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

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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 intensities3,4. 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 opioids3,6. Researchers have already demonstrated persistent opioid use after surgical procedures3-7.

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?
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 statement.

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.

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. 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 flaws.

RESULT
In total, 1,847 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 review. The reference list of the included articles was analyzed to identify relevant articles, but no new articles were included in this process. 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 articles. The results were favorable to the group without an opioid in six articles. Kaiser et al. reported the effectiveness of the group without opioids [intercostal nerve infusion of 0.5% bupivacaine (20 mL) + continuous infusion of 0.5% bupivacaine...
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 | Meflumennaminic 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 thoracotomy surgery | Japan | No indication that hypothesis test was used in some analysis |

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

| Author (year) | Participants | n | Intervention | Comparison | Type of surgery | Country | Critical appraisal |
|---------------|--------------|---|--------------|------------|-----------------|---------|-------------------|
| El-Dawlatly et al.20 | 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.21 | 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.22 | 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.23 | 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.24 | Miastenia Gravis | 200 | Flurbiprofen (50 mg intravenously) | Tramadol (100 mg intramuscular) | Thymectomy via mediastinal | China | Tramadol was administered intramuscularly |
| Biçer et al.25 | 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.26 | 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 |
| Mia et al.27 | 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.
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vomiting in the opioid group. Dabir et al.\textsuperscript{19} reported no serious complications in both groups. Bauer et al.\textsuperscript{20} and Miao et al.\textsuperscript{25} reported no differences between groups. Li et al.\textsuperscript{22} reported more complications in the opioid group.

Degree of satisfaction was evaluated in one study\textsuperscript{24}. 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\textsuperscript{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 ornipressin\textsuperscript{15}, ketoprofen via intramuscular and interpleural bupivacaine\textsuperscript{16}, continuous paravertebral thoracic infusion of ropivacaine\textsuperscript{20}, flurbiprofen via intravenously\textsuperscript{22}, paravertebral block of bupivacaine and dexmedetomidine\textsuperscript{23}, and ketorolac or paracetamol via intramuscular\textsuperscript{24}.

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\textsuperscript{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 power\textsuperscript{13}. The other statistical flaw was the inappropriate choice of statistical tests that could lead to false-positive results\textsuperscript{13}.

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.

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