum group and TAP group. The time for the first analgesic requirement was 243 ± 97.36 min in the TAP group and 447.00 ± 62.52 min in the quadratus lumborum group. The total amount of morphine consumption was 5.65 ± 1.55 mg in the TAP group and 3.25 ± 0.78 mg in the quadratus lumborum group, with the difference being statistically significant. This difference was explained in our study based on the effect of surgical incision, which opened the plane where the local anesthetic was injected, spilling a part of the injected volume and thus decreasing its effective time postoperatively. In addition, the use of morphine in that study as rescue analgesia compared to pethidine used in our study resulted in longer duration of action. Moreover, significant differences in postoperative pain scores at rest were observed between both groups up to 16 hours.[16]

Limitations

The flank incision opened the plane where the local anesthetic was injected in both block groups, thus limiting its

postoperative efficacy. Moreover, the period of testing of postoperative analgesia was limited to the first 12 hours postoperatively. However, both quadratus lumborum block and TAP block are known to produce analgesia for at least 48 hours postoperatively. In addition, the exact extent of the blocks was not clinically evaluated as the patients received the blocks after the induction of general anesthesia. The fixed intervals to evaluate VAS scores did not allow the maximum accuracy of determination of analgesia requirements of patients.

Recommendations

It is recommended that further studies be performed on a larger number of patients to confirm our study findings. Longer postoperative follow-up period up to 48 hours is recommended for better assessment of the postoperative analgesic effects of both blocks. Moreover, introduction of a catheter with continuous infusion of local anesthetics appears to provide potentially strong postoperative analgesia. The catheter can be introduced percutaneously or through a surgical incision in situ.

Conclusion

Transmuscular quadratus lumborum block provides more effective perioperative analgesia than posterior TAP block in patients undergoing nephrectomy through flank incision. However, both blocks are effective in achieving pain control perioperatively, with significant reduction of opioid consumption compared with the control group.

Conflicts of interest

The authors declare no conflicts of interest.

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CLINICAL RESEARCH

Does local anesthetic temperature affect the onset and duration of ultrasound-guided infraclavicular brachial plexus nerve block?: a randomized clinical trial



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KEYWORDS
Local anesthetic;
Temperature;
Nerve block;
Brachial plexus;
Interventional ultrasonography

Abstract
Background: Infraclavicular brachial plexus nerve block is a commonly performed anesthesiology technique in the upper extremity. Local anesthetics may be administered at different temperatures for both neuraxial and peripheral nerve blocks. We aimed to evaluate the effects of the temperature of the local anesthetic at the time of administration on the onset and duration of sensory and motor blocks in infraclavicular brachial plexus nerve block.
Methods: A total of 80 patients undergoing elective upper extremity surgery were randomly assigned to one of the following groups using a computer-based randomization software; low temperature (4 °C) (Group L, n = 26), room temperature (25 °C) (Group R, n = 27) and warmed (37 °C) (Group W, n = 27). A 1:1 mixture of 2% lidocaine and 0.5% bupivacaine was used as local anesthetic. Infraclavicular brachial plexus nerve block was performed under ultrasound guidance in all patients preoperatively. The onset and duration of sensory and motor blocks were recorded.
Results: Each group had different onset of motor ($p < 0.001$) and sensory ($p < 0.001$) blocks. The duration of motor block was similar between groups ($p = 221$). However, a significant difference was found in the duration of sensory block between group L (399.1 ± 40.8 min) and group R (379.6 ± 27.6 min) ($p = 0.043$). There was no complication related to nerve block procedure.
Conclusions: The administration of the local anesthetic at lower temperatures may prolong the onset of both motor and sensory blocks in infraclavicular brachial plexus nerve block.
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Introduction

Infraclavicular brachial plexus nerve block is commonly used to facilitate upper extremity surgeries.[1] This technique was proposed to have several advantages over general anesthesia including providing a longer postoperative pain relief and decreased opioid consumption, a lower complication rate, and being more cost efficient.[2] The disadvantage of single shot blocks is that the duration of the block is highly dependent on the local anesthetic agent.[3] Also, blocks may have a late onset of action due to the long latency period.[4] Though a continuous catheter may be used to prolong the duration of effect, it also poses some risks such as increased infection rate and higher toxicity.[5]

Various adjuvants (e.g., epinephrine, morphine, fentanyl, clonidine, dexmedetomidine, buprenorphine, tramadol, dexamethasone, neostigmine, ketorolac, magnesium, sodium bicarbonate, and ketamine) were shown to prolong the duration of the effect of the peripheral nerve block and reduce the latency period, but each of these agents has its own side effects.[5,6] The effect of pre-warmed local anesthetic solution on the onset of sensory block was shown in epidural and spinal anesthesia in earlier studies.[7–9]

Outcomes of studies on intra-articular injection of local anesthetics and infiltration blocks are controversial. The number of studies investigating the effect of temperature of the local anesthetic solution on infraclavicular brachial plexus nerve block is limited. In this study, we aimed to evaluate the effect of the temperature of the local anesthetic at the time of administration on the onset and duration of sensory and motor blocks in infraclavicular brachial plexus nerve block.

Materials and methods

Setting and study population

Institutional review board (IRB) approval was obtained for the study (B.30.2.ATA.O.Ol.00/137). The sample size was calculated using NCSS-PAS. The primary outcome of the study was the onset of sensory block. According to study by Heath et al, based on a 2-minutes difference was accepted as significant between the groups and standard deviation of 1.39 and 1.12 minutes in the onset of sensory block of median nerve between study groups, 26 patients per group was calculated to achieve 80% power with an alpha error of 0.05.[4]

Patients who were between 18–65 years old, with an American Society of Anesthesiologists (ASA) physical status I–II and undergoing elective upper extremity surgery between August 2016 and August 2017 were included. Patients who declined to participate, having a history of ipsilateral peripheral nerve damage of the upper extremity, bleeding disorder, chronic renal or liver disease, drug allergy, and an active infection at the local anesthetic injection site were excluded. Ninety-five patients underwent elective upper extremity surgery during the study period. Of these, 12 patients declined study participation and 3 patients were lost to follow-up. A total of 80 patients were included in this study (Fig. 1). Patients were randomly assigned to one of the 3 groups using a computer-based randomization software. The local anesthetic mixture was administered to patients in group L (n = 26), group R (n = 27) and group W (n = 27) at 4 °C, 25 °C and 37 °C, respectively (Fig. 1).

Patients were routinely monitored for oxygen saturation, arterial blood pressure, and electrocardiography (ECG) intraoperatively. All blocks were performed preoperatively by an anesthesiologist under the ultrasound (US) guidance (Esaote MyLab30®, Florence, Italy) in a room reserved and equipped for peripheral nerve blocks. The anesthesiologist who performed the blocks was unblinded to the study since it was easily felt the temperature of the local anesthetic during injection it by anesthesiologist. The investigator anesthesiologists who collected to the data was blinded for the study.

After placing the patient in a supine position, a bolus of 1 mg of midazolam was administered via IV cannula (Zolamid® 5 mg/5 mL, Defarma, Istanbul, Turkey), and oxygen was delivered through a nasal cannula. The site around the entry point of the needle of peripheral nerve block was draped in a sterile fashion. The high frequency linear ultrasound probe (Esaote MyLab30® high frequency linear probe) was covered with a sterile ultrasound cover. A 10-cm sonovisible sterile needle (Stimuplex® Ultra, Braun, Germany) was used for the nerve block. Brachial plexus and surrounding structures including axillary artery and vein, and infraclavicular muscles were visualized under US guidance.

Local anesthetic was warmed up to 37 °C for group W, stored at room temperature (25 °C) for group R and stored at 4 °C for group L before use. For each patient, a 20 ml of local anesthetic solution containing a 1:1 mixture of 2% lidocaine and 0.5% bupivacaine was administered. The patients were unblinded for the study since they could feel the cold or warmed local anesthetic during injection.

Sensory block was evaluated using a cold ice pack every 2 minutes. The onset of sensory block was recorded as the time when a total loss of cold sensation on radial, median, ulnar, and musculocutaneous nerve dermatomes was confirmed by the patient. Duration of the motor block was evaluated for each nerve individually using the Lovett Rating Scale at 15 and 30 minutes, 1, 2, 4, 8, 12, 16, 20, and 24 hours. Motor strength was scored between 0 and 6, with 0 representing complete paralysis, 1 almost complete paralysis, 2 impaired mobility, 3 slightly impaired mobility, 4 pronounced reduction of muscular force, 5 slightly reduced muscular force, and 6 normal muscular force. Strength of thumb abduction was evaluated as a reference for the radial nerve motor block, as thumb opposition for the median nerve and thumb adduction for the ulnar nerve.

Statistical analysis

Data is presented as mean, standard deviation, median, minimum, maximum, percentage, and in numbers. Normality of the distribution of continuous data was tested using Shapiro-Wilk test. In the comparison of continuous variables with more than two independent groups, the ANOVA test was used when the normal distribution condition was met and the Kruskal Wallis test was used when the normal distribution condition was not met. After the ANOVA test, post-hoc tests were performed using the Tukey test

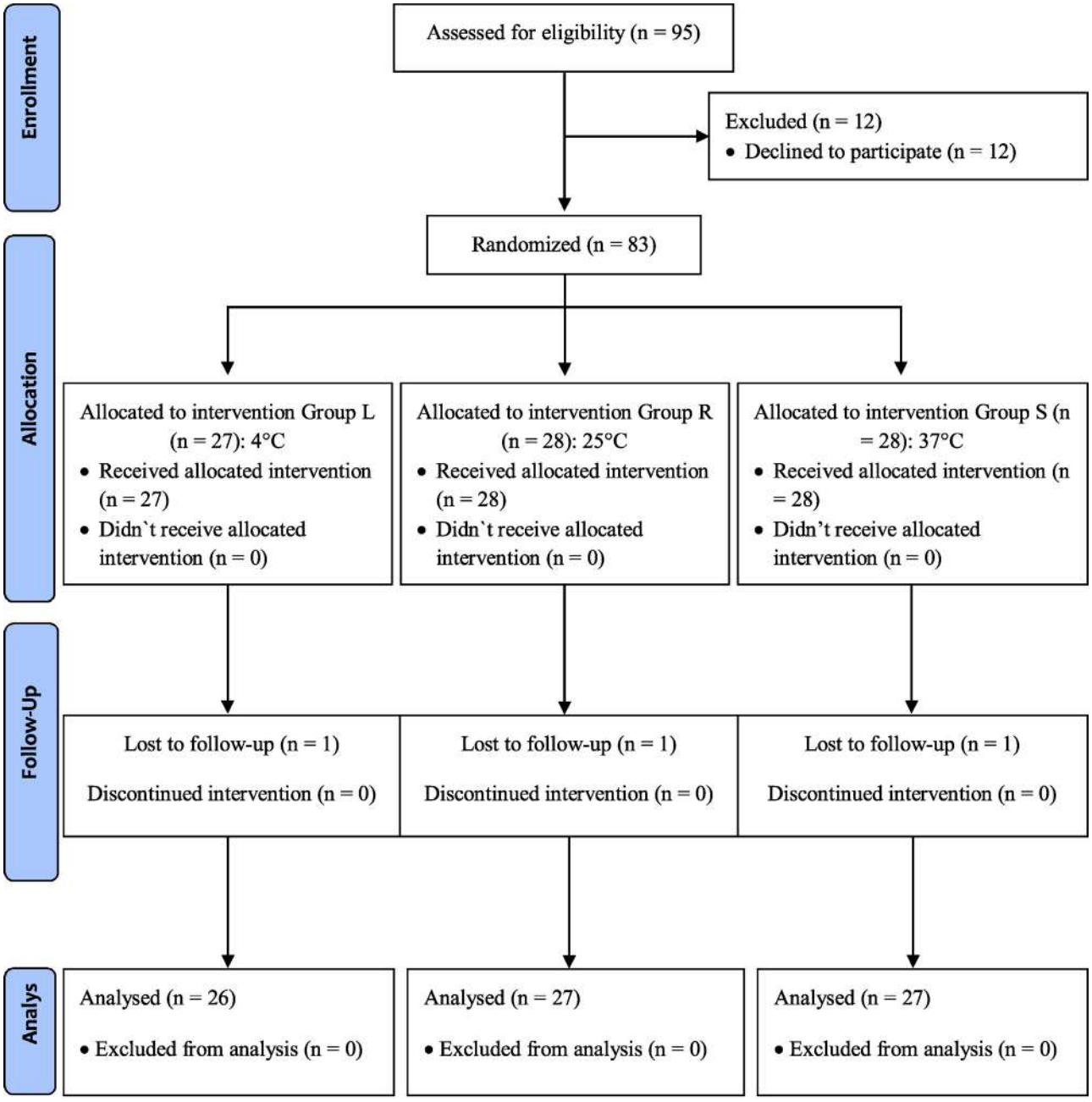

Figure 1 Consort flow diagram.

when the variances were homogeneous and Tamhane's T2 test when the variances were not homogeneous. The Kruskal Wallis test was performed using the Kruskal Wallis one-way ANOVA (K samples) test for post-hoc tests. Categorical data was compared using Chi-Square test. Statistical analysis was performed using SPSS v20 (IBM, NY, USA). A p-value < 0.05 was defined as significant.

Results

Demographic data, body temperature, and operative time were similar between groups (Table 1). Mean onset of sensory block in group L, R, and W were 10.9 ± 1.3, 9.6 ± 1.2, and 8.6 ± 1.8 minutes, respectively. Significant differences were detected in the onset between groups (p < 0.01), and subgroup analysis revealed a significant difference between each group (Table 2). Mean onset of motor block in group L, R, and W were 13.1 ± 2.2, 11.6 ± 1.5, and 9.8 ± 2.2 minutes, respectively. Significant differences were detected between groups (p < 0.05), and subgroup analysis revealed a significant difference between each group (Table 2).

Duration of sensory block in group L, R, and W were 399.1 ± 40.8, 379.6 ± 27.6, 381.8 ± 29.6 minutes, respectively. A significant difference was detected between groups (p = 0.043), and a subgroup analysis revealed a difference between groups L and R (Table 3). Duration of motor block

Table 1 Demographic and operation-related data.

	Group L (n = 26)	Group R (n = 27)	Group W (n = 27)	*p*-value
Age (years)	42.8 ± 16.2	36.5 ± 9.4	37.9 ± 11.9	0.176[a]
Weight (kg)	72.1 ± 13.4	72.8 ± 13.4	76.3 ± 13.3	0.464[a]
Height (cm)	169.5 ± 6.9	170.1 ± 8.4	171.4 ± 8.8	0.670[a]
Gender (male/female)	14/12	16/11	21/6	0.162[b]
Body Temperature (°C)	36.4 ± 1.1	36.7 ± 0.4	36.4 ± 0.6	0.412[a]
Duration of Surgery (min)	41.1 ± 19.7	55.2 ± 23.8	63.7 ± 57.1	0.096[a]

Group L: Low Temperature (4 °C) group, Group R: Room temperature (25 °C) group, Group W: Warmed (37 °C) group.
Values are expressed in mean ± SD.
[a] $p > 0.05$, One-way ANOVA.
[b] $p > 0.05$, Chi-Square Test.

Table 2 Onset of motor and sensory block.

	Group L (n = 26)	Group R (n = 27)	Group W (n = 27)	*p*-value
Onset of Motor Block (min)	13.1 ± 1.2	11.6 ± 1.5	9.8 ± 2.2	< 0.001[a]
Onset of Sensory Block (min)	10.9 ± 1.3	9.6 ± 1.2	8.6 ± 1.8	< 0.001[b]

Group L: Low Temperature (4 °C) group, Group R: Room temperature (25 °C) group, Group W: Warmed (37 °C) group.
Values are expressed in mean ± SD.
Significant difference between all groups after post-hoc test.
[a] $p < 0.05$, Kruskal Wallis.
[b] $p < 0.05$, One-way ANOVA.

Table 3 Duration of motor and sensory block.

	Group L (n = 26)	Group R (n = 27)	Group W (n = 27)	*p*-value
Duration of Motor Block (min)	276.5 ± 16.7	273.8 ± 14.9	269.4 ± 12.5	0.221[a]
Duration of Sensory Block (min)	399.1 ± 40.8	379.6 ± 27.6	381.8 ± 29.6	0.043[b]

Group L: Low Temperature (4 °C) group, Group R: Room temperature (25 °C) group, Group W: Warmed (37 °C) group.
Values are expressed in mean ± SD.
[a] $p > 0.05$, One-way ANOVA.
[b] $p < 0.05$, Significant difference between Group L and Group R, after Post-Hoc test, Kruskal Wallis.

in group L, R, and W were 276.5 ± 16.7, 273.8 ± 14.9, and 269.4 2 ± 12.5 minutes, respectively and were similar ($p = 0.221$) (Table 3). No complication was reported due to nerve block during the follow-up.

Discussion

A major finding of this randomized controlled study is that the onset of sensory and motor blocks may be delayed when administered at lower temperatures. Effects of temperature on peripheral blocks have been reported in earlier studies, in which local anesthetics were administered at a low, room, or body temperature.[9,10] However, there is no study to compare the effect of local anesthetic solution administered at low, room, and body temperature on block characteristics. Although potentiation of the action of the local anesthetic by either cooling or warming have been described, to date there is no conclusive evidence showing superiority of one group (cold/room temp/warm) over another.[9,10]

Heath et al found that the onset of effect the subclavian brachial plexus block using 0.5 $mL.kg^{-1}$ of 0.5% bupivacaine was significantly shorter at body temperature compared to room temperature.[4] We found that the onset of both sensory and motor blocks after infraclavicular brachial plexus block were significantly earlier in the warm group (37 °C), and the duration of sensory and motor blocks were similar.

In a prospective, randomized, doubled-blind study, Svigum et al investigated the effect of temperature of anesthetic agent in epidural anesthesia (bupivacaine 0.125% with fentanyl 2 $\mu g.mL^{-1}$ (20 mL initial and 6 mL hourly boluses) on 54 nulliparous laboring women. They administered anesthetic solution at 20 °C and 37 °C. They found that the onset of action was shorter in the warm group (37 °C) and suggested this provided improved analgesia for the first 15 minutes.[11]

Various factors determine the final outcome when physical properties of a drug are studied in vivo. Increasing the temperature causes a decrease in dissociation constant of the drug,[12] which in turn increases the unionized fraction.

This leads to increased lipid solubility and hence, increases the membrane permeation.[11,13]

In another double-blind, controlled trial, Chilvers et al investigated the effect of warming the local anesthetic on the onset of axillary brachial plexus block.[14] They suggested that injecting the solution close to the axillary artery may possibly increase the temperature of the solution from room temperature to body temperature quickly. Their results opposed to our findings, in that our study showed a significant difference in the onset of both motor and sensory blocks between all groups.

In a study on patients undergoing transurethral prostate resection (TUR-P) surgery, Nazli et al performed spinal anesthesia at two different temperatures and demonstrated that the onset of action of the block (3 mL of 0.5% levobupivacaine solution) was shorter and its duration was longer at body temperature (37 °C) compared to room temperature (25 °C).[9] They noted that increasing the temperature of the solution resulted in an increase in the unionized fraction of the drug available to penetrate the nerve, and increased the molecular kinetic energy which leads to increased distribution of drug in CSF. The overall effect was an earlier onset of action and sensory block at more levels of medulla spinalis. It is unclear whether their outcome could be translated to the infraclavicular brachial plexus nerve block. Tomak et al reported that compared to room temperature group, spinal anesthesia using an anesthetic solution at 5 °C caused a delayed onset of action, effected fewer sensory levels of medulla spinalis, and had shorter duration of sensory and motor blocks.[15] They reported a higher success rate of unilateral spinal anesthesia and lower hemodynamic complications in the cold group.

In an interesting study, Dabarakis et al compared the effect of the temperature of the local anesthetic solution (0.25 mL of 3% plain mepivacaine) on pulpal anesthesia.[16] They reported that there was no difference in the onset of block between 4 °C and 20 °C, while the duration of block was longer in the 4 °C group. They suggested that the vasoconstrictive effect of cooling was responsible for the result. Cooling also decreases the amplitude, and increases the duration and latency of the action potential.[10] Recovery of inactivated fibers at low temperatures is slow.[17]

Although we found that administering local anesthetic at a higher temperature shortened the onset of both sensory and motor blocks, and this finding was similar in many earlier studies, the clinical importance of this effect is not clear. Also, storing local anesthetic at room temperature is more cost-effective compared to storing it at a higher temperature. Similarly, we detected a significant difference in the duration of the sensory block between L (4 °C) and R (25 °C) groups. Considering that both groups had over 6 hours of action and there was only a 20-minute difference between groups, the clinical significance of this difference is equivocal.

Conclusions

Warming the local anesthetic solution to body temperature shortens the onset of action of sensory, and motor blocks in infraclavicular brachial plexus block with no effect on the duration of sensory or motor block. This approach is desirable as it shortens the onset by utilizing the physical properties of the solution without unnecessarily exposing the patient to additional drugs.

Conflicts of interest

The authors declare no conflicts of interest.

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CLINICAL RESEARCH

Effect of ketamine on emergence agitation following septoplasty: a randomized clinical trial

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KEYWORDS
Emergence agitation;
General anesthesia;
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Abstract
Background and objectives: The risk of emergence agitation (EA) is high in patients undergoing nasal surgery. The aim of the present study was to investigate the incidence of EA in adults undergoing septoplasty and the effect of ketamine on EA.
Methods: In this randomized study, a total of 102 ASA I–II patients who underwent septoplasty between July 2018 and April 2019 were divided into two groups: ketamine (Group-K, n = 52) and saline (Group-S, n = 50). After anesthesia induction, Group-K was intravenously administered 20 mL of saline containing 1 mg kg^{-1} ketamine, whereas Group-S was administered 20 mL of saline. Sedation and agitation scores at emergence from anesthesia, incidence of cough, emergence time, and response to verbal stimuli time were recorded. The sedation/agitation and pain levels were recorded for 30 minutes in the recovery unit.
Results: There was no significant difference between the groups in terms of the incidence of EA (Group-K: 15.4%, Group-S: 24%). The incidence of cough during emergence was higher in Group-S than in Group-K, but the response time to verbal stimuli and emergence time were shorter in Group-S. The sedation and agitation scores were similar after surgery. Pain scores were higher in Group-S at the time of admission to the recovery unit and were similar between groups in the other time points.
Conclusion: Administration of 1 mg kg^{-1} ketamine after anesthesia induction does not affect the incidence of EA in patients undergoing septoplasty, but it prolongs the emergence and response time to verbal stimuli and reduces the incidence of cough.
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Introduction

Postanesthesia emergence agitation (EA) is an important clinical problem that occurs during the early period of recovery from anesthesia, and it causes problems such as self-extubation, catheter removal, bleeding and injury to patients and healthcare personnel, and a prolonged hospital stay.[1,2] Although EA is commonly observed in children after inhalation anesthesia, its incidence has been reported to be high in adults after certain surgeries, particularly ear, nose and throat surgeries. The pathophysiology of EA is still unclear, but a sense of suffocation can be the cause of the increased incidence of emergence agitation after nasal surgeries.[2]

Various anesthetic and analgesic drugs are used in the treatment of EA. However, the potential respiratory depression effect of such drugs may pose a risk to patients during the recovery period. Therefore, the prevention of EA is safer and of greater priority than its treatment.[3]

While several studies have shown that ketamine, a NMDA receptor antagonist frequently used for anesthesia, may reduce the incidence of EA in children, studies investigating the effect of ketamine on EA in adults are limited.[4,5] Therefore, the aims of the present study were to evaluate the incidence of EA in adults undergoing septoplasty and to investigate the effect of the administration of ketamine on EA.

Methods

After approval for the study was obtained from the hospital's ethics committee (FSM EAH-KAEK 2018/35) and informed consent was obtained from the patients, a total of 102 ASA (American Society of Anesthesiologists) physical status I–II adults who underwent septoplasty between July 2018 and April 2019 were included in the study.

Patients with a history of ketamine allergy, hypertension, coronary artery disease, arrhythmia, seizure, obstructive sleep apnea, glaucoma, kidney disease, or liver disease, as well as those with a body mass index of $> 30\,kg\,m^{-2}$ or cognitive dysfunction were excluded from the study.

The sealed envelope technique was used for randomization, and each randomization result was written on paper and kept in an opaque sealed envelope that was labeled with a serial number. The sealed envelope was opened once the patient consented to participate in the study. Therefore, the patients were randomly divided into two groups: ketamine (Group-K) and saline (Group-S) (Figure 1). The patients were not informed about the group to which they were assigned. Their demographic data were recorded. The patients were taken to the operating room without premedication. After monitoring the peripheral capillary oxygen saturation level, noninvasive blood pressure, heart rate (HR), and Bispectral Index (BIS), anesthesia was induced with $2.5\,mg\,kg^{-1}$ propofol, $2\,mcg\,kg^{-1}$ fentanyl, and $0.6\,mg\,kg^{-1}$ rocuronium, and the patients were intubated. Anesthesia was maintained by administering a mixture of 50% oxygen and 5–7% desflurane in air at a flow rate of $2\,L\,min^{-1}$ with $0.05–0.5\,mcg\,kg^{-1}\,min^{-1}$ remifentanil infusion such that the BIS remained between 40 and 60. The ventilator parameters were adjusted at a tidal volume of $7–8\,mL\,kg^{-1}$ and a respiratory rate of 10–12 breaths.min^{-1} so that the end-tidal CO_2 level remained between 30 and 35. Immediately after anesthesia was induced, 20 mL of normal saline containing $1\,mg\,kg^{-1}$ ketamine was intravenously administered to Group-K in 10 minutes, whereas 20 mL of normal saline was intravenously administered to Group-S in 10 minutes. The solutions were prepared according to the relevant envelope containing the randomization result for each patient that was provided by a specialist physician who participated in the study randomization process but was not involved in the follow-up. The perioperative follow-up of the patients was performed by an anesthesiologist blinded to the administered drug. The oxygen saturation level (SPO_2), mean arterial pressure (MAP), and HR were recorded every 15 minutes while the patient was under anesthesia. At 20 minutes before the end of the surgery, 1000 mg paracetamol and $1\,mg\,kg^{-1}$ tramadol were intravenously administered. The total surgical duration was recorded after integral airway nasal packing was placed at the end of the surgery and inhalation anesthesia was discontinued. The patients were ventilated with 80% oxygen at a flow rate of $6\,L\,min^{-1}$, and $0.03–0.05\,mg\,kg^{-1}$ neostigmine and $0.02\,mg.kg^{-1}$ atropine were intravenously administered to reverse the neuromuscular block. Patients who met the extubation criteria were extubated. The period between the discontinuation of inhalation anesthesia and 3 minutes after extubation was considered the emergence period, and this time was recorded. The agitation/sedation level during the emergence period was evaluated and recorded using the Riker Sedation/Agitation Scale (SAS) (Table 1), and patients with a SAS score ≥ 5 were considered agitated. Patients with an agitation score of 7 were intravenously administered $0.4\,mg\,kg^{-1}$ propofol. The incidence of cough during emergence was scored as follows: 0, no cough; 1, a single cough; 2, nonpersistent cough lasting ≤ 5 s; and 3, persistent cough lasting > 5 s. The response time to verbal stimuli (the response to the question ''how are you?'') was also recorded.

In the postanesthesia care unit (PACU), the sedation/agitation levels were evaluated with the SAS, whereas the pain scores were evaluated with the visual analogue scale (VAS) at 0, 10, 20 and 30 minutes. The SpO_2, MAP, and HR were recorded at the same time points. The patients were also evaluated for nausea and other side effects. Patients with nausea and/or vomiting during the PACU follow-up were intravenously administered $0.1\,mg\,kg^{-1}$ ondansetron. Patients with a modified Aldrete score of ≥ 9, 30 minutes after emergence were transferred to wards.

Statistical analysis

Continuous variables are presented as the mean $\pm$ standard deviation or the median (minimum-maximum), and categorical variables are presented as the frequency and percentage. The Shapiro–Wilk test was used to test the normality of the data. Continuous variables were compared using Student's *t*-test when the data were normally distributed and the Mann-Whitney *U* test when the data were non-normally distributed. For the response times to verbal stimuli at the different time points, the percent change values were calculated according to the baseline measure-

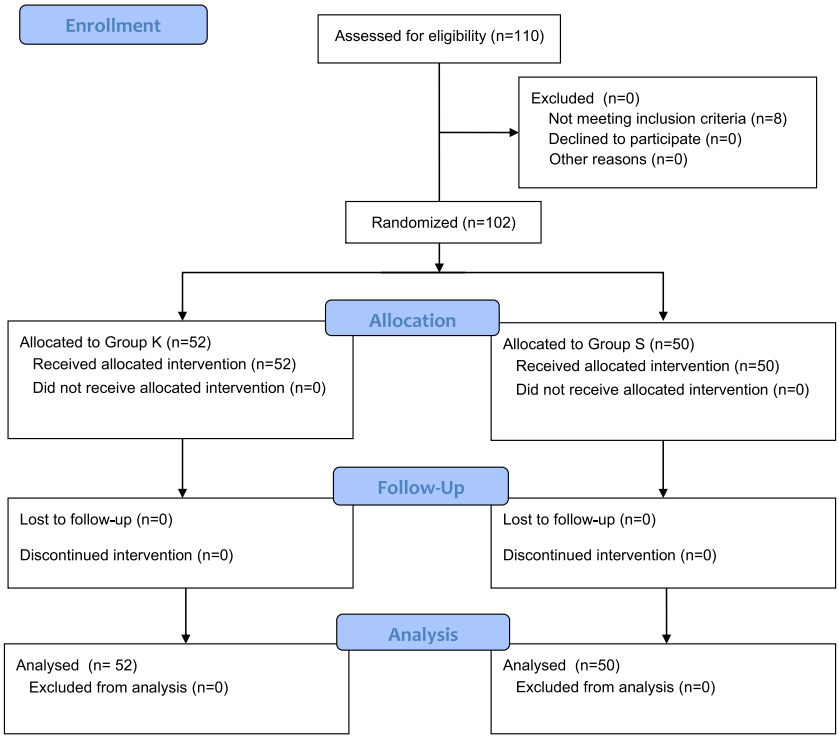

Figure 1 CONSORT flow diagram.

Table 1 Riker Sedation/Agitation Scale (SAS).

Score	Term	Descriptor
7	Severely agitated	Remove endotracheal tubes, attempt to remove catheters, climb over bedrail, attack staff, thrash sideways
6	Very agitated	Do not calm down despite frequent verbal reminders of limits, require physical restraints, bite endotracheal tubes
5	Agitated	Display anxiety or mild agitated, attempt to sit up, calm down on verbal instructions
4	Calm, cooperative	Calm, easily arousable, follow verbal instructions
3	Sedated	Difficult to arouse, awaken to verbal stimuli or gentle shaking but drifts off again, follow simple verbal instructions
2	Highly sedated	Arouse to physical stimuli but do not communicate or follow verbal instructions, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, do not communicate or follow verbal instructions

ments. These percent change values were compared using the Mann-Whitney *U* test for the two groups. The Friedman test was used to assess the overall change in the variables. Post hoc analysis with the Wilcoxon signed-rank test was performed with Bonferroni's correction. Categorical variables were compared using Pearson's chi-squared test and Fisher's exact test. McNemar's test was used for the dependent categorical data. All statistical analyses were performed using IBM SPSS (v 23.0; IBM Corp. Released 2015; IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

The primary study outcome was the incidence of EA. Yu et al reported the incidence of EA to be 55.4% after ear, nose and throat surgeries.[6] In a study conducted with nefopam, another NMDA antagonist, the authors accepted a significant decrease by 50% at this previously reported incidence.[7] After performing a power analysis, we found that a sample size of 49 patients was needed in each group to detect a 50% reduction in the incidence of EA, with a power of 80% and an alpha value of 0.05. We enrolled 52 patients in Group-K and 50 in Group-S after considering that patients may drop out from the study.

Results

A total of 102 patients (Group-K: 52, Group-S: 50) were included in the present study. The patient demographics and surgical durations are summarized in Table 2.

The intraoperative and postoperative SpO_2 values were similar between the two groups. In both groups, the intraoperative MAP and HR were significantly lower than the baseline measurements. At 45 minutes, the decrease in MAP

Table 2 Comparison of patient demographics and surgical duration.

	Group K (n = 52)	Group S (n = 50)	*p*
Age, years (mean ± SD)	33.54 ± 10.71	32.80 ± 10.35	0.724[a]
Female sex, n (%)	15 (28.8%)	18 (36.0%)	0.440[b]
BMI, kg.m^{-2} (mean ± SD)	24.33 ± 3.30	24.08 ± 3.58	0.717[a]
ASA, n (%)			0.422[b]
I	41 (78.8%)	36 (72.0%)	
II	11 (21.2%)	14 (28.0%)	
Surgical duration, minutes (median [min–max])	64.00 (27–210)	55.00 (20–121)	0.136[c]

[a] *t*-test.
[b] Pearson's Chi-Squared test.
[c] Mann-Whitney *U*-test, $p < 0.05$ was considered statistically significant.

compared with the baseline measurement was significantly higher in Group-K than in Group-S ($p = 0.024$); the MAP values were similar between the two groups at the other time points. The intraoperative HR was similar between the two groups at all time points.

The incidence of EA was similar between the two groups (Group-K: 15.4%, Group-S: 24%; $p = 0.273$). The patients' age, ASA score and sex had no effect on the incidence of EA ($p = 0.195$, 1.000, and 0.064, respectively). The incidence of cough during emergence was higher in Group-S than in Group-K, whereas the emergence and response to verbal stimuli times were longer in Group-K (Table 3).

During the PACU follow-up period, the patients had similar agitation incidence. Compared with Group-K, Group-S had a higher VAS score at the time of admission to the PACU (postoperative 0 min), but the pain level was similar at the other time points (Table 4). The MAP and HR values were similar between the groups in the postoperative follow-up.

During the postoperative follow-up period, nausea was observed in 2 patients (3.8%) in Group-K and 5 (10%) in Group-S ($p = 0.265$). Bleeding was observed in 1 patient (1.9%) in Group-K, hallucination was observed in 1 patient (1.9%) in Group-K, and cough was observed in 3 patients (6%) in Group-S. The complication rates were similar between the two groups ($p = 0.145$).

Discussion

In this study, we investigated the effect of ketamine on EA in adults undergoing septoplasty and found that the incidence of EA was 24% in Group-S and that ketamine did not reduce the incidence of EA. Group-K had a lower incidence of cough during emergence but longer emergence and response to verbal stimuli times than Group-S.

Although the mechanism underlying the occurrence of EA has not been fully elucidated, several factors are known to trigger its occurrence. One such factor is the sense of suffocation caused by nasal packing placed after nasal surgery.[6] Practices such as those not involving the use of nasal packing or the use of integral airway nasal packing may reduce the risk of EA. Studies have reported that the incidence of EA after nasal surgery may be > 50%.[3,6] In our study, the incidence of EA was found to be 24%; this discrepancy may be due to the use of integral airway nasal packing in our study, which reduced the sense of suffocation experienced by the patients. Furthermore, to the best of our knowledge, the present study is the first to investigate the effect of ketamine on EA in adults undergoing septoplasty. The fact that only patients who underwent septoplasty were included in this study, rather than all patients who underwent any type of nasal surgery, might have been a factor that reduced the sense of suffocation experienced by the patients and led to a low incidence of EA because this subset of patients is more used to, or familiar with, experiencing chronic nasal obstruction.

Although EA may occur after painless procedures, pain has been defined as one of the most important factors causing EA. In their study examining EA after nasal surgery, Kim et al reported that an NRS of ≥ 5 was an independent risk factor for EA.[8] Some studies have reported that the use of drugs with analgesic properties, such as nefopam, dexmedetomidine, and opioids, reduces the risk of EA.[4,7,9] In a study that investigated rhinoplasties, it was reported that severe postoperative pain was an important risk factor for the development of EA and that the use of ketamine at subanesthetic doses was useful in reducing the incidence of EA.[3] In another study, nefopam, an NMDA antagonist, was reported to reduce EA after nasal surgery.[7] Pediatric studies have also reported that ketamine can reduce the incidence of EA.[4,5] In a previous study, it was reported that the administration of ketamine was not effective in preventing the occurrence of EA after inhalation anesthesia in children subjected to caudal blocks and that pain is the primary factor in the development of EA.[10] In our study, the pain score was found to be low in both groups. The VAS score was higher in Group-S than in Group-K at the time of admission to the PACU (postoperative 0 min). The terminal plasma half-life of ketamine after intravenous administration is reportedly 186 minutes.[11] A low VAS score at the time of admission to the PACU may be due to the analgesic effect of ketamine. However, although the VAS score of Group-S was significantly higher than that of Group-K, the median VAS score of Group-S was 1 (0–8). Therefore, the absence of a difference between the groups in terms of the incidence of EA can be attributed to the low postoperative pain levels in both groups. A young age, the male sex, and a high ASA score were reported to be factors that increase the incidence of EA.[8] In our study, the patients' age, ASA score and sex did not have an effect on the incidence of EA. Furthermore, the age and sex distributions were similar between the two groups. Hence, it is concluded that the incidence of EA was not affected by demographic factors.

Table 3 Riker Sedation/Agitation Scale (SAS) scores at emergence from anesthesia, incidence of cough and response time to verbal stimuli.

		Group K (n = 52)	Group S (n = 50)	*p*
		n (%)	n (%)	
Emergence SAS	Agitated	8 (15.4%)	12 (24.0%)	0.273[a]
	Calm/Sedated	44 (84.6%)	38 (76.0%)	
Cough incidence	None	41 (78.8%)	26 (52.0%)	0.036[a]
	Present	11 (21.2%)	24 (48.0%)	
Emergence time (min)	Mean (SD)	11.79 (4.65)	7.54 (3.21)	<0.001[b]
Response to verbal stimuli time (min)	Mean (SD)	13.48 (4.90)	9.22(3.45)	<0.001[b]

Agitated, SAS score of 5/6/7; Calm/Sedated, SAS score of 1/2/3/4; Cough classification, (0) – none; (1 to 3) – present.
[a] Pearson Chi-Square test.
[b] *t*-test, $p < 0.05$ was considered statistically significant.

Table 4 Riker Sedation/Agitation Scale (SAS) and Visual Analogue Pain Scale (VAS) scores after surgery.

	Postoperative time (min)		Group K (n = 52)	Group S (n = 50)	*p*
			n (%)	n (%)	
SAS	0	Agitated	0 (0.0%)	1 (2.0%)	0.490[a]
		Calm/Sedated	52 (100%)	49 (98%)	
	10	Agitated	0 (0.0%)	0 (0.0%)	–
		Calm/Sedated	52 (100%)	50 (100%)	
	20	Agitated	1 (1.9%)	0 (0.0%)	1.000[a]
		Calm/Sedated	51 (98.1%)	50 (100%)	
	30	Agitated	1 (1.9%)	0 (0.0%)	1.000[a]
		Calm	51 (98.1%)	50 (100%)	
VAS	0	Median (min–max)	0 (0–5)	1 (0–8)	0.001[b]
	10	Median (min–max)	0 (-1–5)	0 (-2–3)	0.108[b]
	20	Median (min–max)	0 (-2–6)	0 (-2–5)	0.213[b]
	30	Median (min–max)	0 (-2–6)	0 (-5–5)	0.181[b]

Agitated, SAS score of 5/6/7; Calm/Sedated, SAS score of 1/2/3/4.
[a] Fisher's exact test.
[b] Mann-Whitney *U*-test, $p < 0.05$ was considered statistically significant.

The dose and time of administration tend to differ among studies investigating the effect of ketamine on the incidence of EA. In some studies, ketamine was administered after anesthesia induction or before the end of surgery.[4,12] In a study conducted in children, it was reported that ketamine administered at a dose of 0.25 mg kg^{-1} 10 minutes before the end of surgery decreased the incidence of EA without affecting the recovery period.[9] It was reported that the administration of a 1 mg kg^{-1} bolus and 1 mg kg^{-1}.h^{-1} ketamine decreased the incidence of EA in children, but it delayed their mental orientation.[4] Demir et al administered 0.5 mg kg^{-1} ketamine 20-minutes before the end of surgery to adults undergoing rhinoplasty and reported that the duration of anesthesia was longer in this group than that in the control group.[3] In our study, the infusion of 1 mg kg^{-1} ketamine for 10 minutes after anesthesia induction was preferred, and the emergence and response to verbal stimuli times were found to be longer in Group-K than in Group-S. This effect might not have been observed if lower doses of ketamine had been administered.

The incidence of EA during extubation in the operating room is reportedly higher than that of EA in the PACU.[13] In our study, all patients were followed for 30 minutes during the postoperative period, and EA was evaluated during emergence and in the PACU. After surgery, the SAS score distribution was found to be similar between the two groups, and the number of agitated patients was lower in the PACU as compared to the emergence from anesthesia.

Reducing the incidence of cough during emergence after nasal surgery is important for preventing bleeding at the surgical site. Studies have reported that ketamine reduces fentanyl-induced cough.[14,15] In our study, the incidence of cough during emergence was found to be lower in Group-K than in Group-S. We believe that the administration of a low dose of ketamine is a good alternative method for preventing bleeding complications in surgeries wherein cough prevention is important, such as nasal and endoscopic sinus surgery.

In a study conducted in adults, it was reported that ketamine had no effect on the incidence of nausea and vomiting after rhinoplasty.[3] In another study conducted on children, a placebo and different doses of ketamine (0.2 and 0.5 mg kg^{-1}) were used, and the rates of postoperative nausea and vomiting were found to be similar across all groups.[12] In our study, no difference was found between the groups

in terms of the occurrence of nausea/vomiting and other complications during the PACU follow-up period.

