







Opioid-free postoperative analgesia compared to traditional analgesia after thoracic surgery: scoping review

Raul Ribeiro de Andrade^{1*} , Natália de Oliveira Lima² , Marina Viegas Moura Rezende Ribeiro³ , Fernando Wagner da Silva Ramos⁴ , Célio Fernando de Sousa-Rodrigues¹ , Fabiano Timbó Barbosa⁵ 

INTRODUCTION

Patients receiving opioids for pain treatment can paradoxically become more sensitive to pain stimuli¹. This condition is known as opioid-induced hyperalgesia¹. It can explain why some patients require more opioid agents to treat their pain¹. Some factors in animal studies have been identified as a potential explanation: activation of neuroexcitatory mechanisms, long-term potentiation, and descending pain facilitation². Nociception process can be increased by neuroinflammation due to the activation of microglia and astrocytes². It also identified other factors that can be a potentiate nociception, such as toll-like receptor 4, excitatory molecules, and the anti-opioid systems².

Opioid prescription is common after surgical procedures, but it can be excessive for many patients with different pain intensities^{3,4}. Although opioids have great benefits for postoperative analgesia, adverse events and nonmedical uses can occur, and the experience can be catastrophic^{5,6}. The routine use of opioids cannot be justified for all types of surgeries, because alternative drugs can be used and low-risk surgical procedures are included in the treatment with opioids^{5,6}. Researchers have already demonstrated persistent opioid use after surgical procedures⁵⁻⁷.

Some strategies have been developed in thoracic surgery before this manuscript⁸. The guideline has been associated with reduced opioid usage, but it seems to be more appropriate to avoid opioid usage in postoperative thoracic surgery. Strategies for this purpose have to be explored further in research and disclosed in anesthesiology journals.

So, it is reasonable to identify drugs or protocol treatments to avoid the use of opioid drugs. Randomized controlled trials were published testing the effectiveness of thoracic surgery,

but until this moment, these findings have not been proven effective to be disseminated in clinical practice. The objective of this scoping review was to identify and describe the effectiveness of opioid-free postoperative analgesia when compared to opioid analgesia after thoracic surgery.

METHODS

A scoping systematic review was done to examine the available research on opioid-free postoperative analgesia after thoracic surgery. A review protocol was developed before the research and is available at <https://tinyurl.com/protocol001>.

We used the methodology proposed by Arksey and O'Malley⁹. Our protocol followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scoping Review Protocols (PRISMA-ScR) guidelines¹⁰. The method followed five consecutive stages: identifying the research question; identifying relevant studies; study selection; charting the data; and collating, summarizing, and reporting the results⁹.

The authors defined opioid-free analgesia as any postoperative pain management regimen that does not involve action on opioid receptors. It can be multimodal or unimodal, and pharmacological or nonpharmacological.

Stage 1: Identifying the research question

We planned to answer the following specific questions:

1. What drugs or combinations of them are being used effectively for opioid-free postoperative analgesia after thoracic surgery to avoid the use of opioid drugs?
2. What is the duration of postoperative analgesia?

¹Universidade Federal de Alagoas, Institute of Health and Biological Sciences – Maceió (AL), Brazil.

²Universidade Federal de Alagoas – Maceió (AL), Brazil.

³Centro Universitário CESMAC, Faculty of Medicine – Maceió (AL), Brazil.

⁴Centro Universitário CESMAC, Faculty of Biomedicine – Maceió (AL), Brazil.

⁵Universidade Federal de Alagoas, Faculty of Medicine – Maceió (AL), Brazil.

*Corresponding author: raulandrade.med@gmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on May 20, 2022. Accepted on May 22, 2022.

Stage 2: Identifying relevant studies

This review was planned to use data from systematic reviews, randomized controlled trials, and cohort studies to compare two techniques of postoperative analgesia (analgesia with opioid versus analgesia without opioid) for thoracic surgery. The following databases were searched: MEDLINE (Medical Analysis and Retrieval System Online) via PubMed (1966 to May 2021), LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde – 1982 to May 2021), and Scopus. We used terms to scan PubMed and adapted them for other databases. The search strategy for PubMed was: ((“thoracic surgical procedures”[MeSH Terms] OR “thoracic surgery”[MeSH Terms] OR thoracic surgery[Text Word]) and (“analgesics, opioid”[All Fields] OR “analgesics, opioid”[MeSH Terms] OR opioid[Text Word]) and (“analgesics”[All Fields] OR “analgesics”[MeSH Terms] OR analgesic agents[Text Word]) AND (“Pain, Postoperative”[Mesh])).

