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Erector Spinae Plane Block compared to Paravertebral Block in the post-operative pain management of patients undergoing elective Video-Assisted Thoracic Surgical lobectomy for lung cancer: a randomized, non-inferiority clinical trial protocol

Wilson Fandino[1]

[1]*Guy's and St Thomas' NHS Foundation Trust. London, United Kingdom.*
**Corresponding authors: Wilson Fandino. Anaesthetics Department, Guy's and St Thomas NHS Foundation Trust. Westminster Bridge Road. Lambeth, SE1 7EH. London, United Kingdom. Phone number: +44 07701372374. e-mail address: wilson.fandino@hotmail.com*

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Abstract:
Background and aim: *Erector spinae plane (ESP) block is a regional anesthesia technique recently described, that has gained growing interest because of its relative safety, versatility and simplicity, when compared to other approaches, including paravertebral block (PVB). In the context of thoracic surgery, clinical trials are warranted to evaluate the potential efficacy of this new technique. This clinical trial aims to test the non-inferiority of ESP block compared to PVB, in patients with early-stage lung cancer admitted to a tertiary referral center for elective pulmonary lobectomy, under video-assisted thoracic surgery (VATS).*
Design: *Parallel, randomized, controlled, single-blinded, non-inferiority clinical trial protocol for a pilot study.*
Participants: Patients aging between 18 and 85 years old, diagnosed of early-stage non-small cell lung cancer, and admitted for elective VATS lobectomy.
Measurements and procedures: *All participants will be blinded to the intervention. After undergoing general anesthesia, they will receive either ESP block or PVB, according to their randomized allocation. The primary outcome will be pain intensity at 30 minutes after the operation, which will be measured by an 11-point (0 to 10) Visual Analogue Scale (VAS). Secondary outcomes will include VAS score at 30 min and at 6, 12 and 24 hours after arrival to the recovery area, morphine consumption at 24 hours, time of performance of the block, and complications related to the procedure.*
Ethical aspects: *For the development of this protocol, all ethical principles outlined in the last version of the Declaration of Helsinki (Fortaleza, Brazil, 2013) have been followed. Approval from local ethical committee and written informed consent from all participants will be obtained.*

Keywords: *Thoracic surgery video-assisted, non-small-cell lung carcinoma, anesthesia recovery period, pain management.*

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INTRODUCTION

In the United States, lung cancer is currently the leading cause of mortality among all types of cancer. By the end of 2017, it has been estimated that in this country there were over 116.000 and 105.000 new cases of lung cancer diagnosed in men and women, respectively, thus becoming the second most frequent type of cancer in both genders (Siegel et al., 2017). In patients with diagnose of early-stage non-small cell lung cancer, lobectomy under video-assisted thoracic surgery (VATS) seems to decrease the perioperative mortality, when compared to conventional open lobectomy (Cao et al., 2018).

Furthermore, VATS is one of the main cornerstones of the enhanced recovery pathway, a combination of multiple interventions that, along with administration of short-acting anesthetic drugs, minimal invasive

monitoring and optimal pain management, has proven to shorten the hospital length stay and improve the patient satisfaction (Scarci et al., 2016). Among pain management strategies for VATS procedures, thoracic epidural analgesia (TEA) continues to be the first choice in the United States (El-Tahan, 2017). Though, this technique has deleterious effects on the cardiac output, stroke volume and right ventricular contractility. Furthermore, TEA has been associated with increased incidence of postoperative hypotension, nausea, vomiting and urinary retention, and there still remain some concerns regarding its routine use for patients under one-lung ventilation (El-Tahan, 2017).

In this setting, paravertebral block (PVB), a technique that was first described in the early twentieth century, has gained renewed interest after the publication of successful cases reported by Eason and Wyatt, in 1979 (Eason & Wyatt, 1979). With the advent of ultrasound into the clinical practice of anesthesia, the performance of PVB evolved from a loss of resistance technique (Eason & Wyatt, 1979) to an ultrasound-guided approach (Pace et al., 2016). Nonetheless, the proximity with pleura and vascular structures makes the PVB challenging, even in expert hands (Pace et al., 2016). Thus, there is a need for including basic and simpler approaches for regional blocks in anesthetic training programs, so most patients can obtain benefit of the regional anesthesia techniques (El-Boghdadly & Pawa, 2017).