In nasal surgery, controlled hypotension is important for preventing bleeding, facilitating the application of surgical techniques, and reducing the surgical duration. Ketamine leads to central sympathetic activation by preventing neuronal catecholamine reuptake and stimulating norepinephrine, dopamine, and serotonin release from noradrenergic neurons, which in turn increases the individual's blood pressure and HR.[16] In our study, the intraoperative MAP and HR decreased in both groups compared with the baseline measurements. The vital signs during the postoperative period were similar between the two groups. Therefore, the administration of a low dose of ketamine did not have any negative hemodynamic effects in patients undergoing septoplasty.

The present study has some limitations. In the postoperative period, all patients were followed only until discharge from the PACU. Therefore, a significant difference might have been observed in the pain scores between the groups, if the patients were followed over a longer period of time after surgery. Furthermore 102 patients were included in the study; although the number of patients included in the study was not small, a larger sample size might have revealed a difference between the groups in terms of the incidence of EA.

Conclusion

The intraoperative administration of ketamine does not reduce the incidence of EA following septoplasty, but it is effective in reducing the incidence of cough during emergence. In surgery wherein hypotensive anesthesia is performed, the administration of 1 mg kg^{-1}, ketamine does not have any negative effects on hemodynamics.

Conflicts of interest

The authors declare no conflicts of interest.

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CLINICAL RESEARCH

Impact of age on the incidence of complications after liver transplantation: A single-center retrospective study

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Abstract
Background and objective: Advances in surgical technique, postoperative management, and immunosuppressive therapy have led to a steady increase in the number of patients undergoing organ transplantation. This study aimed to compare the incidence of postoperative complications between young and elderly patients undergoing liver transplantation (LT) at a single university hospital.
Method: The medical records of 253 patients who underwent LT between January 2010 and July 2017 were retrospectively reviewed. The patients were divided into two groups: those younger than 65 years (group Y, n = 231) and those older than 65 years (group O, n = 22). Data on patient demographics, perioperative management, and postoperative complications were collected.
Results: The patients' baseline characteristics, including underlying diseases and the Model for End-Stage Liver Disease scores, were not different between groups. Preoperative laboratory findings were not significantly different between the two groups, except for hemoglobin level. The total amounts of infused fluid and packed red blood cells were higher in group O than in group Y. The postoperative plasma creatinine level was higher in group O than in group Y; however, the incidence of postoperative complications was not considerably different between the two groups. In addition, there was no difference in the survival rate after LT depending on age.

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Introduction

Liver transplantation (LT) has been recognized as the standard treatment for patients with end-stage liver disease based on accumulated experience and improvements in long-term outcome.[1] The prolongation of life span has increased the number of patients waiting for organ transplantation, and the median age of liver transplant recipients has also increased owing to advances in surgical technique, intensive care, postoperative surgical treatment, and immunosuppressive therapy.[2,3] However, the reported outcomes among elderly liver transplant recipients have varied widely. An early study from a single center reported a longer hospital stay and lower survival rate in patients aged >60 years.[4] The causes of high mortality were as follows: comorbidities before surgery, malignancy, cardiovascular and/or neurological disease after LT, increased risk of infection, increased resource utilization, and lower life expectancy.[5,6] Consequently, most of the recently published studies showed similar outcomes in elderly recipients compared with younger recipients, with elderly patients showing a significantly lower incidence of acute rejection but higher incidences of infection and cancer.[7–10] Advanced age alone is not a cause of transplant rejection; however, several studies have shown that the risk of complications is higher in elderly liver transplant recipients because of their high physiological age, functional status, and preoperative comorbidities.[11]

Although the number of candidates for LT has increased, organ availability does not fully meet the demand. Therefore, proper organ allocation and utilization are necessary, and it is important to determine whether there would be any difference in the risk of complications and outcomes after LT in elderly patients compared with younger patients. To clarify this issue, we aimed to evaluate the relationship between age and the risk of post-LT complications and to identify the important factors for safely performing LT in elderly patients.

Methods

This study was approved by the institutional review board (n. 2017–156). The medical records of patients who underwent LT from January 1, 2010 to July 31, 2017 were computer-searched, and data from 360 patients were collected (Figure 1).

A total of 253 patients were ultimately included in the study, after excluding 107 patients because of cerebral disease that could affect mental status, missing data about mental status after LT, retransplantation, or additional surgery.

The patient records were reviewed retrospectively, including hospitalization records, progress reports, consultation records, preoperative evaluation reports, anesthesia records, intensive care unit (ICU) records, nursing records, and discharge records. A preoperative examination was performed within 1 day before surgery, and postoperative tests were carried out within 1 day after transfer to the ICU.

Postoperative complications after surgery and before discharge were assessed by referring to the discharge records. Cardiac complications were defined as cardiac-related diseases such as angina and arrhythmia that needed treatment. Respiratory complications were defined as respiratory infections such as pneumonia that required management. Neurological complications included neurological problems such as cerebral hemorrhage that required treatment. The incidence of delirium was assessed in cases in which delirium was diagnosed in patients under psychiatric consultation and needed medical treatment with haloperidol or other drugs for delirium. In accordance with the Acute Kidney Injury Network (AKIN) criteria,[12] patients with postoperative acute kidney injury were diagnosed. The infection rate was reviewed in cases with surgical site infection and sepsis. Acute rejection after LT was confirmed by pathologic biopsy results within 6 months after transplantation. Mortality was also evaluated in cases of deaths in the postoperative period before discharge.

Induction of anesthesia was performed with propofol and rocuronium or cisatracurium. Inhalation anesthesia was applied with sevoflurane or desflurane in an oxygen/air mixture with 40–50% inspired oxygen. Remifentanil (range 0.5–1 $\mu g.kg^{-1}.min^{-1}$) and a neuromuscular blocking agent (rocuronium [range 0.3–0.6 $mg.kg^{-1}.h^{-1}$] or cisatracurium [range 0.1–0.2 $mg.kg^{-1}.h^{-1}$]) were continuously infused. All patients underwent standard anesthetic monitoring, including electrocardiography and end-tidal carbon dioxide concentration, bispectral index, peripheral oxygen saturation, cerebral oxygenation using INVOS 5100 C (COVIDIEN, Mansfield, MA, USA), and invasive arterial blood pressure monitoring in the radial and femoral arteries. An oxygen monitoring central venous catheter (PreSep; Edwards Lifesciences, Irvine, CA, USA) was inserted and used to evaluate circulation using an EV1000 platform (Edwards Lifesciences) for monitoring cardiac output, cardiac index, stroke volume, stroke volume index, central venous oxygen saturation, and systemic vascular resistance. Transfusion was performed to maintain the hematocrit level at 25–30%. Norepinephrine (0.01–0.4 $\mu g.kg^{-1}.min^{-1}$) was used to maintain adequate blood pressure during surgery (systolic blood pressure > 90 mmHg, mean arterial pressure > 60 mmHg). If norepinephrine was not effective, dobutamine, vasopressin, and epinephrine were used, depending on the condition of the patient.

Data were analyzed using SAS (Statistical Analysis System version 9.3; SAS Institute, USA) and R software version 3.3.2 (R Project for Statistical Computing, Austria). All data are presented as the mean ± standard deviation, median (25th–75th percentile), or number of patients (%). The normality test was performed with the Shapiro-Wilk W-test or the Kolmogorov-Smirnov test. The independent *t*-test or Wilcoxon rank-sum test was used for continuous variables for comparison between the two groups. The chi-square test or Fisher's exact test was used for categorical variables. The survival difference was assessed by the log rank tests and Kaplan-Meier curves. A p-value < 0.05 was considered statistically significant.

The effect of the age on the death or not after LT using univariate analysis and multivariate analysis were analysed. Typical factors associated with the death after LT were analysed by univariate analysis, and multivariate analysis was performed using 8 factors with p-value < 0.1.

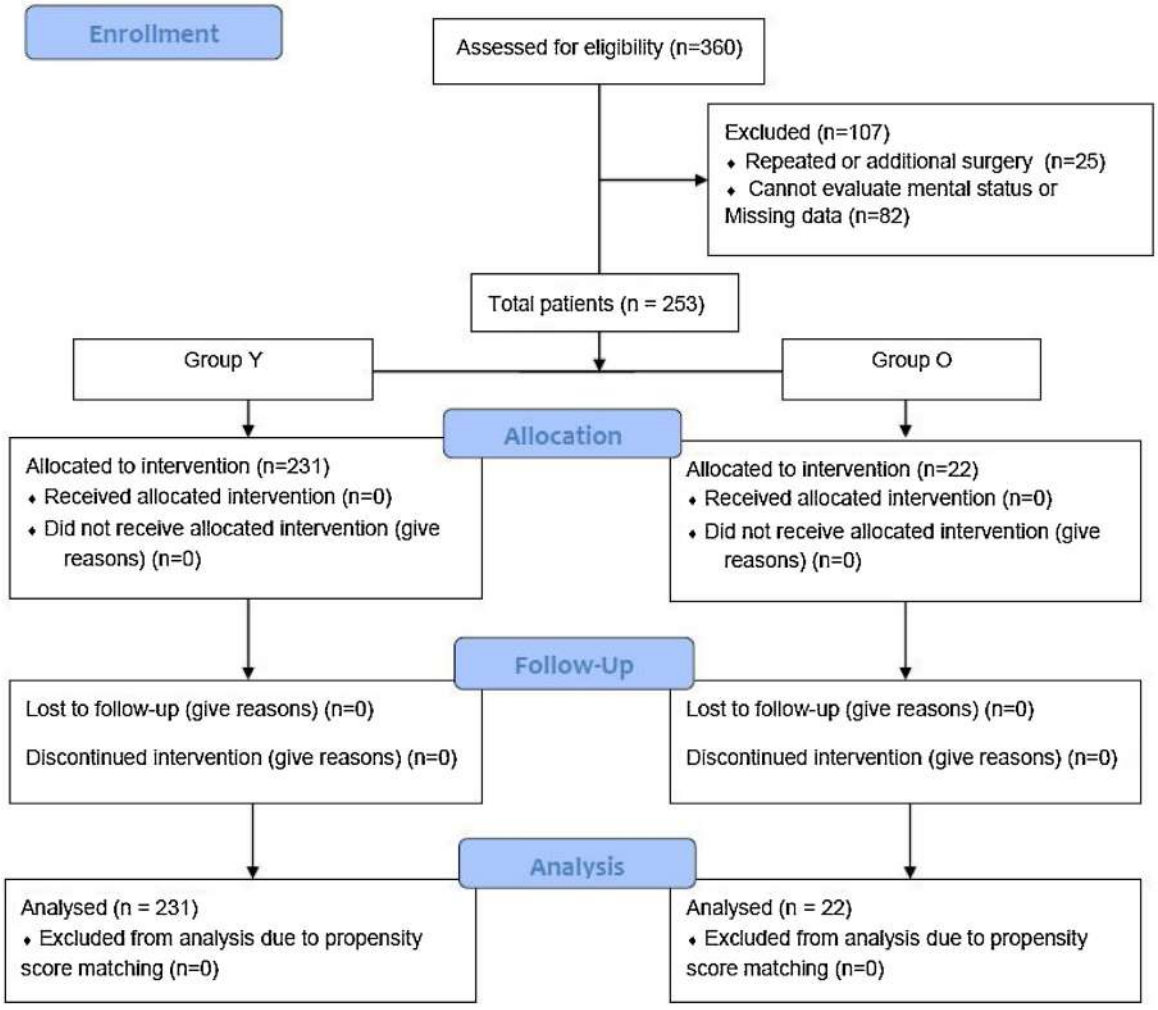

Figure 1 Flow diagram of the study.

Results

We retrospectively analyzed the data of 360 LT cases in Figure 1. Of these patients, 107 were excluded. Twenty-five patients were excluded due to repeated or additional surgery. Twenty patients were excluded as mental status could not be evaluated, while perioperative laboratory data were missing in 62 patients. Among the excluded patients, seven were aged 65 years or more: one patient was excluded due to repeated surgery, and six patients were excluded due to missing perioperative blood coagulation test data.

The preoperative characteristics of the patients are summarized in Table 1. The patients were divided into two groups: those aged < 65 years (group Y, n = 231) and those aged ≥ 65 years (group O, n = 22). The patients' characteristics, such as body mass index (BMI), use of diuretics or insulin, use of psychiatric medication, and underlying diseases, were not significantly different between group Y and group O. Moreover, the reasons for LT and the Model for End-Stage Liver Disease (MELD) scores also showed no difference between the two groups.

In the preoperative laboratory findings, most of the results showed no difference between the two groups, except for hemoglobin (p = 0.001), which was slightly lower in group O than in group Y (Table 2).

During the surgery, patients in group O had a longer anesthetic duration than patients in group Y (p = 0.033). In addition, the intraoperative estimated blood loss was higher in group O than in group Y (p = 0.027). The total amounts of infused fluid (p = 0.042) and packed red blood cells (p = 0.008) were higher in group O than in group Y (Table 3).

No notable differences in postoperative data were found between the two groups except for creatinine level. The plasma creatinine level after LT was higher in group O than in group Y (Table 4). However, there were no significant differences in the incidence of postoperative complications, including ICU stay and time from surgery to discharge.

Thirty-eight patients died after LT, five of whom were aged 65 years or older. In the group O, two patients died within 3 months of the liver transplant. One patient died of respiratory failure due to tuberculosis and the other died of multiple organ failure due to sepsis. In addition, there was no difference in the survival rate after liver transplantation depending on age using Kaplan-Meier curves (log-rank p-value = 0.20) as depicted in Figure 2. In the univariate analysis in Table 5, LDLT or CDLT, hypertension, diabetes

Table 1 Patients' characteristics.

Characteristics	Group Y (n = 231)	Group O (n = 22)	*p*-value[a]
Age (y)	53 (22–64)	66 (65–74)	0.865
Sex (M/F)	62 (26.84)/169 (73.16)	8 (36.36)/14 (63.64)	0.340
Body mass index ($kg.m^{-2}$)	22.49 ± 3.21	21.09 ± 3.15	0.051
LDLT/CDLT	153 (66.23)/78 (33.77)	11 (50)/11 (50)	0.635
MELD score	18.32 ± 11.29	20.00 ± 9.93	0.500
Cause for LT			
Alcoholic cirrhosis	50 (21.65)	3 (13.64)	0.294
HBV and HCV	155 (67.10)	13 (59.09)	
NBNC LC	8 (3.46)	2 (9.09)	
Toxic hepatitis	13 (5.63)	3 (13.64)	
Primary biliary cirrhosis	5 (2.16)	1 (4.55)	
Ascites	76 (32.90)	10 (45.45)	0.235
Hepatic Encephalopathy	37 (16.02)	5 (22.73)	0.381
Varices	37 (16.02)	4 (18.18)	0.764
HRS	20 (8.66)	3 (13.64)	0.433
Hypertension	44 (19.05)	7 (31.82)	0.167
Diabetes mellitus	61 (26.41)	5 (22.73)	0.707
Ischemic heart disease	1 (0.43)	1 (4.55)	0.167

Values are presented as mean (standard deviation), median (range) or number (%). SD, standard deviation; LDLT, living donor liver transplantation; CDLT, cadaveric donor liver transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC LC, non-HBV non-HCV liver cirrhosis; HRS, hepatorenal syndrome; Group Y, patients < 65 years; Group O, patients ≥ 65 years.
[a] $p < 0.05$ compared between groups.

Table 2 Perioperative laboratory data in patients undergoing liver transplantation.

Variables	Preoperative data			Postoperative data		
	Group Y (n = 231)	Group O (n = 22)	*p*-value[a]	Group Y (n = 231)	Group O (n = 22)	*p*-value[a]
Hb ($g.dL^{-1}$)	10.88 ± 2.29	9.65 ± 1.42	0.001[a]	8.93 ± 1.49	9.25 ± 1.31	0.331
Bilirubin ($\mu mol.L^{-1}$)	2.70 (1.30–1.80)	3.30 (1.80–7.00)	0.253	4.00 (2.10–6.80)	4.90 (3.00–7.50)	0.307
Protein ($g.dL^{-1}$)	5.97 ± 0.87	5.66 ± 0.84	0.108	5.27 ± 0.69	5.17 ± 0.55	0.470
Albumin ($g.dL^{-1}$)	3.13 ± 0.56	3.04 ± 0.50	0.446	3.64 ± 0.46	3.61 ± 0.39	0.731
K ($mmol.L^{-1}$)	3.98 ± 0.54	3.95 ± 0.61	0.817	3.99 ± 0.41	4.12 ± 0.49	0.166
Cr ($mg.dL^{-1}$)	0.78 (0.61–1.00)	0.90 (0.77–1.19)	0.099	1.04 ± 0.47	1.26 ± 0.54	0.044[a]
PT (INR)	1.55 (1.24–2.20)	1.75 (1.40–2.31)	0.203	1.79 ± 0.37	1.67 ± 0.30	0.139

Values are expressed as mean ± standard deviation or median (25th–75th percentile). Hb, hemoglobin; K, potassium; Cr, creatinine; PT, prothrombin time; INR, international normalized ratio; Group Y, patients < 65 years; Group O, patients ≥ 65 years.
[a] $p < 0.05$ compared between groups.

Table 3 Patients' perioperative factors.

Variables	Group Y (n = 231)	Group O (n = 22)	*p*-value[a]
Anesthetic duration (h)	10.75 (9.20–12.50)	10.00 (8.50–11.00)	0.033[a]
Intraoperative EBL (L)	2.80 (1.50–5.00)	4.00 (2.50–6.00)	0.027[a]
Total fluid (L)	7.06 (5.32–10.09)	9.42 (6.40–13.26)	0.042[a]
pRBC (units)	4.00 (0.00–10.00)	7.00 (4.00–12.00)	0.008[a]
FFP (units)	4.00 (0.00–10.00)	6.50 (4.00–12.00)	0.076
Cryo (units)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.330
PLT (units)	0.00 (0.00–0.00)	0.00 (0.00–8.00)	0.257

EBL, estimated blood loss; pRBC, packed red blood cells; FFP, fresh frozen plasma; PLT, platelet; Group Y, patients < 65 years; Group O, patients ≥ 65 years. Values are expressed as mean ± standard deviation or median (25th–75th percentile).
[a] $p < 0.05$ compared between groups.

Table 4 Postoperative data of patients undergoing liver transplantation.

Variables	Group Y (n = 231)	Group O (n = 22)	*p*-value[a]
ICU stay (days)	8.00 (5.00–12.00)	14.00 (5.00–23.00)	0.112
Time from surgery to discharge (days)	28.00 (22.00–42.00)	34.00 (22.00–70.00)	0.118
Postoperative complication			
Cardiac complication	6 (2.60)	0 (0.00)	1.000
Atrial fibrillation	5 (2.16)		
Infectious endocarditis	1 (0.43)		
Respiratory complication	19 (8.23)	3 (13.63)	1.000
Neurologic complication			
Brain hemorrhage	0 (0.00)	1 (4.55)	0.087
Seizure	1 (0.43)	0 (0.00)	1.000
Brain injury	2 (0.87)	1 (4.55)	1.000
Delirium	31 (13.42)	5 (22.73)	0.215
Postoperative AKI	54 (23.38)	10 (45.45)	0.043[a]
Infectious complication			
Abscess	3 (1.31)	1 (4.55)	1.000
Sepsis	3 (1.31)	1 (4.55)	1.000
Reoperation	20 (8.66)	5 (22.73)	0.060
Acute rejection	6 (2.60)	0 (0.00)	1.000
Death during hospitalization	10 (4.32)	2 (9.09)	0.879

ICU, intensive care unit; AKI, acute kidney injury; Group Y, patients < 65 years; Group O, patients ≥ 65 years. Values are expressed as number (%) or median (25th–75th percentile).
[a] $p < 0.05$ compared between groups.

Table 5 Logistic Regression Analysis for death after liver transplantation.

Variables	OR	95% CI		*p*-value	OR	95% CI		*p*-value
		Lower	Upper			Lower	Upper	
Age	1.025	0.980	1.071	0.283				
Age (Group Y/O)	1.765	0.610	5.109	0.295				
Sex	0.928	0.433	1.990	0.848				
Body mass index	0.989	0.888	1.101	0.836				
LDLT/CDLT	2.670	1.325	5.383	0.006[a]	1.808	0.741	4.41	0.193
Hypertension	2.422	1.137	5.160	0.022[a]	2.402	1.028	5.612	0.043[b]
Diabetes mellitus	2.742	1.342	5.603	0.006[a]	2.497	1.145	5.443	0.021[b]
Alcoholic cirrhosis	0.399	0.135	1.178	0.096[a]	0.309	0.096	0.999	0.050
MELD score	1.009	0.979	1.040	0.545				
Anesthetic duration	1.072	0.965	1.191	0.197				
Intraoperative EBL	1.078	0.974	1.193	0.146				
Total fluid	1.032	0.978	1.088	0.256				
pRBC	1.014	0.981	1.049	0.409				
Hb after surgery	1.195	0.958	1.492	0.114				
Cr after surgery	1.911	1.020	3.581	0.043[a]	0.966	0.421	2.217	0.935
ICU stay	1.064	1.031	1.098	< 0.001[a]	1.038	0.999	1.079	0.059
Cardiac complication	6.057	1.175	31.218	0.031[a]	4.669	0.456	47.828	0.194
Respiratory complication	1.765	0.610	5.109	0.295				
Postoperative AKI	2.209	1.071	4.559	0.032[a]	1.754	0.746	4.123	0.198
Infection	1.910	0.193	18.859	0.580				
Reoperation	1.477	0.518	4.209	0.465				
Acute rejection	2.931	0.518	16.593	0.224				

OR, odds ratio; CI, confidence interval; CDLT, cadaveric donor liver transplantation; MELD, Model for End-Stage Liver Disease; Hb, hemoglobin; Cr, creatinine; EBL, estimated blood loss; pRBC, packed red blood cells; ICU, intensive care unit; AKI, acute kidney injury; Group Y, patients younger than 65 years; Group Y, patients < 65 years; Group O, patients ≥ 65 years.
[a] $p < 0.1$ in univariate analysis.
[b] $p < 0.05$ in multivariate analysis.

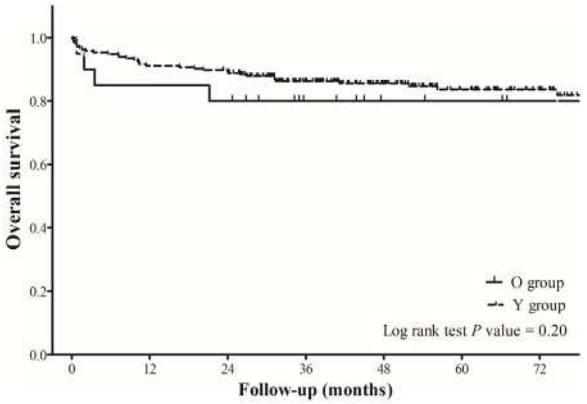

Figure 2 Overall survival rate according to the follow-up period in O and Y groups. Group Y, patients < 65 years; Group O, patients ≥ 65 years.

mellitus, alcoholic disease, ICU stay, cardiac complication, postoperative AKI showed lower *p*-values than 0.1. The multivariate analysis revealed that hypertension, diabetes mellitus were independent risk factors for death after LT ($p < 0.05$). However, age ($p = 0.283$) or groups classified by age ($p = 0.295$) were not related with death after LT.

Discussion

As the number of elderly patients undergoing transplantation has increased, we analyzed the data on the occurrence of age-related complications in liver transplant recipients. Although the preoperative hemoglobin level was lower and the requirement for blood transfusion was more common in the elderly patients, there were no notable differences in postoperative complications, including ICU stay and time from surgery to discharge, between the two groups. In addition, there was no difference in survival rate after liver transplantation based on age.

Early studies have reported higher mortality rates in elderly recipients than in younger patients because more complications occurred after transplantation in elderly recipients even when the MELD score was the same between the 2 groups.[5,6] The causes of high mortality in elderly recipients were as follows: comorbidities before surgery, malignancy, cardiovascular and/or neurological events after LT, renal failure, and secondary infections due to the use of immunosuppressants. The prognosis was poor in patients with renal insufficiency before surgery, especially in patients undergoing dialysis. Renal replacement therapy before surgery has been shown to have a strong association with poor outcomes.[13] Furthermore, the rate of bacterial or fungal infection, post-transplantation sepsis, and the duration of ICU stay also increased in recipients with renal insufficiency before surgery.[14] The second most influential comorbidity was cardiovascular diseases such as coronary artery disease, atherosclerosis in major vessels, and arrhythmia.[11] Niazi et al.[15] reported the impact of psychosocial factors on the outcomes associated with LT. Depression and anxiety are known to be related to poor outcomes after LT. In addition to these general complications, it was reported that elderly recipients had increased resource utilization owing to weak pulmonary function and low life expectancy.[9,11] Thus, many authors recommend screening elderly recipients with associated comorbidities and malignancy and performing LT only in elderly patients without significant comorbid conditions.[16–18]

Recently, with accumulated experience and successful LT cases, several studies have reported that graft survival and mortality did not differ significantly between young and elderly liver transplant recipients.[7,15,19–21] These studies suggested that functional status rather than chronological age had a greater impact on outcomes. Functional status depends not only on advanced patient age but also on behavioral factors, including exercise, BMI, smoking and alcohol use, and psychosocial factors. Moreover, regardless of age, high MELD scores, alcoholic liver disease, and medical comorbidities such as congestive heart failure, coronary artery disease, and renal insufficiency requiring dialysis were significantly associated with poor outcomes in liver transplant recipients.[11] Furthermore, the utilization of medical resources after transplantation was similar in the two groups.[22] However, those studies had limitations. They found that elderly liver transplant recipients had lower MELD scores, lower BMI, fewer comorbidities, and higher serum albumin than younger recipients. This shows that elderly patients with relatively preserved physiological conditions and low MELD scores selectively underwent LT.[23]

Blood transfusions are one of the known causes of postoperative complications such as infection, respiratory complications, myocardial infarction, and renal insufficiency.[24,25] Our study showed that group O had lower preoperative hemoglobin and more intraoperative transfusions than group Y. Blood transfusions are known to affect postoperative complications by directly increasing the plasma concentration of inflammatory mediators[26] and amplifying the inflammatory response induced by surgery.[27] However, our study showed that although there were differences in transfusion doses, there was no difference in the incidence of complications. Similar results have been obtained in other studies. Postoperative complications were reduced by the use of red blood cells that were irradiated or depleted of leukocytes by filtration during surgery.[28–31]

In our study, there was no significant difference in the occurrence of complications after LT between group O and group Y, and the patient characteristics, preoperative laboratory findings except for hemoglobin level, and comorbidities also did not differ significantly. The total amounts of infused fluid and packed red blood cells were higher, and the postoperative creatinine level was higher in the elderly group than in the younger group; however, there was no significant difference in the incidence of acute kidney injury after transplantation. Moreover, the ICU length of stay and time from surgery to discharge also showed no notable differences between the two groups. Altogether, these findings suggest that elderly patients may be considered adequate candidates for LT.

There are several risk factors for mortality after LT. Dialysis patients are known to have the highest risk of death regardless of age, and the number of fresh frozen plasma units transfused and re-transplantation have a statistically significant association with early death due to sepsis.[9,32] Previous studies have indicated that the risk of mortality is increased in liver transplant recipients aged ≥ 60

years-old, especially patients undergoing renal replacement therapy.[9,32] However, our study failed to demonstrate any association of advanced age and an increased mortality rate. Although this study has shown that the elderly group had a higher incidence of AKI after LT, serum creatinine levels were similar in both groups after surgery and any clinical difference between groups seems to be negligible.

This study has important limitations. The number of patients aged ≥ 65 years was small (22 patients); therefore, the outcomes of postoperative complications in elderly patients cannot be considered completely similar to those in younger patients. Because of the small number of ''exposed'' patients, the probability of type 2 error cannot be ignored, and the findings may not be sufficient to conclude that LT is safe in elderly patients.

Second, our study did not investigate long-term prognosis. It is an important issue that elderly recipients have a relatively short life expectancy and may have other critical diseases compared with younger patients, regardless of the severity of liver function before transplantation. Thus, long-term follow-up is necessary for a more accurate comparison between young and old patients.

Another limitation is our inability to collect data on vascular and biliary complications since the relevant data were missing. Vascular and biliary tract complications are known to be common in elderly patients,[33] increasing the risk of type 2 error in relation to the mortality rate.

In conclusion, despite the limitations imposed by the small number of patients, our study has demonstrated positive results for the safety indication of LT in elderly patients. Therefore, to improve the prognosis of elderly patients who require LT in the future, it is necessary to focus on the main strategies and new protocols in order to identify potential risk factors, and improve outcomes in elderly patients undergoing liver transplantation.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgement

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CLINICAL RESEARCH

Evaluation of lightwand-guided endotracheal intubation for patients with missing or no teeth: a randomized controlled study

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KEYWORDS
Endotracheal intubation;
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Abstract
Background: Unhealthy teeth can seriously affect general health and increase the risk of death in elderly people. There has been no confirmation of which device is most effective for elderly patients with teeth loss. Therefore, we compared four intubation devices in elderly patients with partial and total tooth loss aiming to reduce risk during anesthesia.
Methods: Two hundred patients were randomized to undergo tracheal intubation with the Macintosh laryngoscope, the Glidescope, the Fiberoptic bronchoscope or the Lightwand as part of general anesthesia. A unified protocol of anesthetic medications was used. HR and BP were measured at T_0, T_1, T_2, T_3, T_4 and T_5. Catecholamine (epinephrine and norepinephrine) blood samples were drawn at T_0, T_1 and T_2. Intubation time and postoperative complications, including dental damage and losses, were recorded.
Results: Reduced fluctuations in HR, DBP, and SBP were observed in the Lightwand group. Intubation time was significantly shorter in the Lightwand group ($p < 0.05$). There was no statistically significant difference between the groups in epinephrine levels, but norepinephrine levels were less volatile in the Fiberoptic bronchoscope and Lightwand groups. Fewer patients in the Lightwand group experienced dental damage and other postoperative complications than in the other three groups. Although a higher success rate on the first attempt was as high as in the Fiberoptic bronchoscope group, shorter intubation time was observed only in the Lightwand group.
Conclusion: The Lightwand offers less hemodynamic stimulation than the Macintosh laryngoscope, Glidescope, and Fiberoptic bronchoscope. Because it had the shortest intubation time, the Lightwand caused the least damage to the teeth and throat of elderly patients. Our findings showed that tracheal intubation with the Lightwand was advantageous for preventing cardiovascular stress responses with short intubation times and fewer postoperative complications.
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Introduction

As the aging of society intensifies, more elderly patients with multisystem complications will require general tracheal intubation anesthesia for surgery.[1] However, following laryngoscopy and endotracheal intubation, undesired pathophysiological effects and postoperative complications frequently occur.[2,3] Although healthy and young patients generally tolerate these responses well, elderly patients can experience worse outcomes.[4] Dental injury, including fracturing or dislocating of teeth, is known to be a common feature of claims in anesthetic practice.[5–7] Many studies have demonstrated that poor dental health is associated with mental impairment, physical disability, rheumatoid arthritis, and even increased mortality among elderly people.[8–12] Moreover, endotracheal intubation leads to a reflexive increase in sympathetic activity, including arrhythmia, hypertension, and tachycardia.[13–15] Additionally, changes in plasma catecholamine concentrations have been reported from the stress of endotracheal intubation.[4,16,17] Therefore, reducing dental damage and stress responses during surgery are important for elderly patients' postoperative health.

The risks of anesthesia and mortality for patients could be significantly increased by traditional laryngoscopy.[18,19] Thus, alternative devices are used to facilitate laryngoscopy and improve the glottic view to reduce postoperative complications and mortality.[20] The Glidescope has a digital camera at its tip, which can improve the view of the glottis and is beneficial in patients with difficult airways.[21] The Fiberoptic bronchoscope has a small, soft and bendable lumen for guidance and clear vision. Fiberoptic bronchoscope-guided intubation can be performed without stimulation of oropharyngeal structures.[22] The Lightwand is a stick featuring a light bulb at its tip that can be used to perform tracheal intubation blindly after confirmation that the bulb has passed the glottis and is illuminating the anterior neck clearly.[23]

Although Fiberoptic bronchoscopy or video laryngoscopes are used more commonly in patients with difficult laryngoscopic intubation,[24] the Lightwand can be used as a multimodal approach to difficult intubation. However, no studies have compared the effects of using different intubation equipment on elderly patients. The purpose of this study was to evaluate whether Lightwand-guided tracheal intubation was more suitable for elderly patients than other endotracheal intubation equipment.

Materials and methods

After approval from the institutional ethics committee, written informed consent was obtained from all patients before participating in the study. Two hundred patients were enrolled (aged 64–82 years old) with American Society of Anesthesiologists (ASA) I–II physical status requiring general anesthesia with endotracheal intubation undergoing surgery. Patients were excluded if they were at risk for regurgitation and aspiration or lacked informed consent. Patients with Mallampati scores of 3 or those with congenital or acquired abnormalities of the upper airway were also excluded.

All study subjects were randomized by a researcher blinded to the study, and envelopes containing randomization numbers were used to allocate the patients to the following four groups (n = 50 per group) according to the airway device used: group M (intubation attempt using a Macintosh laryngoscope), group G (intubation attempt using a Glidescope), group F (intubation attempt using a Fiberoptic bronchoscope), and group L (intubation attempt using a Lightwand). In all cases, intubation was performed by several experienced anesthesiologists who were familiar and trained (performed at least 30 intubations prior to the study) with all four devices. In the operating room, the patients were monitored using electrocardiography, noninvasive and invasive arterial blood pressure, oxygen saturation, and end-tidal carbon dioxide concentration.

For the four groups of patients, the tube size was chosen based on the manufacturers' recommendations. The endotracheal tube size for female and male patients was 7.0 and 7.5 mm, respectively. The laryngoscope blades used for female and male patients were sizes 3 and 4, respectively. The Lightwand was bent 6.5 cm from the distal end at a 90° angle similar to a hockey stick.

The patients underwent preanesthetic oxygenation by mask before standardized general anesthesia induction (0.4 $\mu g.kg^{-1}$ sufentanil, 0.05 $mg.mL^{-1}$ midazolam, 0.2 $mg.kg^{-1}$ etomidate followed by 0.6 $mg.kg^{-1}$ rocuronium) and 3-minute mask ventilation with 100% oxygen. After adequate neuromuscular blockade (TOF = 0) was confirmed, we checked the laryngeal view and the Modified Cormack and Lehane grade of the patients. The depth of sedation was monitored by Narcotrend (MonitorTechnik, Bad Bramstedt, Germany), and intubation was prepared when the Narcotrend index was 45–55.

In group M, the endotracheal tube was inserted and advanced blindly into the nasal cavity and passed into the pharynx. In group F, the Fiberoptic bronchoscope (Olympus LF-DP; Olympus, Tokyo, Japan) was inserted via the nasal cavity, and its passage past the intranasal structures and through the nasopharynx, oropharynx, larynx, and carina was observed with a jaw lift by the caregiver through the eyepiece of the scope. In group G, the Glidescope (Glidescope videolaryngoscopy, Verathon, Bothell, WA, USA) was inserted along the middle of the tongue and positioned at the epiglottis vallecula. Intubation was then performed with a stylet-inserted tracheal tube using the lift blade and confirmation of the glottis on the monitor. In group L, the tip of the Lightwand (Surch-LiteTM Orotracheal Lighted Intubation Stylet, Bovie, Melville, NY, USA) was bent similar to a hockey stick before the jaw lift. Up to 3 attempts were allowed before tracheal intubation was performed. Insertion time was defined as the time elapsed from opening the mouth until the first appearance of a square waveform on the capnograph.

Hemodynamic measurement

Heart Rate (HR), Blood Pressure (BP), and Oxygen Saturation (SpO2) were recorded preinduction (T_0), preintubation (T_1), immediately postintubation (T_2) and then 1, 3, and 5 minutes postintubation (T_3, T_4, and T_5).

Table 1 Demographic data in four groups.

	Group M (n = 50)	Group G (n = 50)	Group F (n = 50)	Group L (n = 50)
Age (y)	73.44 ± 5.17	72.66 ± 4.67	72.94 ± 5.19	73.00 ± 5.60
Sex (M/F)	23/27	25/25	24/26	21/29
BMI (kg.m^{-2})	23 ± 3.9	22 ± 2.7	23 ± 2.1	23 ± 2.8
ASA class 1/2	41/9	44/6	42/8	46/4

All data were presented as mean ± SD or numbers, $p > 0.05$.

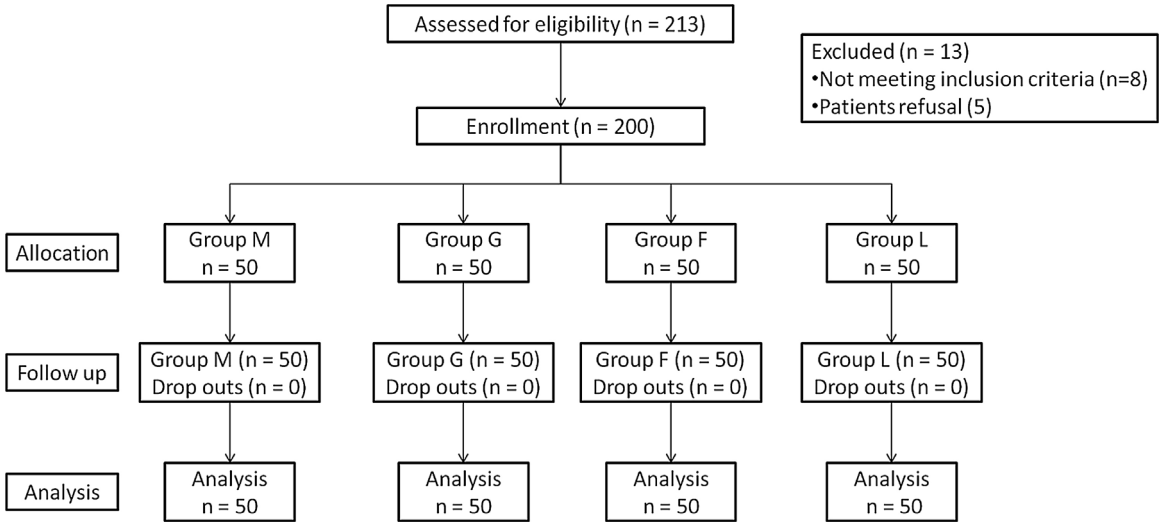

Figure 1 CONSORT flow diagram.

Table 2 Changes in Systolic (SBP) and Diastolic (DBP) Blood Pressures, and Heart Rate (HR) in four groups.

Group	Pre- induction (T_0)	Pre-intubation (T_1)	Post-intubation (T_2)	Minutes post-intubation		
				1 (T_3)	3 (T_4)	5 (T_5)
Group M						
SBP (mmHg)	132 ± 10.12	113 ± 15.72	135 ± 9.36	124 ± 13.69	115 ± 12.91	109 ± 15.38
DBP (mmHg)	86 ± 10.12	73 ± 13.29	93 ± 14.12	87 ± 14.66	82 ± 15.39	75 ± 13.34
HR (bpm)	75 ± 12.54	71 ± 12.59	92 ± 13.92	84 ± 10.22	82 ± 11.38	80 ± 10.29
Group G						
SBP (mmHg)	129 ± 15.38	112 ± 12.72	133 ± 16.29	125 ± 17.48	116 ± 16.25	110 ± 18.21
DBP (mmHg)	84 ± 14.63	75 ± 15.27	92 ± 14.61	85 ± 12.42	80 ± 13.21	74 ± 15.73
HR (bpm)	74 ± 13.51	71 ± 10.63	93 ± 10.91	82 ± 9.41	82 ± 10.43	81 ± 11.40
Group F						
SBP (mmHg)	133 ± 14.29	112 ± 16.94	132 ± 12.40	118 ± 17.25	113 ± 14.90	109 ± 16.30
DBP (mmHg)	83 ± 13.53	74 ± 14.37	91 ± 12.62	86 ± 14.85	81 ± 15.84	73 ± 14.39
HR (bpm)	76 ± 12.62	70 ± 13.82	95 ± 11.47	81 ± 9.92	80 ± 12.34	77 ± 13.24
Group L						
SBP (mmHg)	129 ± 16.39	114 ± 13.51	116 ± 14.32[a]	113 ± 16.25	110 ± 14.38	107 ± 15.23
DBP (mmHg)	84 ± 15.57	75 ± 14.38	80 ± 15.41[a]	79 ± 16.25	76 ± 15.39	73 ± 16.18
HR (bpm)	77 ± 13.05	74 ± 11.60	82 ± 12.58[a]	80 ± 9.03	79 ± 12.67	78 ± 12.91

Group M, Macintosh laryngoscope; Group G, Glidescope; Group F, Fiberoptic bronchoscope; Group L, Lightwand.
[a] $p < 0.05$ compared to Group M, G and F (Only intergroup significances are showed).

Catecholamine measurement

Plasma catecholamine levels were drawn at T_0, T_1 and T_2. Catecholamine blood samples for measuring Epinephrine (E) and Norepinephrine (NE) were collected into Ethylenediaminetetraacetic Acid (EDTA) tubes. Plasma catecholamines were determined by High-Performance Liquid Chromatography (HPLC) with electrochemical detection using methods that were previously described.[25] The reference blood lev-

els were up to 0.45 nmoL.L^{-1} for E and up to 2.40 nmoL.L^{-1} for NE.