There were no restrictions on any language, date, or document format. The references of the studies included studies that were analyzed to identify other relevant studies.

Stage 3: Study selection

Titles, abstracts, and keywords were scanned to identify studies through the search strategy for all databases. Two reviewers identified studies independently. The papers identified as a possibility to answer our research questions were obtained and read in full. Discordances were settled through consensus meetings. This stage followed the PRISMA statement¹¹.

Stage 4: Charting the data

Studies identified and read in full were charted into an Excel spreadsheet. A standardized form was developed by the review team to collect data. We contacted the authors of the relevant studies when data were not clear or understandable.

Outcomes considered important for this review were as follows:

1. Primary outcomes: length of analgesia or pain scores, length of hospital stay, length of stay in the intensive care unit (ICU), frequency of complications in the postanesthesia care unit (PACU), frequency of complications during hospitalization, and degree of satisfaction.
2. Secondary outcomes: therapeutic schemes of analgesic drugs.
3. Complementary data: characteristics of the studies including design, country, year, surgical procedures, and interventions.

Outcomes in this review were defined as follows:

1. Length of analgesia is time without pain. When these data were absent, we used data from pain scores.
2. Length of hospital stay is the time elapsed between hospital admission and discharge. It was considered in days.
3. Length of stay in the ICU is the time elapsed between ICU admission and discharge. It was considered in hours.
4. Frequency of complications in the PACU is the number of adverse events that occurred in the PACU. It was described in percentages.
5. Frequency of complications during hospitalization is the number of adverse events that occurred during the time elapsed between ICU discharge and discharge from the hospital. It was considered in percentages.
6. Degree of satisfaction is the level of satisfaction with respect to the hospital stay, surgical procedures, and anesthesia received. It was considered as described by the authors of the included studies.
7. Therapeutic schemes are the combinations of drugs used and their mode of administration.

Stage 5: Data summary and synthesis of results

The characteristics of the included studies were summarized. Studies were classified according to the outcomes reported. According to some guidelines, the risk of bias is not necessary for scoping reviews^{10,12}. The authors of this review believe that general information can provide a general idea of quality assessment. The statistical analysis of the included studies was evaluated to identify statistical sources of flaws¹³.

RESULT

In total, 1847 articles were identified from the search strategy, and 20 articles were identified as relevant to this scoping review. In the selection process, eight articles were excluded due to inadequate comparators or incomplete data. Thus, 12 articles were included in this scoping review¹⁴⁻²⁵. The reference list of the included articles was analyzed to identify relevant articles, but no new articles were included in this process (Figure 1). The therapeutic regimens can be seen in Table 1, and the characteristic of included studies and critical appraisal are listed in Table 1.

Length of analgesia was evaluated in all included articles¹⁴⁻²⁵. The results were favorable to the group without an opioid in six articles^{15,18,20-24}. Kaiser et al.¹⁵ reported the effectiveness of the group without opioids [intercostal nerve infusion of 0.5% bupivacaine (20 mL) + continuous infusion of 0.5% bupivacaine

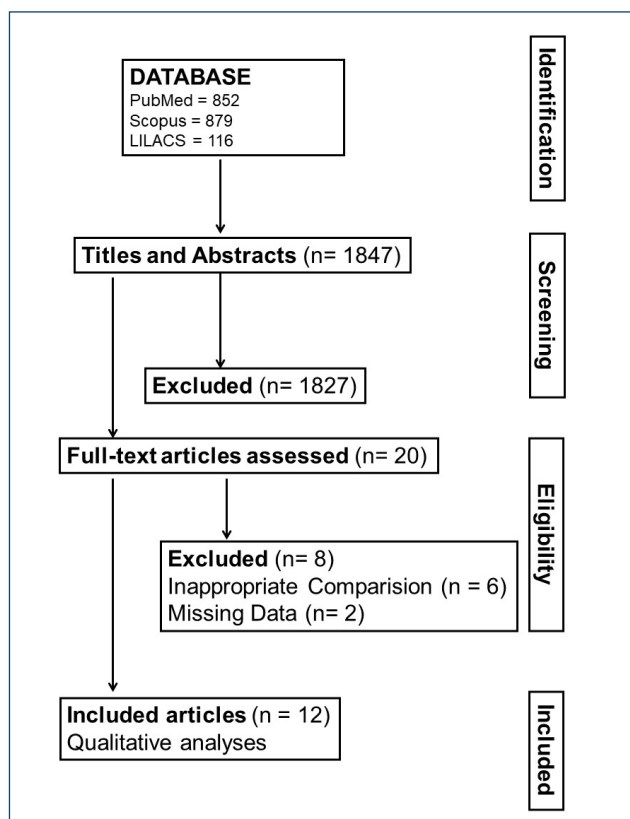


Figure 1. Flowchart of the selection process of the included articles.