Accordingly, there has been a growing interest in the potential benefit of erector spinae plane (ESP) block in the context of postoperative pain management. Although this technique was first proposed by Forero et al. for the management of thoracic neuropathic pain (Forero et al., 2016), recently it has emerged as an alternative to PVB for the postoperative pain management of patients undergoing VATS, in which TEA or PVB are contraindicated (Forero et al. 2016, Wilson et al. 2018). Despite the novelty of this technique, ultrasound-guided ESP block has been reported to be successfully used in a wide range of procedures, depending on the level of the spine blocked.

In the context of thoracic surgery, case reports and cases series have been published to document the successful application of ESP block for VATS lobectomies (Forero et al. 2016, Luis-Navarro et a. 2017 & Scimia et al. 2017) and excision of thoracic tumors (Wilson et al. 2018, Cesur et al. 2018). However, clinical trials are warranted to confirm the potential benefit of ESP block in patients undergoing VATS lobectomy, as the current evidence continues to be scarce. Therefore, a randomized, single blinded, non-inferiority clinical trial will be conducted to evaluate the role of ESP blocks in the postoperative pain management of VATS lobectomies, when compared with PVB.

METHODS

Study design and recruitment

This is a prospective, parallel, randomized, single-blinded, non-inferiority clinical trial protocol for a pilot study. In the context of a non-inferiority design, the null hypothesis of ESP block inferiority as compared to PVB will be tested in patients admitted in hospital with diagnosis of early-stage lung cancer, and eligible to undergo pulmonary lobectomy under VATS. Thus, using a convenience sampling strategy, participants will be enrolled consecutively by a research nurse, who will gain the consent of patients at the time of admission (Figure 1).

Randomization

A random 1:1 ratio allocation sequence will be computer generated by principal investigator, in order to randomize participants to receive either ESP block or PVB. To diminish the risk of selection bias, the randomization will use random block sizes, using computer-generated sequences. To assure allocation concealment, patients will be randomly assigned to either group using sequentially numbered, opaque and sealed envelopes, which will be opened by a recruiting research nurse, and revealed to the anesthesiologist assigned for the case, immediately before starting the block. .

Blinding

All participants will be blinded to the intervention. Likewise, research nurses in charge for the electronic data recording and statisticians involved in the data analysis will not be aware of the treatment allocation. Although anesthesiologists will not be blinded, they will be told not to disclose the allocation of the patient to the theatre and recovery staff, when possible. Emergency unblinding will only take place, should the patient present a life-threatening complication (i.e., cardiopulmonary arrest, accidental intravascular injection of local anesthetics, or pneumothorax).

Eligibility criteria

Inclusion criteria: -Patients with age ranging between 18 and 85 years old and weight between 50 and 90 kg, diagnosed of early-stage non-small cell lung cancer, and admitted for elective VATS lobectomy to the thoracic unit of a tertiary referral hospital.

Exclusion criteria: -Morphine allergy. -Local anesthetics allergy. -Patients in treatment with opioids. -

Patients with history of chronic pain. -Refusal of having a PVB or ESP block.

Outcomes

The Primary outcome (Figure 1): - Pain score, measured by an 11-point (0 to 10) Visual Analogue Scale (VAS) score for pain intensity at rest and on movement (Todd & Funk 1996, Luis-Navarro et al. 2017).

Secondary outcomes: -Pain score, measured by an 11-point (0 to 10) VAS score for pain intensity at 30 min, and at 6, 12 and 24 hours after arrival to the recovery area (Todd & Funk 1996, Luis-Navarro et al. 2017). -Morphine consumption at 24 hours. -Time of performance of the block, from needle insertion until needle removal. -Rate of immediate complications: block failure (VAS score >=5 at 30 minutes), vascular puncture (aspiration of blood), pleural puncture (aspiration of air), epidural or intrathecal spread (aspiration of cerebrospinal fluid), and hypotension or bradycardia (decrease of blood pressure or heart rate, respectively, of more than 25%, compared with the baseline measurement recorded immediately after the block).

Procedures

Considering that ESP block is a novel and evolving technique, a clinical trial protocol for a pilot study is described. Four thoracic anesthesiologists with experience in PVB, who are to be involved in the performance of all blocks, will be specifically trained for three months in the ESP block technique by a colleague with expertise in regional anesthesia, before the recruitment of patients.