Sample size and statistical analysis

The sample size was calculated by the PASS software (version 11.0; NCSS, Kaysville, UT). Power studies suggested that a sample size of 44 patients per group was required to achieve a power of 90% at a 0.05 level of significance for detection of differences across the four groups. Therefore, we *a priori* decided to include 200 patients (50 patients per group), in case of a general 15% of patients' dropouts.

All data were analyzed using ANOVA in SPSS software, version 19.0 for Microsoft Windows (Chicago, IL, USA). The quantitative variables are represented as the mean ± SD, and the qualitative variables are shown as case numbers (percentages, %). The χ^2 test was used to analyze qualitative variables. All tests were 2-tailed, and the significance level for the statistical analysis was set to $p < 0.05$.

Results

A total of 213 patients were assessed for eligibility, 13 patients were excluded on the grounds of the patient's refusal to participate and the risk for regurgitation and aspiration. Eventually, a total of 200 patients were enrolled in this study. There were 50 patients in each group. The characteristics of the patients are presented in Table 1. There were no significant differences among the four groups in age, sex, gender, or ASA status ($p > 0.05$).

SBP, DBP and HR data analysis revealed that, after anesthetic induction (T_1), there were significant decrease in SBP, DBP and HR in all patients compared with T_0, as seen in Fig. 1A, 1B, and 1C, respectively ($p < 0.05$). SBP, DBP and HR values significantly increased with the completion of intubation at T_2 for groups M, G and F, but group L showed only a slight increase. SBP, DBP and HR values finally returned to almost the same level in the four groups. SBP, DBP and HR were not significantly different at any measurement time for group L and showed a stable profile across the entire study period. The intergroup comparison showed that group L had significantly lower SBP, DBP and HR values at T_2 than the other groups. All inter- and intragroup comparisons of SBP, DBP and HR data are shown in Table 2.

Catecholamine plasma levels are shown in Figures 2D and 2E. Preinduction (T_0) catecholamine concentrations decreased significantly after the induction of anesthesia. There was no significant difference in epinephrine levels among the groups at the matched time points. The plasma norepinephrine levels in groups F and L at T_2 showed less fluctuation than those of the other two groups. Catecholamine plasma data are presented in Table 3.

All intubations were completed within two attempts through the assigned intubation equipment. Groups F and L had higher success rates on the first attempt than groups M and G ($p < 0.05$) (Table 4). However, only group L had a significantly different duration of intubation compared to the other groups ($p < 0.05$) (Table 4 and Fig. 2F).

Table 3 Serum catecholamine changes.

	Group M		Group G		Group F		Group L	
	E (nmoL.L^{-1})	NE (nmoL.L^{-1})	E (nmoL.L^{-1})	NE (nmoL.L^{-1})	E (nmoL.L^{-1})	NE (nmoL.L^{-1})	E (nmoL.L^{-1})	NE (nmoL.L^{-1})
Pre-induction	0.191 ± 0.07	1.63 ± 0.35	0.228 ± 0.04	1.59 ± 0.31	0.211 ± 0.07	1.69 ± 0.48	0.205 ± 0.09	1.55 ± 0.32
Pre-intubation	0.124 ± 0.05	1.14 ± 0.41	0.136 ± 0.09	1.03 ± 0.42	0.118 ± 0.04	1.21 ± 0.30	0.137 ± 0.06	1.13 ± 0.27
Post-intubation	0.091 ± 0.008	1.43 ± 0.37	0.083 ± 0.003	1.49 ± 0.26	0.092 ± 0.005	1.19 ± 0.31[a]	0. 101 ± 0.004	1.10 ± 0.37[a]

E, Epinephrine; NE, Norepinephrine.
Group M, Macintosh laryngoscope; Group G, Glidescope; Group F, Fiberoptic bronchoscope; Group L, Lightwand.
[a] $p < 0.05$ compared to Group M, G and F (Only intergroup significances are showed).

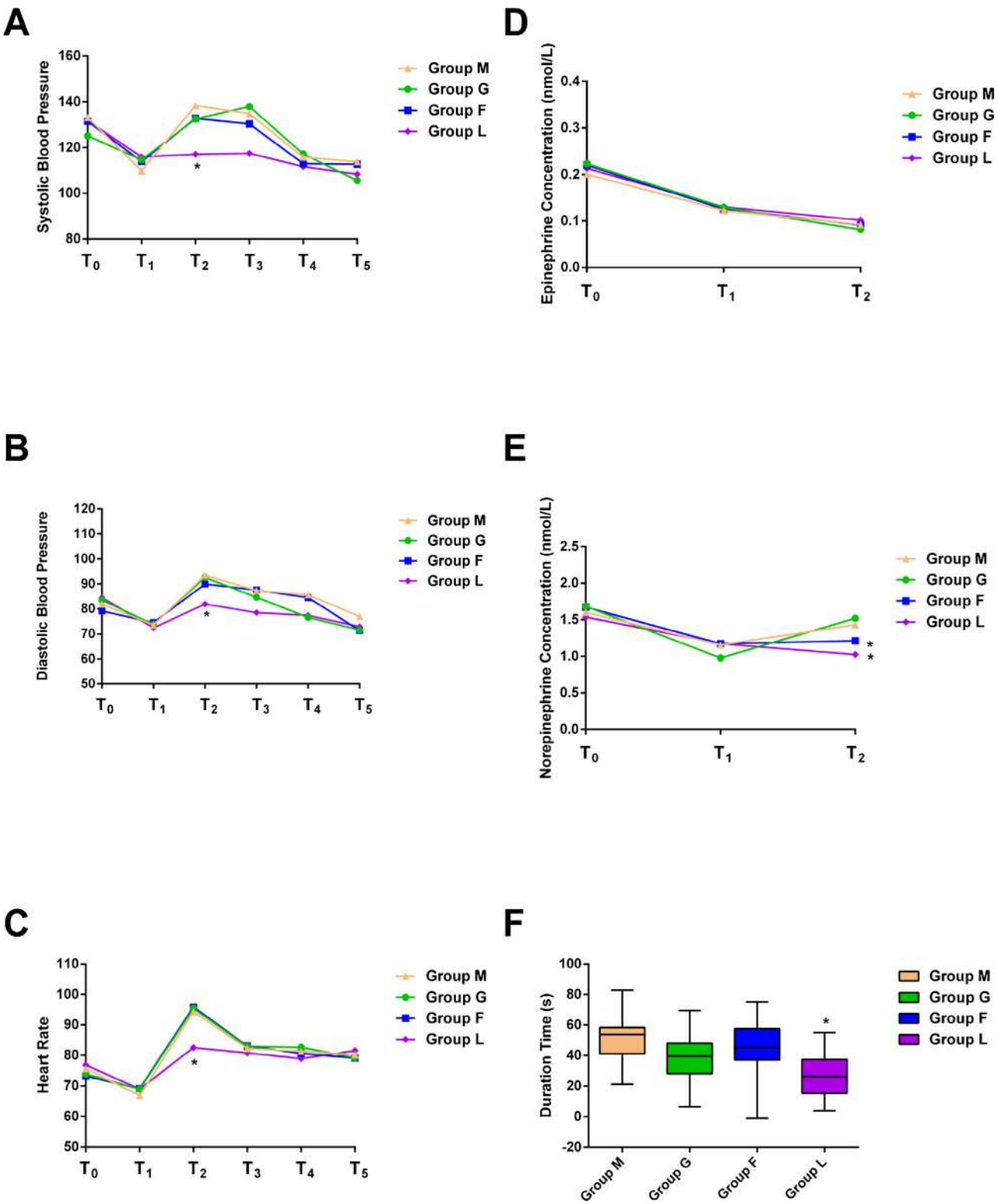

Figure 2 (A, B and C) Systolic blood pressure, diastolic blood pressure and heart rate changes, respectively, during the study period. (D and E) Epinephrine and norepinephrine concentrations (nmoL.L^{-1}). (F) Total intubation time using each intubation device, mean ± SD. Group M, Macintosh laryngoscope; Group G, Glidescope; Group F, Fiberoptic bronchoscope; Group L, Lightwand.

Postoperative complications for dental or gum injury, hoarseness, and sore throat are described in Table 4. There were no statistically significant differences among groups M, G and F, but group L had lower incidences of complications than the other three groups ($p < 0.05$) (Table 4).

Table 4 Success rate, duration of intubation, and post-operation complications.

	Group M	Group G	Group F	Group L
Success rate at first time	10/40 (80%)	11/39 (82%)	5/45 (90%)[a]	3/47 (94%)[a]
Duration time	46.24 ± 14.35	39.71 ± 11.94	41.39 ± 13.28	25.47 ± 11.58[a]
Hoarseness	4/46 (8%)	3/47 (6%)	0[a]	0[a]
Sore throat	12/38 (24%)	7/43 (12%)	2/48 (4%)[a]	3/47 (6%)[a]
Loss of teeth	5/45 (10%)	6/44 (12%)	5/45 (10%)	0[a]
Dental or gum injury	7/43 (14%)	5/45 (10%)	4/46 (8%)[a]	0[a]

Group M, Macintosh laryngoscope; Group G, Glidescope; Group F, Fiberoptic bronchoscope; Group L, Lightwand.
[a] $p < 0.05$ Group F or L compared to Group M or G (Only intergroup significances are showed).

Discussion

Due to the poor conditions of elderly patients, they often suffer more than younger people during general surgery because of intubation stimulation. Therefore, there is an urgent need to seek safer intubation devices to reduce the risk for elderly patients.

In our study, we compared the effects of the four different intubation devices for elderly patients during general anesthesia and observed reduced fluctuations in HR, SBP and DBP in group L. While reductions in sore throat, dental injury, hoarseness, and loss of teeth and a higher success rate were shared with group F, shorter intubation time was solely found for group L. Moreover, norepinephrine levels in groups L and F were also more stable than in the other groups after intubation. Therefore, elderly patients' stress responses to tracheal intubation using the Lightwand seem to be less than in the other groups, and the Lightwand had a shorter intubation duration.

A growing number of research studies have demonstrated that dental disease causes a large difference in nutrition intake, arrhythmias, and cognitive disorders, including Alzheimer's disease and dementia.[26,27] This point highlights the importance of tooth protection during surgery to prevent postoperative complications. Elderly patients always suffer from more severe dental abnormalities, emphasizing the need for appropriate intubation devices to prevent diseased teeth or tooth loss.[28] Our data showed that the Lightwand had considerable advantages for protecting elderly patients' teeth and causing fewer postoperative complications. These differences might occur because the Lightwand is smaller and softer. The shorter intubation time could also be a reason for this finding.

The hemodynamic response associated with intubation tubes and intubation is transient and ends within minutes; however, it can be harmful to some groups of patients, especially elderly patients. There is already literature demonstrating that the hemodynamic response to a tracheal cannula was not significantly different between the Lightwand and the Glidescope with a normal airway.[29] However, it was also reported that the Lightwand caused less stimulation of hemodynamic responses in patients with difficult airways.[30] In our study, our results were similar to studies of difficult airways since the incidence of hypertension was higher in the other three groups than in the Lightwand group. There are several possible explanations for this outcome. First, elderly people have greater sensitivity to stimulation. Second, intubation using the Glidescope, the Macintosh laryngoscope, and the Fiberoptic bronchoscope requires more time than that using the Lightwand.

In our study, plasma catecholamine levels did not increase after induction of general anesthesia in any group. There have been other papers that evaluated plasma catecholamines using two intubation techniques, and these results agreed with our results for plasma catecholamine levels.[4,16,31] Although a correlation among HR, SBP, DBP and catecholamines might be anticipated, this idea still requires further evaluation because our results did not show any correlations.

Our results demonstrated that the success rate on the first attempt in groups L and F was higher, but the total intubation time was significantly shorter using only the Lightwand than when using the other intubation techniques. There were no significant differences among the Macintosh laryngoscope, the Glidescope and the Fiberoptic bronchoscope in total intubation time. These differences were likely due to the different procedural methods required during the intubation process compared to the procedures for familiar devices.

There were some limitations of our study. First, the number of study patients was not very large, and the patients' experience with the specific devices varied. Second, we studied only these four devices in our department's facilities. There are several alternatives for other hospitals, and this study cannot draw conclusions about all intubation equipment. Finally, it is also possible that hemodynamics repercussions and time to insert the tracheal tubes can differ with nasal intubation compared to oral intubation and techniques being blinded with possible risk of damage to soft tissues by the Lightwand.

Conclusion

This study was the first study to compare four different types of intubation devices for their influence on hemodynamic responses and postoperative complications in elderly patients with normal airways. Our results demonstrated that the Lightwand might be the best choice for anesthetists to conduct tracheal intubation in elderly patients who are more vulnerable to operative complications.

Conflicts of interest

None of the authors of this paper has a financial or personal relationship with other people or organizations that could

inappropriately influence or cause bias in the content of the paper.

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CLINICAL RESEARCH

Remifentanil reduces glutamate toxicity in rat olfactory bulb neurons in culture

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KEYWORDS
Remifentanil;
Olfactory bulb neuron;
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Abstract
Background: Opioids are widely used as an analgesic drug in the surgical setting. Remifentanil is an ultra-short acting opioid with selective affinity to the mu (μ) receptor, and also exhibits GABA agonist effects. The aim of this study was study of the neurotoxic or neuroprotective effect of different doses of remifentanil in glutamate-induced toxicity in olfactory neuron cell culture.
Materials and methods: Olfactory neurons were obtained from newborn Sprague Dawley rat pups. Glutamate 10^{-5} mM was added to all culture dishes, except for the negative control group. Remifentanil was added at three different doses for 24 hours, after which evaluation was performed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), Total Antioxidant Capacity (TAC), Total Oxidant Status (TOS), and Annexin V.
Results: The highest and lowest viability values were obtained from the low and high remifentanil doses at approximately 91% and 75%, respectively. TAC and TOS were correlated with the MTT results. TAC, TOS and MTT most closely approximated to the sham group values in the remifentanil 0.02 mM group.
Conclusions: Our results suggest that remifentanil has the potential to reduce glutamate toxicity and to increase cell viability in cultured neuron from the rat olfactory bulb.
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Introduction

Olfactory neurons regulate complex biological functions and coordinate complex motor and sensory behavior. These neurons largely function by means of glutamate and GABA.[1,2] Opioids are commonly used for the treatment of any acute or chronic pain perioperatively.[3] Remifentanil is widely used as an analgesic, including in young children and parturient/pregnant women exposed to surgical anesthesia.[4] Remifentanil is ultra-short-acting opioid with selective affinity to the mu receptor, and also exhibits GABA agonist effects.[5] Recent studies have shown that remifentanil can be employed in various settings, from anesthesia to organ protection (kidney and heart).[6] However, there is disagreement concerning whether remifentanil exhibits neuroprotective or neurotoxic effects.

Glutamate is the principal excitatory neurotransmitter in the central nervous system.[7] Elevated extracellular glutamate levels induce neuronal damage.[8] In cerebral hypoxia/anoxia, and in most nervous system diseases glutamate transporter function is impaired, and extracellular glutamate levels increase and result in irreversible neuronal damage.[9] In addition, by attaching to N-Methyl-D-Aspartate (NMDA) and AMPA receptors for longer than physiological levels, glutamate causes Ca++ and Na+ influx.[10] Zhao and Joo demonstrated that remifentanil induced acute concentration-dependent and receptor subtype-dependent increases in NMDA responses.[5] Strong evidence also exists that glutamate toxicity is significantly associated with NMDA receptors.[11] These receptors are also significantly involved in the central sensitization processes associated with hyperalgesia.[12]

The purpose of the present study was to evaluate different doses of remifentanil to determine its applicability in a glutamate toxicity model.

Materials and methods

Chemicals and reagents

Remifentanil (Ultiva) was purchased from (Genval, Belgium), while Dulbecco's modified Eagle's medium (DMEM), Fetal calf serum (FCS), Neurobasal medium (NBM), 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT), phosphate buffer solution (PBS), antibiotic antimitotic solution (100×), L-glutamine and trypsin–EDTA and dimethyl sulfoxide (Sigma, USA) were obtained from Sigma-Aldrich (St. Louis, MO, USA). Total Antioxidant Capacity (TAC) and Total Oxidant Status (TOS) were obtained from Rel Assay Diagnostics (Turkey), and Annexin V was purchased from bioVision (San Francisco, USA).

In vitro studies

Ethical permission

This study was conducted at the Medical Experimental Research Center in Ataturk University (Erzurum, Turkey). The ethical committee of Ataturk University approved the study protocol (36643897-000-E.1800108979) according to the ARRIVE guidelines 2.0.

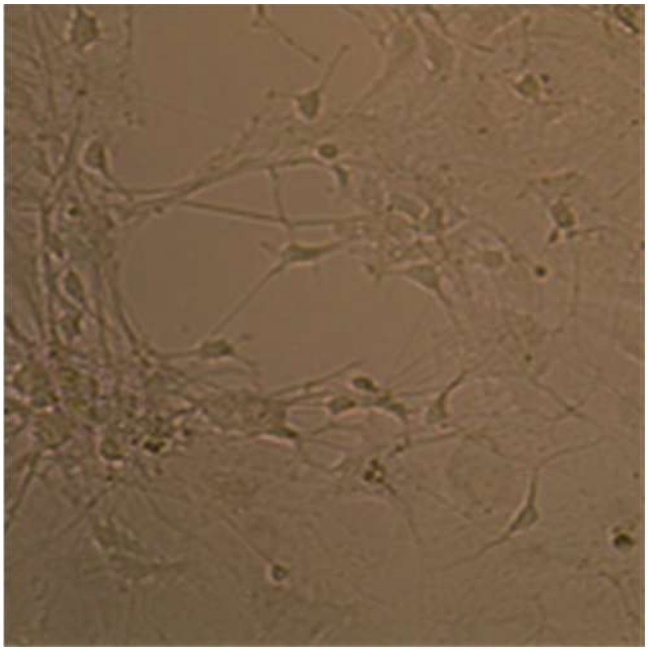

Figure 1 Harvested cell line ×10: Olfactory neuron cells.

Cell cultures

Briefly, the neuron cells isolation and centrifugation were done at 1200 rpm for 5 minutes. The collapsed cells were suspended with fresh medium (Neurobasal medium, FBS 10%, B27 2%, and antibiotic 0.01%) and then the cells were seeded in 24-well plates (Corning, USA). The plate was stored in an incubator (5% CO_2; 37 °C)[13,14] (Fig. 1).

Glutamate toxicity

Adequate branches were observed to have formed in the cells by day 10. Medium and glutamate 10^{-5} mM for toxicity induction were then added to each well, except for the negative controls (sham group). After 10 minutes, final remifentanil concentrations (2-, 0.2-, and 0.02-mM remifentanil) were added to each well, except for the sham groups, and incubated for 24 hours (5% CO_2; 37 °C). In addition, 150 μL of NBM was only added as a negative control to each well, while the positive controls contained only 10^{-5} mM glutamate, and left for 24 hours.[15]

3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) assay

MTT assay was according to the commercial kit protocol. Briefly, MTT reagent (10 μL) was added to each well and incubated (5% CO_2; 37 °C) for 4 hours. The medium was removed, then 100 μL of dimethyl sulfoxide was added to each well. The optical density was evaluated at 570 nm using a Multiskan™ GO Microplate Spectrophotometer reader (Thermo Scientific, Canada, USA). the cell viability (%) was calculated[16] using the formula: $\text{Viability \% ratio} = \frac{\text{sample absorbance value}}{\text{control group absorbance value}} \times 100 = \frac{\text{sample absorbance value}}{\text{control group absorbance value}} \times 100$.

Total oxidant status (TOS)

TOS assay was done according to the commercial manufacture kit protocol. Briefly, 500 μL Reactive 1 solution was added to wells and the initial absorbance value at 530 nm.

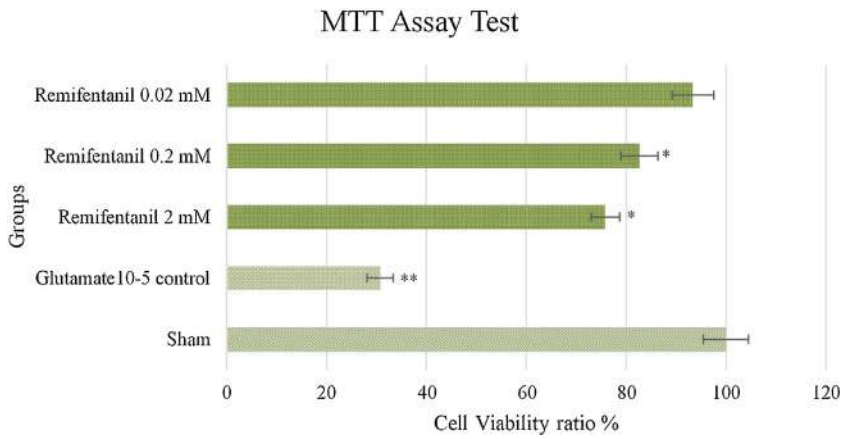

Figure 2 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay results for the olfactory cell line after 24-h remifentanil treatment *$p < 0.05$), **$p < 0.001$ compared to sham group.

then 25 μL Reactive 2 solution was added to the same well, and the second absorbance was read at 530 nm. TOS levels were determined as mmoL Trolox equiv/mmoL^{-1}.

The evaluation was done according to the formula[17] $TOS = \Delta \text{example}/\Delta ST2 \times 20$; Δ ST2 (Δ standard 2 = ST2 second reading - ST2 first reading), Δ Sample (Δ Sample = Sample second reading- Sample first reading).

Total Antioxidant Capacity (TAC)

TAC assay was done according to the commercial manufacture kit protocol. Briefly, 500 μL Reactive 1 solution was added to wells and the first absorbance was read at 660 nm. Next, 75 μL Reactive 2 was added to the same wells and the second absorbance value was read at 660 nm. TAC levels were expressed as mmol equiv/mmoL^{-1}.

The evaluation was done according to the formula[18]; $TAC = (\Delta ST1 - \Delta \text{example})/(\Delta ST1 - \Delta ST2)$; Δ ST1 (Δ standard 1 = ST1 second reading - ST1 first reading), Δ ST2 (Δ standard 2 = ST2 second reading - ST2 first reading), Δ Sample (Δ Sample = Sample second reading- Sample first reading).

Annexin V-FITC (Fluorescein Isothiocyanate) and Propidium Iodide (PI) staining assay

The experiment was done according to the manufacturer's protocol. Briefly, (1×10^5) cells washed with PBS. 500 μL binding buffer was added and then annexin v-FITC and PI were added for 10 minutes at room temperature. The stained samples were then analyzed on a CytoFLEX flow cytometer (Beckman Coulter, USA).[19]

Statistical analysis

Statistical analysis was performed using One-Way Analysis of Variance (ANOVA) and Tukey's HSD test on SPSS 21.0 software.

Results

MTT assay

Olfactory culture was first prepared. After a 24-hour exposure to remifentanil (at doses of 2-, 0.2- or 0.02-mM remifentanil), the experiment was concluded with the addition of MTT solution. The data were subject to analysis, and the results are shown in Figure 2. The highest viability ratio was observed at the lowest remifentanil dose. In addition, the positive control group (receiving only 10^{-5} mM glutamate) had a viability ratio close to 30%. Remifentanil at 2 and 0.2 mM exhibited viability rates of 75% and 82%, respectively. In addition, 0.02 mM remifentanil exhibited the highest cell viability ratio, at up to 92% ($p < 0.05$) (Fig. 2).

TAC assay

The neuron Total Antioxidant Capacity (TAC) is shown in Figure 3. The sham group exhibited the highest antioxidant capacity among all the study groups. There is no significant difference in 0.02- and 0.2-mM remifentanil groups in comparison with control group ($p > 0.05$). Statistically difference was observed only at 2 mM remifentanil ($p < 0.05$) group compared to the sham group. The lowest Antioxidant capacity was measured in the glutamate control group (Fig. 3).

TOS Assay

The neuron total oxidant level is shown in Figure 4. The lowest and highest oxidant level was observed in the sham group and the glutamate control group, respectively. Only remifentanil at 0.02 mM remifentanil exhibited no significant difference compared to the sham group ($p < 0.05$) (Fig. 4).

Flow cytometry

After 24 hours, olfactory neuron cultures were stained, and the results are shown in Figure 5. The sham group exhibited viability of 95.69%, with early and late apoptosis rates

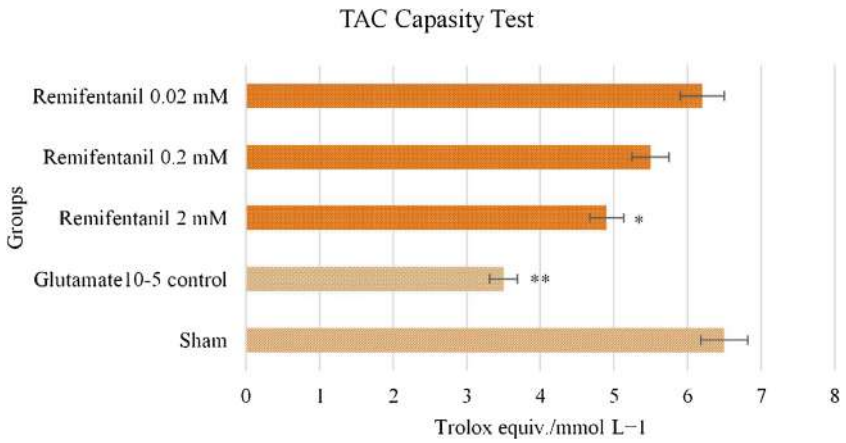

Figure 3 Total antioxidant capacity assay results for olfactory cell lines after 24-h remifentanil treatment. *$p < 0.05$, **$p < 0.001$ compared to sham group.

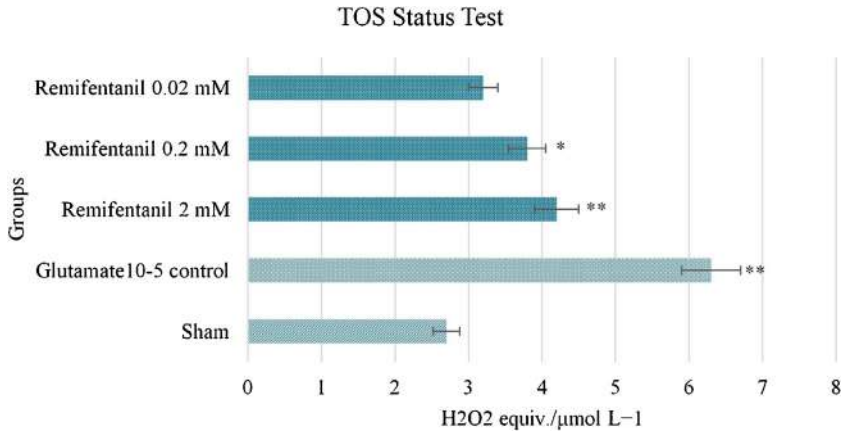

Figure 4 Total oxidant status assay results for olfactory neuron cell lines after 24-h remifentanil treatment. *$p < 0.05$, **$p < 0.001$ compared to sham group.

of 0.1% and 0.4%, respectively. The glutamate control group (positive control group) exhibited 57.7% viability, with 28.5% and 11.9% early and late apoptosis rates. Our data show a correlation with the MTT results. According to our findings, the early apoptosis level was higher than that in late apoptosis in all treatments except for 2 mM remifentanil. Treatment with 2 mM remifentanil produced lower viability, while 0.02 mM remifentanil resulted in a higher viability ratio. Late apoptosis levels and necrosis were higher in the glutamate toxicity group than in the other study groups (Fig. 5).

Discussion

Neurons have different types and functions in the olfactory system. The olfactory neurons regulate complex motor patterns and are also involved in sensory functions. Those neurons operate through glutamate and GABA neurotransmitters. Remifentanil is a mu receptor agonist and regulates pain-related information. Mu receptor agonists increase postoperative hyperalgesia by affecting glutamate-mediated NMDA receptors.[20] In addition, remifentanil is widely used as a painkiller in brain-related complications. The current study provides strong evidence that remifentanil hydrochloride has a protective effect on glutamate toxicity.

There is strong evidence that N-Methyl-D-Aspartate (NMDA) receptors play a major role in the central sensitization processes associated with hyperalgesia.[10] Recent animal[8,11] and human studies[12–16] confirmed this hypothesis, providing evidence that blocking NMDA receptors can prevent opioid-induced hyperalgesia. Studies by Guntz et al.[21] showed remifentanil has no direct effect on NMDA receptors but increases NMDA current mediated by μ-opioid receptor activation, probably through an intracellular pathway. Those studies involved electrophysiological and NMDA receptor current analysis. This finding is particularly significant because elevated NMDA receptor current induced neuron toxicity by reducing the action potential threshold.[22] Additionally, remifentanil binding to μ-opioid receptor indirectly increases glutamate toxicity, thus leading to neuron degeneration and epilepsy in patients.

Zhao M and Joo DT showed that remifentanil concentrations of 4, 6 and 8 mM increased NMDA current in the healthy rat dorsal root ganglion culture by up to 37%. However, there are some differences between Zhao and Joo's study and the present research. For example, those authors

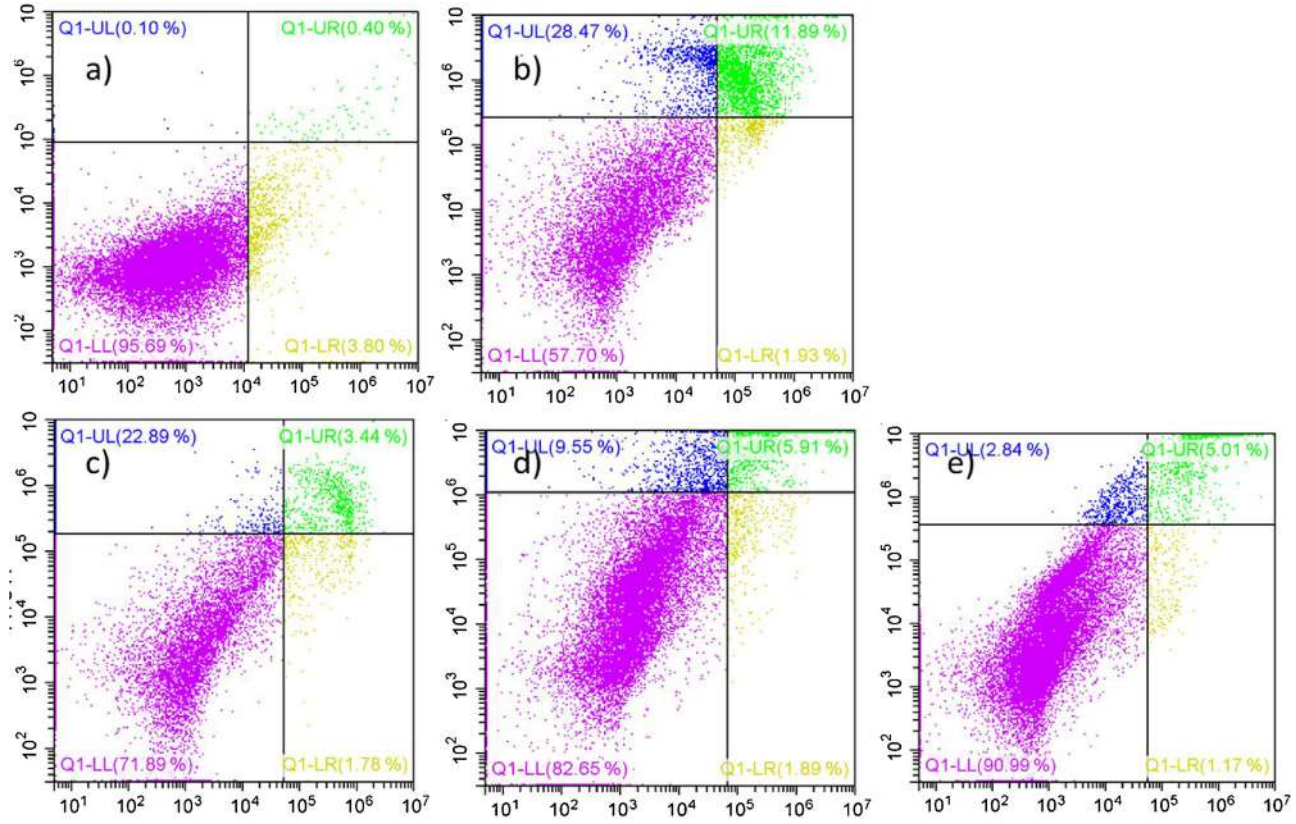

Figure 5 Flow cytometry results for olfactory neurons stained with fluorescein isothiocyanate (annexin V-FITC) and propidium iodide (PI) after a 24-h remifentanil treatment. (a) sham group; (b) glutamate control 10^{-5} mM; (c) remifentanil 2 mM; (d) remifentanil 0.2 mM; (e) remifentanil 0.02 mM.

did not induce glutamate toxicity in those neurons, and our dose concentration was also higher.[5] In the present study, remifentanil reduced glutamate toxicity mainly caused by the NMDA receptors.

Neuropathic pain models can be induced by activation of the NMDA receptor via reactive oxygen species that was administrated in the spinal cord.[22] In the present study we investigated total neuron antioxidant and oxidant capacity of cells after a 24-hour exposure time. The observation showed remifentanil act differently in high and low doses. In high doses we found a significant decrease in antioxidant capacity reversed to oxidant status (oxidant status was elevated).

Ji-Young Yoon et al. showed that remifentanil prevents hydrogen peroxide-induced apoptosis in cos 7 cells.[23] This finding is compatible with our study data. The findings of the present study show that a lower dose of remifentanil effectively reduced TOS levels and late apoptosis rates. Especially 0.02 mM remifentanil showed neuroprotective effect. But remifentanil high dose act reversed and increased oxidant status. Our findings further indicated that protection occurred not only by increasing TAC levels, but also by reducing TOS status.

Bo Pan et al. investigated the neuroprotective effects of remifentanil on isoflurane-induced apoptosis in the neonatal rat brain.[24] The findings of that study showed that remifentanil alone shows light neuroprotective effects. However, after isoflurane administration, remifentanil reduced apoptotic cell formation in the cortex and thalamic area.

In summary, this study has demonstrated that low concentration of remifentanil may cause neuroprotective effects by preventing glutamate-induced toxicity in cultures of rat olfactory bulb neuron. However, new studies are still warranted and should further investigate the role of glutamate transporters and the glutamine enzymatic pathways in the remifentanil-induced neuroprotection.

Conflicts of interest

The authors declare that there are no conflicts of interest. The article has not been previously published elsewhere, either totally or partly.

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CLINICAL RESEARCH

Use of second generation supraglottic airway device for endovascular treatment of unruptured intracranial aneurysms: a retrospective cohort

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KEYWORDS
Intracranial aneurysm;
Endovascular procedure;
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Abstract
Background: We aimed to assess the feasibility of using supraglottic devices as an alternative to orotracheal intubation for airway management during anesthesia for endovascular treatment of unruptured intracranial aneurisms in our department over a nine-year period.
Methods: Retrospective single center analysis of cases (2010–2018). Primary outcomes: airway management (supraglottic device repositioning, need for switch to orotracheal intubation, airway complications). Secondary outcomes: aneurysm complexity, history of subarachnoid hemorrhage, hemodynamic monitoring, and perioperative complications.
Results: We included 187 patients in two groups: supraglottic device 130 (69.5%) and orotracheal intubation 57 (30.5%). No adverse incidents were recorded in 97% of the cases. Three supraglottic device patients required supraglottic device repositioning and 1 supraglottic device patient required orotracheal intubation due to inadequate ventilation. Three orotracheal intubation patients had a bronchospasm or laryngospasm during awakening. Forty-five patients (24.1%) had complex aneurysms or a history of subarachnoid hemorrhage. Thirty-three of them (73.3%) required orotracheal intubation compared to 24 of the 142 (16.9%) with non-complex aneurysms. Two patients in each group died during early postoperative recovery. Two in each group also had intraoperative bleeding. A post-hoc analysis showed that orotracheal intubation was used in 55 patients (44%) in 2010 through 2014 and 2 (3.2%) in 2015 through 2018, parallel to a trend toward less invasive blood pressure monitoring from the earlier to the later period from 34 (27.2%) cases to 5 (8.2%).

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Conclusion: Supraglottic device, like other less invasiveness protocols, can be considered a feasible alternative airway management approach in selected patients proposed for endovascular treatment of unruptured intracranial aneurisms.
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Introduction

The efficacy of endovascular intracranial aneurysm treatment has been recognized since the 1970s, and although its safety has been demonstrated in Unruptured Intracranial Aneurysms (UIAs), little has been published about perioperative anesthetic care in this setting.[1–3] The standard of care calls for general anesthesia with Orotracheal Intubation (OTI), muscle paralysis, controlled ventilation, and standard monitoring plus invasive arterial pressure recording to provide absolute immobility and strict hemodynamic control.[2]

However, OTI is associated with hemodynamic effects that may increase the risk of aneurysm rupture prior to occlusion. Furthermore, OTI is also associated with more coughing episodes and potentially deleterious hemodynamic changes during emergence compared to Supraglottic Devices (SGD), which have less impact in the sympathetic nervous system.[4–6] Nevertheless, there is concern that SGD may not provide the same degree of airway protection and safety as OTI during these long procedures.[3]

Only a few case series, including a limited number of patients, have reported the feasibility of SGD during endovascular treatment of UIAs.[7,8] We present the analysis of our 9-year experience with using SGD as an alternative to assess the feasibility of this approach to airway management in patients undergoing endovascular treatment in UIAs.

Materials and methods

This retrospective cohort study was approved by the research ethics committee at our university hospital (reference HCB/2018/0691) and registered at clinicaltrials.org (NCT03632902). The committee waived the requirement for specific written informed consent for use of data; thus, consent was obtained only for anesthesia and radiology procedures.

We reviewed the records of all patients who underwent endovascular treatment of a UIA from January 2010 to March 2018. Ruptured intracranial aneurysms were excluded.

Anesthetic procedures and monitoring

Our institutional protocol included premedication with 5 mg of oral diazepam the night before and 2 hours before surgery, continuation of corticosteroids or anticonvulsants throughout the procedure and antibiotic prophylaxis (intravenous [IV] ceftriaxone, 2 g).

Continuous monitoring consisted of blood pressure (arterial cannulation or use of a noninvasive monitor [ccNexfin, BMEYE, Irvine, CA, USA]), electrocardiogram, and the Bispectral Index monitoring (BIS, Brain Monitoring System; Covidien, Mansfield, MA, USA), pulse oximetry (S/5; Datex Ohmeda, Helsinki, Finland); and bilateral regional Oxygen Saturation (SrO_2) (INVOS 5100C Cerebral/Somatic Oximeter, Minneapolis, MN, USA). Each patient was preoxygenated (100% oxygen) through a face mask. All procedures were performed under general anesthesia. Intravenous anesthesia was administered through a target-controlled infusion system (Orchestra Infusion Workstation, Primea Base; Fresenius Vial, Bad Homburg v.d.H., Germany) with propofol (target concentration, 4–6 $\mu g.mL^{-1}$) and remifentanil (target, 2–4 $\eta g.mL^{-1}$) adjusted to keep the bispectral index close to 50. Rocuronium bolus 1 $mg.Kg^{-1}$ followed by continuous perfusion (0.1 $mg.Kg^{-1}.h^{-1}$) was administered to maintain one response of a train-of-four (S/5 Datex Ohmeda®, Helsinki, Finlandia). The anesthesiologist, who was experienced in airway management, was free to choose either SGD (I-gel, Intersurgical Ltd, Wokingham, Berkshire, UK) or OTI airway management, according to their own clinical criteria, always following current airway management guidelines.

A bolus dose of heparin (100 $IU.kg^{-1}$ IV) was administered at the start of the procedure. The level of anticoagulation was monitored with the activated clotting time (ACT, GEM PCL plus, Bedford, MA, USA), and doses of heparin were repeated if necessary.

In the absence of complications, a dose of 2 $mg.Kg^{-1}$ sugammadex was administered, patients were to be awakened and extubated (or the SGD removed) immediately after the end of the procedure for early neurological examination and then transferred to the stroke unit or the postanesthetic care unit.

Data collection

The main goal was to analyze the type of airway management technique used (SGD or OTI) and airway related events and complications: laryngospasm, bronchospasm, arterial oxygen desaturation (< 95% measured by pulse oximetry), gastric content aspiration and airway symptoms within the first month (during hospitalization or outpatient follow-up). We also collected whether a difficult airway had been anticipated during the preanesthetic assessment. For SGD-managed airways, we recorded the need to reposition it to optimize ventilation or to switch to OTI because of failed SGD insertion. Details of airway management strategies were also extracted for intubated patients.

The analysis included demographic data, aneurysm characteristics, history of arterial hypertension, type of anesthesia, and method of arterial blood pressure monitor-

Table 1 Patient and aneurysm characteristics.