(0.1 mL/kg/h) + ornipressin (0.05 U/mL) for 5 days] on the second day after surgery. El-Dawlatly et al.¹⁸ reported no difference at rest, but ketoprofen (100 mg IM) associated with bupivacaine 0.5% interpleural (0.4 mL/kg) showed effectiveness at inspiration and coughing up to 24 h. Li et al.²² reported that effectiveness of the group without opioids [flurbiprofen (50 mg intravenously)] occurred up to 8 h after surgery. Biçer et al.²³ reported greater effectiveness in the group where there was a combination of 0.5% bupivacaine (20 mL) + dexmedetomidine (100 µg) for up to 24 h. Deng et al.²¹ reported effectiveness for up to 48 h with ultrasound-guided continuous serratus plane block with patient-controlled nerve analgesia (continuous infusion of 0.2% (30 mL) and 0.3% (for maintenance) ropivacaine). Dastan et al.²⁴ reported superior analgesia with ketorolac (90 mg/24 h) and paracetamol (3 g/24 h) in the anesthetic recovery room and at other times up to 24 h. There was no difference between the groups when considering rest, but the result was favorable to the group without opioids during times of coughing.

Length of hospital stay was evaluated in two studies^{20,21}. Bauer et al.²⁰ reported no difference between groups. Deng et al.²¹ reported a shorter time in the opioid-free group.

Complications during hospitalization were evaluated in five studies^{17,19,20,22,25}. Yoshioka et al.¹⁷ reported more nausea and

Table 1. Characteristics of the included studies and therapeutic regimens.

Author (year)	Participants	n	Intervention	Comparison	Type of surgery	Country	Critical appraisal
Dauphin et al. ¹⁴	Inappropriate description	72	Intercostal infusion of 0.5% bupivacaine (0.3 mL/kg bolus + 0.1 mL/kg/h infusion) for 3 days	Epidural infusion of morphine (70 g/kg bolus + 7 g/kg infusion) for 3 days	Thoracotomy	Canada	Missing data
Kaiser et al. ¹⁵	Adults scheduled for anterolateral thoracotomy (lobectomy or bilobectomy without pleural resection)	30	Intercostal nerve infusion of 0.5% bupivacaine (20 mL) + continuous infusion of 0.5% bupivacaine (0.1 mL/kg/h) + ornipressin (0.05 U/mL) for 5 days	Meflumenaminic acid (500 mg 6/6 h) + continuous infusion into the epidural space of 0.25–0.375% bupivacaine (4–6 mL/h) with 2 mg/ml fentanyl	Thoracotomy (fourth intercostal space)	Switzerland	Possible failure in pain analysis
Tuncel et al. ¹⁶	ASA I and II, lung tumor, one patient with hydatid cyst in each group	60	ropivacaine 0.2% dose (mL)=height (cm) – 100/10 Infusion continues for 3 days	Ropivacaine 0.2% + sufentanil 0.75 mcg/mL dose (mL)=height (cm) – 100/10 Infusion continues for 3 days	Toracotomia posterolateral	Turkey	Postoperative infusion regimen was not clearly described
Yoshioka et al. ¹⁷	Adults, lobectomy, or partial lung resection	46	There was no detailed description of the drugs	Epidural anesthesia with 0.25% bupivacaine (5 mL in initial dose + continuous infusion associated with 1 mg fentanyl)	Video-assisted thoracic surgery	Japan	No indication that hypothesis test was used in some analysis

Continue...