Standard cardiovascular monitoring will be used for all patients. Irrespective the block technique used, all participants will undergo a VATS lobectomy under general anesthesia, using a target-controlled infusion (TCI) of propofol. After the anesthetic induction and intubation, participants will be turned to the lateral position, with the hemithorax to be blocked uppermost, to facilitate the performance of the block (Scimia et al., 2017). The skin will be prepared with a 2% chlorhexidine and 70% isopropyl alcohol solution, and the T5 spinous process will be identified by palpating the C7 spinous process and counting down the thoracic vertebrae. For all cases, a SonoSite S-Nerve ultrasound machine (SonoSite Inc., Bothell, USA) will be used with a 13-6 MHz frequency linear probe, to identify the T5 transverse process and advance an echogenic, 18G, 90 mm short beveled block needle (Pajunk SonoTAP, Geisingen, Germany). Depending on the allocated group, unilateral ESP block or PVB will be performed by one of four investigators, by administering 30 ml of 0.25% bupivacaine without

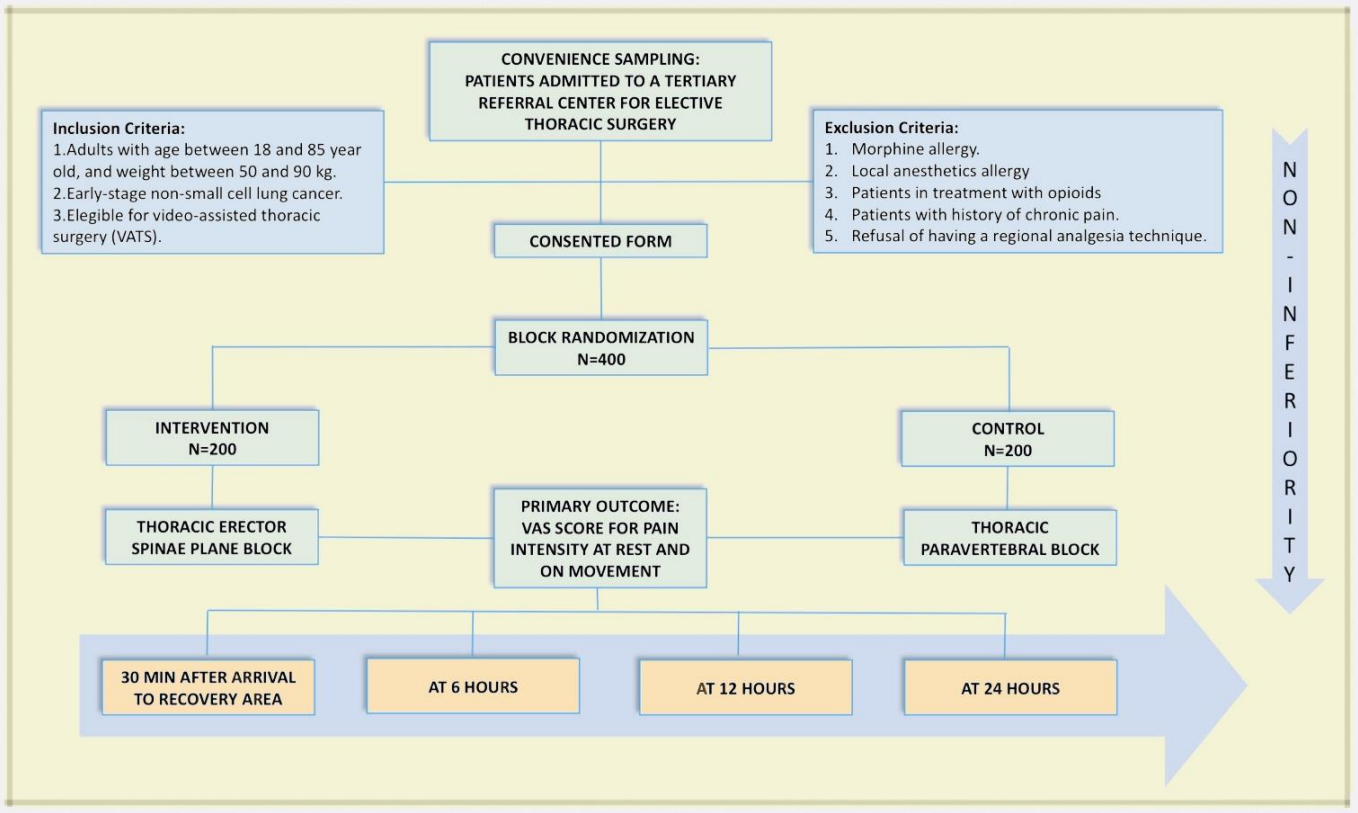

Fig. 1. Study timeline. VAS: Visual Analogue Scale for pain intensity. See text for further details.