		OTI	SGD	Total	*p*
Nº of patients		57	130	187	
Sex,	F	40 (89.5)	100 (76.9)	140 (74.9)	0.31
n (%)	M	17 (10.5)	30 (23.1)	47 (25.1)	
Age, mean (SD), y		61 (10.5)	57.8 (11.0)	58.8 (10.9)	0.07
BMI, mean (SD), $kg{\cdot}m^{-2}$		25.6 (5.25)	24.5 (4.2)	24.7 (4.5)	0.24
Anticipated difficult airway, n (%)		6 (10.5)	7 (5.4)	13 (6.8)	0.19
Hypertension, n (%)[a]		26/57	50/130	77 (41.2)	0.36
Aneurysm location, n (%)					0.65
Anterior circulation		45 (79)	99 (76.2)	144 (77)	
Posterior circulation		12 (21)	31 (23.8)	43 (23)	
Complexity, n (%)[b]		33 (57.9)	12 (9.2)	45 (24.1)	0.001

Quantitative and qualitative variables were compared with the *t* test or χ^2 test, respectively.
BMI, Body Mass Index; OTI, Orotracheal Tube; SGD, Supraglottic Device.
[a] Past medical history of hypertension in medical treatment.
[b] Previous history of subarachnoid haemorrhage or aneurism complexity score $\geq$ 4 on a scale of 0 to 7.

ing. To assess the procedure potential risks, previous history of subarachnoid hemorrhage and aneurysm complexity were also recorded. Complexity was defined by a score of 4 or more points on a scale of 0 to 7 derived by giving one point to each of the following characteristics: wide neck, significant lobulation, calcifications, intra-aneurysmal thrombosis, tortuosity or stenosis of proximal vessels, small size (less than 3 mm), and presence of branches in the sack.

Statistical analysis

Quantitative variables were expressed as mean (SD) and qualitative variables as absolute frequency and percentage. Statistics were compared between groups with the *t*-test or χ^2 test, as appropriate. In a post-hoc analysis we also explored variables that might be associated with differing airway management decisions in two consecutive time periods: 2010 to 2014 and 2015 to 2018.

IBM SPSS Statistics 23 for Windows (IBM Corp, Armonk NY, USA) was used for all analyses. A value of $p < 0.05$ was considered statistically significant.

Results

A total of 187 patients were treated during the study period, 130 (69.5%) of them received a SGD group and 57 (30.5%) were managed with OTI. There were no differences in demographic characteristics, history of hypertension, or anticipated difficult airway rates between the two airway management groups (Table 1).

All incidents during airway management are described in Table 2. In the 3 SGD patients whose device required repositioning, adequate ventilation was achieved on the second attempt. No episodes of desaturation or gastric content aspiration developed in SGD patients. The single laryngospasm in the OTI group occurred during awakening and was associated with intense coughing. The 2 fiberoptic bronchoscope insertions in the OTI group were performed in patients with predicted difficult intubation.

Three postoperative pneumonias (1 in the SGD group and 2 in the OTI group) were diagnosed. All 3 pneumonias were in patients that remained intubated when transferred to the intensive care unit.

OTI was the preferred technique for patients with increased risk of complications either due to previous history of subarachnoid hemorrhage or to the presence of a complex aneurysm. Tracheal intubation was performed in 33 of the 47 high-risk patients (73.3%), but only in 24 of the 142 patients (16.9%) without these risk factors ($p < 0.0001$) (Table 1).

Four patients, 2 in each group, died while in the postoperative period (2.1% of the cohort of 187 patients). Three of the deaths (2 of them in the OTI group) had complex aneurysms. Two OTI patients bled during the procedure and remained intubated when transferred to the intensive care unit, where they died. Postoperative bleeding was detected in 2 SGD patients. The first presented with mild right paresis that progressed to diminished consciousness over the next few hours. This patient was immediately intubated, a pericallosal artery bleed was observed with cranial tomography, and transferred to the ICU. The second developed a headache and experienced vasospasm after being asymptomatic for the first 6 hours after awakening. Subarachnoid bleeding was diagnosed by cranial tomography and the patient was admitted in the ICU. Eleven days later, a bilateral cerebral stroke involving the middle cerebral and anterior cerebral arteries was observed and he died a few days later.

There was a parallel trend toward the use of less invasive airway management and less invasive blood pressure monitoring over the period of study. A post-hoc analysis showed that OTI was used in 55 patients (44%) from 2010 to 2014 and 2 (3.2%) from 2015 to 2018, parallel to a trend toward less invasive blood pressure monitoring from the earlier to the later period; from 34 (27.2%) cases to 5 (8.2%).

Discussion

In our case series, the use of SGD provided effective airway management during endovascular treatment of UIAs

Table 2 Events during airway management by group and anticipated difficult airway classification.

	No ADA	ADA	Total
SGD group			
No incidences, n (%)	119 (91.5%)	7 (5.4%)	126 (96.9%)
Incidents, n (%)			
Repositioning[a]	3 (2.3%)	0	3 (2.3%)
Switch to OTI	1 (0.8%)	0	1 (0.8%)
Total, n (%)	124 (95.4%)	7 (5.4%)	130
OTI group			
No incidences, n (%)	49 (86%)	3 (5.3%)	52 (91.2%)
Incidents, n (%)	2 (3.5%)	1 (1.7%)	3 (5.3%)
Laryngospasm	0	1 (1.7%)	
Broncospasm	2 (3.5%)	0	
Fiberoptic intubation, n (%)	0	2 (3.5%)	2 (3.5%)
Total, n (%)	51 (89.5%)	6 (10.5%)	57

ADA, Anticipated Difficult Airway; SGD, Supraglottic Device; NA, Not Applicable; OTI, Orotracheal Intubation.
[a] SGD repositioning or adjustment manoeuvres were needed to improve ventilation.

and was associated with a low incidence of airway-related events or complications. No major airway complications occurred in the patients whose airways were managed with SGD. Post-procedure pneumonia was diagnosed in 3 patients under prolonged mechanical ventilation due to neurological complications that cannot be attributed to airway instrumentation during the procedure. To date, no randomized trials or prospective studies comparing OTI to SGD management in neuroradiological interventions have been published; only data from two retrospective observational studies in this setting are available, including 3 and 26 cases of uneventful SGD use,[7,8] which is consistent with our findings.

During endovascular embolization of intracranial aneurysm, the transmural pressure gradient of the aneurysm sac must remain constant[2,9,10] to decrease the risk of rupture, estimated to be 1.4% of the cases.[11] Furthermore, preventing the ischemia and bleeding that can occur at different moments, during or shortly after the procedure, requires a strict and continuous control of the hemodynamic and respiratory parameters, in particular during the induction of anesthesia and the awakening period. As studies in other settings have demonstrated the benefit of using SGD to reduce the deleterious hemodynamic impact of airway manipulation during induction and emergence of anesthesia in comparison to OTI, it could be speculated that they may contribute to reduce the risk of aneurysm rupture and postoperative intracranial bleeding.[6,12,13] The data of our retrospective analysis do not allow drawing conclusions because more patients with high risk for complication were managed with OTI. In our series, 4 cases of aneurysm rupture and bleeding occurred. The 2 patients in the OTI group were still intubated. The 2 patients in the SGD group were intubated postoperatively and transferred to the intensive care unit when neurological status declined after several hours. Although complications after uneventful endovascular procedures seem to be rare,[14] it appears very important to monitor these patients very closely and evaluate neurological function often during the first 6 hours of recovery to detect events early, as we did in our series. An additional advantages of SGD use is that the early and smooth recovery from anesthesia, facilitating the immediate assessment of neurological status after the procedure, which has been found to be beneficial.[15]

The shift toward SGD in our series progressed alongside a transition to minimally invasive periprocedural protocols, including the use of noninvasive continuous monitoring, as better equipment became available. This evolution in clinical practice also reflects the consolidation of our collective experience in the use SGD in neuroanesthesia.[6,16,17]

However, controversy still exist over the use SGD for endovascular treatment of UIAs, as for other neurosurgical procedures, based on concerns over their efficacy and safety on protecting the airway. In our 9-year experience, no complication related to the use of SGD, such as severe hypoxemia or aspiration of gastric contents, were detected and all airway related events were easily solved by repositioning or adjusting the device. These encouraging results could be explained by a prudent patient selection considering several factors. First, patients estimated to be at risk for carotid rupture or cervical bleeding and those with decreased level of consciousness were managed with OTI. Second, patients with predicted difficult airways were managed according to institutional protocols, performing awake tracheal intubation if indicated by the preanesthetic airway evaluation findings. Notwithstanding, 7-patients with criteria for difficult intubation, but not for difficult ventilation or SGD placement, were managed uneventfully with such devices. Third, the number of patients managed with SGD increased steadily as the members of the neuroanesthesia team gained expertise in their use, to include the vast majority of patients scheduled for embolization of unruptured aneurysms. Fourth, an SGD that is appropriate for the indication should be used, and a second-generation device is recommended for advanced uses. Only second-generation SGD were used in our case series, the I-gel was the most commonly available in the radiological suite as it does not have metal components.

Our retrospective analysis has several limitations. First, the number of patients and the severity of their risk factors for complications were not evenly distributed between the groups of patients. Second, data related to hemody-

namic and respiratory changes, particularly during induction and emergence from anesthesia, was not precise enough to draw conclusions about the benefits of SGD use over the OTI. Finally, our single center study, with a limited sample size, is not large enough to support the safety of SGD use during the endovascular treatment of UIAs.

In conclusion, our experience suggests that the use of SGD I-gel is a feasible airway management approach for patients proposed for endovascular treatment of UIAs under minimally invasive periprocedural management protocols.

Conflicts of interest

The authors declare no conflicts of interest.

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SYSTEMATIC REVIEW

Dexmedetomidine reduces postoperative cognitive and behavioral dysfunction in adults submitted to general anesthesia for non-cardiac surgery: meta-analysis of randomized clinical trials

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KEYWORDS
Dexmedetomidine;
Delirium;
Psychomotor agitation;
General anesthesia;
Meta-analysis

Abstract Introduction and objectives Dexmedetomidine (DEX) have been associated with a decrease in postoperative cognitive and behavioral dysfunction in patients submitted to general anesthesia, whether inhalation or total intravenous anesthesia. Consequently, the DEX effects on postoperative agitation and delirium in patients submitted to general anesthesia for non-cardiac surgery have been investigated.

Method: We performed a meta-analysis of randomized and double-blind clinical trials assessing adults submitted to elective procedures under general anesthesia that received DEX or placebo. We searched articles published in English in the Pubmed and Web of Science databases using keywords such as dexmedetomidine, delirium, and agitation. We excluded duplicate publications, studies involving cardiac surgery or that used active control (other than saline solution). A random effects model was adopted using the DerSimonian-Laird method and estimate of Odds Ratio (OR) for dichotomous variables, and weighted mean difference for continuous variables, with their respective 95% Confidence Intervals (95% CI).

Results: Of the 484 articles identified, 15 were selected comprising 2,183 patients (1,079 and 1,104 patients in the DEX and control group, respectively). The administration of DEX was considered a protective factor for postoperative cognitive and behavioral dysfunction (OR = 0.36; 95% CI 0.23–0.57 and $p < 0.001$), regardless of the anesthesia technique used.

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Conclusion: Dexmedetomidine administration reduced by at least 43% the likelihood of postoperative cognitive and behavioral dysfunction in adult patients submitted to general anesthesia for non-cardiac surgery.
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Introduction

Delirium is an acute inability to sustain attention associated with cognitive dysfunction, impairment in mental status and in the sleep-wake cycle, as well as in behavior, which can lead the patient into a hypo or hyperactive state.[1,2] It has risk factors such as older age, postoperative period, past comorbidities, previous neurological deficits and sensory impairments.[1,3] As reported both in pivotal studies and in more updated publications, delirium is associated with longer hospital stay, functional reduction, less likelihood of regaining autonomy, and greater morbidity and mortality.[4–6] It is estimated that approximately 20% of hospitalized patients over 65 years of age develop postoperative delirium.[1]

Agitation is a mental state in which the patient is restless, uncooperative, and incoherent.[7] It can be related to a paranoid ideation associated with time disorientation and misinterpretation of neurosensory stimuli, resulting from residual effect of anesthetic drugs.[8] Postoperative agitation is associated with adverse events such as surgical site bleeding, accidental removal of drains or vascular catheters, and even damage to the surgery performed.[9]

Dexmedetomidine (DEX) is an α_2 adrenoceptor agonist, with selectivity ratio of 1600:1 (α_2:α_1). It acts on α_2 receptors of the locus coeruleus, promoting sedation, and on the spinal cord dorsal horn, decreasing the release of substance P and producing analgesia.[10] DEX provides excellent sedation and analgesia, with minimal respiratory depression.[11,12] DEX is also associated with reduction in delirium and postoperative stress, and increased patient satisfaction.[13]

Decreased postoperative agitation[14,15] and delirium[16,17] has been attributed to DEX, promoting a beneficial effect on morbidity and mortality associated with both conditions, which, in the present study, will be denominated postoperative cognitive and behavioral dysfunction. Therefore, the aim of the study was to evaluate the effects of dexmedetomidine on postoperative agitation and delirium in patients submitted to general anesthesia for non-cardiac surgery.

Method

We conducted a systematic review with meta-analysis of clinical trials on the effects of DEX on postoperative cognitive and behavioral dysfunction in adult patients submitted to general anesthesia for non-cardiac surgery. We complied with Prisma guidelines[18] for the construction of a systematic review and meta-analysis of randomized clinical trials. We searched PubMed and Web of Science database English language articles published between January 2013 and March 2020. The search was performed using the keywords ''dexmedetomidine, delirium and agitation'' or their synonyms, separated by AND and OR interlocutors with the following search strategy: (((((Deliri *) OR agitat *) AND dexmedetomidine))). To complement the search, we carried out a manual analysis of the references of the studies that complied with the inclusion criteria, aiming to detect original articles not recovered previously.

We included randomized, double-blind clinical trials with participants over 18-years of age, submitted to elective procedures under general anesthesia and receiving DEX or placebo. We excluded duplicate articles, studies comprising cardiac surgery patients or studies that used active control (other than saline solution).

Two independent investigators carried out a preliminary assessment of the titles/abstracts and extracted the data. After selecting the articles in conformity with the inclusion and exclusion criteria, there was full-text reading of the article. In case of disagreement, a third investigator made the final arbitration. Using a standardized form previously prepared by the authors, data were recorded on patient age, anesthesia technique, dosage and method administration of DEX, type of procedures and outcomes. For this study, the primary outcome was postoperative cognitive and behavioral dysfunction, comprising delirium and/or agitation (present or absent). Secondary outcomes included the interval in minutes for anesthesia awakening and tracheal extubation (awakening time and tracheal extubation time, respectively).

Sensitivity analysis was conducted to explore sources of heterogeneity among studies in the overall and in the subgroup analysis that evaluated cognitive outcome regarding patient age and the anesthesia technique. Statistical heterogeneity was calculated using the chi-square method (χ^2) and the Higgins test (I^2).[19] The presence of heterogeneity was deemed to occur when $p < 0.05$ and $I^2 \geq 50\%$. The Odds Ratio (OR), with a 95% Confidence Interval (95% CI), was used to quantify the statistical difference between groups for dichotomous variables and Mean Difference (MD) for continuous variables (time in minutes). Following the qualitative analysis of the studies and statistical heterogeneity assessment, the random effects model was implemented using the DerSimonian-Laird[20] method, and the statistical analysis was performed using the Comprehensive Meta-analyses® software v.3.3. Assessment of potential publication bias was performed by visual analysis of the funnel plot and by using the Begg[21] and Egger[22] tests. The statistical significance adopted was 5%. To assess the impact of the study (Grading of Recommendations, Assessment, Development and Evaluations), we used the GRADEpro Guideline Development Tool (GRADEpro GDT®) software according to the methodological guidelines of the GRADE system provided by the Brazilian Ministry of Health.[23]

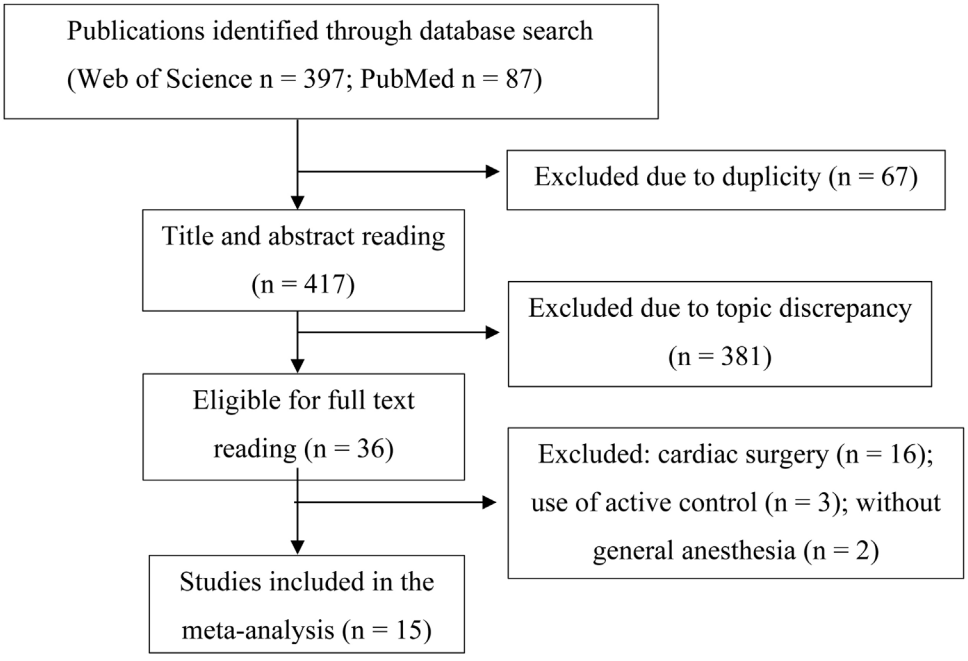

Figure 1 Flowchart of the selected studies.

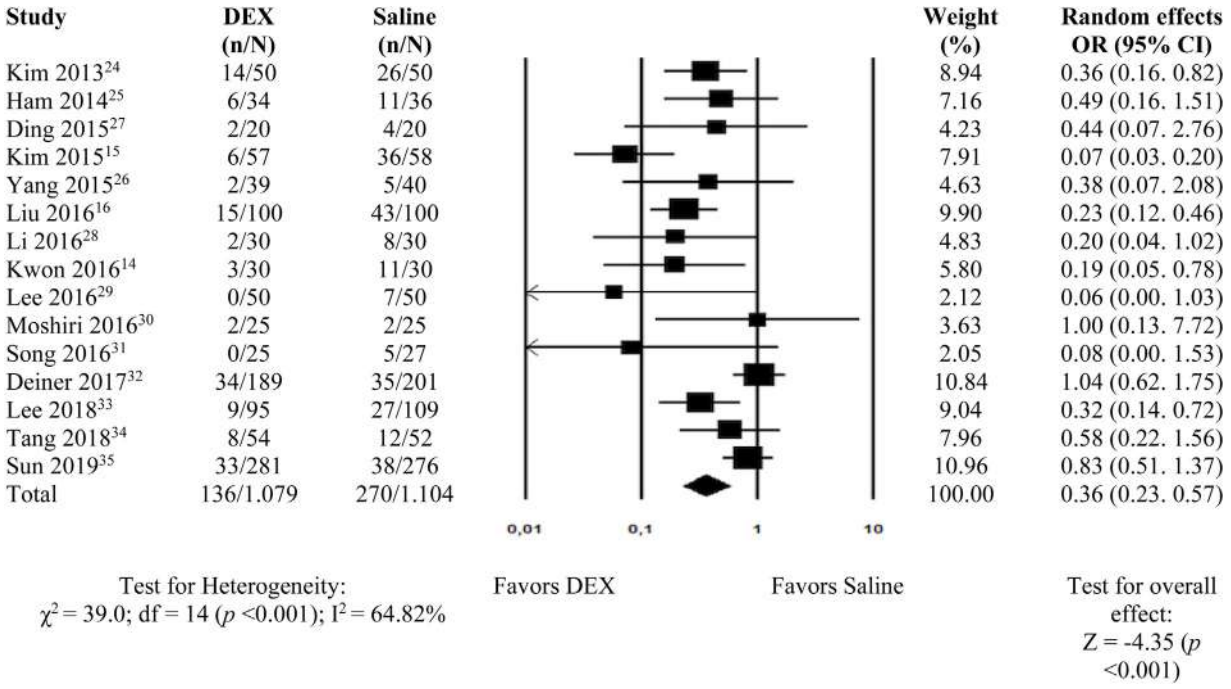

Figure 2 Meta-analysis of the effect of dexmedetomidine on postoperative cognitive and behavioral dysfunction in adults submitted to general anesthesia for non-cardiac surgery. df, Degrees of freedom.

Results

As depicted in Fig. 1, 484 studies (397 on Web of Science and 87 on PubMed) were identified, from which 15 were selected to constitute this meta-analysis.

Table 1 details the characteristics of the 15 trials selected.[14–16,24–35] They comprised 2,183 patients (1,079 in the intervention group and 1,104 in the control group). Seven studies were carried out in China, six in South Korea, one in the United States, and one in Iran.

Postoperative cognitive and behavioral dysfunctions were assessed in the 15 studies,[14–16,24–35] and as shown in Fig. 2, the administration of DEX was considered a protective factor (OR = 0.36; 95% CI 0.23–0.57 and $p < 0.001$). Postoperative delirium and agitation were separately evaluated,

Table 1 Description of the selected studies.

Year of publication of the study	Details of the study	n	Age range (years)	Procedure
Kim 2013[24]	DEX 0.4 mcg.kg^{-1}.h^{-1}	50	20–58	Nose surgery
	Salina	50		
Ham 2014[25]	DEX 0.1 mcg.kg^{-1}	34	20–45	Orthognathic
	Salina	36		surgery
Kim 2015[15]	DEX 0.4 mcg.kg^{-1}.h^{-1}	57	≥65	Orthopedic
	Saline	58		surgery
Yang 2015[26]	DEX 0.5 mcg.kg^{-1}.h^{-1} and 0.2–0.7 mcg.kg^{-1}.h^{-1}	39	18–80	Oral and maxillofacial
	Salina	40		surgery
Ding 2015[27]	DEX 0.8 mcg.kg^{-1}.h^{-1}	20	45–80	Cystectomy
	Salina	20		
Liu 2016[16]	DEX 0.2–0.4 mcg.kg^{-1}.h^{-1}	100	65–80	Orthopedic
	Salina	100		surgery
Li 2016[28]	DEX 0.6 mcg.kg^{-1}.h^{-1}	30	18–65	Open gastrectomy
	Salina	30		
Lee 2016[29]	DEX 0.1 mcg.kg^{-1}.h^{-1}	50	≥20	Thoracoscopy
	Salina	50		
Kwon 2016[14]	DEX 0.5 mcg and 0.5 mcg.kg^{-1}.h^{-1}	30	30–80	Transurethral resection
	Salina	30		of the prostate
Moshiri 2016[30]	DEX 0.5 mcg.kg^{-1}.h^{-1}	25	18–50	Electroconvulsive
	Salina	25		therapy
Song 2016[31]	DEX 0.5 mcg.kg^{-1}.h^{-1}	25	18–60	Craniotomy
	Salina	27		
Deiner 2017[32]	DEX 0.5 mcg.kg^{-1}.h^{-1}	189	≥68	Non-cardiac
	Salina	201		elective surgery
Lee 2018[33]	DEX 0.1 mcg.kg^{-1} and 0.2–0.7 mcg.kg^{-1}.h^{-1}	95	≥65	Non-cardiac
	Salina	109		surgery
Tang 2018[34]	DEX 0.1 mcg.kg^{-1} and 0.3 mcg.kg^{-1}.h^{-1}	54	18–70	Neurosurgery
	Salina	52		
Sun 2019[35]	DEX 0.1 mcg.kg^{-1}.h^{-1}	281	≥65	Non-cardiac
	Salina	276		surgery
Total		2,183		

and DEX was effective in reducing both complications (6 studies[16,27,32–35]; OR = 0.53; 95% CI 0.31–0.92 and $p = 0.023$; and 9 studies[14,15,24–26,28–31]; OR = 0.24; 95% CI 0.13–0.42 and $p < 0.001$, respectively).

Fig. 3 depicts the age sub-group analysis (adults under 6-years vs. elderly above 60-years of age), and shows that administering DEX reduced the rate of postoperative cognitive and behavioral dysfunction in adults under 60-years of age (4 studies[24,25,30,31]; OR = 0.40; 95% CI 0.22–0.75 and $p = 0.004$), and in the elderly (5 studies[15,16,32,33,35]; OR = 0.52; 95% CI 0.39–0.69 and $p = 0.018$).

Regarding anesthesia technique sub-groups (intravenous vs. inhalational), two studies[28,35] were excluded because they involved patients undergoing both techniques indistinctly. Conversely, one study[15] was included in the sub-analysis of both techniques, as they were discriminated between groups. DEX was shown to be beneficial against postoperative cognitive and behavioral dysfunction in both procedures: intravenous anesthesia (5 studies[15,16,28,30,31]; OR = 0.18; 95% CI 0.08–0.40 and $p < 0.001$) and inhalational anesthesia (9 studies[14,15,24–27,29,33,34] OR = 0.28; 95% CI 0.17–0.47 and $p < 0.001$) (Fig. 3).

Awakening time was assessed in five studies[14,25,28,29,34] and there was no significant difference between the groups (MD = 1.19; 95% CI −0.97–3.36; $p = 0.280$). Fig. 4 shows that tracheal extubation time was different between groups, with a lengthier duration for the DEX group (4 studies[24,28,29,31]; MD = 1.43; 95% CI 0.76–2.11; $p < 0.001$).

The funnel plot analysis (Fig. 5) shows an asymmetry with absence of studies with small and medium samples to the right of the Summary of Findings, however the Begg ($p = 0.458$) and Egger ($p = 0.050$) tests refute the hypothesis of publication bias. The evaluation by the GRADE protocol demonstrated that, regarding search execution, the study has high safety.

Discussion

This meta-analysis included 15 randomized clinical trials published between 2013 and 2019, evaluating the effect of DEX on cognitive and behavioral dysfunction in the postoperative period of adult patients submitted to general anesthesia.

We observed variation in the dosage and method administration of DEX, with studies administering DEX throughout the intraoperative period, while others used it only at anesthetic induction, and others that maintained the drug

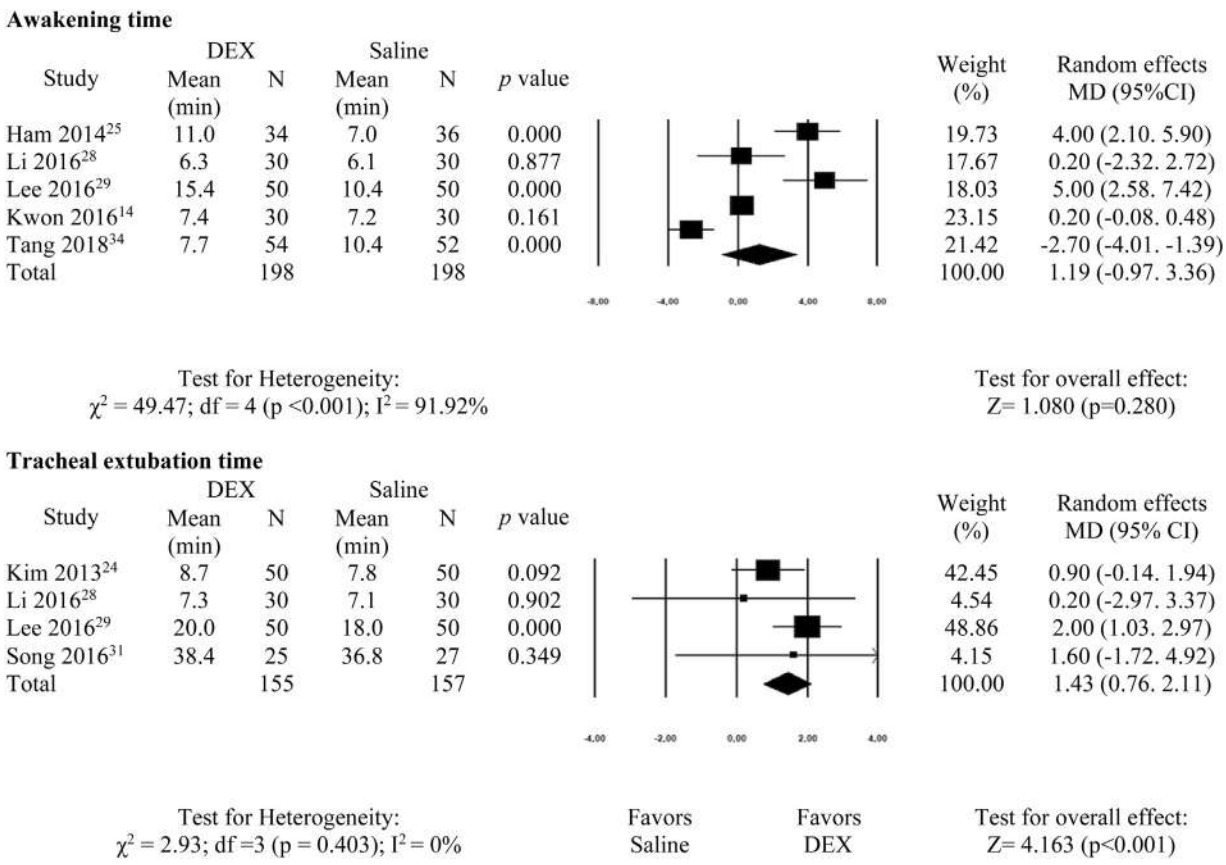

Figure 3 Meta-analysis of the effect of dexmedetomidine on postoperative cognitive and behavioral dysfunction according to age sub-groups and type of anesthesia in adults submitted to general anesthesia for non-cardiac surgery. df, Degrees of freedom.

postoperatively. Such studies have achieved similar results regarding the rate of postoperative cognitive and behavioral dysfunction, suggesting there is no recommended time for the administration of DEX regarding its beneficial effect against such events.

Delirium is a multifactor event and the most effective prevention strategies comprise pharmacological and non-pharmacological approaches.[1–3] Among the pharmacological options, DEX was effective in reducing the delirium rate when compared to placebo.[16,33]

This meta-analysis shows DEX as a protective factor against delirium and postoperative agitation in adults submitted to general anesthesia for non-cardiac surgery and a similar result has been found by other authors.[15,24,26,28] Although the actual mechanism for this effect remains unknown, the analgesic and sedative effects of DEX are thought to be contributing factors.[13,36] Studies have suggested a perioperative anti-inflammatory activity of DEX as they reported a decrease in plasma concentration of interleukin 6 and the tumor necrosis factor alpha.[37] There is also evidence that DEX decreases plasma concentration of neuron-specific enolase and S100β protein, both neural injury biomarkers perioperatively, and promotes neuroprotective effect.[34] Therefore, one should consider that DEX, additionally to its known action at the locus coeruleus, has inherent neurocytological protection activity,[28,34,37] reducing postoperative agitation and delirium and thus contributing to preservation of preoperative neurological status.[32]

Elderly people are more prone to delusions and to cognitive dysfunction postoperatively, nonetheless DEX acted as a beneficial anesthetic adjunct agent as it prevented these events in both age sub-groups analyzed, adults below 60-years and the elderly sub-group. This result was also found elsewhere, however, when trials assessed the DEX effect in patients submitted to cardiac and non-cardiac surgery.[38] Thus, DEX effectiveness in preventing cognitive and behavioral dysfunction revealed to be age independent.

Regarding the analysis by subgroup of anesthetic technique, we observed that DEX was a protective factor for cognitive and behavioral dysfunction in both intravenous and inhalation general anesthesia. This finding underlines the concepts that lessening the endocrine-metabolic stress and providing analgesia play a more prominent role than choosing the anesthetic technique itself.[39]

This study revealed no difference in awakening time with administration of DEX, conflicting with the literature.[25,29] Due to its elimination half-life of 2 to 2.5 hours and upward context-sensitive half-life, DEX sustains sedative activity through its sympatholytic properties.[40] Additionally, due to DEX capability of intensifying the effects of other analgesics simultaneously administered,[41] there is the likelihood of extending anesthesia effects and thus prolonging awakening time. Conversely, a significant difference was found in tracheal extubation time, but with irrelevant clinical sig-

Awakening time

Study	DEX		Saline		*p* value	Weight (%)	Random effects MD (95%CI)
	Mean (min)	N	Mean (min)	N			
Ham 2014[25]	11.0	34	7.0	36	0.000	19.73	4.00 (2.10. 5.90)
Li 2016[28]	6.3	30	6.1	30	0.877	17.67	0.20 (-2.32. 2.72)
Lee 2016[29]	15.4	50	10.4	50	0.000	18.03	5.00 (2.58. 7.42)
Kwon 2016[14]	7.4	30	7.2	30	0.161	23.15	0.20 (-0.08. 0.48)
Tang 2018[34]	7.7	54	10.4	52	0.000	21.42	-2.70 (-4.01. -1.39)
Total		198		198		100.00	1.19 (-0.97. 3.36)
Test for Heterogeneity: $\chi^2 = 49.47$; df = 4 ($p < 0.001$); $I^2 = 91.92\%$							Test for overall effect: Z= 1.080 ($p = 0.280$)

Tracheal extubation time

Study	DEX		Saline		*p* value	Weight (%)	Random effects MD (95% CI)
	Mean (min)	N	Mean (min)	N			
Kim 2013[24]	8.7	50	7.8	50	0.092	42.45	0.90 (-0.14. 1.94)
Li 2016[28]	7.3	30	7.1	30	0.902	4.54	0.20 (-2.97. 3.37)
Lee 2016[29]	20.0	50	18.0	50	0.000	48.86	2.00 (1.03. 2.97)
Song 2016[31]	38.4	25	36.8	27	0.349	4.15	1.60 (-1.72. 4.92)
Total		155		157		100.00	1.43 (0.76. 2.11)
Test for Heterogeneity: $\chi^2 = 2.93$; df =3 ($p = 0.403$); $I^2 = 0\%$						Favors Saline / Favors DEX	Test for overall effect: Z= 4.163 ($p < 0.001$)

Figure 4 Meta-analysis of the effect of dexmedetomidine on awakening and tracheal extubation time in adults submitted to general anesthesia for non-cardiac surgery. df, Degrees of freedom.

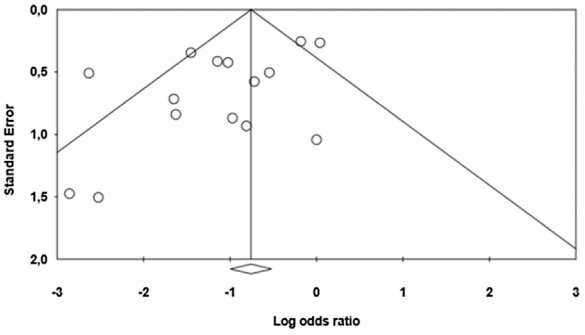

Figure 5 Funnel plot of the effect of dexmedetomidine on cognitive and behavioral dysfunction in adults submitted to general anesthesia for non-cardiac surgery.

nificance, or less than two minutes. This effect coincides with the literature.[38] The reason for not observing a greater difference may lie in the heterogeneity of the methods and timing of drug administration in the primary studies included here.

The quality of the meta-analysis depends on the selection of relevant studies, heterogeneity, and detection bias.[18] Despite the different strategies adopted in this study to minimize possible biases, they cannot be ruled out. A search was performed using two important databases, complemented by manual search, and the selected works were submitted to the appreciation of two independent investigators. We included only clinical, double-blind, randomized trials. The present study adds an important contribution in demonstrating the protective effect of DEX against cognitive and behavioral dysfunction in patients submitted to non-cardiac surgery. Additional systematic reviews with meta-analysis can be found in the literature, however, they include patients admitted in intensive care units, undergoing cardiac surgery or only elderly patients.[38,42,43]

The authors of this meta-analysis considered that the studies were heterogeneous, due to the variation of DEX dose between groups, and the type of surgery the patients were submitted to. Nonetheless, the heterogeneity was tested and confirmed with a high χ^2 value and an I^2 greater than 64%, which indicate medium heterogeneity.

As they followed the GRADE protocol,[23] the authors considered that the study has no significant publication bias, because the search was conducted using two important databases and was complemented by manual analysis of the references. The GRADE outcome indicates that the study has a considerable impact and high consistency concerning the DEX protection effect on postoperative cognitive and behavioral dysfunction.

DEX provides reliable hemodynamic stability and has been increasingly administered in anesthetic practice due to its straightforward use in the pre-anesthetic, intraoperative and even postoperative period, as well as its wide range of dosage formulations.[11] In addition to the beneficial effects on cognitive and behavioral dysfunction evaluated in this study, there is a reported sparing effect on the use of volatile agents and opioids.[31]

Conclusion

This systematic review with meta-analysis reveals that the administration of dexmedetomidine reduced from 43% to 77% the likelihood of cognitive and behavioral dysfunction in the postoperative period of adult patients submitted to general anesthesia for non-cardiac surgery.

Conflicts of interest

The authors declare no conflicts of interest.

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NARRATIVE REVIEW

Renal and cardiovascular repercussions in preeclampsia and their impact on fluid management: a literature review



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Abstract Preeclampsia is a multifactorial condition associated with significant morbidity and mortality. Fluid therapy in these patients is challenging since volume expansion may precipitate pulmonary edema, and fluid restriction may worsen renal function. Furthermore, cardiac impairment may introduce an additional component to the hemodynamic management. This article reviews the repercussions of preeclampsia on renal and cardiovascular systems and the development of pulmonary edema, as well as to discuss fluid management, focusing on the mitigation of adverse outcomes and monitoring alternatives. The literature review was carried out using PubMed, Embase, and Google Scholar databases from May 2019 to March 2020. Papers addressing the subjects of interest were included regardless of the publication language. There is a current trend towards restricting the administration of fluids in women with non-complicated preeclampsia. However, patients with preeclampsia may experience hemorrhagic shock, requiring volume resuscitation. In this case, hemodynamic monitoring is recommended to guide fluid therapy while avoiding complications.
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Introduction

Preeclampsia is a multifactorial condition characterized by new-onset hypertension and proteinuria, or hypertension associated with significant organic dysfunction after 20-weeks of pregnancy.[1] Worldwide, it complicates 2% to 8% of pregnancies and is responsible for up to 14% of maternal deaths.[2,3] Preeclampsia is also a significant cause of morbidity; patients presenting with severe disease are at a higher risk of developing severe complications, including Acute Kidney Injury (AKI), cardiovascular diseases, and Pulmonary Edema (PE).[4]

The current knowledge in physiopathology of preeclampsia relies on abnormal placentation and imperfect invasion

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of the uterine spiral arteries by cytotrophoblast cells, causing inadequate blood flow and relative placental ischemia.[5,6] In consequence, a state of oxidative stress is established, leading to defective fetoplacental angiogenesis and endothelial dysfunction.[7]

The endothelial dysfunction in preeclampsia is associated with an increase in both peripheral vascular resistance and vascular permeability, which ultimately results in a state of relative intravascular hypovolemia.[8] Fluid therapy in this scenario may be challenging, especially during cesarean delivery. Although volume expansion may precipitate fluid overload and PE, fluid restriction may worsen tissue hypoperfusion and increase the risk of AKI (Fig. 1).[9–11] Furthermore, cardiac impairment may play an essential role in preeclampsia, introducing an additional component to the hemodynamic management.[12,13]

This article reviews the repercussions of preeclampsia on renal and cardiovascular systems, and the development of pulmonary edema, as well as to discuss fluid management, focusing on the mitigation of adverse outcomes and monitoring alternatives.

Methodology

The literature review was carried out by searching the PubMed, Embase, and Google Scholar databases from May 2019 to March 2020. Eligible studies were identified by using different combinations of the following search terms: ''preeclampsia'', ''pathogenesis'', ''acute kidney failure'', ''cardiovascular'', ''pulmonary edema'', and ''fluid management''.

Articles were initially selected after reviewing the title and the abstract. Papers addressing the subjects of interest were selected for a full review and included regardless of the publication language.