Table 1. Continuation

Author (year)	Participants	n	Intervention	Comparison	Type of surgery	Country	Critical appraisal
El-Dawlatly et al. ¹⁸	ASA I and II	40	Three groups: 1 – ketoprofen (100 mg intramuscular), 2 – bupivacaine 0.5% interpleural (0.4 mL/kg), 3 – Ketoprofen (100 mg intramuscular) + bupivacaine 0.5% interpleural (0.4 mL/kg)	Pethidine 1.5 mg/kg (intramuscular)	Thoracoscopic sympathectomy	Saudi Arabia	Repeated measures analysis was not performed
Dabir et al. ¹⁹	ASA I and II	36	Intercostal space infusion of 0.25% bupivacaine (30 mL) + 10 ml of saline solution. Repeating the same solution every hour for 24 h	Intercostal space infusion of 0.2 mg/kg morphine in 40 ml of saline solution. Repeating the same solution every hour for 24 h	Posterolateral thoracotomy	Iran	Repeated measures analysis was not performed
Bauer et al. ²⁰	18 years of age and scheduled for planned video-assisted thoracic surgery under general anesthesia with thoracic paravertebral block	70	Continuous paravertebral thoracic infusion of ropivacaine (2 mg/mL)	Continuous paravertebral thoracic infusion sufentanil (0.25 mcg/mL) and ropivacaine (2 mg/mL)	Video-assisted thoracic surgery	France	Final analysis contains patients who received morphine in both groups
Deng et al. ²¹	Inappropriate description	60	Ultrasound-guided continuous serratus plane block with patient-controlled nerve analgesia – continuous infusion of 0.2% (30 mL) and 0.3% (for maintenance) ropivacaine	Patient-controlled intravenous analgesia with continuous infusion of sufentanil (sufentanil 1.5 µg/kg) + tropisetron (5 mg – diluted with normal saline to 100 mL) at a flow rate of 2.0 mL/h	Single-port thoracoscopic surgery	China	Repeated measures were analyzed with inadequate testing
Li et al. ²²	Miastenia Gravis	200	Flurbiprofen (50 mg intravenously)	Tramadol (100 mg intramuscular)	Thymectomy via mediastinal	China	Tramadol was administered intramuscularly
Biçer et al. ²³	ASA I and II, aged between 18 and 65 years old	93	Two groups of paravertebral block: 0.5% bupivacaine (20 mL) and 0.5% bupivacaine (20 mL) + dexmedetomidine (100 µg)	Intravenous morphine via patient-controlled analgesia	Thoracotomy	Turkey	Repeated measures were analyzed with inadequate testing
Dastan et al. ²⁴	ASA I and II in a referral hospital	101	Two groups: ketorolac (90 mg/24 h) and paracetamol (3 g/24 h)	Morphine 10 mg in intravenous bolus and infusion within 24 h (0.5 mg/h with a total of 10 mg)	Video-assisted thoracoscopy	Iran	Sample size may overestimate the results
Miao et al. ²⁵	ASA I and II, 18–65 years old, BMI less than 30, and lung cancer	54	Dexmedetomidine and patient-controlled postoperative intravenous analgesia with 0.1 µg/kg/h dexmedetomidine + 3 mg/kg ketorolac	Postoperative patient-controlled intravenous analgesia with 1.5 µg/kg sufentanil + 3 mg/kg ketorolac	Thoracoscopic surgery	China	Sample size cannot be verified

ASA: American Society of Anesthesiologists; BMI: Body mass index in kg/m².

vomiting in the opioid group. Dabir et al.¹⁹ reported no serious complications in both groups. Bauer et al.²⁰ and Miao et al.²⁵ reported no differences between groups. Li et al.²² reported more complications in the opioid group.

Degree of satisfaction was evaluated in one study²⁴. The authors reported no statistical difference between groups.

Length of ICU stay and frequency of complications in the PACU were not analyzed in the included articles.

DISCUSSION

This scope review demonstrated that some drugs are being used to promote opioid-free analgesia after thoracic surgery. The duration of analgesia was up to 48 h. Statistical analysis of primary studies demonstrated the presence of flaws in the choice of statistical tests. These flaws can lead to inconclusive results when considering protocols tested in the included studies. More studies are needed to clarify the controversy identified in this scope review.

Effectiveness of analgesia was seen as length of analgesia. Six studies reported favorable results^{15,18,20,22-24}, however, the time of analgesia was different between studies. Some authors of the included studies reported effectiveness in rest position and others in the cough effort. The authors of this review believe that the difference in pathologies and in surgical techniques led to different intensities of pain. It can justify differences between studies.

We identified the following therapeutic schemes as effective: intercostal nerve infusion of bupivacaine followed by continuous infusion of bupivacaine and ornipressin¹⁵, ketoprofen via intramuscular and interpleural bupivacaine¹⁸, continuous paravertebral thoracic infusion of ropivacaine²⁰, flurbiprofen via intravenously²², paravertebral block of bupivacaine and dexmedetomidine²³, and ketorolac or paracetamol via intramuscular²⁴.