vasoconstrictor. Standard multimodal analgesia, including intravenous paracetamol, non-steroidal anti-inflammatory drugs, dexamethasone and morphine will be administered to all patients, at the discretion of the anesthesiologist. Additionally, intravenous boluses of morphine will be prescribed as required in the recovery period, followed by intravenous morphine patient-controlled analgesia (PCA) and paracetamol on a regular basis (15 mg/kg every 6 hours, with a maximum dosage of 4 grams a day).

Interventions

Paravertebral block: After a proper identification of the T5 transverse process, the ultrasound probe will be placed perpendicular to the long axis of the spine, keeping the medial edge of the probe in contact with the T5 spinous process, to obtain a transverse view of the corresponding rib. After moving the probe caudally, the intercostal space will be identified by visualizing the external intercostal muscle, along with the internal intercostal membrane. Immediately deep to this structure, and superficial to the pleura, the apex of the paravertebral space will be identified as a wedge-shaped structure (Shibata & Nishiwaki, 2009). Then, using the in-plane approach (i.e., keeping the long axes of the probe and the needle aligned), the block needle will be advanced with the bevel facing the probe, until it penetrates the internal intercostal membrane, and after a negative aspiration to confirm the absence of blood or air, the local anesthetic will be administered, and adequate spread along the paravertebral space will be confirmed by turning the probe to obtain a parasagittal view of the transverse processes, and visualize the cephalo-caudal spread of the anesthetic eliciting a ventral displacement of the pleura (Shibata & Nishiwaki, 2009).

Erector spinae plane block: The ultrasound probe will be placed aligned with the thoracic transverse processes, approximately 3 cms away from the midline, and parallel to the long axis of the spine. After localizing the T5 transverse process, the erector spinae muscle will be identified lying above the thoracic transverse processes, and below the rhomboid major muscle (which, in turn, is located deep to the trapezius muscle) (Forero et al., 2016). The block needle will be advanced from cranial to caudal direction, using the in-plane approach with the needle tip targeting the T5 transverse process, until the bone is gently contacted. The correct position of the needle will be confirmed by dissecting the deep fascia of the erector spinae muscle with 0.5-1 ml of saline, thus creating a space between the muscle and the T5 transverse process (Scimia et al., 2017). Then, the local anesthetic will be administered as described for PVB, and adequate spread will be confirmed by visualizing the dissection of the plane between the erector spinae and external intercostal muscles (Forero at al. 2016, Scimia et al 2017).

Data management

Data will be recorded by a research nurse, in a pro forma specifically designed for this trial. All the forms and collected files will be stored, numbered and kept in a secure and accessible place. Only authorized staff will be granted access, to protect confidentiality of patients. Subsequently, two research nurses, who will be blinded for the intervention, will be in charge for the electronic recording of data in an Excel spreadsheet. To protect electronic data, the Excel file will be password-secured. The password will be changed on a regular basis, and only accredited staff will be allowed to edit data, previous authorization and justification. Additionally, typos and missing data will be monitored, and a backup copy of data will be generated monthly.

Data monitoring

An independent data monitoring committee (DMC) will be constituted before the recruitment of patients. The committee will be integrated by two anesthesiologists with expertise in the field of regional anesthesia, who will not be involved in the trial, one statistician, and one representative of patients. None of them will have any conflict of interest on the study. The purpose of this committee is to raise potential ethical issues, to monitor side effects related to the anesthetic blocks, and to assess the efficacy or futility of the intervention, based on the information provided by researchers in masked data. To this end, there will be mandatory meetings every six months until the end of the trial, and three interim analyses will be held upon completion of 25%, 50% and 75% of the sample size. Stopping boundaries for efficacy or futility will be 0.0006, 0.015 and 0.046, respectively, following the O'Brien-Fleming methodology for alpha spending (O'Brien & Fleming, 1979). At the committee discretion, further interim analyses can be triggered (with the necessary adjustments to the stopping boundaries), and sample size can be modified, based on the estimated standardized effect size and statistical power of available data. Likewise, data may be unmasked upon request of the committee, should there be any safety concerns.