Preeclampsia-related renal repercussions

Preeclampsia is the leading cause of pregnancy-related AKI,[14,15] a condition associated with high rates of maternal mortality and fetal loss.[16] In the United States, between 1998 and 2009, up to 17% of deaths during hospitalized deliveries occurred among women with AKI.[11] Additionally, women who develop AKI during pregnancy, regardless of etiology, are at higher risk of poor outcomes, including obstetrical hemorrhage, placental abruption, and intensive care unit admission.[17,18] Approximately 2% of women with severe preeclampsia and 15% of women with HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, a variant of severe preeclampsia, will develop AKI.[15,18–21]

The diagnosis of pregnancy-related AKI is challenging. During pregnancy, the physiological increase in Glomerular Filtration Rate (GFR) decreases the concentration of serum creatinine.[22,23] Thus, serum creatinine that is within the normal range for the general population may actually mask a significant impairment in renal function.[24] Pregnant women may experience 30% to 40% reduction in GFR before a significant increase in serum creatinine occurs.[15]

An additional issue is the absence of consensus regarding the diagnostic criteria for pregnancy-related AKI. Several classifications have been developed for application in the general population, including the RIFLE (Risk, Injury, Failure, Loss, and End-Stage Kidney Disease – ESKD)[25] and the AKIN (Acute Kidney Injury Network)[26,27] criteria. They are commonly used in the obstetric population, even without validation. The American College of Obstetricians and Gynecologists (ACOG) has its definition for AKI as a pregnancy-related hypertensive disorder (Table 1).[1]

AKI management during pregnancy is focused on providing supportive measures, dialysis, and correction of the underlying etiology.[28] Avoidance of nephrotoxic drugs and correction of complications, such as hypertension, hyperkalemia, and metabolic acidosis, should be promptly initiated along with judicious fluid management, aiming to provide adequate uteroplacental perfusion and fetal well-being while avoiding volume overload and PE.[29]

In the presence of uremic symptoms (encephalopathy, pericarditis, or neuropathy) or complications that are refractory to pharmacological interventions, renal replacement therapy is indicated. Dialysis prescription during pregnancy should minimize hemodynamic fluctuations; in this scenario, longer and more frequent sessions are preferred.[24,29] As many as 30% to 50% of those who develop AKI associated with HELLP syndrome will require dialysis temporarily.[30]

The identification of the underlying etiology of pregnancy-related AKI is essential; however, since several causes may share similar clinical and laboratory findings, the exact etiology may remain indefinite.[24] Regarding preeclampsia, diagnosis relies on the presence of Blood Pressure (BP) > 140/90 mmHg with proteinuria of $\geq$ 300 mg/day after 20 weeks of gestation in a previously normotensive woman or the evidence of organ damage.[31]

Specific treatment depends on the illness severity, fetal well-being, and gestational age. Before 24 weeks, pregnancy is discontinued because no fetal survival benefit is observed.[32] Between 24 and 32 weeks, expectant management is recommended[32,33]; after 32-weeks, delivery is the treatment of choice.[34] Development of severe preeclampsia, HELLP syndrome, or fetal compromise are indications for prompt delivery regardless of gestational age.[33]

In the past, preeclampsia-related AKI was considered completely reversed after delivery. Although the risk of ESKD after pregnancy is low, recent studies indicate that AKI during pregnancy increases the risk of long-term renal dysfunction.[18,22,35–37] A study that followed women with HELLP syndrome and AKI for up to one year after delivery reported that 21% of the patients needed dialysis.[35] Patients with preexisting hypertension or renal disease have a higher likelihood of requiring long-term dialysis.[38]

Preeclampsia-related cardiovascular repercussions

Preeclampsia and cardiovascular diseases share several predisposing conditions, such as obesity, smoking, sedentary lifestyle, diabetes, chronic kidney disease, chronic hypertension, and abnormal serum lipid profile.[39] For a long time, the overlap of risk factors for both illnesses was thought to be spurious. However, recent studies hypothesize that disorders of the cardiovascular system may have a direct effect

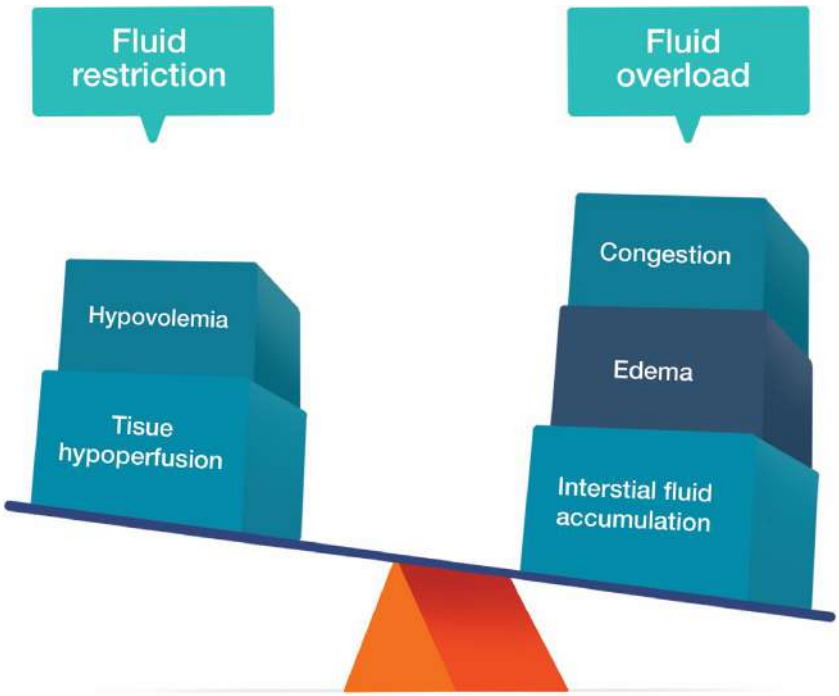

Figure 1 Considerations while choosing the fluid management strategy in women with preeclampsia.

Table 1 RIFLE, AKIN, and ACOG definitions for AKI.

RIFLE[25]	
Risk	1.5-fold increase in serum creatinine OR 25% decrease in GFR OR < 0.5 mL.kg^{-1}.h^{-1} for > 6 h
Injury	2-fold increase in serum creatinine OR 50% decrease in GFR OR UO < 0.5 mL.kg^{-1}.h^{-1} for > 12 h
Failure	3-fold increase in serum creatinine OR 75% decrease in GFR OR UO < 0.3 mL.kg^{-1}.h^{-1} for > 24 h OR no UO for 12 h
Loss of kidney function	Complete loss of kidney function (> 4 weeks)
ESKD	Complete loss of kidney function (> 3 months)
AKIN[26]	
Absolute increase in serum creatinine 0.3 mg.dL^{-1} or more OR 1.5-fold increase in baseline serum creatinine OR UO < 0.5 mL.kg^{-1}.h^{-1} for > 6 h	
ACOG[1]	
Baseline serum creatinine > 1.1 mg.dL^{-1} OR 2-fold increase in baseline serum creatinine in the absence of renal disease	

ESKD, End Stage Kidney Disease; GFR, Glomerular Filtration Rate; UO, Urinary Output.

on preeclampsia pathogenesis and that preeclampsia is an independent risk factor for cardiovascular disease.[12,13,40–42]

Preeclamptic women experience a derangement in renin-angiotensin-aldosterone system regulation when compared to their healthy counterparts. While refractoriness to angiotensin II is found in uncomplicated pregnancies,[43] an increase in vascular sensitivity to angiotensin II occurs in preeclampsia.[44,45] This imbalance, which is clinically expressed as high BP and peripheral arterial resistance, is present long before the diagnosis of preeclampsia.[39] Likewise, when compared to healthy women, those who develop preeclampsia may have a lower cardiac output and cardiac index, impaired myocardial relaxation, and increased prevalence of abnormal heart geometry even before conception.[46–48]

Besides the compelling evidence that preeclampsia has a cardiovascular etiology, the American Heart Association now recognizes that this condition is a risk factor for long-term postpartum cardiovascular diseases.[49] A cohort study that included over one million maternities demonstrated that preeclamptic women have a higher risk of major adverse cardiovascular events and that this risk remains significantly higher long after the delivery.[50] Another study found that recurrent preeclampsia is associated with increased rates of hypertension, ischemic heart disease, heart failure, and cerebrovascular accident.[51] There is also evidence for increased cardiovascular risk in the offspring of the preeclamptic mother.[52]

The cardiovascular management in uncomplicated preeclampsia is focused on BP control. Although BP thresholds and goals vary in international guidelines, there is a consensus that BP should be treated when it is severe (systolic BP $\geq$ 160 mmHg or diastolic BP $\geq$ 110 mmHg).[42] In complicated preeclampsia, delivery after stabilization of the patient is the only specific treatment.[31] During labor,

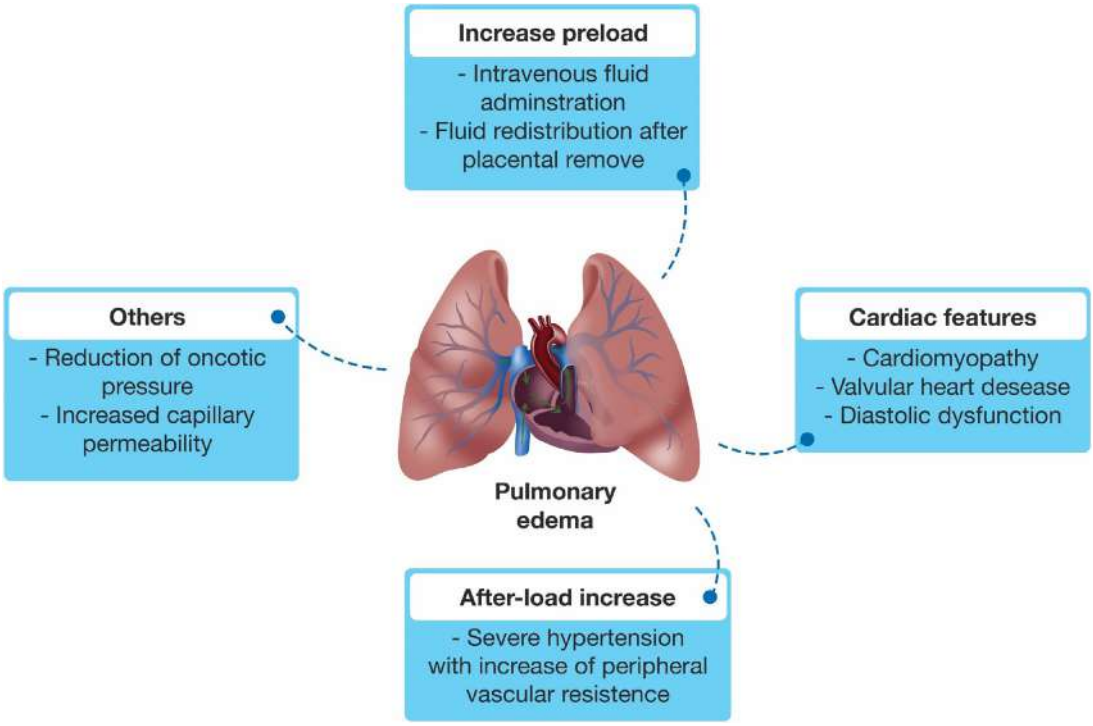

Figure 2 Multifactorial etiology of pulmonary edema in preeclampsia.

the use of invasive hemodynamic monitoring might be considered to guide fluid therapy, especially if severe cardiac disease, PE, persistent oliguria, and severe hypertension are present.[10,53]

In the postpartum period, women should be followed during the first 6 to 8 weeks; patients with a persistent need for antihypertensive medication require a referral to a cardiologist.[54] It is known that cardiovascular diseases have a slow progression, from asymptomatic to symptomatic stage. In this setting, the diagnosis of preeclampsia, which typically occurs in young women, poses an opportunity for early identification of high-risk patients when they are still in the asymptomatic stage. At this point, lifestyle and therapeutic interventions are more effective in controlling other cardiovascular risk factors.[42]

Pulmonary edema in preeclampsia

PE is the most common cardiopulmonary complication of preeclampsia, occurring in 3% to 5% of preeclamptic pregnancies, mainly in the peripartum or postpartum stage.[42,55,56] Despite the low rate of incidence, PE is a life-threatening event, being a frequent cause of admission to the intensive care unit and the leading cause of death among preeclamptic women.[57,58]

The etiology of PE in preeclampsia is multifactorial (Fig. 2). The decrease in oncotic pressure secondary to preeclampsia-related hypoproteinemia, the disruption in pulmonary endothelium leading to increased capillary permeability, and the increase in afterload due to severe hypertension all appear to play a role.[10,59] As previously discussed, preeclampsia may be associated with cardiac function impairment, which may contribute to PE.[60] PE is also related to preeclampsia severity, with higher rates among women who develop AKI, HELLP syndrome, and eclampsia.[18,61,62]

Nearly 70% of the PE events occur in the postpartum period.[61] Following the placental removal, a fluid shift from the extravascular space restores the intravascular volume, increasing the preload.[63,64] Furthermore, the inadvertent administration of fluid, frequently used to increase plasma volume or treat oliguria, may also exacerbate the preload and trigger PE.[10] It is recognizable that iatrogenic fluid administration is a major preventable cause of PE.[65]

The management of preeclampsia complicated by PE poses a significant challenge to the medical team. The superimposed issues of the physiological changes of pregnancy, the presence of the fetus, and the knowledge gaps regarding the physiopathology of preeclampsia all contribute to the high rates of morbidity and mortality associated with this condition.[10]

The initial goal while treating PE during preeclampsia relies on the reduction of BP with intravenous antihypertensive agents (Table 2).[42] Rapid reduction of blood pressure may be accomplished with the use of intravenous labetatol or hydralazine.[42,66] Some authors also recommend the use of nitroglycerine in hypertensive crises, despite the risk of aggravate the depletion of intravascular volume.[42,67,68] Furosemide should be used with caution because it may worsen the placental perfusion.[69]

In the case of left ventricular systolic dysfunction, inotropic support should be considered.[10] There is a gap in the literature regarding the choice of a specific inotrope to manage acute heart failure during pregnancy, especially due to safety concerns.[70] Therefore, the selection of an inotrope should be based upon the clinical scenario.

Table 2 Intravenous antihypertensive medications used in hypertensive pulmonary edema during preeclampsia.

Drug	Starting dose	Repeating doses and intervals	Maximum total dose	Comments
Labetalol[42,66]	20 mg	40 mg after 10 minutes	220 mg	Avoid in asthma, chronic obstructive airways disease, and heart failure; associated with neonatal bradycardia and hypoglycemia
Hydralazine[42,66]	5 mg	5–10 mg after 20 minutes	20 mg	Risk of sudden hypotension and maternal tachycardia; may need preloading or simultaneous fluid infusion
Nitroglycerine[10,42,67,68]	5 $\mu g.min^{-1}$	Gradually increase every 3–5 minutes	100 $\mu g.min^{-1}$	Considered the drug of choice by some authors; may aggravate the depletion of intravascular volume
Furosemide[10]	20–40 mg	40–60 mg after 30 minutes	120 mg	May worsen placental perfusion

Regarding ventilatory support, noninvasive modalities are initially preferred due to the risks associated with tracheal intubation in hypertensive pregnant women, such as intracerebral hemorrhage.[10,71,72]

After stabilization of the patient, consideration needs to be given to the delivery of the fetus if PE occurs in the antenatal period. Assessment of fetal well-being and multidisciplinary planning for safe birth is necessary.[10]

Fluid management and hemodynamic monitoring

Despite the lack of paramount evidence favoring a specific fluid management protocol, current guidelines advocate a restrictive approach, with additional fluid administration only recommended in selected scenarios (Table 3).[73–75]

Usually, preeclamptic women admitted for delivery may need fluid therapy for maintenance of water and electrolyte balance, or replacement of lost intravascular volume.[73] A routine fluid bolus should not be administered before neuraxial anesthesia, or to treat oliguria.[73,74,76,77] The available data do not suggest an absolute maternal or fetal benefit of colloids over crystalloids in preeclamptic women.[75,78,79]

Maintenance fluid therapy is required in uncomplicated patients who are expected to fast for several hours during labor. The infusion rate of crystalloids may be fixed 60 to 80 $mL.h^{-1}$, or calculated to match the Urinary Output (UO) combined with stool and insensible losses (lungs and skin).[73,80] It is also important to consider the volume used as a vehicle for drug administration when calculating the total amount of fluid. Given the low risk of complications following slow administration of intravenous fluids, hemodynamic monitoring may be based only upon clinical observation.[73]

Patients with severe preeclampsia may experience hemorrhagic shock due to several causes, such as placental abruption, operative blood loss, and rupture of subcapsular liver hematoma.[81–83] These women require immediate resuscitative measures, including intravenous volume replacement and blood typing.[84] The primary goal in this setting is to maintain a systolic BP above 90 mmHg.[73]

The shock index may also be considered as a predictor of adverse maternal outcomes. A threshold $\geq$ 0.9 indicates rigorous monitoring, $\geq$ 1.4 indicates an urgent need for intervention, and $\geq$ 1.7 indicates a high chance of adverse outcomes, including severe end-organ dysfunction and death.[85] UO is not a good predictor of fluid responsiveness in preeclamptic women and should not be routinely used as a therapeutic guide.[86]

The possibility of fluid overload and PE should be considered in the case of over-transfusion, especially when the fluid balance is above 2,000 mL.[58,73] However, inadequate resuscitation may increase the likelihood of AKI.[9] To balance the risks of both complications, hemodynamic monitoring is recommended to guide replacement therapy.[87]

Arterial line insertion is valuable in the presence of severe bleeding or difficult BP control. Other invasive methods, such as central venous pressure and pulmonary artery catheterization, are not routinely encouraged.[53,74] Ultimately, particular attention has been given to the use of noninvasive methods. Transthoracic echocardiography is recommended as a diagnostic and monitoring tool for hemodynamic complications, such as PE, severe arterial hypertension, and chest pain.[88] Lung ultrasound is another modality with growing importance. It can indicate both PE and increased left ventricular end-diastolic pressures.[89]

Conclusion and future directions

Preeclampsia is an important complication in pregnancy, resulting in significant rates of morbidity and mortality worldwide. Given its intricate and not still completely understood renal and cardiovascular repercussions, the management of fluid administration in preeclamptic women

Table 3 Intravenous fluid indications in preeclampsia.

Maintenance[73,80]	
60 to 80 mL.h^{-1} OR	Consider the volume used for drug administration
UO + stool + insensible losses	Monitoring based on clinical observation
Replacement[73,74,88,89]	
Titrate to systolic BP > 90 mmHg	Consider arterial line insertion if pressure control is difficult or there is severe bleeding
OR Shock index < 0.9	Consider noninvasive hemodynamic monitoring
Preload before neuraxial anesthesia[73,74,76,77]	
300 mL fluid challenge	Not routinely indicated
	Consider if high dose of anesthetic is administered
	Consider if hydralazine is the antenatal antihypertensive
Oliguria[73,74,77]	
300 mL fluid challenge	Not routinely indicated
Maintain UO $\geq$ 100 mL/4 h	If persistent oliguria, consider repeat the fluid challenge (in case of negative fluid balance)
	Consider noninvasive hemodynamic monitoring

BP, Blood Pressure; UO, Urinary Output.

can be challenging. Fluid restriction may precipitate or accentuate ischemic kidney lesions, while fluid overload may increase the hydrostatic pressure in the pulmonary capillaries, leading to PE.

Despite the lack of paramount evidence, there is a current trend towards restricting the administration of fluids in women with non-complicated preeclampsia. However, patients with severe preeclampsia may experience hemorrhagic shock, requiring volume resuscitation. In this case, hemodynamic monitoring is recommended to guide fluid therapy while avoiding complications. Noninvasive methods, such as transthoracic echocardiography and lung ultrasound, are preferred.

Future studies should focus on the influence of fluid management on patient outcomes. A randomized controlled trial could help to define the appropriate volume, as well as to describe which outcomes are significantly impacted by different volume management strategies. Additionally, basic sciences research could help to clarify the physiopathology of preeclampsia.

Conflicts of interest

The authors declare no conflicts of interest.

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NARRAGTIVE REVIEW

Clinical protocols for oral anticoagulant reversal during high risk of bleeding for emergency surgical and nonsurgical settings: a narrative review

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Prothrombin complex concentrates;
Idarucizumab;
Andexanet alfa

Abstract
Background and objectives: Oral anticoagulants prevent thromboembolic events but expose patients to a significant risk of bleeding due to the treatment itself, after trauma, or during surgery. Any physician working in the emergency department or involved in the perioperative care of a patient should be aware of the best reversal approach according to the type of drug and the patient's clinical condition. This paper presents a concise review and proposes clinical protocols for the reversal of oral anticoagulants in emergency settings, such as bleeding or surgery.
Contents: The authors searched for relevant studies in PubMed, LILACS, and the Cochrane Library database and identified 82 articles published up to September 2020 to generate a review and algorithms as clinical protocols for practical use. Hemodynamic status and the implementation of general supportive measures should be the first approach under emergency conditions. The drug type, dose, time of last intake, and laboratory evaluations of anticoagulant activity and renal function provide an estimation of drug clearance and should be taken into consideration. The reversal agents for vitamin K antagonists are 4-factor prothrombin complex concentrate and vitamin K, followed by fresh frozen plasma as a second-line treatment. Direct oral anticoagulants have specific reversal agents, such as andexanet alfa and idarucizumab, but are not widely available. Another possibility in this situation, but with less evidence, is prothrombin complex concentrates.

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Conclusion: The present algorithms propose a tool to help healthcare providers in the best decision making for patients under emergency conditions.
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Introduction

Oral anticoagulants are broadly used in the prevention of thromboembolic events and stroke in patients with atrial fibrillation and mechanical heart valves, those undergoing treatment for deep venous thrombosis, and patients with pulmonary embolism, as well as in the prevention of venous thromboembolism in medical and orthopedic surgery patients.[1,2] Oral anticoagulants have been used for more than 60 years, and its use is tending to increase worldwide as the population ages.

The vitamin K antagonist (VKA) warfarin was the pioneer oral anticoagulation drug and still has clinical importance. Its prescription has increased by 3.6 times in a 15-year period.[3] Warfarin is a VKA that inhibits the synthesis of factors II, VII, IX, X and the anticoagulant proteins C and S.[1] Warfarin has a very high bioavailability and a long half-life, and its elimination is almost entirely via hepatic metabolism[4,5] (Table 1).

More recently, direct oral anticoagulants (DOACs) have become available as an alternative to warfarin. They provide direct, selective, and reversible inhibition of the coagulation factors showing similar efficacy and a safer bleeding profile with a faster onset of action, shorter duration after discontinuation, fewer food and drug interactions, easier administration with a fixed dose, and no need for routine laboratory monitoring of the anticoagulant effect.[6–9] The drugs available are factor Xa inhibitors (rivaroxaban, apixaban, betrixaban, and edoxaban) and direct thrombin inhibitors (dabigatran). Rivaroxaban, apixaban, and edoxaban have high bioavailability, short half-lives, and a high plasma protein binding ability (54–95%).[10–12] The direct thrombin inhibitor dabigatran is rapidly absorbed after oral administration, and it has low bioavailability, a longer half-life than Xa inhibitors, and low protein-binding ability[13] (Table 1).

Nonetheless, warfarin continues to be the most commonly used anticoagulant in the world because DOACs are not globally accessible, are expensive, and have not yet been extensively studied with regard to their use for all VKA indications.[14]

Patients taking oral anticoagulants could face situations in which the acute reversal of therapy is necessary, such as life-threatening bleeding due to treatment or acute injury, prior to invasive procedures, or other emergency circumstances with a high risk of bleeding. Coagulation factor replacement with prothrombin complex concentrates (PCCs), which consist of 3-factor PCC (II, IX, and X), 4-factor PCC (II, VII, IX, and X), and activated PCC (aPCC) with four coagulation factors (in inactive and activated forms), as well as fresh frozen plasma (FFP), are well-known nonspecific reversal agents for oral anticoagulants.[15] Recently, specific reversal agents for DOACs were approved, including andexanet alfa for the reversal of apixaban and rivaroxaban, and idarucizumab for dabigatran.[16]

Clinicians and surgeons working in emergency departments or involved in the perioperative care of a patient taking oral anticoagulants must know the best approach to the rapid reversal of anticoagulant activity and should choose the safest and most efficient protocol according to the type of drug, its pharmacokinetic profile, and the patient's medical history and clinical condition. This paper provides a concise narrative review regarding the reversal of anticoagulants and recommends clinical algorithms for patients taking oral anticoagulants who need urgent reversal of the therapy. These protocols include emergency surgical and nonsurgical scenarios and provide algorithms for both VKA and DOAC reversal.

Methods

In this review, the authors searched national and international literature to identify currently available data on the main points of the management of oral anticoagulant reversal for the development of this clinical protocol.

The authors included systematic and nonsystematic literature reviews, randomized clinical trials, prospective and retrospective cohort studies with or without a control group, case reports, case series, and guidelines addressing the reversal of oral anticoagulation in humans under emergency circumstances. The studies were written in Portuguese or English, and published in the last 12 years up to September 2020. They excluded in vitro investigations as well as studies using animals.

The PubMed, LILACS, and Cochrane Library databases were used with the following search terms (keywords and delimiters): oral anticoagulant and reversal, warfarin and reversal, nonvitamin K antagonists, direct oral anticoagulants and reversal, prothrombin complex concentrates, idarucizumab, and andexanet alfa.

Results

The authors chose 82 articles jointly according to their relevance, with full agreement among the reviewers. Table 2 summarizes the most relevant evidence identified on the reversal of anticoagulants: clinical trials, systematic reviews, cohorts, and case series studies. A flow chart documenting the process of selecting the studies is presented in Figure 1.

Table 1 Pharmacological properties of oral anticoagulants.

	Warfarin[4,5]	Rivaroxaban[10]	Apixaban[11]	Edoxaban[12]	Dabigatran[13]
Target	Vitamin K-dependent factors	Factor Xa	Factor Xa	Factor Xa	Thrombin
Prodrug	No	No	No	No	Yes
Bioavailability (%)	79-100	63-79	66	50	3-7
Tmax (hrs)	3-9	2-4	1-2	1-2	1-3
T½ (hrs)	36-42	7-13	8-15	9-11	12-17
Protein binding (%)	99	95	87	54	35
Dialysis	No	No	14%	No	50-60%
Renal elimination (%)	80	33	25	35	80
Reversal agents	Vitamin K PCC FFP	Andexanet alfa PCC	Andexanet alfa PCC	Andexanet alfa PCC	Idarucizumab PCC
Laboratory	INR PT	Anti-factor Xa	Anti-factor Xa	Anti-factor Xa	ECT DTT

Tmax, time to maximum plasma concentration; T½, half-life; PCC, prothrombin complex concentrate; FFP, fresh frozen plasma; INR, International Normalized Ratio; PT, prothrombin time; ECT, ecarin clotting time; DTT, diluted thrombin time.

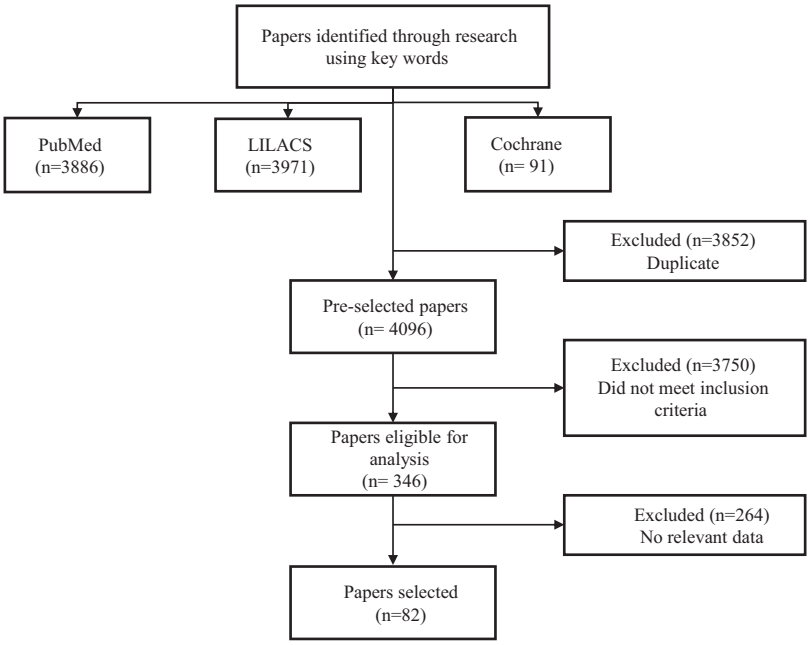

Figure 1 Study selection process.

Emergency anticoagulation reversal: general considerations

In an emergency scenario, the strategy for oral anticoagulant reversal depends on the type of drug; the presence, location, and level of bleeding; and the need for and type of invasive procedure.

Patients taking oral anticoagulants have a higher risk of spontaneous bleeding due to treatment or trauma. Attention should be given to head injuries; most anticoagulated patients are elderly, with a high risk of intracerebral hemorrhage (ICH).[17]

The first approach in a bleeding situation in anticoagulated patients is the identification of the bleeding source and severity of bleeding (Fig. 2). Evaluation of the patient's hemodynamic status should be performed and must be closely monitored.

General measures providing supportive care with hemostatic procedures (mechanical compression, use of topical hemostats, sutures, vessel clipping, etc.), volume replacement and/or transfusions should be established, with an evaluation of the necessity for an invasive procedure as treatment (surgery/embolization) and the risk of bleeding due to the procedure on its own versus the thrombotic risk due to anticoagulant withdrawal.

Concomitant medications, such as antiplatelet therapy, could interfere with anticoagulant activity. Patients taking warfarin should be questioned about the use of antibiotics,

Table 2 Summarized evidence regarding the reversal of warfarin and DOACs.

References	Study design	Population	Reversal agents	Results
Warfarin studies				
Steiner, 2016[40]	Prospective, randomized, open-label, blinded-endpoint clinical study	50 VKA-ICH patients	4F-PCC vs FFP	67% of PCC group vs 9% of FFP group, $p = 0.0003$
Goldstein, 2015[30]	Prospective, randomized, open-label, clinical study	181 VKA-treated patients needing urgent surgical or invasive procedures	4F-PCC vs FFP	90% of the PCC group vs 75% of the FFP group. Rapid INR reduction in 55% of the PCC group vs 10% of the FFP group
Kerebel, 2012[37]	Prospective, randomized, open-label study	59 VKA-associated intracranial hemorrhage	4F-PCC	40 IU.kg^{-1} of 4F-PCC significantly decreased the INR compared to that of the 25 IU.kg^{-1} group ($p = 0.001$).
Demeyere, 2010[55]	Prospective, randomized, open-label, clinical study	40 cardiac surgery patients	4F-PCC vs FFP	Faster target INR with PCC ($p = 0.007$), and less additional dose ($p < 0.001$)
Burburry 2011[33]	Prospective single-arm clinical study	178 presurgical patients under warfarin	Vitamin K	94% with INR levels 1.5 or less on the day of surgery
Chausson, 2018[41]	Pilot clinical study	26 acute ischemic stroke patients	4F-PCC and vitamin K	No symptomatic ICH or thrombotic events
Pautas, 2011[34]	Prospective, observational study	239 elderly hospitalized patients with over-anticoagulation	Vitamin K	Decrease in INR levels, achieving 2.7 $\pm$ 1.3 on Day 1 ($p < .0001$)
Bhatia, 2010[32]	Prospective, observational study	45 proximal hip fracture patients	Vitamin K	INR levels decreased to 1.5 or less in 2 days (mean, 38 h; range, 15–64 h
Rimsans, 2018[42]	Prospective, observational study	37 patients with continuous flow left ventricular assistive devices	4F-PCC	Efficient reversal, no case of thromboembolism, mean INR from 2.9 to 1.7 ($p < 0.0001$)
Yank, 2011[62]	Systematic review	64 studies included	rFVIIa vs placebo or usual care	No mortality reduction Increased thromboembolism risk
Dentalli, 2011[38]	Systematic review	27 studies included	3F-PCC and 4F-PCC	Incidence of thromboembolic complications: 1.8% (95% CI 1.0-3.0) with 4F-PCC and 0.7% (95% CI 0.0-2.4) with 3F-PCC
Matino, 2015[63]	Systematic review	2 studies, with 69 patients	rFVIIa vs aPCC	Similar hemostatic effect No increase in thromboembolic risk
Chai-Adisaksopha, 2016[35]	Systematic review	13 studies included	PCC vs FFP	PCC: significant reduction in mortality, more rapid INR reduction, less volume overload. No statistically significant difference in VTE risk
Milling, 2016[39]	Post hoc analyses of pooled data	2 randomized trials, with 388 patients	4F-PCC vs FFP	Incidence of thromboembolic complications: 7.3% in the 4F-PCC group and 7.1% in the FFP group

Table 2 (*Continued*)

References	Study design	Population	Reversal agents	Results
				Risk difference 0.2%; 95% CI -5.5% to 6.0%
Barton, 2018[60]	Retrospective cohort study	195 patients with life-threatening bleeding	4F-PCC vs 3F-PCC and rFVIIa	Faster and longer duration of reversal with 4F-PCC ($p < 0.01$) Higher mortality and VTE with 3F-PCC and rFVIIa ($p < 0.01$)
Rowe, 2016[51]	Retrospective cohort study	158 patients with warfarin-associated hemorrhage	aPCC vs 4F-PCC	No difference in effectiveness and safety between treatments
Holt, 2018[48]	Retrospective cohort study	134 patients with warfarin-associated bleeding	4F-PCC vs 3F-PCC	INR normalization: 84.2% with 4F-PCC vs. 51.9% with 3F-PCC, $p = 0.0001$
Mattisson, 2018[44]	Retrospective case-control study	Patients with hip fractures: 99 taking warfarin and 99 controls	4F-PCC and vitamin K	No significant differences in blood loss, adverse events or mortality
Hedges, 2015[45]	Retrospective chart review	193 patients taking warfarin and DOACs	PCC, 4F-PCC	65.8% achieved target INR in 8.03 h (IQR 3.38–34.07) 4.1% with acute VTE
Voils, 2015[49]	Retrospective chart review	165 patients requiring emergency reversal	4F-PCC vs 3F-PCC	No difference in VTE events. Higher mortality in 3F-PCC group ($p < 0.01$)
Mehringer, 2018[61]	Retrospective chart review	129 cardiac surgery patients with significant bleeding	rFVIIa vs 4F-PCC	No difference in bleeding, thromboembolic events, or re-exploration
Chapman, 2014[58]	Retrospective chart review	106 patients needing emergency reversal	3F-PCC vs low-dose rFVIIa	71.9% rFVIIa patients achieved target INR vs. 33.8% 3F-PCC, $p = 0.001$ No difference in VTE risk
Carothers, 2018[50]	Retrospective chart review	89 patients with traumatic ICH	aPCC vs FFP	Reversal achieved in 90.3% with aPCC vs 69.7% with FFP, $p = 0.029$ Faster reversal with aPCC, $p = 0.003$. No difference in mortality and VTE risk
Woo, 2014[57]	Retrospective chart review	63 VKA-ICH patients	FFP vs rFVIIa vs PCC	PCC and rFVIIa reached target INR faster than FFP ($p < 0.05$). More rebound with FFP and rFVIIa ($p = 0.001$)
Sarode, 2012[59]	Retrospective chart review	46 VKA-ICH patients	3F-PCC and rFVIIa	Rapid and effective reversal
Astrup, 2018[47]	Retrospective chart review	37 patients with urgent reversal	Single fixed dose of 1500 IU of 4F-PCC	75% achieved INR $\leq$ 1.5 100% achieved INR $\leq$ 2
Mačiukaitienė, 2018[43]	Retrospective chart review	35 VKA-ICH requiring urgent neurosurgical procedures	4F-PCC and vitamin K	Decrease in INR ($p < 0.01$), PT ($p < 0.01$), and PTT ($p = 0.02$), no adverse effect
Scott, 2018[46]	Retrospective cohort study	31 VKA-ICH patients	4F-PCC	No significant difference between the fixed and weight-based doses of 4F-PCC
DOACs studies				
Pollack, 2017[91]	Multicenter, prospective, open-label study	503 patients under dabigatran with bleeding or urgent surgical intervention	Idarucizumab	100% of median maximum percentage reversal
Siegal, 2015[68]	Prospective, randomized, double-blind, placebo-controlled study	101 healthy older volunteers taking Xa inhibitors	Andexanet alpha	Efficient reversal within minutes after administration

Table 2 (*Continued*)

References	Study design	Population	Reversal agents	Results
Connolly, 20196[69]	Prospective, open-label, single-group study	352 patients who had acute major bleeding within 18 hours after administration of a factor Xa inhibitor	Andexanet alpha	92% reduction in anti-factor Xa activity.
Eerenberg, 2011[71]	Prospective, randomized, double-blind, placebo-controlled study	12 healthy volunteers taking rivaroxaban or dabigatran	4F-PCC	Immediate and complete reversal of rivaroxaban anticoagulation activity (p = 0.0001) No effect on dabigatran
da Luz, 2017[72]	Systematic review and meta-analysis	12 studies included DOAC reversal	PCC Andexanet alfa Idarucizumab	PCC reversed the prothrombin time and endogenous thrombin potential (p < 0.01) Andexanet alfa, idarucizumab: completed reversal was achieved
Piran, 2019[80]	Systematic review and meta-analysis	10 case series with 340 patients presenting direct Xa inhibitor–related major bleeding	4F-PCC	Effective management of bleeding: 0.69 (95% CI 0.61-0.76). Mortality: 0.16 (95% CI: 0.07-0.26), VTE: 0.04 (95% CI: 0.01-0.08)
Majeed, 2017[74]	Prospective cohort study	84 patients under Xa inhibitors presenting major bleeding events	4F-PCC	Efficacy in 69.1% of patients
Dybdahl, 2019[79]	Retrospective cohort study	62 patients taking factor Xa inhibitors with traumatic ICH	4F-PCC vs no reversal	No difference in mortality, functional recovery, hospitalization duration or thromboembolic events
Allison, 2018[36]	Retrospective, observational study	33 patients taking Xa inhibitors with major bleeding requiring emergent reversal	4F-PCC	83.8% achieved hemostasis No VTE event
Green, 2019[82]	Retrospective chart review	421 patients with DOAC-related major bleeding	4F-PCC	Low-dose PCC: lower mortality (hazard ratio: 0.5; 95% CI: 0.02–1.19; p = 0.07)
Piran, 2018[73]	Retrospective chart review	247 Xa inhibitors patients undergoing emergency surgery or an invasive procedure	4F-PCC	85.7% achieved good hemostasis. No VTE events occurred.
Dager, 2019[81]	Retrospective analysis	64 patients with DOAC-related bleeding	aPCC	Thromboembolic complications: 8%.
Tao, 2018[77]	Retrospective chart review	43 patients under Xa inhibitors needing emergency reversal	4F-PCC	VTE: 2.1%, 95% CI: 0.1-12.3
Harrison, 2018[76]	Retrospective chart review	42 factor Xa inhibitor anticoagulant and VKA-ICH	4F-PCC	No difference in the mortality, rates of hemorrhagic expansion, VTE, between Xa inhibitors and VKA patients receiving 4F-PCC
Engelbart, 2019[84]	Retrospective case series study	42 patients with emergent reversal of DOAC for life-threatening hemorrhage or urgent surgical interventions	aPCC	Thrombotic events: 10%; hemorrhage progression: 10%; mortality: 29%

Table 2 (*Continued*)

References	Study design	Population	Reversal agents	Results
Sheikh-Taha, 2019[75]	Retrospective chart review	29 patients taking factor Xa inhibitors with major bleeding	4F-PCC	72.4% patients achieved clinical hemostasis
Grandhi, 2015[78]	Retrospective chart review	18 patients with Xa inhibitors-ICH	4F-PCC	No hemorrhagic complications after surgery. One VTE event
Senger, 2016[81]	Retrospective chart review	17 patients under dabigatran or rivaroxaban with ICH	4F-PCC	Of 6 patients who underwent immediate surgery, 50% presented severe intraoperative hemorrhage
Dibu, 2016[87]	Prospective observational study	127 patients with spontaneous ICH under DOAC: 5 patients receiving aPCC	aPCC	No ICH expansion, hemorrhagic, or thrombotic complications
Schulman, 2014[92]	Case series	4 patients under DOAC with a major bleeding episode	aPCC	Recovery, no effect on hemostatic parameters

VKA, vitamin K antagonist; ICH, intracerebral hemorrhage; INR, international normalized ratio; IVT, intravenous thrombolysis; DOACs, direct oral anticoagulants; VTE, venous thromboembolism; CI, confidence interval.

nonsteroidal anti-inflammatory drugs, acetaminophen, metronidazole, amiodarone, antiepileptic drugs, and selective serotonin reuptake inhibitors and the ingestion of foods that prolong the international normalized ratio (INR).[1] Patients taking DOACs have fewer drug interactions, but a pharmacokinetic study showed that azole-antimycotics, HIV protease inhibitors, phenytoin, rifampin, and amiodarone could interfere with drug activity.[18–20]

Laboratory evaluations help guiding the management of patients during emergencies by detecting and quantifying the remaining anticoagulant activity, and are essential for the assessment of hemostasis before surgery. These evaluations must include the coagulation status, blood cell count, blood group, and hepatic and renal function. Abnormal renal and liver functions affect the metabolism and elimination of the drug. Renal perfusion and urine output should be maintained to help eliminate anticoagulant drugs. Laboratory evaluation of anticoagulation activity will be further discussed in this paper.

The type, dosage, and time of the last intake of an oral anticoagulant provide the time for elimination according to its half-life and patient renal function. The drug must be suspended immediately after a bleeding episode. At the time of reintroduction of the drug, the need for dose adjustment must be evaluated in cases of spontaneous bleeding.

The anticoagulant should not be suspended in cases of a small invasive procedure with minimal bleeding risk, such as blood tests, dental extraction, dermatological biopsies, and gastrointestinal endoscopic procedures without the risk of bleeding.[21] However, in cases of moderate to major bleeding or surgical indication, the balance between the risk of bleeding and the risk of a thromboembolic event must be considered, and withdrawal of the drug is recommended in cases of a high-risk scenario such as ICH; neuraxial anesthesia; and abdominal, cardiothoracic, intracranial, orthopedic operations.[22–24] The possibility of postponing surgery should be evaluated, with a delay long enough to promote drug clearance. Surgery with a high risk of bleeding must be postponed as long as possible. In patients taking VKAs, drug withdrawal is necessary for at least 5 days prior to surgery for drug clearance.[24] The withdrawal of DOACs will vary according to the risk of bleeding, and it is recommended 2 days before a high-risk procedure and 1 day before a low-risk procedure.[25] For patients under dabigatran with a clearance of creatinine less than 50 $mL.min^{-1}$, the withdrawal is 4 days before surgery with a high-risk of bleeding and 2 days for low-risk procedures.[25]

A reversal agent should be used in cases of bleeding not responding to supportive measures, uncontrolled, major, life-threatening bleeding, bleeding located in critical organs (central nervous system, abdominal, thoracic), trauma, or urgent surgery.[26] Urgent surgery requires immediate reversal, clotting factor supplements (provided by PCCs), and intensive care support.[26]

The use of tranexamic acid (TXA) as a hemostatic agent significantly reduces mortality in bleeding trauma patients,[27] and it is inexpensive with few side effects.[28] TXA can be used in cases of major bleeding in patients taking oral anticoagulants and/or trauma patients within 3 hours. Its mechanism of action is based on competitive inhibition of the activation of plasminogen to plasmin, preventing clot lysis.