Length of hospital stay analysis demonstrated that the difference between groups was only significant for a few hours, so it does not contribute to decision-making in clinical practice.

Five studies evaluated the complications^{17,19,20,22,25}. The authors considered that there was no difference between the groups or

there were reports of complications that were already expected for the group with opioids, such as nausea and vomiting. The authors of this review did not link complications to mortality.

The contribution to clinical practice from this scope review was the identification of potential drugs that can be used in daily clinical practice. The statistical flaws prevented the choice of one protocol to guide physicians. Physicians must first consider the similarity between the populations assessed in the included studies and drugs used in their daily clinical practice. The choice of analgesic protocols has to be individualized.

The contribution to future research lies in the identification of statistical flaws and the absence of data for some variables. The main statistical flaw is the lack of sample size calculation description. The description of the sample size allows the analysis of statistical power¹³. The other statistical flaw was the inappropriate choice of statistical tests that could lead to false-positive results¹³.

The main limitation of scope reviews is the absence of risk of bias analysis; however, the conclusions of this review took into account the statistical analysis used in the included studies. The other limitation of this research was considering data from different surgeries, but the purpose of the scope review is to provide a broad description of the findings for further systematic reviews and randomized clinical trials.

The opioid-free analgesia may be more effective after 2–48 h in postoperative thoracic surgery. However, there are still controversies and good quality future studies are needed to assess the effectiveness of drugs in this clinical setting. We suggest some outcomes in future studies to test effectiveness: mortality, degree of satisfaction, quality of life, and complications in patient follow-up.

AUTHORS' CONTRIBUTIONS

RRA: Conceptualization, Supervision, Writing – original draft. **NOL:** Supervision, Writing – review & editing. **MVMRR:** Writing – original draft, Writing – review & editing. **FWSR:** Data curation, Formal Analysis. **CFSR:** Data curation, Formal Analysis. **FTB:** Conceptualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician*. 2011;14(2):145-61. PMID: 21412369
2. Roeckel LA, Le Coz GM, Gavériaux-Ruff C, Simonin F. Opioid-induced hyperalgesia: cellular and molecular mechanisms. *Neuroscience*. 2016;338:160-82. <https://doi.org/10.1016/j.neuroscience.2016.06.029>
3. Hill MV, McMahon ML, Stucke RS, Barth RJ Jr. Wide Variation and excessive dosage of opioid prescriptions for common general surgical procedures. *Ann Surg*. 2017;265(4):709-14. <https://doi.org/10.1097/SLA.0000000000001993>
4. Bicket MC, Brat GA, Hutfless S, Wu CL, Nesbit SA, Alexander GC. Optimizing opioid prescribing and pain treatment for surgery: review and conceptual framework. *Am J Health Syst Pharm*. 2019;76(18):1403-12. <https://doi.org/10.1093/ajhp/zxz146>