Statistical analysis

All statistical analyses will be performed using Stata® 14.2 (Stata Corp, USA), applying both intention-to-treat

and per protocol methodologies. Pain scores at 30 minutes after arrival to recovery area, and morphine consumption, will be evaluated with t-test or Mann-Whitney U test, depending on the distribution of data. Likewise, pain scores at 6, 12 and 24 hours will be tested with repeated measures ANOVA (Analysis of variance) or Friedman method. To analyze the occurrence of side effects, a Fisher exact test will be preferred over chi-squared test, when possible. No post-hoc analyses are considered in advance for this clinical trial.

Based on the overall sample size estimation of 400 subjects, a total number of participants of 40 (20 per group) has been considered appropriate for this pilot study, which is in accordance to the recommended number of subjects for a pilot randomized clinical trial (Whitehead, 2016). An original sample size of 400 (200 per group) has been calculated, based on the following estimations: standard deviation of the VAS score of 2 points, statistical power of 85%, one-sided alpha critical value of 0.025, and non-inferiority margin of 0.6 (Flight & Julious 2016, Duttchen et al. 2017). This last value represents the 30% of the reported minimum clinically significant decrease in VAS score for pain intensity (Todd & Funk 1996, Duttchen et al. 2017). Since this trial will involve patients eligible for elective surgery, and the perioperative mortality following VATS for lung lobectomy is deemed to be low (Cao et al., 2012), the expected rate of dropouts is minimal, and consequently, no additional increments of the sample size has been considered.

Missing data

The rate of dropouts is expected to be low, owing to the design of the study and the short follow-up period (only 24 hours). Nonetheless, a variable amount of missing information recorded in the pro forma templates is anticipated. To diminish the impact of these missing data, every efforts will be made to enroll highly motivated staff, and train research nurses responsible for the collection of data. The potential mechanisms of missing data are expected to be missing completely at random (MCAR) or missing at random (MAR). In line with these assumptions, a regression imputation technique will be used to replace data. To assess the robustness and plausibility of this process, a sensitivity analysis will be also presented (Little et al., 2012).

Ethical aspects

This trial will be registered on the website clinicaltrials.gov. Approval from local ethical committee and written informed consent from all participants will be obtained. For the development of this protocol, all ethical principles outlined in the last version of the Declaration of Helsinki (Fortaleza, Brazil, 2013) have been followed. In particular, it is important to highlight that all patients will receive multimodal analgesia at the discretion of the anesthetist, and rescue morphine delivered via a patient-controlled analgesia (PCA) infusion will be available when needed. In addition, this protocol will need the approval of the Institutional Review Board and the local ethical committee, which will include one representative of the patients.

DISCUSSION

In this paper, a study protocol has been described to evaluate the potential role of ESP block, in the pain management of patients with lung cancer undergoing pulmonary lobectomy under VATS. For this target population, this is the first clinical trial aiming to explore the potential benefits of the technique.

Although described as early as 1912 (Eason & Wyatt, 1979), PVB has not gained popularity among anesthetists. This may be explained by the fact that the successful performance of this block demands advanced training and continuous practice to consolidate the ultrasound skills, which may be only afforded by a few anesthetists. Being aware of the significant amount of time needed to learn a single regional anesthesia technique (McCartney & Mariano, 2016), efforts should be focused on the learning of essential techniques that could be potentially included in all anesthetic training programs (El-Boghdadly & Pawa, 2017). In this context, ESP blocks emerge as an alternative to PVB.

The mechanism of action of ESP block is a matter of current debate. As a result of the proximity to the intervertebral foramen, the local anesthetic spreads into the ventral and dorsal rami and rami communicantes of the thoracic spinal nerves (Forero et al., 2016). In a cadaveric model, extensive lateral and cephalo-caudal spread, both superficial and deep to the erector spinae muscle has been reported, which is consistent with the spread of the dye along the dorsal rami (Ivanusic et al., 2018). This is explained by the close proximity of the needle to the costo-transverse foramen, and the involvement of nerves located posterior to this structure. In contrast, no involvement of the paravertebral space, the ventral rami or dorsal root ganglia was reported (Ivanusic et al., 2018). These findings suggest that, although some authors have described the ESP block as an "indirect" technique of PVB (Ueshima & Hiroshi 2017, Cornish 2018), the mechanism of action of ESP block may be different.