The reversal of warfarin

The reversal of warfarin is based on the clinical scenario and the evaluation of INR, with a therapeutic range of 2 to 3. For these patients, the prothrombin time (PT) and INR provide the status of VKA activity.[29] Warfarin reversal is accomplished with the administration of PCCs, preferably 4-factor PCC, and vitamin K.[30] If those are not available, fresh frozen plasma (FFP), 3-PCC, or aPCC could also be used (Fig. 3).

Patients at very high risk of a thromboembolic event should use low molecular weight heparin (LMWH) after warfarin discontinuation as a bridging anticoagulation strategy.[24]

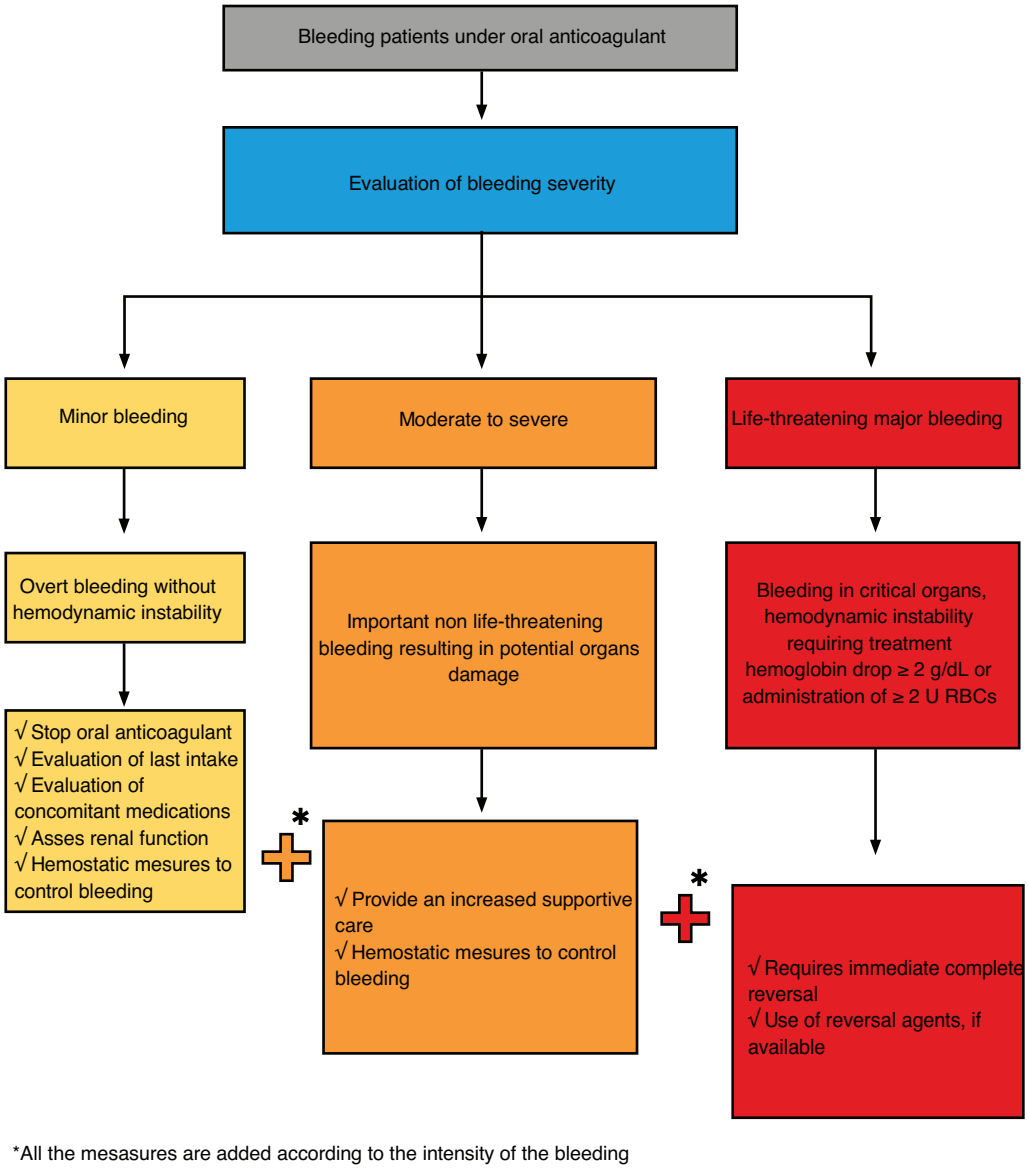

Figure 2 Assessment of bleeding in patients taking oral anticoagulants. * All the measures are added according to the intensity of the bleeding.

Vitamin K is not a direct hemostatic agent but rather a cofactor for the activation of factors II, VII, IX, X, and the anticoagulant proteins C and S.[31] The usual dose of vitamin K varies from 5 to 10 mg or an even lower dose (1 to 3 mg) via the intravenous route, and it should be combined with coagulation factor administration in an emergency setting because, alone, it could take from 4 to 24 hours to normalize coagulation.[32–34]

PCCs are considered the treatment of choice for VKA reversal in emergency settings, such as in patients with significant bleeding.[35] Four-factor PCC is a plasma-derived product that restocks the vitamin K-dependent proteins, factors II, VII, IX, X, and proteins C and S. It is used for warfarin reversal, and it shows efficacy in factor Xa inhibitor reversal but limited evidence for thrombin inhibitor reversal.[36]

The administration of 4-factor PCC is performed intravenously with rapid infusion and low volume, promoting reversal of warfarin in 10 minutes.[37] The risk involved in the use of PCCs is mainly allergic reactions, heparin-induced thrombocytopenia (HIT, for preparations containing heparin), and thromboembolic complications;[38,39] however, proteins C and S in 4-factor PCC may improve its safety profile as they are coagulation inhibitors, decreasing the risk of thromboembolic events after reversal.

Prospective, randomized clinical trials show the clinical efficacy of 4-factor PCC in the reversal of warfarin as being superior to that of FFP in patients presenting VKA-related ICH[40] and achieving faster homeostasis in patients needing reversal for surgical interventions.[30] A retrospective observational study demonstrated the efficacy and safety of warfarin reversal using 4-factor PCC and vitamin K in acute ischemic stroke patients before undergoing

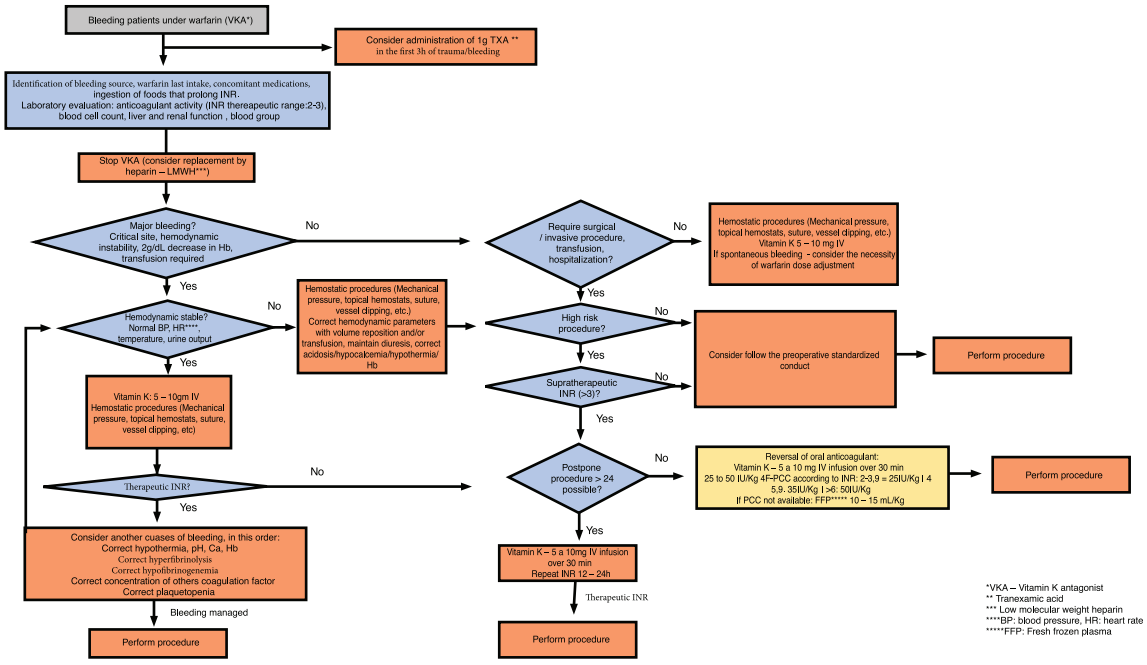

Figure 3 Reversal due to bleeding after trauma, due to spontaneous bleeding and/or before surgery in patients taking warfarin. VKA, Vitamin K antagonist; BP, Blood pressure; HR, Heart rate; FFP, Fresh frozen plasma.
** Tranexamic acid.
*** Low molecular weight heparin.

intravenous thrombolysis;[41] in patients with continuous flow left ventricular assistive devices presenting bleeding or the need for urgent surgery, with no thromboembolic event observed;[42] in patients with intracranial bleeding requiring urgent neurosurgical intervention;[43] and in patients undergoing early orthopedic surgery (within 24 hours) due to hip fractures.[44] In an observational study of 143 patients on warfarin, the use of 4-factor PCC was safe as a reversal agent mainly for bleeding and prior to surgery, with 5 cases of thromboembolic complications.[45] Evidence regarding fixed doses of 1000 units and 1500 units of 4-factor PCC showed a similar efficacy compared to weight-based dosing.[46,47]

Four-factor PCC is preferred over 3-factor PCC because 4-factor PCC leads to a more significant reduction in the INR,[48] and the survival rate is higher.[49] aPCC proved to be more effective and faster than FFP for warfarin reversal in patients with traumatic ICH,[50,51] but it is not indicated for all patients because it may present a higher thrombotic risk compared to 4-PCC due to a high content of both prothrombin and thrombin; however, no comparative safety study has been identified.

Although FFP is much less expensive than 4-PCC, current guidelines recommend the use of 4-factor PCC over FFP.[52–54,70] Four-factor PCC has a safer profile and faster action than FFP in patients undergoing cardiopulmonary bypass surgery.[55] A systematic review and meta-analysis of 13 studies showed that PCC significantly reduces all-cause mortality, reduces the INR faster and is effective in smaller volumes compared to FFP, without an increased risk of thromboembolic events.[35] FFP is a human product that contains all coagulation factors, including fibrinogen, and it should be administered with Vitamin K.[31] To use FFP, it is essential to verify ABO compatibility. A larger infused volume is required (15 mL.kg^{-1}), increasing the risk of transfusion-associated circulatory overload and worsening renal function in patients with renal impairment.[35] All the characteristics of FFP, including long defrosting time and long infusion time, show that it is not an ideal therapy for urgent or emergency settings. Additionally, the use of FFP requires consideration of the risk of venous thromboembolism, allergic reactions, anaphylactic reactions, transfusion-related acute lung injury (TRALI), hemolysis, and infections.[56]

Recombinant activated factor VII (rFVIIa) is a hemostatic agent that increases thrombin generation by activating factor X at the site of vascular injury. It should not be used as a single agent to reversal because it is usually not capable of restoring hemostasis. The actual recommendation is not to use rFVIIa for warfarin reversal unless no other option is available, or in case of failure with previous treatments. A review of 63 patients with warfarin-ICH showed that both rFVIIa and PCC, in addition to vitamin K, are more effective with faster reversal than FFP but are associated with more INR rebound with rFVIIa.[57] rFVIIa seems superior to 3-factor PCC for warfarin reversal,[58] and their joint administration could be an option because 3-factor PCC has a lack of adequate levels of factor VII; however, their efficacy remains inferior to 4-factor PCC alone.[59,60] rFVIIa is more expensive than PCCs and has a rapid but short duration of action. Data from a literature review show that the use of rFVIIa as a prothrombotic agent could result in an increased risk of thromboembolic events, especially in elderly patients and when used for off-label indications such as the reversal of anticoagulant agents.[61–64]

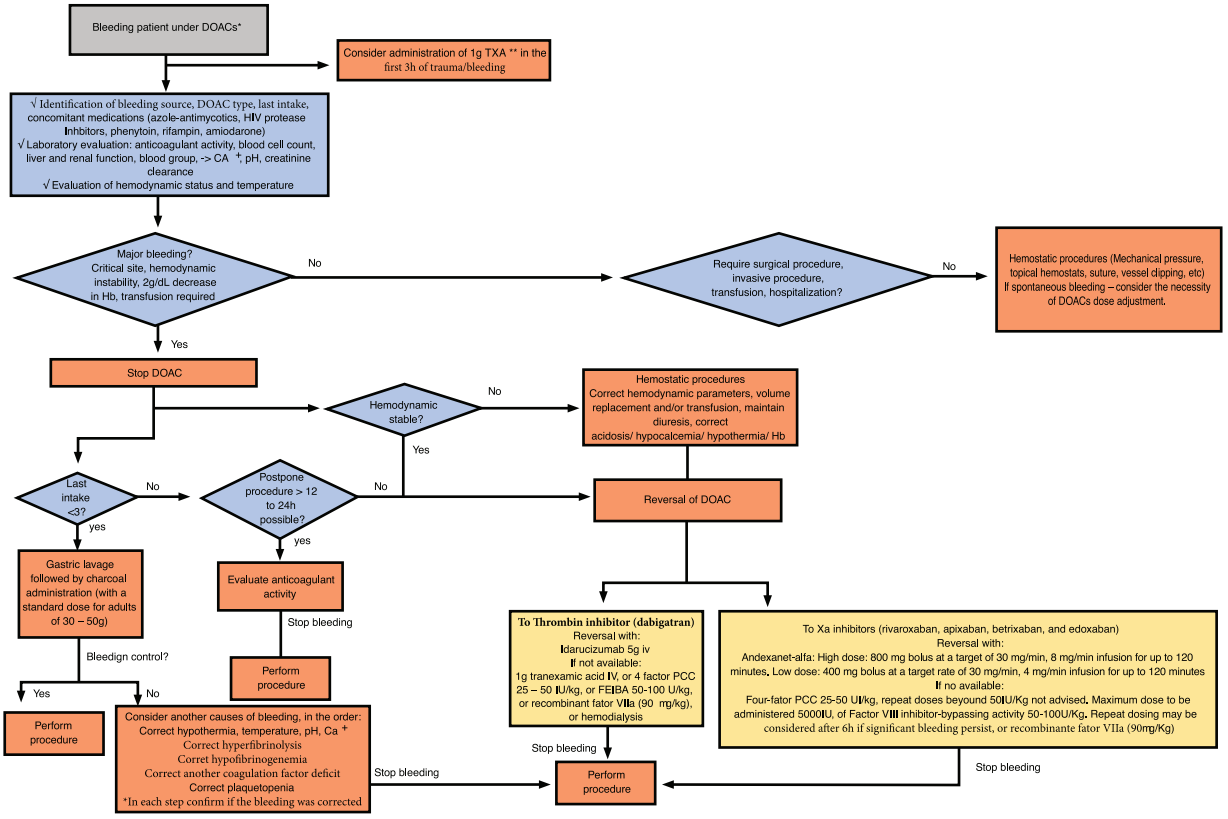

Figure 4 Reversal due to bleeding after trauma, due to spontaneous bleeding and/or before surgery in patients taking DOACs. BP, Blood pressure; HR, Heart rate; Hb, Hemoglobin.
* Direct oral anticoagulant.
** Tranexamic acid.

The reversal of DOACs

Active charcoal could be useful by helping reduce the absorption of DOACs (if the last dose was less than 2 hours before an emergency).[65] Hemostatic strategies using specific DOACs reversal agents should always be considered for patients with major bleeding, if available.[70]

The factor Xa inhibitors

Rivaroxaban, apixaban, and edoxaban anticoagulant action can be monitored by anti-FXa activity.[18] The factor Xa inhibitors at on-therapy or above on-therapy levels may not affect PT values or may induce a significant prolongation of the PT.[66,67]

Andexanet alfa is the specific Xa inhibitor that is currently on the market. Literature reports the use of 4-factor PCC or aPCC as non-specific, off-label, Xa inhibitor reversal agents, if andexanet alfa is not available (Fig. 4).

Andexanet alfa binds Xa inhibitors competitively with high affinity. It is indicated only for patients with severe, life-threatening bleeding, 18 hours within the last dose of anticoagulant.[68] The administration is performed intravenously, as a bolus and via infusion, and the effect is observed 5 minutes after intravenous administration, up to 2 hours after administration of the bolus and 1 to 2 hours after a 2-hour infusion.[68] The efficacy of andexanet alfa regarding the reversal of rivaroxaban and apixaban was first evaluated in 101 healthy volunteers, showing at least 80% reversal of anti-factor Xa activity.[68] This effect started 2 to 5 minutes after the bolus and lasted 2 hours after the bolus. In patients receiving Xa inhibitors (n = 352) presenting with major acute bleeding (mostly gastrointestinal or intracranial), treatment with andexanet alfa in a bolus followed by a 2-hour infusion showed that effective hemostasis was achieved in 82% of patients after 12 hours of reversal administration, and 10% of patients presented thromboembolic events within 30 days.[69]

High cost, limited availability, and the lack of clinical experience limit the use of andexanet alfa and other specific reversal agents. Anti-factor Xa is almost all protein bound; therefore, it is not possible to remove it by dialysis. Four-factor PCC is the non-specific agent most commonly used for reversal and guidelines support its use despite low evidence level.[22,70,71] Data on the use of PCC for anti-factor Xa are still limited. A single bolus of 50 IU.kg^{-1} of 4-factor PCC completely reversed the effect of rivaroxaban in 12 healthy subjects, with normal PT in 12.8 $\pm$ 1.0 seconds and maintained this effect for 24 hours.[72] In a meta-analysis, PCCs efficiently reversed the factor Xa inhibitors, represented by a significantly decreased PT and increased endogenous thrombin potential.[73] Four-factor PCC promoted hemostasis without any thromboembolic event in trauma patients (n = 33) presenting major bleeding using direct factor Xa inhibitors, mostly rivaroxaban,[36] and in 21 patients undergoing emergency surgery/procedures.[74] The use of a fixed dose of 2000 IU (approximately 25 IU.kg^{-1}) of 4-factor PCC

in 84 patients with major bleeding, mostly ICH and gastrointestinal bleeding, was effective in 69.1% of patients for the reversal of rivaroxaban and apixaban, with a low incidence of thromboembolic events and death (3 ischemic strokes leading to death).[75] In a prospective cohort of 66 patients on rivaroxaban or apixaban with major bleeding, 65% achieved good hemostasis with 2000 IU 4-factor PCC, but 8% presented thromboembolic events.[76] A dose-weight-based 50 IU.kg^{-1} to a maximum of 5000 IU of 4-factor PCC was evaluated in the reversal of apixaban and rivaroxaban action in 29 bleeding patients (most of them exhibiting ICH and gastrointestinal bleeding)[77] and 14 ICH patients,[78] with no thromboembolic events observed. Forty-three patients received 25 to 50 IU.kg^{-1} 4-factor PCC for the reversal of rivaroxaban or apixaban due to major bleeding or invasive emergency procedures, with only one thromboembolic event.[79] The efficacy and safety of 4-factor PCC for the reversal of Xa inhibitors were demonstrated in 18 patients presenting with traumatic ICH, hemorrhage stroke, subarachnoid hemorrhage, and tumoral hemorrhage, with one thromboembolic event.[80] In a retrospective cohort, reversal of direct factor Xa inhibitors with 4-factor PCC did not increase mortality or thromboembolic events in patients with traumatic ICH.[81] A meta-analysis with ten case series including 340 patients receiving 4-factor PCC showed that it was safe and effective for the reversal of factor Xa inhibitor in patients with major bleeding. However, the authors classified this meta-analysis as low-quality evidence because they did not identify comparative studies.[82] The use of PCCs for the reversal of factor Xa inhibitors before immediate neurosurgery was reported in six cases, but 50% of the cases presented severe bleeding during the operation, with three deaths due to bleeding.[83] In the observation of the reversal of DOACs using PCC to manage bleeding, the dose of 25 IU.kg^{-1} seemed to result in a better outcome than did a higher dose.[84] Preference should be given to nonactivated PCC because it presents more data available in the literature and probably has lower prothrombotic activity. Reports of case series studies and retrospective analyses show that aPCC was effective for the reversal of rivaroxaban in a patient with subdural hematoma[85] and in the setting of hemorrhage or the need for urgent surgical procedures.[86–89]

The thrombin inhibitor

The diluted thrombin time (DTT) and the ecarin clotting time (ECT) are the assays suitable for quantification of dabigatran.[66,67,90] The ECT test provides a consistent direct measurement of thrombin inhibitor activity, but it is not widely available. Patients under dabigatran may present normal or increased aPTT and TT. A normal range of these parameters does not rule out the anticoagulation effect, and an increased range may not indicate a more imminent bleeding risk.[90]

Removal through dialysis is possible, taking at least 4 hours to eliminate approximately 60 to 70% of the drug.[91,92] Therefore, patients who are hemodynamically unstable due to bleeding are not candidates for dialysis.

Reversal of dabigatran is achieved with idarucizumab. If this drug is not available, limited evidence supports the use of aPCC or PCC at 50 U.kg^{-1} (maximum dose 4000 units) (Fig. 4). Idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran and acts as a specific reversal agent in cases of emergency surgery or urgent procedures, or major bleeding, life-threatening bleeding, or uncontrolled bleeding.[93] It takes 2.5 hours for bleeding cessation after the intravenous administration of 5 g and 24 hours for complete reversal.[93] However, some patients, especially those with comorbid renal failure, may rebound and need a repeated dose.[93] Idarucizumab was evaluated for the reversal of dabigatran in a clinical study with 461 patients exhibiting uncontrolled bleeding or presenting before an urgent procedure.[93] The results showed 100% of the median maximum percentage reversal, assessed by either DTT or ECT. Of 203 patients assessed for bleeding, 67.7% had confirmed bleeding cessation within 24 hours, and periprocedural hemostasis was normal in 93.4%.

The literature shows controversial results for the use of PCCs as a reversal agent for dabigatran. Limited evidence of efficacy was observed in reported case series in which aPCC reversed dabigatran, controlled bleeding, with no thromboembolic events.[94,95] One patient was reported to have a rapid response after the administration of aPCC during cardiac ablation,[96] and one patient responded to PCCs and FFP.[97] Other reported cases showed the inefficacy of PCCs and aFVII.[72,98]

Conclusion

Emergency situations, such as trauma, bleeding, and urgent surgery, involve the reversal of anticoagulants. Reversal is achieved by the administration of hemoderivatives such as PCCs and FFP, and specific agents for DOACs. PCCs and vitamin K have the highest benefit-risk ratio for warfarin reversal in emergency settings; the preferred choice is 4-factor PCC. Patients taking DOACs should receive specific reversal agents (andexanet alfa, idarucizumab). In cases of non-availability of specific reversal agents, PCC or aPCC could be considered based on limited evidence.

Conflicts of interest

Carlos Galhardo Jr received honoraria for consulting and lecture fees from ASPEN Pharma and CSL Behring. Dr Hugo Dantas has received honoraria for lecture fees from CSL Behring and Merck Sharp & Dohme. Luiz Henrique Ide Yamauchi and Dr João Carlos de Campos Guerra declare that they have no conflicts of interest relevant to the manuscript submitted to the Brazilian Journal of Anesthesiology.

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CASE REPORTS

Oxygen delivery failure due to improper installation of carbon dioxide absorbent canister: a case report

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KEYWORDS
Anesthesiology;
Carbon dioxide;
Positive pressure respiration;
Soda lime;
Ventilators, mechanical

Abstract The CLIC system in the Dräger Apollo anesthesia workstation allows a successful pre-use machine checkout without the presence of a carbon dioxide absorbent canister. It also allows the canister to be changed without interrupting controlled ventilation. However, this canister can be easily installed improperly with the CLIC adapter. We report a case in which a patient could not be ventilated by mask after the induction of general anesthesia, resulting in oxygen desaturation before successful ventilation was achieved with a bag valve mask. This case illustrates the importance of a leak test after components of the breathing circuit are changed.
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Introduction

The CLIC adapter (Drägersorb CLIC system; Dräger, Inc, Telford, Pennsylvania) on the Apollo anesthesia workstation (Dräger, Inc) allows the disposable soda lime carbon dioxide (CO_2) absorbent canister (Drägersorb 800+ CLIC disposable absorber; Dräger, Inc) to be changed without interrupting controlled ventilation. The CLIC adapter is fitted with a spring-loaded rubber valve.[1] A release button on the CLIC adapter is pressed to detach the CO_2 absorbent canister, activating a valve mechanism that bypasses the absorber and thus maintains a seal in the internal breathing circuit to allow controlled ventilation while changing the canister. For anesthesia workstations without this feature, replacing the CO_2 absorbent canister during a procedure interrupts the patient's controlled ventilation and the administration of volatile anesthetics. However, the design has a flaw that becomes apparent when the CO_2 absorbent canister can be secured without being seated correctly, failing to seal the breathing circuit. Another problem is that the CLIC system allows a successful pre-use machine checkout without the presence of the absorbent canister. Anesthesiologists should be aware of potential problems with the CLIC system to troubleshoot a machine circuit leak. As described in the present case report, the use of a functioning bag valve mask (BVM)

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Figure 1 Installation of the carbon dioxide absorbent canister.

allowed timely ventilation and oxygenation of the patient, minimizing harm.

This case report focuses solely on the designs of the anesthesia workstation, not on patient demographics. The Case Reports (CARE) guidelines were used in writing the article. Patient information has been deidentified in accordance with the institutional review board policy and the Health Insurance Portability and Accountability Act (HIPAA). The patient completed an institutional HIPAA authorization form to give written authorization to use existing protected health information.

Case report

A 70-year-old man was brought to the operating room for repair of a right inguinal hernia. After induction of general anesthesia and placement of a laryngeal mask airway, manual ventilation with a reservoir bag in the anesthesia machine breathing circuit was not possible because of a lack of positive pressure. Oxygen (O_2) desaturation occurred (from 100% to 62%) before a BVM connected to the auxiliary O_2 source was used for ventilation. When the patient was successfully oxygenated and ventilated, the machine was inspected. On inspection, controlled mechanical ventilation with the ventilator provided positive pressure ventilation, but manual ventilation with the reservoir bag did not. It was then discovered that the CO_2 absorbent canister was not completely inserted. The canister was secured with the CLIC adapter system but was not fully seated in the absorbent canister bracket (Fig. 1), creating a large leak where the top of the canister pressed on the spring-loaded rubber valve. An air leak could be felt near the canister. When the problem was identified, the canister was unclamped with a push of the CLIC adapter button, completely inserted into the bracket, and then secured by reengaging the adapter with a click. Correct installation of the CO_2 absorbent canister stopped the air leak (Fig. 1), and the case continued uneventfully. On further investigation, the pre-use automated machine checkout had been successfully completed without a CO_2 absorbent canister in place. The CO_2 absorbent canister was installed after checkout, and no additional leak test was performed after canister installation. At the end of the procedure, the laryngeal mask airway was removed, and the patient was awake and alert without any signs of complications approximately 20 minutes after arriving in the recovery room.

Discussion

With the CLIC adapter, the Dräger Apollo anesthesia machine allows the disposable CO_2 absorbent canister to be changed without interrupting the patients' controlled ventilation.[1] It also allows the automated checkout to be passed without a CO_2 absorbent canister in place.[2] This anesthesia workstation lacks a mechanism to ensure that the replaceable CO_2 absorbent canister is fully inserted into the canister bracket before engaging the *U*-shaped CLIC adapter clamp. When the canister is secured with the *U*-shaped clamp but not fully inserted into the absorbent canister bracket, the top of the canister presses on the spring-loaded rubber valve

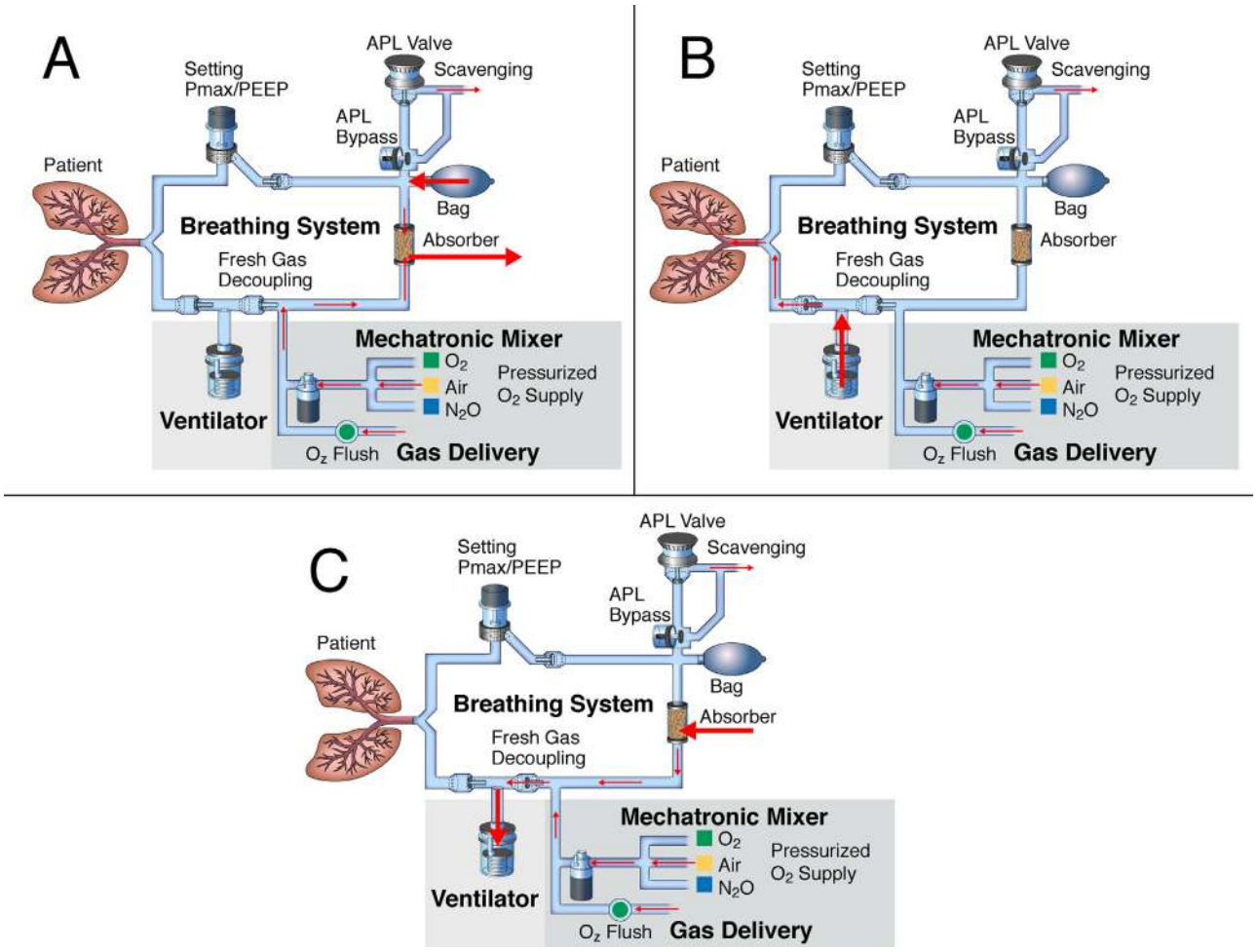

Figure 2 Gas flow diagrams. A, Manual ventilation mode. B, In controlled ventilation during the inspiratory phase, the fresh gas decoupling valve closes and allows positive pressure ventilation to the lungs. C, In controlled ventilation during the expiratory phase, room air is drawn into the breathing circuit. Red arrow indicates the gas flow. APL indicates adjustable pressure-limiting; N_2O, nitrous oxide; O_2, oxygen; PEEP, positive end-expiratory pressure; Pmax, maximum expiratory pressure.

and causes a large gas leak where the machine connects to the CO_2 absorbent canister. The result is minimal preoxygenation to the patient when the machine is in spontaneous ventilation mode, and manual positive pressure ventilation is not possible (Fig. 2A).

The location of the fresh gas decoupling valve in the Dräger Apollo design allows positive pressure ventilation to be provided if the machine is switched to controlled ventilation. The fresh gas decoupling valve excludes machine leaks between the ventilator and the exhalation valve, preventing retrograde gas flow through the CO_2 absorbent canister (Figs. 2B and 2C). However, concentrations of O_2 and inhalational agents will vary depending on the degree of gas leak. The leak may also cause volatile anesthetics to be in the working environment without being properly scavenged. Without a functioning CO_2 absorbent, the patient's end tidal CO_2 partial pressure may increase.

In addition to the disposable CLIC absorber, the Apollo workstation allows the optional use of a reusable CO_2 absorbent canister (Drägersorb CLIC Free) without the *U*-shaped CLIC adapter. We are not aware of published reports on safety issues with the CLIC Free design.[2] The CLIC Free design lacks the CLIC adapter, so the anesthesia workstation would not pass the pre-use machine leak check without a properly seated CO_2 absorbent canister because of the gas leak at the CO_2 absorbent canister site. With the *U*-shaped CLIC adapter present, as in our case, the anesthesia machine checkout will pass with the CO_2 absorbent canister either absent or properly placed.[2] The canister can be easily changed after the machine checkout is completed and passed. It is acceptable to change the CO_2 absorbent canister during the case, but proper placement of the canister must be ensured.

The Apollo workstation manual recommends a leak test after replacing the absorbent canister. However, the CLIC system is designed to allow absorbent canister replacement during use, and an automatic leak test is not possible when the workstation is being used. The location of the CO_2 absorbent canister on the Apollo workstation may make visual identification of an improperly installed absorber canister difficult because it is low in the machine and is obscured by the workstation table. A manual pressure check of the breathing circuit must be performed immediately before the induction of anesthesia to ensure proper machine function-

ing and to avoid relying solely on the automated pre-use machine leak test.

Besides Apollo, other Dräger workstations that are compatible with the CLIC adapter, such as the Fabius Tiro, all have the similar design concern. Anesthesia machine manufacturers may want to review CO_2 absorbent bypass designs to verify their safety and to identify other possible operating issues. In fact, when the incident was reported to the manufacturer, the Dräger representative mentioned that the company's newer Perseus anesthesia workstation has an optional radio frequency identification sensor for the CO_2 absorbent canister to ensure that a canister is present and properly seated in the workstation.

When the risk with the CO_2 absorbent canister was identified, our anesthesiologists, nurse anesthetists, and anesthesia technicians were given education and reminders on proper installation of the canister. This case is a reminder of the importance of performing the additional manual pressure leak check of the machine immediately before the beginning of each procedure. It consists of setting the machine to spontaneous-manual ventilation mode, setting all gas at minimum flow, occluding the Y-piece of the breathing circuit, closing the adjustable pressure-limiting valve, and inflating the breathing bag with O_2 from the O_2 flush valve. A sustained pressure of 30 cm H_2O for more than 10 seconds confirms the integrity of the system.[3] A BVM must always be available and functioning in the operating room.[4]

Conclusions

Although modern anesthesia workstations conduct automated pre-use checks for machine and breathing circuit leaks, the anesthesiologist is responsible for ensuring proper machine function before each procedure. Anesthesiologists should be aware that the presence of the fresh gas decoupling valve on the machine side of the ventilator enables positive pressure ventilation during controlled ventilation despite the presence of a leak because it closes as the piston ventilator generates positive pressure. During manual ventilation, a leak in the CO_2 absorbent canister will prevent positive pressure ventilation because gas flow follows the path of least resistance and escapes through the leak rather than creating positive pressure to inflate the lungs. Although the design flaw may be limited to only the Dräger Apollo anesthesia machine, this case report provides important lessons for a proper machine check and the need for a functioning BVM in the operating room. The breathing circuit should undergo a manual pressure check immediately before induction of anesthesia to ensure proper machine functioning. The presence of a functioning BVM in operating rooms is essential because it can allow timely ventilation and oxygenation of the patient if the machine malfunctions.

Conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORTS

Near ideal anesthetic technique for tracheal stenting in central airway obstruction with dexmedetomidine-ketamine infusion: a case report

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Ketamine;
Dexmedetomidine;
Central airway obstruction;
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Case report

Abstract Central airway obstruction presents as an emergency with dyspnea and stridor. Anesthetic management of rigid bronchoscopy-guided tracheal stenting is highly stimulating procedure requiring general anesthesia. But it may lead to life threatening airway obstruction and cardiovascular collapse after induction. Total intravenous anesthesia based on propofol-remifentanil is an optimal anesthetic technique, but remifentanil is not available in many countries. Although dexmedetomidine-ketamine has been used for procedural sedation, its use for rigid bronchoscopy in the setting of central airway obstruction has not been described in literature. We describe near ideal anesthetic technique for management of central airway obstruction using dexmedetomidine-ketamine combination.
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Introduction

Anesthetic management of Rigid Bronchoscopy (RB) guided tracheal stenting in patients with Central Airway Obstruction (CAO) poses unique challenges because the patient present as an emergency with high grade dyspnea and stridor with impaired oxygenation which provides us minimal time for optimization. It is a highly stimulating procedure and requires General Anesthesia (GA). But it may lead to life-threatening airway obstruction and cardiovascular collapse after induction of anesthesia. Total Intravenous Anesthesia (TIVA) based on propofol and remifentanil combination (intermittent boluses or continuous infusion)[1–3] is an optimal anesthetic technique but remifentanil is not available in many countries like ours. Remifentanil and propofol both cause hypotension and bradycardia and the effect

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Figure 1

of their combination on hemodynamics can be synergistic. Ketamine, on the other hand, increases blood pressure and heart rate and is a good bronchodilator and analgesic but causes delirium, hallucinations, and increased salivation. Dexmedetomidine (DXM) reduces the side effects of ketamine and their combination provides hemodynamic stability. There are a few reports on the use of ketamine and DXM combination for procedural sedation.[4] DXM-ketamine infusion has not been reported to be utilized for GA in the setting of rigid bronchoscopy. We describe the use of combination of DXM-ketamine infusions for RB guided tracheal stenting in a patient with CAO.

Case report

A 55-year-old American Society of Anesthesiologists (ASA) physical status II patient weighing 56 kg presented to the emergency with cough, breathlessness (modified medical research council Grade 3)[5,6] and stridor. He was in respiratory distress with tachypnea (respiratory rate 22/minute) and usage of accessory muscles for respiration. On auscultation, patient had decreased air entry with bilateral inspiratory crackles with expiratory wheeze and audible stridor. Hemodynamic parameters were stable except tachycardia (pulse rate 120 min). Arterial Blood Gas (ABG) exhibited pH 7.31, PaO_2 63 mmHg, $PaCO_2$ 58 mmHg, and oxygen saturation (SpO_2) 89% on room air. Chest X-ray revealed mediastinal mass with tracheal compression and homogenous opacity in right middle lobe (Fig. 1). Computed Tomography (CT) scan demonstrated a large conglomerated lymph nodal mass in right paratracheal location (7 × 5 cm) infiltrating into tracheal lumen with significant narrowing of tracheal lumen with minimum diameter 3.5 mm (Grade 3 tracheal stenosis)[7] (Fig. 2). He was posted for RB-guided tracheal stenting under GA.

After confirming fasting status (6 hours) and obtaining written informed consent, the patient was taken to operation theatre. Preoperative counselling was done, and anesthesia risks related to loss of airway control, need of intubation and mechanical ventilation, need of intensive care unit, and perioperative pulmonary complications were explained to relatives. He was started on nebulization with salbutamol (2 mL, 2.5 mg) and budesonide (2 mL, 0.5 mg), and standard ASA monitors including Bispectral Index (BIS) monitor were attached. Preoxygenation was done with 10 L of 100% oxygen for 5 minutes in head-up position.



Figure 2

He received 0.2 mg glycopyrrolate, 8 mg dexamethasone and 75 μg fentanyl Intravenously (IV). Thereafter, 0.5 $\mu g.kg^{-1}$ DXM was given over 10 minutes, and anesthesia was induced with 75 mg IV ketamine. Subsequently, 1 $mg.kg^{-1}$ intravenous (IV) succinylcholine was given and RB (Karl storz, size 11) was introduced in the trachea 60 seconds later. During maintenance phase, DXM (0.2–0.5 $mcg.kg^{-1}.h^{-1}$) and ketamine (0.5–1 $mg.kg^{-1}.h^{-1}$) infusions were titrated to achieve a BIS between 40–60. The patient was ventilated intermittently through anesthesia circuit attached to the ventilating port of the RB. Intraoperative ABG revealed improvement in oxygenation (PaO_2 75 mm) with slight increase in $PaCO_2$ (63 mm). The procedure lasted for 30 minutes and the patient was hemodynamically stable throughout the procedure. After the stent was placed, bronchoscope was removed, and I-gel size 4 was inserted. The infusion of DXM and ketamine was stopped, and the patient was extubated after ensuring good respiratory efforts with BIS of 80 after about 6 minutes of stopping the infusions. Postoperative ABG revealed Ph 7.37, PaO_2 80 mm, $PaCO_2$ 52 mm, and SpO_2 95%. He was conscious, oriented, pain free and was following commands. He was shifted to post anesthesia care unit for one day. Patient remained stable while maintaining SpO_2 95–96% on room air with normal neurocognition in the postoperative period. He was discharged the next day. His immediate postoperative period and follow up at one week was uneventful.