5. Waljee JF, Zhong L, Hou H, Sears E, Brummett C, Chung KC. The use of opioid analgesics following common upper extremity surgical procedures: a national, population-based study. *Plast Reconstr Surg*. 2016;137(2):355e-64e. <https://doi.org/10.1097/01.prs.0000475788.52446.7b>
6. Wunsch H, Wijeyesundera DN, Passarella MA, Neuman MD. Opioids prescribed after low-risk surgical procedures in the United States, 2004-2012. *JAMA*. 2016;315(15):1654-7. <https://doi.org/10.1001/jama.2016.0130>
7. Lee JS, Hu HM, Edelman AL, Brummett CM, Englesbe MJ, Waljee JF, et al. New persistent opioid use among patients with cancer after curative-intent surgery. *J Clin Oncol*. 2017;35(36):4042-9. <https://doi.org/10.1200/JCO.2017.74.1363>
8. Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, Brunelli A, Cerfolio RJ, Gonzalez M, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). *Eur J Cardiothorac Surg*. 2019;55(1):91-115. <https://doi.org/10.1093/ejcts/ezy301>
9. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol*. 2005;8:19-32. <https://doi.org/10.1080/1364557032000119616>
10. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018;169(7):467-73. <https://doi.org/10.7326/M18-0850>
11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6:e1000100. <https://doi.org/10.1371/journal.pmed.1000100>
12. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol*. 2018;18:143. <https://doi.org/10.1186/s12874-018-0611-x>
13. Rodrigues CFS, Lima FJC, Barbosa FT. Importância do uso adequado da estatística básica nas pesquisas clínicas. *Rev Bras Anestesiol*. 2017;67:619-25. <https://doi.org/10.1016/j.bjan.2017.01.003>
14. Dauphin A, Lubanska-Hubert E, Young JE, Miller JD, Bennett WF, Fuller HD. Comparative study of continuous extrapleural intercostal nerve block and lumbar epidural morphine in post-thoracotomy pain. *Can J Surg*. 1997;40(6):431-6. PMID: 9416252
15. Kaiser AM, Zollinger A, De Lorenzi D, Largiadèr F, Weder W. Prospective, randomized comparison of extrapleural versus epidural analgesia for postthoracotomy pain. *Ann Thorac Surg*. 1998;66(2):367-72. [https://doi.org/10.1016/s0003-4975\(98\)00448-2](https://doi.org/10.1016/s0003-4975(98)00448-2)
16. Tuncel G, Ozalp G, Savli S, Canoler O, Kaya M, Kadiogullari N. Epidural ropivacaine or sufentanil-ropivacaine infusions for post-thoracotomy pain. *Eur J Cardiothorac Surg*. 2005;28(3):375-9. <https://doi.org/10.1016/j.ejcts.2005.05.017>
17. Yoshioka M, Mori T, Kobayashi H, Iwatani K, Yoshimoto K, Terasaki H, et al. The efficacy of epidural analgesia after video-assisted thoracoscopic surgery: a randomized control study. *Ann Thorac Cardiovasc Surg*. 2006;12(5):313-8. PMID: 17095972
18. El-Dawlatly A, Al-Dohayan A, Almajed M, Turkistani A, Manaa E, Elsayed M, et al. Pain relief following thoracoscopic sympathectomy for palmar hyperhidrosis: a prospective randomised double-blind study. *Middle East J Anaesthesiol*. 2008;19(4):757-65. PMID: 18630763
19. Dabir S, Parsa T, Radpay B, Padyab M. Interpleural morphine vs bupivacaine for postthoracotomy pain relief. *Asian Cardiovasc Thorac Ann*. 2008;16(5):370-4. <https://doi.org/10.1177/021849230801600506>
20. Bauer C, Pavlakovic I, Mercier C, Maury JM, Koffel C, Roy P, et al. Adding sufentanil to ropivacaine in continuous thoracic paravertebral block fails to improve analgesia after video-assisted thoracic surgery: A randomised controlled trial. *Eur J Anaesthesiol*. 2018;35(10):766-73. <https://doi.org/10.1097/EJA.0000000000000777>
21. Deng K, Xu SJ, Qian YF, Chen GD, Yuan XZ, Zhou XY, et al. Application of continuous serratus plane block with patient-controlled analgesia on postoperation analgesia after thoracoscopic surgery. *Zhonghua Yi Xue Za Zhi*. 2018;98(8):570-5. <https://doi.org/10.3760/cma.jissn.0376-2491.2018.08.003>
22. Li Y, Dong H, Tan S, Qian Y, Jin W. Effects of thoracic epidural anesthesia/analgesia on the stress response, pain relief, hospital stay, and treatment costs of patients with esophageal carcinoma undergoing thoracic surgery: a single-center, randomized controlled trial. *Medicine (Baltimore)*. 2019;98(7):e14362. <https://doi.org/10.1097/MD.00000000000014362>
23. Biçer C, Ünal EN, Aksu R, Önal Ö, Güneş I. Addition of dexmedetomidine to bupivacaine in ultrasonography-guided paravertebral blockade potentiates postoperative pain relief among patients undergoing thoracotomy. *Rev Bras Anestesiol*. 2019;69(2):144-51. <https://doi.org/10.1016/j.bjane.2018.12.004>
24. Dastan F, Langari ZM, Salamzadeh J, Khalili A, Aqajani S, Jahangirifard A. A comparative study of the analgesic effects of intravenous ketorolac, paracetamol, and morphine in patients undergoing video-assisted thoracoscopic surgery: a double-blind, active-controlled, randomized clinical trial. *Ann Card Anaesth*. 2020;23(2):177-82. https://doi.org/10.4103/aca.ACA_239_18
25. Miao Z, Wu P, Wang J, Zhou FC, Lin Y, Lu XY, et al. Whole-course application of dexmedetomidine combined with ketorolac in nonnarcotic postoperative analgesia for patients with lung cancer undergoing thoracoscopic surgery: a randomized control trial. *Pain Physician*. 2020;23(2):E185-93. PMID: 32214297