Irrespective the approach used to perform an ESP block, it appears that the extension of local anesthetic

spread is subject to inter-individual variability (Luis-Navarro et al. 2017). Thus, as the ESP block may not reach the same intensity of the block compared with PVB, its effectiveness is not expected to be superior. To offset these potential drawbacks, ESP block may offer interesting advantages, including the relative simplicity and grater safety of the technique (Ivanusic et al., 2018).

In line with these concepts, a non-inferiority design seems to be the best choice to explore the potential benefits of ESP block. The delta margin was selected based on a minimum clinically significant decrease of 18 mm, which has been previously reported for 100-point visual analogue pain scores (Todd & Funk, 1996). Thus, for a proportional VAS threshold of 1.8 points, a delta margin of 0.6 points (⅓ of the reported significant decrease) was considered appropriate (Duttchen et al., 2017).

The VAS score for pain intensity has been long validated as a continuous variable (Price et al., 1983). In spite of the unavoidable subjective nature of this score, it was chosen as the primary outcome, because as an 11-point scale, the definition of the non-inferiority margin is proportional to the magnitude of the scale. On the contrary, outcomes like morphine consumption pose some challenges in the establishment of the margin. For instance, if 3 mg of morphine were chosen as the non-inferiority margin, the clinical relevance of the results would be entirely different if the morphine consumption was 30 mg, as compared to, say, 5 mg. Thus, relative rather than absolute values would have been needed (Macaya et al., 2017). On the other hand, because all patients eligible for the trial are undergoing pulmonary lobectomy under VATS, and participants with history of chronic pain are excluded, the basal surgical pain score is assumed to be zero. Hence, the absolute value of VAS score will be recorded, rather than the difference obtained with the basal score.

The type and volume of local anesthetic used for ESP blocks is variable among studies (Pace et al. 2016, Shibata & Nishiwaki 2009). In this trial, 30 ml of 0.25% plane bupivacaine will be used for all blocks. Since only patients weighing between 50 and 90 kg will be included, this volume will be below the maximum allowed dose for bupivacaine of 2 mg/kg. Patients weighing >90 kg will be excluded of the trial, because the performance of PVB in these patients is usually challenging.

This study design has some limitations. Firstly, since ESP block is a relatively new approach, non-inferiority trials comparing ESP block with another technique are lacking. In addition to this, trials comparing PVB with placebo are unlikely to be conducted, because of important ethical concerns. As a consequence, the choice of the delta margin was not based on existing placebo-controlled studies (D'Agostino et al., 2003), but rather on a recently published non-inferiority trial comparing two doses of a non-steroidal anti-inflammatory drug (Duttchen et al., 2017). Thus, the conditions of assay sensitivity and constancy assumption cannot be verified (D'Agostino et al., 2003). Despite that it seems obvious that PVB is more effective than placebo, it is unknown to which extent it is superior, and therefore, the choice of the delta margin in this context is exceptionally challenging. Secondly, the study may be underpowered to evaluate the secondary outcomes, particularly because the occurrence of complications is expected to be low, and the sample size needed for detecting significant differences would be unaffordable. Thirdly, anesthesiologists involved in the trial will not be blinded. However, since they will not rate the pain scores reported by the patients, it is not expected that this lack of blinding will have any impact on the primary or secondary outcomes. Lastly, because ESP block is an emerging technique, anesthesiologists will not have expertise in the performance of the block. Despite that this may increase the external validity of the results, as most anesthetists do not perform blocks on a routine basis, anesthetists involved in this study will be specifically trained before the recruitment of patients, to prevent any impact on the trial resulting from a lack of experience on the technique.

CONCLUSION

Regional anesthesia is a continuously evolving field. However, in the context of thoracic surgery, the paravertebral block has not gained the popularity that was expected, mainly because the technique is difficult to perform, even in expert hands, and there are some concerns in regard to the occurrence of potential complications, including pneumothorax. With the recent description of the erector spinae plane block, a new and exciting pathway has opened to optimize the pain management of patients undergoing a wide range of procedures, involving thorax and abdomen. Thus, there is a need for high-quality evidence to evaluate the role of erector spinae blocks in such different scenarios.

Conflicts of interest and financial disclosure

The author followed the International Committee of Journal of Medical Journal Editors (ICMJE) form for disclosure of potential conflicts of interest. The listed author concurs with the submission of the manuscript. The final version has been approved by the author. The author has no financial or personal conflicts of interest.

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