Discussion

Tracheal stenting in CAO is an emergency procedure and may not give enough time for preoperative optimization. It can lead to life threatening respiratory complications due to nature of disease, decreased oxygen reserve, or sudden airway collapse after anesthesia induction.

Propofol and remifentanil based TIVA is preferred technique over inhalational anesthesia.[2,8] Propofol is an IV hypnotic agent with short context sensitive half-life but it is painful on injection and does not provide analgesia. It may also cause suppression of airway reflexes, apnea, and hemodynamic instability due to vasodilatation and negative inotropy. Ketamine is an IV anesthetic agent with N-Methyl-D-Aspartate (NMDA) receptor blockade as the primary mechanism of action. Ketamine is a good analgesic with rapid onset of action (30 s) and causes bronchodilatation. But its usefulness is limited as it may cause delirium, hallucinations, emergence reactions, increased salivary secretions and hemodynamic instability (tachycardia and hypertension) due to sympathetic stimulation.[8]

DXM is a centrally acting alpha-2 adrenergic receptor agonist and produces sedation, anxiolysis and analgesia without respiratory depression. It enhances anesthesia produced by other anesthetic drugs, preserves airway reflexes and reduces delirium.[9–11] However, it may cause bradycardia and hypotension and has slow onset of action when used

as sole agent. A combination of DXM and ketamine may provide ideal anesthetic conditions like rapid onset, sedation, analgesia, amnesia, bronchodilation, hemodynamic stability, and maintenance of spontaneous respiration with minimal side effects. It may be an alternative to propofol and remifentanil in countries where remifentanil is not available. Moreover, it obviates the need of additional opioids and opioid related side effects.

DXM-ketamine combination has been used for procedural sedation with minimal cardiorespiratory adverse effects in patients undergoing esophago-gastro-duodenoscopy, in children undergoing minor cardiac procedures, and in pediatric dentistry.[11–13] Tobias has demonstrated descriptive accounts of reports from literature regarding the use of this combination for procedural sedation.[4] Apart from sedation, the effective and safe use of this combination has also been described for anesthesia in patients with uncorrected congenital cyanotic heart disease presenting for non-cardiac surgery.[14]

DXM-ketamine combination provided adequate sedation and comfort[15] with better hemodynamic stability than DXM alone[16] for awake fiberoptic intubation. RB procedure is associated with greater hemodynamic response for a longer time and optimum depth of anesthesia should be maintained throughout the procedure. Our patient presented in CAO with severe dyspnea and had low oxygen saturation that did not improve with any bronchodilators or steroids. As insertion of RB is highly stimulating, therefore depolarizing muscle relaxant was used for providing relaxation[17] due to its rapid onset, short duration, low cost, and better intubating conditions. So, emergency tracheal stenting was planned under general anesthesia with short acting neuromuscular block for induction followed by continuous infusion of DXM-ketamine combination that provided good anesthetic depth (objectively measured by BIS values) and hemodynamic stability without the need of additional doses of muscle relaxants. Further randomized studies are required to validate these findings in such category of patients.

Conclusion

DXM-ketamine based total intravenous anesthesia provides good analgesia, anesthesia, and hemodynamic stability with rapid, smooth induction, and emergence with minimal side effects. Hence it can be an ideal anesthetic technique for rigid bronchoscopic guided tracheal stenting.

Conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORTS

Continuous peripheral nerve block for upper limb ischemic pain: a case report

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KEYWORDS
Phantom limb;
Peripheral arterial disease;
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Regional anesthesia

Abstract Peripheral Arterial Obstructive Disease (PAOD) may course with severe ischemic pain. In low-income health systems, patients may wait for vascular surgery. Continuous peripheral nerve block may be an effective alternative, with fewer side effects, in this scenario. A female patient with acute arterial obstruction of upper limb evolving with severe ischemic pain. She was submitted to a continuous infraclavicular brachial plexus block, which led to a satisfying pain control until the amputation surgery. The early postoperative period evolved with good pain management. This approach may be effective and safe as an analgesia option for ischemic pain.
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Introduction

Nowadays, population aging and atherosclerosis associated comorbidities (smoking, diabetes mellitus, hypertension, and metabolic syndrome) lead to a significant prevalence of vascular diseases in the world.[1] Acute and chronic pain are important symptoms due to Peripheral Arterial Obstructive Disease (PAOD) and lead to important impact on quality of life. The lower limbs are more frequently affected.[1] Treatment should be directed to the reversion of primary cause and regain perfusion, if possible. When this is not possible, amputation of affected limb is a manner to avoid more serious complications. However, many patients require pain management before the ultimate treatment. This may be a challenging issue due to frequent old age and comorbidities. In this scenario, interventional pain management procedures may be useful.[2]

We present a case of an inpatient who presented an acute arterial obstruction in the left upper limb, leading to a challenging pain management, who underwent a continuous

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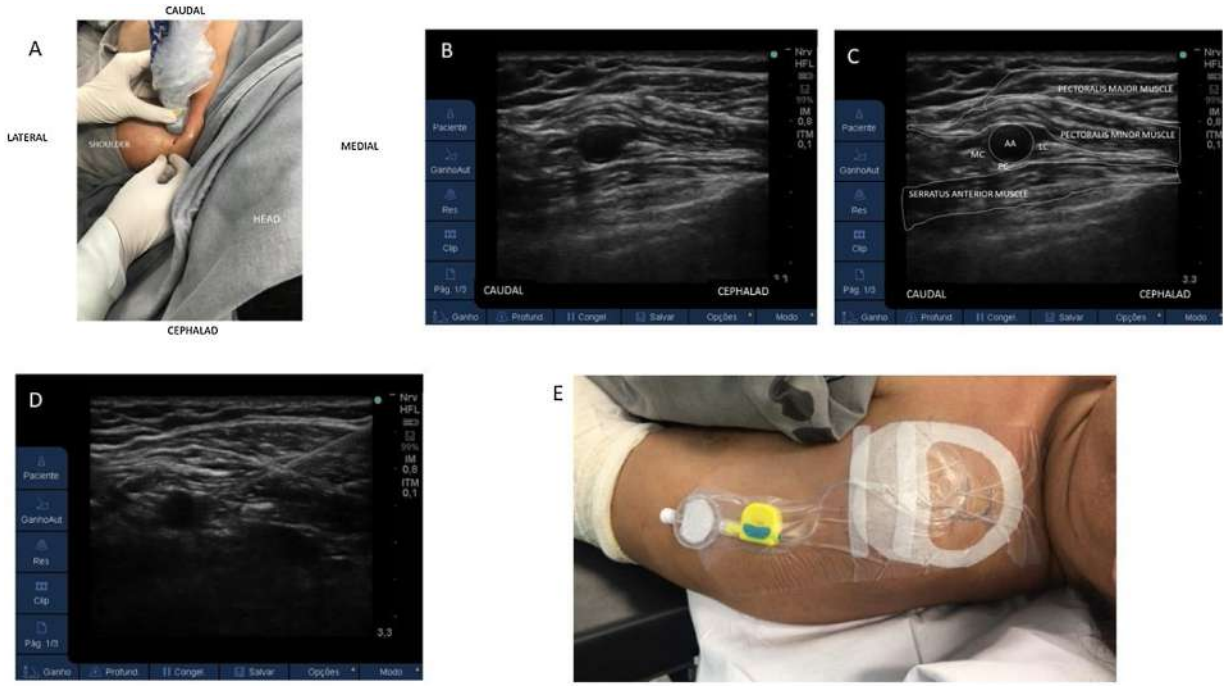

Figure 1 A, Positioning (patient and USG probe); B, Ultrasound image; C, Ultrasonographic anatomy. Axillary Artery (AA), Lateral Cord (LC), Posterior Cord (PC), and Medial Cord (MC). D, Needle in-plane toward the lateral and posterior cord. E, Insertion, and fixation of peripheral nerve catheter in the infraclavicular brachial plexus.

infraclavicular brachial plexus block, resulting in satisfactory analgesia until the definitive surgery.

Case report

Written informed consent to publication was obtained from the patient. Female, 42 years old, 70 kg, 160 cm, no diseases, on an acute arterial obstruction of the left upper limb, with no successful attempts for revascularization (embolectomy, endovascular thrombolysis, and a limb's fasciotomy).

The patient kept severe pain at the left hand and forearm, accordingly to Numeric Verbal Scale (NVS – in which 0 indicates absence of pain and 10 indicates unbearable pain) varying from 8 to 10. She was taking methadone 20 mg peroral (PO) per day; gabapentin 900 mg PO per day; nortriptyline PO 25 mg per day; intravenous (IV) morphine PRN (mean of 10 mg per day); enoxaparin 40 mg twice a day, subcutaneously.

It was decided to perform a continuous brachial plexus, infraclavicular approach, through a catheter. It was performed six hours after the last dose of enoxaparin. In the operation theater, the left shoulder region was cleaned with antiseptic solution and covered with sterile drapes. A high-frequency (6 to 13 Hz) linear Ultrasound (US) probe (M-Turbo® ultrasound system; Sonosite International, Washington, DC, U.S.A.) was placed under the clavicle, at the coracoid process, in a longitudinal plane (Figure 1A). Then axillary vein and artery, pleura, and cords (medial, lateral, and posterior) of brachial plexus (Figure 1 B–C) could be seen. Local anesthesia was then performed at the needle entry point in the skin, with 2 mL of lidocaine 1%.

An in-plane puncture (from cranial to caudal direction) was performed with a Tuohy needle (17G and 80 mm length) (Figure 1D, aiming the posterior cord. After negative aspiration 5 mL of ropivacaine 0.75% and 5 mL of lidocaine 2% without vasoconstrictor were injected. There was a spread in shape of ''U'' around the axillary artery. The patient referred immediate pain relief. Then, an 18G catheter was introduced through Tuohy's needle, 3 cm beyond the needle tip. The needle was then removed, maintaining the catheter in position. Proper spread of injection of 5 mL of ropivacaine 0.375% through the catheter could still be seen with US around the axillary artery. The catheter was covered with a sterile drape (Figure 1E).

A Patient-Controlled Analgesia (PCA) device was installed, with ropivacaine 0.2% solution, programmed as: infusion of 8 $mL.h^{-1}$; bolus of 5 mL; lock-out of 30 minutes.

After 24 hours, methadone dose was reduced in 50% and the patient remained painless. In the following days, pain scores varied between 0 and 4 in NVS. Six days later she was taking no methadone. Average usage of PCA solution was 207 mL per day.

After seven days, a left trans-humeral amputation was performed. Before the surgery, 10 mL of ropivacaine 0.375% was injected through the catheter. Then it was removed by surgeon's request, before the beginning of the procedure, due to sterility concerns. The patient went home, two days after surgery, receiving tramadol 200 $mg.day^{-1}$, gabapentin 900 $mg.day^{-1}$, and nortriptyline 25 $mg.day^{-1}$. She referred no stump or phantom pain at that moment.

Discussion

The treatment of pain due to acute obstructive arterial disease consists basically in the restoration of the tissue perfusion. When revascularization is not feasible, analgesic treatment is imperative to pain management. Such patients, due to the correlated cardiovascular risk, do not tolerate hyperadrenergic and procoagulant states associated with a severe painful condition, and are very sensitive to adverse effects of many analgesic drugs (opioid, anticonvulsant, antidepressants).[1] It is important to highlight that the patient in this case would undergo amputation of the limb, so adequate analgesia prior to the procedure becomes an important condition to maximize a possible prophylactic effect for the occurrence of postoperative phantom limb pain.[3]

Acute ischemic pain represents an intense nociceptive stimulus, often requiring strong opioids for adequate control.[1] Gabapentin and tricyclic antidepressants were also used to modulate central sensitization against intense nociceptive stimuli. Peripheral regional blocks play an interesting role in arterial ischemic disease. It is well known that regional injection of local anesthetics promotes vasodilation, which contributes to improve perfusion of the affected limb, in addition to effective local analgesia, without causing significant hemodynamic instability. This fact is extremely important in these patients, as they present compromised functional capacity related to associated diseases. Another fact that deserves attention is the capacity of the regional blocks to spare opioids and, consequently, their adverse effects. Therefore, a continuous brachial plexus block was performed using an ultrasound-guided infraclavicular approach with effective analgesia. It has been shown to be a safe and easy-to-perform option for localized upper limb pain.[2] Ultrasound-guided needling contributed to safety, reducing the risk of vascular or lung injury. Despite the ongoing anticoagulation, the patient evolved with no related complications (hematoma or bleeding). The infraclavicular approach was chosen because it is a stable site for catheter insertion, once the device is fixed through the pectoral muscles and can remain for long period, with less risk of migration.[2]

Continuous Peripheral Nerve Block (CPNB) is a useful, effective, and already stablished pain management technique for postoperative analgesia in many kinds of surgery, especially in orthopedics. However, most of the studies in this subject are in acute or postoperative pain scenarios. There are few case reports in literature investigating CPNBs for lower limb ischemic pain management.[4,5] The novelty this paper intends to show is that CPNB may be an excellent alternative for managing refractory ischemic pain when a limb is affected.

As a low-income country, with several limitations in public health system, long wait for surgery treatment (revascularization and amputation, for example) is very common. The option for a nerve block is relatively common for postoperative analgesia in case of amputation but is unusual before the procedure. It is here demonstrated that CPNB may be a valuable asset for pain management while waiting for definite surgery treatment in PAOD, especially in institutions with similar limitations.

We do realize there are commercial kits for CPNB and its use would be more suitable for the procedure. However, this material is not available in our institution. We used a Tuohy needle and epidural catheter, which could be an alternative option in places where the specific kit lacks.

Furthermore, the infraclavicular catheter remained in place for 7 days, with no signs of infection or any other complication. The benefits to the patient were very clear: pain control and reduction in opioid use.

This case report demonstrates that this approach may be effective and safe as an analgesia option for pain due to PAOD. However, randomized clinical trials comparing CPNBs with systemic analgesia in ischemic pain syndromes are required.

Conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORTS

Uneventful epidural catheter removal in a patient with postoperative acute coronary syndrome receiving emergency triple antithrombotic therapy: a case report

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KEYWORDS
Epidural anesthesia;
Platelet aggregation inhibitors;
Anticoagulants;
Blood coagulation tests

Abstract
Background and objectives: Neuraxial hematoma is a rare complication of the epidural technique which is commonly used for high quality postoperative pain relief. In case of urgent initiation of multiple antithrombotic therapy, the optimal timing of epidural catheter removal and need for treatment modification may be quite challenging. There are no specific guidelines and published reports are scarce.
Case report: We present the uneventful removal of an indwelling epidural catheter in a patient who was put on emergency triple antithrombotic treatment with Low Molecular Weight Heparin (LMWH), aspirin and clopidogrel in the immediate postoperative period, due to acute coronary syndrome. In order to define the optimal conditions and timing for catheter removal, so as to reduce the risk of complications, various laboratory tests were conducted 3 hours after aspirin/clopidogrel intake. Standard coagulation tests revealed normal platelet count, normal prothrombin time and normal activated partial thromboplastin time, while Platelet Function Analysis (PFA-200) revealed abnormal values (increased COL/EPI and COL/ADP values, both indicating inhibition of platelet function). The anti-Xa level, estimated 4 hours after LMWH administration, was within therapeutic range. At the same time, Rotational Thromboelastometry (ROTEM) showed a relatively satisfactory coagulation status overall. The epidural catheter was removed 26 hours after the last dual antiplatelet dose and the next dose was given 2 hours after removal. Enoxaparin was withheld for 24 hours and was resumed after 6 hours. Neurologic checks were performed regularly for alarming signs and symptoms suggesting development of an epidural hematoma. No complications occurred.

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Conclusion: Point-of-care coagulation and platelet function monitoring may provide a helpful guidance in order to define the optimal timing for catheter removal, so as to reduce the risk of complications. A case-specific management plan based on a multidisciplinary approach is also important.
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Introduction

Neuraxial hematoma is a rare complication of the epidural technique which is commonly used for postoperative analgesia. It usually occurs after epidural catheter removal and may have disastrous neurologic consequences.[1,2] In case of urgent multiple antithrombotic treatment, appropriate timing for epidural catheter removal is not clearly defined by guidelines and remains challenging.

We describe the uneventful removal of an epidural catheter in a patient who was put on emergency triple antithrombotic treatment in the immediate postoperative period. For the presentation of this case, written informed consent was obtained from the patient and the CARE guidelines were followed.

Case report

A 78-year-old male patient (166 cm, 74 kg) was scheduled for pancreaticoduodenectomy (Whipple procedure) for pancreatic cancer. His medical history included coronary artery disease, hypertension, diabetes mellitus and chronic obstructive pulmonary disease. Platelet count and standard coagulation tests were normal.

Surgery was performed under general anesthesia combined with epidural analgesia; preoperatively, a 20G epidural catheter was inserted through an 18G Tuohy needle at the level of T9–T10 interspace. The procedure was very extensive and prolonged (9 hours), including total pancreatectomy, splenectomy, and portal vein reconstruction. It was associated with massive blood loss and transfusion of blood products, hemodynamic instability, and circulatory support with vasoactive agents. Postoperatively, the patient was transferred to the Intensive Care Unit (ICU) and was put on unfractionated heparin 7500 units/12 h as anticoagulation for the portal vein reconstruction.

The following day, T-wave inversion was observed on the electrocardiogram, along with elevation of the high sensitive Troponin-I (hsTnI peak of 8,496 $pg.mL^{-1}$, normal values < 34.2 $pg.mL^{-1}$) and decrease of patient's ejection fraction (from 45% to 30%). The diagnosis of a non-ST-Segment Elevation Myocardial Infarction was made, and emergency dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg) was added to heparin. The patient developed frequent episodes of ventricular tachycardia for which a cardioverter-defibrillator was implanted. On the 6th postoperative day (POD-6), the unfractionated heparin was replaced by Low Molecular Weight Heparin (LMWH), namely enoxaparin 6,000 IU/12 h.

On POD-10, a multidisciplinary medical team (anesthesiologist, cardiologist, hematologist, surgeon) considered the possibility to remove the epidural catheter after weighing the risks and informing the patient and his family. The ongoing triple antithrombotic therapy raised serious concerns regarding potential bleeding complications following catheter removal, but the patient's critical condition would not allow discontinuation of antithrombotic drugs.

Laboratory tests were conducted 3 hours after aspirin/clopidogrel intake and showed a normal platelet count (291,900 μL^{-1}, reference values: 150,000–400,000 μL^{-1}), normal Prothrombin and activated Partial Thromboplastin Time (PT = 12.6 s, aPTT = 34 s, reference values PT = 11–15 s, aPTT = 24–40 s). Platelet function analysis (Platelet function Assay, PFA-200) revealed abnormal values with both agonists COL-EPI > 248 s and COL-ADP > 235 s (reference values < 150 s and <100 s, respectively). The anti-Xa level, estimated 4 hours after LMWH administration, was within therapeutic range (1.32 $IU.mL^{-1}$, local therapeutic reference range: 0.51–1.47 $IU.mL^{-1}$). At the same time, Rotational Thromboelastometry (ROTEM^{TM}, Pentapharm, Munich, Germany) showed a relatively satisfactory coagulation status overall (Figure 1).

The plan was to repeat the PFA on POD-11, at least 24 hours after aspirin/clopidogrel, just before catheter removal. Unfortunately, that was not possible due to technical reasons. Finally, the epidural catheter was removed 26 hours after the last dual antiplatelet dose and the next dose was given 2 hours after removal. Enoxaparin had been withheld for 24 hours and was resumed after 6 hours. Neurologic checks were performed regularly for alarming signs and symptoms suggesting development of an epidural hematoma. No complications occurred.

Discussion

The overall incidence of neuraxial hematoma is about 1:150,000 epidurals, but the risk increases significantly in patients receiving combination therapy with antiplatelets, anticoagulants and/or thrombolytics.[1,2] Epidural hematomas usually occur after epidural catheter removal and may lead to permanent neurologic deficits.[2] The American Society of Regional Anesthesia and Pain Medicine (ASRA) recommends that clopidogrel should be discontinued 5–7 days prior to neuraxial procedures and can be resumed immediately, provided that a loading dose is omitted.[2] There are no restrictions for aspirin.[2] In patients receiving therapeutic doses of LMWH b.i.d., an indwelling catheter should be removed at least 24 hours after the last dose, while LMWH can be resumed 4 hours after catheter removal.[2] However, in the context of emergency combined

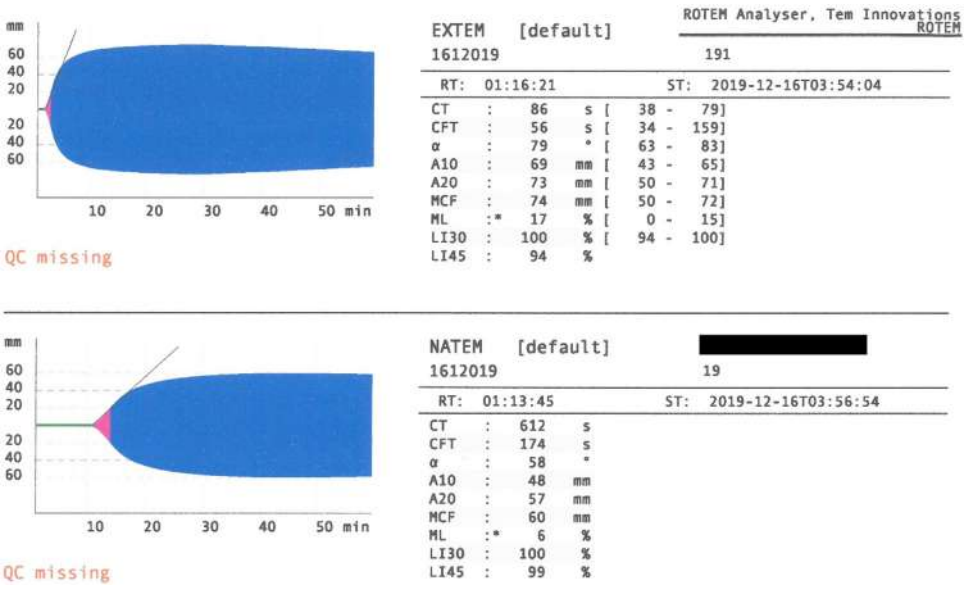

Figure 1 Thromboelastogram obtained by Rotational Thromboelastography (ROTEM). The NATEM was normal with a Clotting Time (CT) of 612 seconds (normal values: 300–999 s), a Clot Formation Time (CFT) of 174 seconds (normal values: 150–700 s), an alpha of 58 (normal values: 30–70), and a Maximum Clot Firmness (MCF) of 60 mm (normal values: 40–65 mm). The EXTEM revealed a Clotting Time (CT) of 86 seconds (normal values: 38–79 s), a Clot Formation Time (CFT) of 56 seconds (normal 34–159 s), an alpha of 79 (normal values: 63–83), and a Maximum Clot Firmness (MCF) of 74-mm (normal values: 50–72 mm).

therapy with anticoagulants/antiplatelets, discontinuation of treatment could be life-threatening.[2]

There are no specific guidelines regarding neuraxial catheter handling in patients receiving multiple antithrombotics, while published reports are scarce.[3–5] In a patient under single antiplatelet therapy (clopidogrel 75 mg) and enoxaparin (30 mg b.i.d.) for acute coronary syndrome, Thromboelastography (TEG) showed hypercoagulability without platelet dysfunction; the in-situ epidural catheter was removed 12 hours after enoxaparin dose without clopidogrel discontinuation.[3]

In another report, the authors were more conservative with a patient who received accidentally one single dose of clopidogrel 75 mg/aspirin 325 mg while being on enoxaparin 90 mg b.i.d. Conventional coagulation tests, platelet function analysis and TEG were normal, and catheter was removed 72 hours after antiplatelets and 24 hours after enoxaparin.[4]

In a more complicated case, similar to ours, the patient underwent urgent postoperative coronary stenting and was put on dual antiplatelet therapy combined with unfractionated heparin infusion.[5] The epidural catheter was removed 24 hours after the last aspirin/clopidogrel dose and 4 hours after discontinuation of unfractionated heparin infusion. Removal was guided by ROTEM which showed normal coagulation and by impedance aggregometry (Multiple Platelet Function Analyzer) at 2 and 24 hours after antiplatelet intake, which demonstrated partial recovery of platelet function over time.[5]

Our patient was under intensive triple antithrombotic therapy with clopidogrel, aspirin and LMWH. We performed a global hemostatic assessment via PT, aPTT, PFA200, anti-Xa and ROTEM close to the time of peak levels of all antithrombotic agents. Although platelet count was normal, platelet function assays performed close to aspirin/clopidogrel administration revealed inhibition of platelet function (increased COL/EPI and COL/ADP values). ROTEM, disclosed a satisfactory clot quality formation ability, when referring to maximum clot formation, despite a subtle prolongation in clot formation time, which was, however, not clinically evaluable. The timing of catheter removal was scheduled by calculating the time corresponding to the lowest levels, and thus activity, of all antithrombotic agents. Due to technical reasons, it was not possible to repeat PFA close to the trough levels of antiplatelets just before catheter removal, as planned. Thus, based on ROTEM results, and considering that the global hemostatic assessment was performed close to the peak enoxaparin, clopidogrel and aspirin levels, we proceeded to epidural catheter removal 24 hours after enoxaparin and 26 hours after the last aspirin/clopidogrel dose, a time-point close to the trough levels of both enoxaparin and antiplatelets. All antithrombotics were resumed early enough to minimize the thrombotic risk.

Apart from standard coagulation tests, we also measured anti-Xa activity; although therapeutic enoxaparin monitoring via anti-Xa is not typically necessary, in special situations such as critically ill patients, anti-Xa levels are often drawn to guide therapy. Additionally, we used the ROTEM and PFA to further assess the coagulation profile of the patient. ROTEM is a point-of-care assay that allows a global assessment of the clotting process but does not measure platelet function. For this purpose, we used PFA, a fast and accurate test that provides quantitative measurement of platelet function. Each test cartridge has a membrane with a 147 μm diameter aperture, coated with type-I Collagen and either Epinephrine (COL/EPI) or Adenosine 5'- Phosphate (COL/ADP). These stimulants cause platelet activation, and finally clot formation and occlusion of the aperture. The

time required for full obstruction of blood flow through the aperture is reported as closure time.[6] Clopidogrel results in both COL/EPI and COL/ADP closure time prolongation, while aspirin causes only COL/EPI prolongation with normal COL/ADP values.[7]

We consider that in analogous cases, useful tests include those employed in the present case, namely Full Blood Count, PT, aPTT, PFA and ROTEM. Ideally, they should be performed at times corresponding to both peak and trough levels of the antithrombotic agents. Multiple Platelet Function Analyzer is another assay that – similarly to PFA – can assess the effects of antiplatelet drugs on platelet aggregation and can be used alternatively. Also, TEG is a point-of-care hemostatic assay that measures the viscoelastic properties of whole blood and may be used as an alternative to ROTEM.

According to ASRA guidelines, the antiplatelet effect of clopidogrel is not immediate if loading dose is omitted, and thus, neuraxial catheters may be left in place for 1–2 days.[2] Unfortunately, there was no early multidisciplinary patient approach to determine the safest practice for epidural catheter handling. Hence, a possible time window for removal was missed and the catheter remained in-situ for several days, complicating things further. The above underlines the need for efficient interdisciplinary collaboration in the management of patients simultaneously treated by multiple different specialties. In the present case, the multidisciplinary care team, which was organized after several days, decided to remove the catheter since it was not in use while the infectious risk was increasing over time, especially after the 4th day.[8] Additionally, there would be no benefit in postponing the removal since the patient's therapy was not expected to change in the near future. The decision was challenging because guidelines are clear only about individual antithrombotic agents, while evidence-based data on drug combinations are not available.[9]

The removal of an epidural catheter in a patient receiving multiple antithrombotic drugs is a challenging decision. The optimal time should correspond to the lowest level, thus the minimum efficacy of antithrombotic treatment. In cases similar to ours, an interval of at least 24–26 hours should elapse between the last dose of antithrombotics (aspirin/clopidogrel/therapeutic LMWH) and catheter removal. Ideally, the timing should be guided by tests and point-of-care coagulation and platelet function monitoring, performed at both peak and trough levels of the antithrombotic agents. The present report also highlights the importance of a case-specific management plan based on a multidisciplinary approach and close cooperation among the involved specialties.

Summary

Neuraxial hematoma is a rare complication of the epidural technique. In case of urgent multiple antithrombotic therapy, the optimal timing of epidural catheter removal may be quite challenging. We present the uneventful removal of an indwelling epidural catheter in a patient who was put on emergency triple antithrombotic treatment with heparin, aspirin and clopidogrel in the immediate postoperative period. Standard coagulation tests, along with Platelet Function Assay (PFA–200) and Rotational Thromboelastometry (ROTEM) provided a helpful guidance in order to define the optimal conditions and timing for catheter removal, so as to reduce the risk of complications.

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Conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORTS

Epidural blood patch for the treatment of liquor hypotension after intrathecal chemotherapy in a 10-year-old: case report

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KEYWORDS
Blood patch, epidural;
Chemotherapy;
Intracranial hypotension;
Cerebrospinal fluid leak

Abstract
Background and objectives: An epidural blood patch is used to treat postdural puncture and liquor hypotension headache. We report the use of an epidural blood patch in a critical pediatric patient.
Case report: A 10-year-old girl with acute leukemia developed venous cerebral thrombosis with hemorrhagic transformation one month after intrathecal chemotherapy. Given the unusual clinical and imagiological evolution even after decompressive craniectomy, we suspected cerebrospinal fluid hypotension. Spine imaging revealed signs of post-lumbar puncture fistula; we hence performed a blind blood patch.
Conclusions: Recognizing cerebrospinal fluid hypotension in critical pediatric patients is important. Less-conventional life-saving measures, such as a blind blood patch, may be considered in such patients.
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Introduction

Epidural Blood Patch (EBP) is a procedure wherein autologous blood is administered in the epidural space, which functions as a patch to the Cerebrospinal Fluid (CSF) leak, raising the epidural space pressure, and causing an inflammatory response that seals the leaking spot. It is used to treat postdural puncture headache and liquor hypotension headache.[1] Only few reports of the use of EBP in pediatric patients, including under general anesthesia, exist.[2]

The use of Intrathecal (IT) chemotherapy, which involves multiple lumbar punctures, is increasing for the treatment of some forms of cancer. The use of IT increases the risk of CSF hypotension.[3]

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We report a case of CSF hypotension in a pediatric patient with clinical instability, who had acute lymphoblastic leukemia and was receiving IT chemotherapy, managed using EBP.

Case report

A 10-year-old girl (weight, 26 kg) received the diagnosis of acute lymphoblastic leukemia and was undergoing induction treatment with triple IT chemotherapy (methotrexate, cytarabine, and hydrocortisone) aimed at preventing central nervous system relapse along with intramuscular PEG-asparaginase and systemic corticotherapy. She had no relevant medical history. The patient was receiving 4 rounds of IT treatment through a serial lumbar puncture (under sedation) per month (one round a week). We observed no complications. However, we had experienced several unsuccessful lumbar punctures in the last round, without CSF leakage, and hence had to postpone the IT chemotherapy. The patient complained of increased orthostatic headaches, neck pain, and scotomas 4 hours after the last lumbar puncture. She developed a single complex focal seizure in the following 24 hours (conjugate deviation of the eyes to the right and clonic movements of the left arm). We administered intravenous diazepam (0.1 $mg.kg^{-1}$), which yielded resolution.

We observed superior sagittal sinus thrombosis and acute subcortical left parietal hemorrhage, with surrounding edematous areas and without signs of hydrocephaly on cranial computed tomography. We transferred the patient to the pediatric intensive care unit under sedation and analgesia and on mechanical ventilation. She was hemodynamically stable.

She presented coagulation abnormalities secondary to chemotherapy-induced myelosuppression; hence, significant bleeding risk was considered. Therefore, we postponed anticoagulant administration despite superior sagittal sinus thrombosis. Considering the possible expansion of intracerebral hemorrhage that could cause intracranial hypertension and clinical deterioration, we considered Intracranial Pressure (ICP) monitoring. Before introducing an ICP monitoring catheter, platelet transfusion was performed. The initial ICP was 8 mmHg (normal ICP for children, 3–12 mmHg).

We observed marked anisocoria (left pupil > right pupil) 1 hour after ICP catheter placement, without any variations in the ICP value. The patient underwent another cranial computed tomography, which revealed a volume increase of the left hemorrhage lesion with a marked shift of the midline structures to the right, although with the same basal cistern patency and a normal cerebellar tonsil position. Subsequently, we performed an urgent left partial decompressive craniectomy. Although a low ICP was maintained, her clinical status 24 hours after surgery did not improve. On the contrary, she experienced bradycardia, with a high arterial pressure and anisocoria persisting. Of interest, these signs improved with the patient supine at 0°. Another cranial computed tomography showed that the right deviation shift persisted; no cerebral herniation at the craniectomy side was observed, as expected.

Considering the initial clinical complaints of orthostatic headaches after several unsuccessful attempts of lumbar puncture and the unusual clinical and imagiological evolution after decompressive craniectomy (normal ICP values despite some neuroradiologic signs of augmented ICP), we suspected post-IT chemotherapy CSF hypotension syndrome.

Magnetic resonance imaging myelography revealed CSF collection in the epidural space, from T4 to the lumbar area, which increased in the lumbar cistern. These findings constituted an indirect evidence of a post-lumbar puncture fistula.

Conservative treatment including maintenance of the supine position at 0°, analgesia, and intravenous fluids was attempted, without improvements, however, by 72 hours.

A multidisciplinary team therefore decided to perform an EBP under sedation and analgesia. A trained anesthesiologist performed the procedure under proper aseptic conditions with the patient in the left lateral decubitus position. A 20G Tuohy needle was used to identify the epidural space at the L4–L5 level using the loss-of-resistance technique with saline. The epidural space was easily identified on the first attempt, and 8 mL of autologous venous blood, collected from the saphenous vein of the left leg, was slowly injected. The anesthesiologist reported mild epidural resistance change after the administration of this volume, however no complications were reported.

The patient had a favorable clinical and imagiological evolution in the first 24 hours after the procedure and was extubated 5 days later. Subsequently, an Ommaya reservoir was placed for IT chemotherapy to avoid further lumbar puncture.

Discussion

Acute lymphoblastic leukemia is the most common neoplasm among pediatric patients. Given the development of new treatment regimens, which often include IT chemotherapy, survival has increased among such pediatric patients. IT chemotherapy involves repeated lumbar puncture that may lead to a CSF fistula formation, which in turn causes liquor hypotension and related symptoms.[3]

With an incidence of 8–25% among children after lumbar puncture with a 22G needle, postdural puncture headache is a relatively common complication. However, it is sometimes neglected by oncologists, particularly in young children with unspecific symptoms and with multiple medications that can lead to the same unexpected adverse effects.

In most extreme cases, like our case, the CSF leak can lead to liquor hypotension, with consequential sagging of the cerebellar tonsils, causing more intense neurologic symptoms.[1] Our patient complained of headache and neck pain after lumbar puncture; however, because of the simultaneous superior sagittal sinus thrombosis with a mass effect, we could not diagnose It earlier. Only when ICP did not increase and even the decompressive craniectomy did not improve the child's clinical status, a magnetic resonance imaging myelography was performed.

Magnetic resonance imaging has significantly improved the detection of CSF leaks, resulting in increased detection of cases and recognition of several clinical or imaging forms of CSF hypotension. We chose to perform a blind EBP at the lumbar region because of the large extension of CSF on magnetic resonance imaging; moreover, there are reports of

successful treatment of postdural puncture headaches with EBP.[4] We performed this procedure at the L4–L5 level considering that IT chemotherapy was attempted in that region.

Traditionally, among adults, EBP is performed with the patient awake; this allows clinical monitoring of symptoms such as neck discomfort, according to which the volume of autologous blood to be administered (typically 15–25 mL) can be adjust. However, performing this technique in children is more complex owing to the procedure being performed under sedation, thus making clinical monitoring and adjustment of volume to be administered impossible. Although few case reports of the EBP technique performed in children under sedation and analgesia do exist, the blood volume to be administered requires further studies. Ylonen and Kokki reported that a blood volume of 0.2–0.3 mL.kg^{-1} should be administered.[5] Roy et al. reported a successful EBP in a 7-year-old with a volume of 10 mL[2] and Kandil et al. reported performing EBP in a 10-year-old boy with a volume of 14 mL; patients were sedated in both the reports. However, reports of successful EBP with a volume as low as 5 mL also exists. We decided to administer 8 mL because the senior anesthesiologist performing the technique noticed a difference in the syringe resistance after this volume was injected.

Central nervous system dissemination is another risk of performing EBP in patients with myeloproliferative disease. Regardless, most studies found that the risk of dissemination is very low. Hence, the benefits outweighed the risks in this case.

To our knowledge, no case reports of EBP use in children with CSF hypotension and similar clinical instability exist.

In conclusion, it is important to recognize CSF hypotension as a differential diagnosis, even in critical pediatric patients. Less-conventional life-saving measures, such as blind EBP, could be considered in similar cases. The optimal volume of blood to be administered in a blind EBP for the treatment of CSF hypotension in children under sedation needs further study.

Conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORTS

A rare complication of continuous positive airway pressure treatment – rectus sheath hematoma: a case report

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KEYWORDS
Bedside ultrasound;
Chronic obstructive pulmonary disease;
Dyspnea;
Emergency medicine;
Noninvasive mechanical ventilation

Abstract Noninvasive mechanical ventilation (NIMV) has a relevant role in the treatment of critically ill patients displaying severe dyspnea. Continuous positive airway pressure (CPAP), a method of NIMV, is also widely used in the management of acute heart failure, chronic obstructive pulmonary disease (COPD) exacerbation, and symptomatic sleep apnea. However, numerous traumatic complications of CPAP treatment in the face region, head, and thorax have been reported and may be related to the application of a continuous positive high pressure to the airway. Conversely, we have observed no complications due to CPAP-related increased intra-abdominal pressure. In this article, we describe a clinical case of a patient with an acute rectus sheath hematoma during CPAP treatment. This previously unreported complication demonstrates that CPAP should be carefully used in patients with exacerbated COPD with difficulty in expiration
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Introduction

The continuous positive airway pressure (CPAP) device, first described by Sullivan et al. in 1981, produces continuous positive pressure due to its high-speed motor, and successfully keeps the upper respiratory tract open.[1] CPAP treatment has a wide sphere of use, particularly in sleep apnea syndrome, as well as acute cardiogenic pulmonary edema (ACPE), chronic obstructive pulmonary disease (COPD), postsurgical lung-protective procedures, and viral bronchiolitis.[2]

Various trauma-related adverse effects resulting from the high pressure to which patients are exposed may be seen in CPAP treatment. CPAP has previously been reported to be

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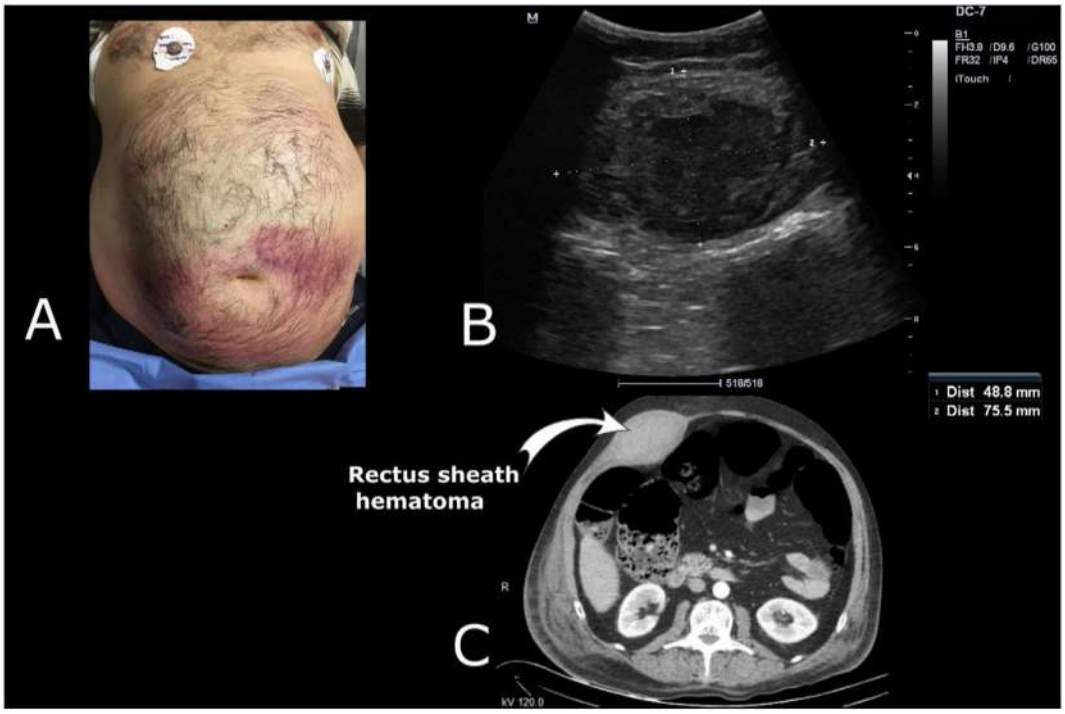

Figure 1 Physical examination finding, ultrasound image, and CT image of the patient with rectus sheath hematoma. A, Redness and ecchymotic areas of abdominal skin that occurred within minutes after abdominal pain; B, Ultrasonographic measurement of the diameter of rectus sheath hematoma with curvilinear probe; C, Computed tomography image showing rectus sheath hematoma that did not invade into the intra-abdominal area.

capable of causing maxilla-facial injuries, increased intraocular pressure and tympanic membrane rupture associated with high pressure developing in the face;[3] pneumothorax-pneumomediastinum and lung herniation associated with high pressure in the thorax;[4] and pneumocephalus associated with increased intracranial pressure. However, we have encountered no previously reported complication developing in association with increased intra-abdominal pressure in CPAP treatment.

This report describes a case of sudden-onset rectus sheath hematoma (RSH) with no provoking factor other than CPAP treatment in a 66-year-old male patient.

Case report

A 66-year-old man presented to the emergency department (ED) with shortness of breath. Diagnoses of COPD and heart failure (HF) were present in his medical history. The patient was taking ipratropium bromide monohydrate plus salbutamol sulfate chronically for COPD, and budesonide in addition to home treatment during attacks. Additionally, he was taking valsartan and hydrochlorothiazide chronically for HF. The patient's respiration rate was 22 with pronounced abdominal breathing, while other vital parameters were within normal ranges, and oxygen saturation was 91%. A physical examination revealed bilateral basal end-inspiratory crackles and rhonchus during the expiratory phase, with prolonged expiration. Cardiomegaly was determined in bedside chest X-ray. CPAP was initiated at a setting of 5 cm H2O external positive end-expiratory pressure (PEEP) via a mask covering the mouth and nose with preliminary diagnoses of COPD exacerbation and HF. No accompanying cough was present, and no significant problems were experienced in terms of CPAP therapy compliance; however, a previously non-existing abdominal pain commenced at approximately the first hour of treatment.

The abdominal pain was exacerbated when the patient was in the expiratory phase and the patient was unable to continue CPAP treatment. Tenderness was present around the umbilical region in an initial examination, and redness and ecchymotic areas around the umbilical region and extending to the lower quadrants appeared within minutes (Fig. 1A). Pancreatic enzymes were requested due to the similarity to Cullen's sign, and bedside ultrasound (USG) was performed. Rapid USG revealed no intra-abdominal free fluid. However, a suspected echogenicity was detected inside the abdominal rectus muscles. The rectus muscle was examined in detail using a curvilinear and linear probe, and a 75*48 mm-diameter hematoma was detected inside the rectus muscle (Fig. 1B). Laboratory tests revealed white blood cells (WBC): 12.53 (10^3uL); platelets: 383 (10^3uL); partial thromboplastin time (PTT): 12.006 (s); activated PTT 23.785 (s); International Normalized Ratio (INR): 1.017; amylase: 64 ($U.L^{-1}$); and lipase: 11($U.L^{-1}$). No bleeding disorder or additional intra-abdominal pathology was determined, and abdominal computed tomography (CT) was performed to confirm the diagnosis of RSH and to confirm the requirement for surgery. The RSH did not open into the abdomen, and no intra-abdominal organ pathology was detected (Fig. 1C).

The patient was hospitalized for 7 days with a diagnosis of HF and COPD exacerbation. During the hospital stay, the patient was given respiratory support with only high-flow

oxygen for the first 24 hours. For the next 3 days, bi-level positive airway pressure (BPAP) and alternating breathing support with high-flow oxygen were administered. The medications of the patient, who did not need respiratory support except nasal oxygen therapy for the previous 3 days, were rearranged. The patient, who did not progress in terms of the RSH, which partially resorbed by the seventh day (70*45 mm), was discharged without undergoing surgery with the recommendation of conservative follow-up.

Discussion

RSH is characterized by an accumulation of blood within the rectus sheath due to a hemorrhage originating from branches of the inferior epigastric artery at its insertion into the rectus abdominis muscle, where branches of the lower epigastric artery are often the most vulnerable. Although RSH is a rare clinical condition, it is more common in elderly and female patients, and the most significant risk has been linked to trauma and anticoagulant therapy.[5] Atherosclerosis, hypertension, cirrhosis, and renal diseases can also increase the risk of rectus sheath hematoma,[5] and coughing episodes in COPD and asthma can also constitute a risk by increasing intra-abdominal pressure. Of these risk factors, trauma and anticoagulant therapy were not present in our case, and values for coagulation tests were within normal limits. No cough capable of increasing intra-abdominal pressure accompanying the clinical manifestation was also present before or during ED follow-up.

CPAP therapy is primarily recommended as a noninvasive mechanical ventilation therapy in ACPE, and BPAP is primarily recommended in acute exacerbations of COPD, although many studies have shown that CPAP might be useful in exacerbations of COPD.[2] CPAP may be particularly suitable for patients with COPD who find bi-level NIV uncomfortable, or who are not synchronized with the ventilator. However, the priority of treatment should be determined according to the clinic in patients with both diseases, like our patient.

Patients undergoing CPAP therapy should be closely monitored for both their underlying diseases and CPAP complications. It has been previously reported that CPAP might increase intracranial[3] and intra-thoracic pressure,[4] causing various complications related to trauma. However, no complications related to the abdomen have been reported by increasing intra-abdominal pressure. During the CPAP treatment of our patient, sudden onset abdominal pain developed with no cough or similar maneuver capable of increasing intra-abdominal pressure. During COPD acute exacerbations, scalene and sternocleidomastoid muscles are used more as accessory muscles in inspiration, and the abdominal respiratory muscles (rectus abdominis, transverse abdominis, and external and internal obliques) are used as accessory muscles in expiration. For this reason, the abdominal respiratory muscles used in expiration during an attack are already under additional pressure load. Also, we think that CPAP treatment could increase the difficulty of expiration in a patient who has an acute exacerbation of COPD. The patient may, therefore, have had to make greater use of the abdominal muscles during expiration. CPAP treatment, which makes expiration difficult for patients with COPD using abdominal muscles due to respiratory difficulties, may increase intra-abdominal pressure and cause rectus sheath hematoma.

Conclusion

CPAP treatment may lead to rectus sheath hematoma by increasing intra-abdominal pressure in patients with COPD with difficulty in expiration. These patients may require attention during CPAP treatment or may be given priority to biphasic noninvasive ventilation methods rather than continuous methods.

Conflicts of interest

The authors declare no conflicts of interest.

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CLINICAL IMAGES

Omega-shaped epiglottis: a challenge

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A heavy smoker 49-year-old man, American Society of Anestesiologists (ASA) physical status III, with positive history of gradually worsening dyspnea was proposed for Suspension Microlaryngoscopy surgery. Airway evaluation showed a grade-III Mallampati score and no apparent or palpable cervical mass. After preoxygenation and induction, orotracheal intubation was performed with C-MAC D blade Videolaryngoscope®, and founded an omega-shaped epiglottis (OSE) (Fig. 1), with vocal cords visualized only after lifting the epiglottis with the tip of the curved blade (Fig. 2). Intubation was accomplished using a 4.0-mm cuffed microlaryngeal orotracheal tube, anesthesia was maintained with sevoflurane and controlled ventilation. Anesthesia emergency was uneventful.



Figure 1 Omega-shaped epiglottis visualized with C-MAC D Blade videolaryngoscope.



Figure 2 Exposition of larynx and vocal cords after lifting epiglottis.

OSE is a variant configuration of epiglottis in which the lateral folds are curled inwards.[1] Although not necessarily pathological, it may be associated with laryngomalacia and supraglottitis.[2] From the anesthetic point of view, potential problems of OSE include variable airway obstruction and compromise. Anatomical changes of the epiglottis should serve as a warning for difficult airway, namely with face-mask ventilation and orotracheal intubation/extubation.[3]

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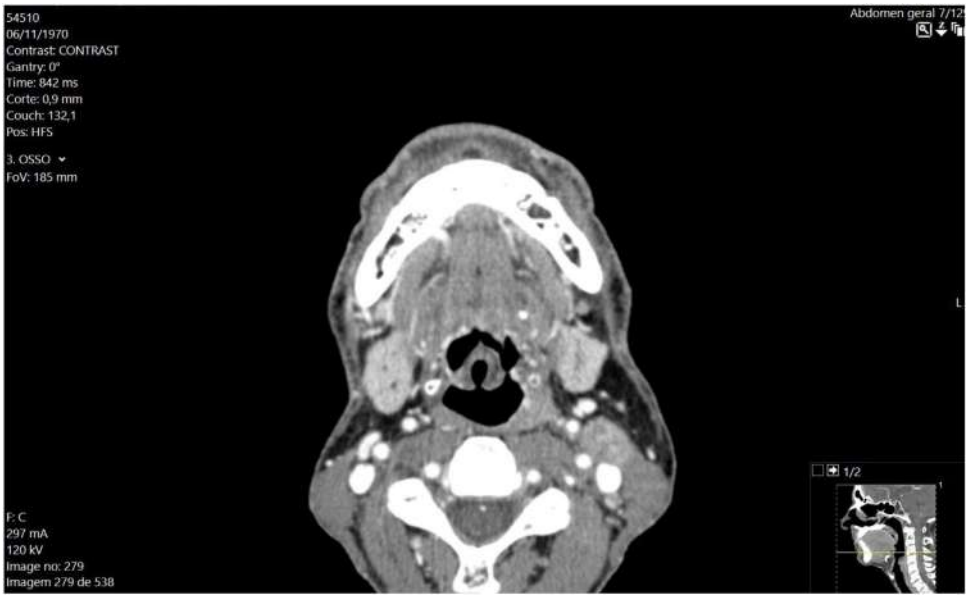

Figure 3 CT-Scan of head and neck showing omega epiglottis.

Preoperative anesthetic evaluation should include investigation symptoms suggestive of intermittent airway obstruction and image evaluation (MRI or CT-scan of the head and neck) (Fig. 3).

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SHORT COMMUNICATION

Anterior scalene plane block at the superior trunk level relieves referred shoulder pain after liver radiofrequency ablation: a technical report



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KEYWORDS
Nerve block;
Phrenic nerve;
Pain, referred: shoulder;
Liver neoplasms;
Radiofrequency ablation

Abstract We report the first case of using an anterior scalene plane block at the superior trunk level achieving phrenic nerve blockade to treat intolerable referred shoulder pain after liver Radiofrequency Ablation (RFA) of a diaphragm-abutting liver tumor despite prevention with a full-dose non-steroidal anti-inflammatory drug. The anterior scalene plane block rapidly alleviated pain without significant complications.
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Introduction

Radiofrequency Ablation (RFA) of diaphragm-abutting tumor results in right shoulder pain in some patients. A hypothesis is that an irritation of the phrenic nerve results in neural hypersensitivity of the third and fourth spinal cervical nerves (C3–C4), and subsequently induces a referred shoulder pain.[1] Management typically requires the early institution of parenteral non-steroidal anti-inflammatory drugs, which may eliminate pain in most patients. However, intractable referred shoulder pain that is unresponsive to the above treatment urges the need for further intervention.

Phrenic nerve block may be challenging, considering the potential complications such as incomplete analgesia when blocking it at the level of diaphragm, unwanted local anesthetic spread toward other nerves, and, above all, nerve injury secondary to mechanical needle trauma, pressure-induced neuropraxia as well as intra-fascicular injection.

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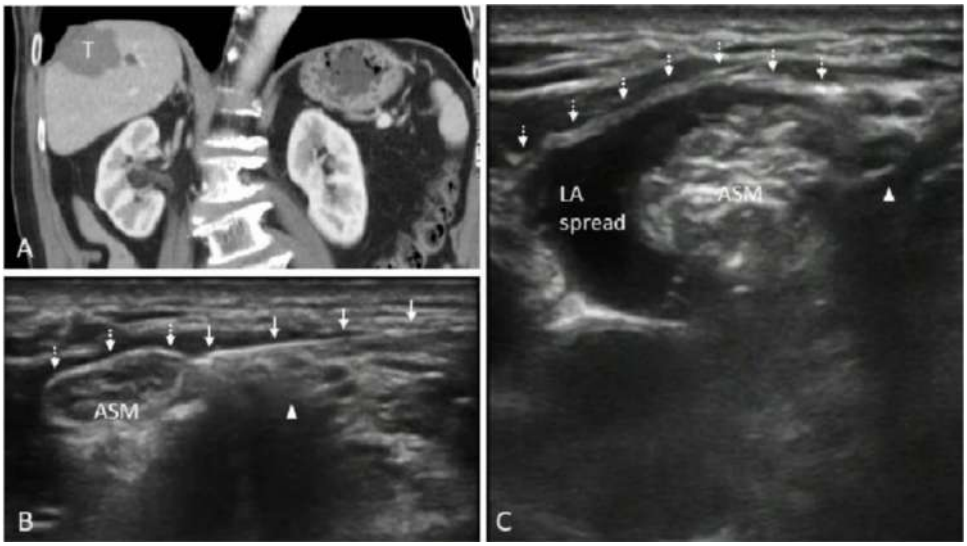

Figure 1 (A) Coronal plane of computed tomography of the diaphragm-abutting tumor. (B) Pre-injection ultrasound image before puncturing the prevertebral fascia. (C) Post-injection ultrasound image with a perimuscular spread beneath the prevertebral fascia. Arrowhead indicates the superior trunk, solid arrow indicates the needle shaft, and broken arrow indicates prevertebral fascia. T, Tumor; ASM, Anterior Scalene Muscle; LA, Local Anesthetic.

Here we proposed an anterior scalene plane approach at superior trunk level under dual guidance (ultrasound and injection pressure) to avoid associated complications as much as possible. Waiver of informed consent has been approved by the TMU-Joint Institutional Review Board (TMU-JIRB nº N201906002).

The technique to manage intractable referred shoulder pain

A 74-year-old man (68 kg) with hepatocellular carcinoma, T2N0M0 (Stage II) and BCLC Stage A previously underwent partial hepatectomy and RFA and received percutaneous ethanol injection. He was otherwise healthy, except for medication-controlled hypertension. This time, he was admitted for a second course of RFA of a recurrent liver tumor approximately 3.5 cm located at segments 7 and 8 adjacent to the liver dome (Fig. 1A).

After being premedicated with intravenous fentanyl (100 mcg) and midazolam (1 mg), 0.15 mL.kg^{-1} of local anesthetic (0.6% ropivacaine with 1:400000 epinephrine) was injected into the T9, T7, and T5 paravertebral spaces. Owing to its diaphragm-abutting property, parecoxib (40 mg) was intravenously administered to prevent referred shoulder pain caused by diaphragm irritation perioperatively. Sedation was maintained with 1% propofol continuous infusion under bispectral index monitoring. Two cool-tip RFA needles were inserted. Total ablation time was approximately 2 -hs, with stable intraoperative blood pressure.

However, after recovery from sedation, he complained of severe pain over the right shoulder region without abdominal discomfort. Cervical phrenic nerve block was planned as preoperative full dose parecoxib failed to prevent referred shoulder pain. The patient was placed in the left lateral decubitus position with scalenus anterior focused sonographically at the superior trunk level to facilitate ergonomic practice. The needle was meticulously advanced from the lateral to medial direction toward the surface of scalenus anterior with the prevertebral fascia punctured immediately medial to the superior trunk (Fig. 1B). Fascial plane dissection was achieved by half-the-air technique. After negative aspiration, 3 mL of 2% lidocaine, followed by 2 mL of 5% dextrose to empty the dead space of the half-the-air setting, was administered into the subfascial plane with continuous pressure monitoring throughout the injection procedure (Fig. 1C).[2]

The patient experienced rapid improvement of his shoulder discomfort immediately after local anesthetic injection. Twenty minutes after the injection, complete pain relief was reported by the patient. No respiratory distress was noted during observation, and phrenic nerve blockade was confirmed by a loss of ipsilateral diaphragmatic movement on ultrasound.

Discussion

Regional blocks targeting the phrenic nerve have been previously proposed to treat referred shoulder pain. Local anesthetic infiltration into the periphrenic fat pad at the level of the diaphragm significantly reduces the incidence of shoulder pain, but still experienced by some patients. The reason responsible for incomplete pain relief might be that the phrenic nerve already branches off into various terminals to innervate the widespread end-targets, which, therefore, is not easily covered by local anesthetic infiltration. Thus, to achieve complete analgesia, it would be reasonable to block the phrenic nerve more proximally at the cervical level. Raft et al. demonstrated the potential of erecter spinae plane block at T3 and T6 level to alleviate right shoulder pain after laparoscopic cholecystectomy, with unilateral sensory loss to cold over C5–T9 dermatomes after 15 mL 0.5% ropivacaine injection at each level.[3] However, its mechanism of action

responsible for shoulder analgesia remains unclear and it is not known whether erector spinae plane block solely at T3 level could provide adequate in-time effect for intractable shoulder pain after liver radiofrequency ablation.

Anterior scalene plane block at the superior trunk level was recommended to block the proximal phrenic nerve without directly getting in touch with the nerve. The phrenic nerve is a predominantly hypoechoic monofascicular structure with a hyperechoic border in the transverse view. The mean diameter of phrenic nerve is only 0.76 mm; therefore, in some cases, tiny nerves cannot be identified using an ultrasound probe with a general resolution.[4] In our patient, the phrenic nerve could not be traced easily even by dynamic up-and-down scanning. Moreover, phrenic nerve is nearly indistinguishable from the C5 ventral ramus at the level of the cricoid cartilage (mean distance: 1.8 mm), but with additional 3 mm separation between the phrenic nerve and brachial plexus for every cm more caudal in the neck.[4] Therefore, to avoid phrenic nerve injury secondary to mechanical needle trauma during cervical phrenic nerve block, we punctured the prevertebral fascia immediately medial to the superior trunk where the phrenic nerve already courses over the medial surface of the anterior scalene muscle. The superior trunk level increases the separation substantially between the phrenic nerve and the brachial plexus because the superior trunk is typically found superficial to the C7 nerve root, and the distance from the cricoid cartilage to the C7 transverse process is estimated to be 1.5 and 2.5 cm in the neutral and extended neck positions, respectively.[5] The transverse scan usually catches the superior trunk at the level caudal to the C7 posterior tubercle. Injection beneath the prevertebral fascia at this level achieves a craniocaudal spread (Fig. 1C) superomedially limited by the fascial attachment of the C3 to C6 anterior tubercles and laterally limited by the outward reflected fascia overlying the superior trunk and subclavian artery in the lower neck. Although whether the phrenic nerve passes onto the surface of prevertebral fascia in the lower neck remains controversial, the proximal portion of the phrenic nerve lies consistently deep to the prevertebral fascia, whose block can be achieved by a cranial spread from injection beneath the prevertebral fascia at the superior trunk level. A perimuscular spread over the anterior scalene plane not only achieved phrenic nerve blockade but also helped minimize unwanted extrafascial spread.

To avoid intrafascicular spread for this invisible tiny string and possible injection pressure-induced neuropraxia, continuous pressure monitoring throughout the injection is mandatory. Among pressure monitors, the half-the-air setting is recommended for cervical phrenic nerve block. Not only can the half-the-air setting continuously monitor injection pressure[2] but it also has additional benefits because 5% dextrose as the test volume is useful for fascial plane dissection before drug deposition[2] to minimize unwanted extra-fascial spread, especially in the complex innervated neck region.

Although our patient experienced complete pain relief after cervical phrenic nerve block, whether a prophylactic phrenic nerve block should be performed as a routine procedure before liver RFA warrants further investigation in terms of a variable incidence of intractable shoulder pain after liver RFA and possible respiratory distress in patients with lung pathology. Furthermore, the optimal drug regimen for anterior scalene plane block needs to be determined.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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SHORT COMMUNICATION

Safe resumption of elective surgery: a Latin American proposal

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The current COVID-19 pandemic has had a disproportionate impact on healthcare practice around the world, imposing a strain on most systems that has exposed weaknesses. As such, in Latin America (LATAM) most countries have experienced suspension of significant schedules surgical procedures to decrease the demand on healthcare services in the face of this pandemic. Therefore, proposals to resume these services are needed, as there is a major backlog to be resolved. This paper intends to generate a basic framework to adapt locally to reinstate scheduled procedures as safely as possible.

This proposal is based on an unstructured review of the current literature, and on Confederación Latinoamericana de Sociedades de Anestesiología (CLASA) webinars on this subject with international experts in the field.

Resumption is recommended when the incidence of local COVID-19 infection rate is decreasing.[1] Institutions should consider these four aspects before resumption:[2] space, stuff, staff, and system, each graded as red, amber, or green. It is recommended that all four should have a green grading to consider resuming activities (Table 1).

There are significant implications regarding perioperative SARS-CoV-2 infections. This is a two-way problem: transmission of infection to a surgical patient and the reverse to healthcare personnel and other patients. Current cohorts have observed that surgical patients who develop COVID-19 infection have unacceptable risks of morbidity and mortality, with rates up to 20%.[3] Also, the risk to healthcare providers, in particular anesthesiologists who deal with the airway, have led to major morbidities with at least a 10% infection rate and tremendous number of deaths (in LATAM, more than 70 anesthesiologists have died as of October 2020, unpublished data).

Dexter et al.[4] have proposed multiple evidence-strategies to diminish the risks of contamination both from and to the patient.

To decrease contamination from the patient:

a) Test patients for nasal SARS-CoV-2 with either a reverse transcriptase Polymerase Chain Reaction (PCR) test or even consider an SARS-CoV-2 antigen test as close to the procedure as possible, ideally hours before the procedure, but no more than 48-hours before.[5] This closes the window to identify infected asymptomatic patients, and could potentially detect whether an infected patient is still not contagious, which could result in false nega-

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Table 1 Institutional considerations as proposed by the Royal College of Anaesthetists, Association of Anaesthetists, and Intensive Care Society.

Institutional considerations as proposed by the Royal College of Anaesthetists, Association of Anaesthetists, and Intensive Care Society	
Space	RED: If Operating Rooms (ORs) or Postanesthesia Care Units (PACU) are used for overflow critical care patients. AMBER: If the process of having isolated COVID+ and COVID- areas is almost completed. GREEN: no current risk of Intensive Care Unit (ICU) overflow.
Staff	RED: Anesthesia staff required for ICU backup support. AMBER: ICU personnel stretched, and anesthesia backup possible. GREEN: No risk of anesthesia support of ICU.
Stuff	RED: Institutional restriction of Personal Protection Equipment (PPEs), medications, and resources like critical care, dialysis machines, and ventilators. AMBER: Available resources but uncertain supplies. GREEN: Good stock of all these resources.
System	RED: If a) independent COVID-19 pathways, b) COVID-19 testing (that has been considered in local protocols as essential), c) structured protocols to care for the patients, or d) ancillary services (preanesthetic assessment, acute pain management, and adequate postoperative follow-up) are NOT available. AMBER: In the process of being available. GREEN: Already available.

tive antigen tests, as these require larger viral loads to detect infection (i.e., significantly less sensitive) than PCR tests. Antigen testing has even been promoted as a more practical way to identify infectious individuals.

b) Decrease nasal contamination (source of viral shedding) with iodine povidone nasal swabs, and oral chlorhexidine washes at concentrations even as low as 0.05%.

To decrease contamination to the patient:

a) Rigorous hand washing after every interaction with the patient and environment.
b) Oropharyngeal decontamination decreases surgical site infections. When caring for the airway, which is highly contaminated, the use of double gloves should become standard, and these should be discarded immediately after use.
c) Periodically wipe the anesthesia work area (a major area for fomite contamination) with hypochlorite (0.1%) or benzalkonium chloride (0.1%) to eliminate Sars-CoV-2.
d) Wipe injection ports with disinfectants before administering medications.

All these interventions, which overall are economically viable, may be culturally difficult to implement in LATAM countries, but if adopted and maintained, this crisis could eventually have some benefit for patients, leading to an overall decrease in general perioperative infectious risks in LATAM.

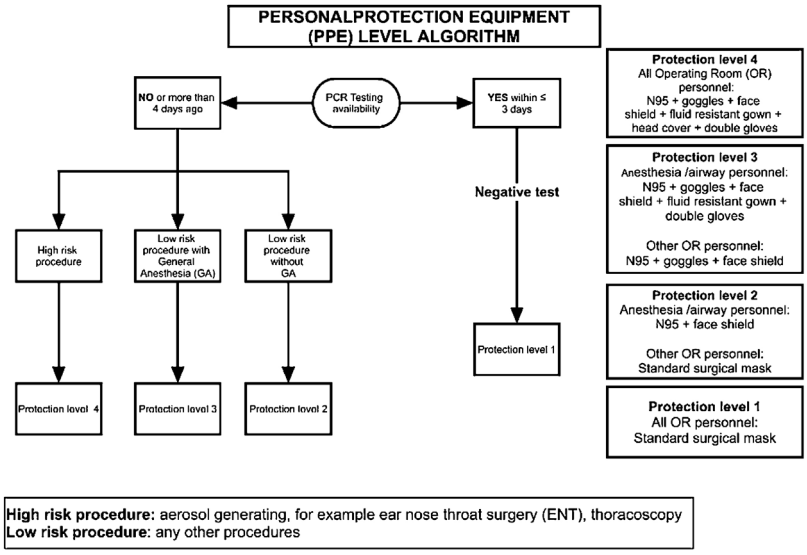
When considering the previous aspects, we have devised three evidence-based algorithms (based on current knowledge) to facilitate the resumption of surgical procedures.

In Figure 1A, we propose a Personal Protection Equipment (PPE) rationalization algorithm. Similar to the coronavirus epidemic of Sars-CoV-1 in 2003, in which airway interventions led to a 13-fold increase in infections in anesthesia personnel, a high risk (10%) of infection has been observed for anesthesiologists involved in the care of current COVID-19 patients. With significant numbers of deceased anesthesiologists worldwide, it seems reasonable to exceed WHO recommendations for PPEs, as proposed by Lockhart, where head and neck coverings are recommended when caring for these patients. Extreme protective measures have been found to be successful at protecting personnel, as shown in an Italian hospital and in the UK where up to May 2020 no anesthesiologists or intensivists had died from COVID-19 infections.

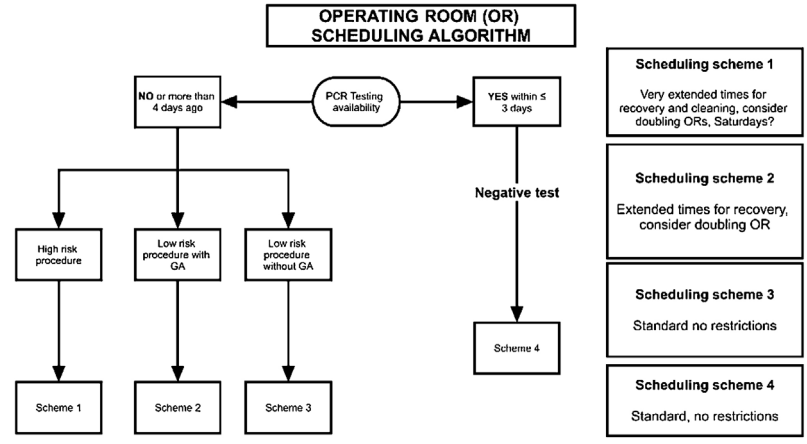
As important as PPE availability is the use of stringent doffing routines to minimize infections. In Figure 1B, we propose a scheduling algorithm. The risk of cross-contamination is a serious aspect to consider; although the ideal, dedicated isolated negative pressure operating rooms are not feasible in LATAM, we propose this scheme to minimize it. This was adapted from the evidence-based approach of Dexter et al in conjunction with the recommendations of the University of California at San Francisco (UCSF).

In Figure 1C, we propose a Postoperative (POP) care flow algorithm. As stated before, it is necessary to decrease the risk of contagion to other patients and healthcare personnel after any surgical procedure. Ideally, the Postanesthetic Care Unit (PACU) should have physically independent modules for each patient with negative pressure ventilation, which is not possible in most LATAM countries, risking cross-contamination in this phase of care. Therefore, it is necessary to define rational approaches to minimize this risk. Infection auditing on behalf of anesthesia departments is still in its infancy in LATAM. This pandemic could be the trigger to establishing them, so that strategies to reduce perioperative infections can be spearheaded by anesthesia department in these institutions.

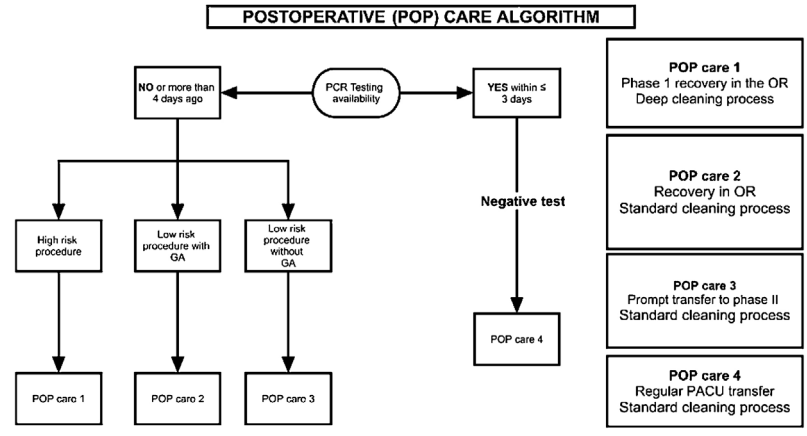
This paper proposes a framework with which anesthesia in LATAM can implement the process of safely resuming scheduled surgical procedures during the Sars-CoV-2 pandemic.



A. Personal protection equiment (PPE) for healthcare personnel



B. Scheduling strategy for procedures



C. Postoperative (POP) management algorithm

Figure 1 Proposed algorithms for PPE use (A), scheduling (B), and postoperative management (C). Based on Dexter et al., and UCSF algorithms.

Authors' contributions

Pedro F Ibarra: MD, MSc was responsible for most of the article.

Juan C Duarte: MD collaborated with ideas and significant text adjustments.

Conflicts of interest

The authors declare no conflicts of interest.

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LETTERS TO THE EDITOR

Blood-soft tissue barrier breach and soft tissue recoil pressure on local anesthetic: two physiological mechanisms for local anesthetic systemic toxicity

Dear Editor,

Local Anesthetics (LA) are safe when limited to the site of therapy, such as tissue infiltration near a nerve or a plexus. However, if a large amount of LA reaches the systemic circulation, supra-therapeutic blood levels can cause Local Anesthetic Systemic Toxicity (LAST). Variables that increase the risk of toxicity include the type and dose of LA, site of injection, patient's age and comorbidities, and muscle mass.[1] The transit of LA into the blood may be due to inadvertent intravascular injection or vascular uptake from local spread.

We hypothesize two physiological mechanisms which may contribute to LAST.

1 Breach of blood–soft tissue barrier due to multiple needle punctures.

Regional anesthesia may require multiple needle punctures to confirm proper needle placement. This may breach the blood–soft tissue barrier due to direct microvascular injury leading to opening of low-pressure vessels (capillaries, venules, and veins). The vascular uptake from local spread gets exaggerated following breach in blood-soft tissue barrier.

2 Elastic recoil force of soft tissue builds a pressure surrounding the capillaries after injection of the LA (Fig. 1).

Injection of the fluid into soft tissue creates a small pocket of free fluid, the pressure in this isolated pocket of fluid is measured as interstitial fluid pressure. Brace et al.[2] used the needle technique to detect negative pressure in the tissue space if no fluid was injected. However, positive pressure was detected when fluid was injected. This changes in interstitial fluid pressures were in accordance with Starling's hypothesis. This pressure corresponds to the total tissue pressure, which is the sum of fluid and solid pressure. There is a constant absorption of the fluid from the created pocket of free fluid into the surrounding tissues,

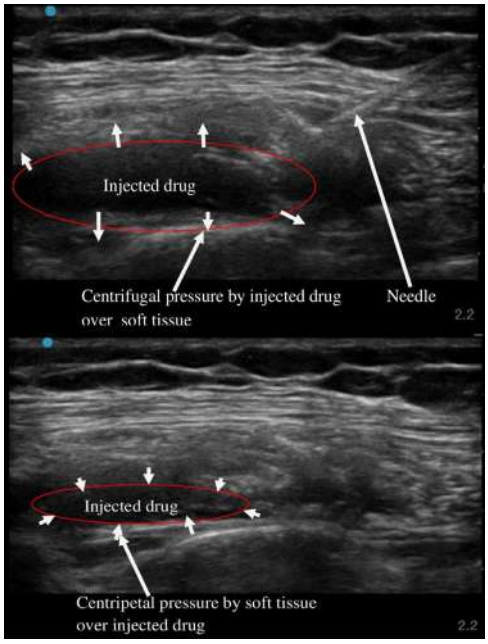

Figure 1 Soft tissue recoil force over the injected LA.

indicating that the fluid pressure in the surrounding tissues is more negative than in the pocket of free fluid.[2] The recoil pressure depends upon volume and site of injection, besides the elastance of tissue near the nerve. Whenever pressure surrounding the capillaries after injection of the LA exceeds the capillary pressure, then it would cause increased convective flux of LA due to increased inward interstitial fluid pressure gradient.

The two mechanisms above might also explain the mechanism of LAST despite negative blood aspiration before drug injection even at submaximal doses. Aydin[3] detected unexpected LAST during the Ultrasonography-Guided (USG) peripheral nerve block despite negative blood aspiration before injecting the drug. The exact cause of LAST in this case was not found out. The possible cause behind rapid absorption of LA into the system circulation could have been multiple needle punctures while using peripheral nerve stimulator before USG drug injection. The maneuver of aspirating prior to injection can yield a false negative result in 2% of the population.[1]

We would require contrast-enhanced ultrasound LA spread,[4] ultrasound microbubble behavior and sonoporation study or targeted microbubbles for molecular imaging study

to validate our hypothesis.[5] There is no facility to do contrast enhanced local anesthetic spread in the animal or human models at our centre. Hence, further studies might be required to validate our hypothesis.

Conflicts of interest

The authors declare no conflicts of interest.

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Quadratus lumborum block in supine position for postoperative pain management in acetabular fracture surgeries: cadaveric and clinical experience

Dear Editor,

We read with interest the case report by Sandeep Diwan et al on supine coronal midaxillary approach to anterior quadratus lumborum block (SCAQLB).[1] Acetabular fractures are usually painful medical conditions. Positioning the patient for regional anesthesia is challenging due to the localization of the fracture and severe pain. Quadratus lumborum block (QLB) in supine position gives advantageous in acetabular fracture surgeries for being both easily applicable and potentially effective in postoperative pain management.

In our clinical practice we started to utilize QLB in supine position for acetabular fracture surgeries with a methodology explained by Blanco et al. since 2019 in caesarean section cases.[2] After seeing the effectiveness of it first in four clinical cases, we investigated the distribution of local anesthetic in a fresh cadaver.[3] According to the results of cadaver dissection, we observed that there was no dyeing in the sacral plexus region. On contrast the branches of the lumbar plexus which are femoral nerve, ilioinguinal nerve, lateral femoral cutaneous were dyed (Fig. 1). This spread of methylene blue dye may explain the mechanism of effectiveness of QLB in asetebular region.

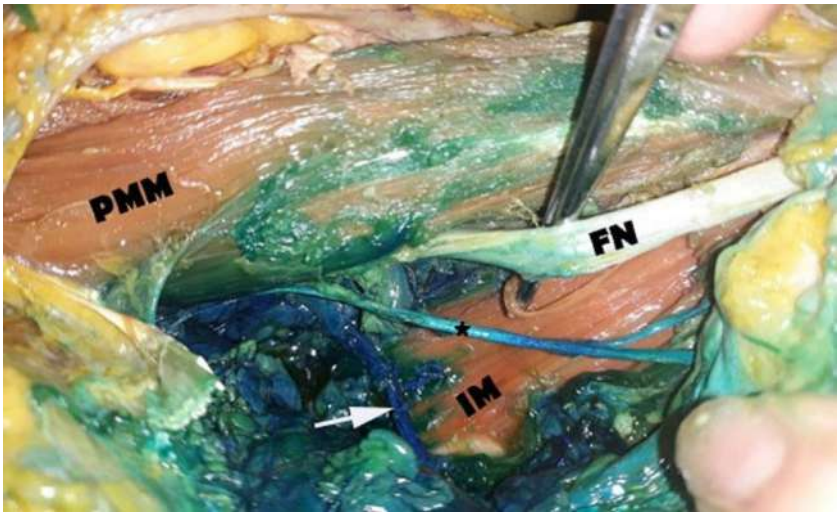

Figure 1 Distribution of the methylene blue in supine QLB. PMM, Major Psoas Muscle; FN, Femoral Nerve; IM, Iliacus Muscle. White Arrow, Ilioinguinal Nerve; *, Lateral Femoral Cutaneous Nerve.

The use of QLB in the supine position can be an efficient option in postoperative pain management in acetabular fractures. The block does not require the repositioning of the patient. In literature lumbar plexus block was reported to be effective in acetabular fracture pain management, since the primary innervation of the acetabular region originates from the lumbar plexus.[4] As QLB is a fascial plane block, unlike the lumbar plexus block, it is not directly applied to the nerve site; therefore, the risk of intraneural injection is lower.

We found an opportunity to perform SCAQLB in three patients. We can say that SCAQLB is easy to perform and has some advantageous for visualization of quadratus lumborum muscle than Blanco et al methodology.[2] Further studies on fresh cadavers may reveal the effectiveness of SCAQLB.

Conflicts of interest

The authors declare no conflicts of interest.

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The mid-point transverse process to pleura (MTP) block in chest trauma: a game-changer

Dear Editor,

Road traffic accidents have emerged as a pandemic of the modern world. Chest trauma, being commonly associated with these road traffic accidents, becomes the leading cause of morbidity and mortality. Management of pain is essential in these trauma patients as, along with patient comfort, it also decreases patient's respiratory complications.[1] Various techniques are designed to reduce pain-related complications, including pharmacological drug therapies, and regional or neuraxial nerve blocks techniques. Thoracic Epidural Analgesia (TEA) is considered as gold standard for relieving rib fracture pain. However, it is not free of complications, including dural puncture, accidental hypotension, and cardiovascular collapse.[2] Likewise, the thoracic paravertebral block might also lead to inadvertent vascular puncture, hypotension, epidural or intrathecal spread, pleural puncture, and pneumothorax.[3]

Mid-point transverse process to pleura (MTP) block is a recently described ultrasound-guided novel technique that involves injecting the drug at mid-point between the transverse process and the pleura.[4] In this block, a high frequency (8–15 MHz) linear ultrasound probe is placed obliquely approximately 3 cm laterally from the midpoint of the spinous process. The block needle (50 mm long) is advanced from caudal to cranial direction of the paravertebral space. When the needle tip reaches the midpoint between the transverse process and the pleura, the drug is given. The drug spreads to the dorsal and ventral rami in the paravertebral space through the fenestrations in the superior costotransverse ligament at the level of injection (Fig. 1).[4] Being a superficial block, landmarks are quickly and easily felt.[5] Thus, it is comparatively easy to insert. It can be easily applied to obese traumatic patients with a compromised position. Due to these advantages, MTP block is much safer than thoracic epidural and thoracic paravertebral blocks by minimizing the risk of pleural puncture and inadvertent intrathecal injections.

Management of acute pain is highly advantageous for enhanced recovery after trauma to prevent the neuroendocrine stress response and thus combat the cascade of events occurring after activation of the sympathetic nervous system and catecholamine release. Therefore, we believe that MTP block can be a game-changer for the chest trauma patients due to an easy approach and reduced risk profile.

Conflicts of interest

The authors declare no conflicts of interest.

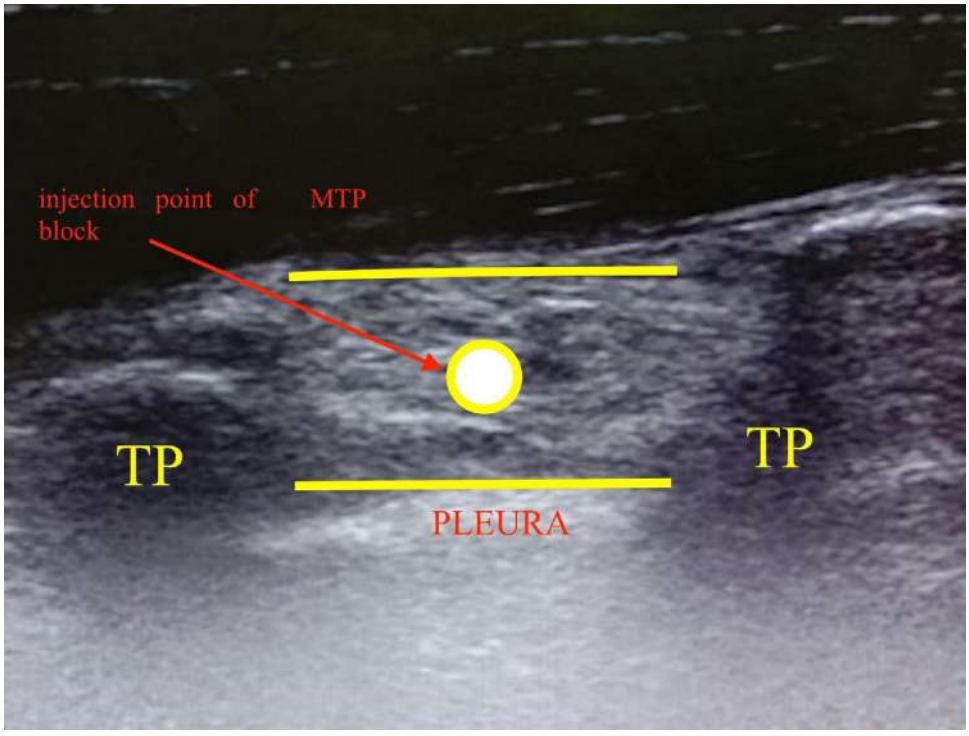

Figure 1 Depicts the ultrasound image of MTP block. The white circle represents the point of injection of MTP block. TP, transverse process; MTP, mid-point transverse process to pleura.

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