

## Peer Review File

**Article Information:** <https://dx.doi.org/10.21037/jtd-23-241>

### Reviewer A

**We would like to thank this reviewer for the critical appraisal and valuable comments on our manuscript.**

This is the review for the postoperative analgesia after esophagectomy. This review described several kinds of analgesia for esophagectomy, including regional analgesia such as paravertebral block, erector spinae plane block, intercostal block and serratus anterior block. Because there was a small number of studies of postoperative analgesia after esophagectomy, the author explained the characteristic of regional analgesia by referring the study of postoperative analgesia after thoracotomy. It is difficult to follow and understand the usefulness of regional analgesia after esophagectomy. **Comment 1** I recommend the authors to create an additional table summarizing regional analgesia after esophagectomy to help reader understand the optimal analgesia after esophagectomy.

**Reply 1:** We agree with the reviewer that the information on the anesthesia techniques can be difficult to follow. We have added the requested table.

### Changes manuscript page 19

An overview of the benefits and disadvantages can be found in table 3. Table 4 shows an overview of studies focusing specifically on analgesia after esophagectomy.

Major comments:

#### 1) Multimodal systemic analgesia

The author described the roll of opioids as only two sentences. However, IV PCA with opioids is widely used for analgesia after esophagectomy. **Comment 2** The author should describe the roll of opioids compared with other analgesia modalities, and as rescue analgesics for poorly controlled analgesia during multi-modal non-opioid medications.

**Reply 2:** IV PCA with opioids are indeed widely used as rescue analgesics. However, systemic opioids alone after esophagectomy are usually only used when regional anesthesia is not possible. Current literature mostly compares systemic opioids alone with regional anesthesia. We have elaborated on the use of systemic opioids alone.

### Changes manuscript page 6:

Fares et al. described mean VAS scores at rest below 30 in patients with systemic opioids during the first three postoperative days after Ivor Lewis esophagectomy.<sup>25</sup> The mean VAS

score at rest in the study by Flisberg et al. for patients after thoracoabdominal esophagectomy (exact approach not described) with PCA morphine was also low: below 20.12

2) Paravertebral block was written focused on video assisted technique. Recently ultrasound-guided paravertebral block has become popular. Ultrasound-guided paravertebral block has a high success rate with few adverse effects. **Comment 3** The author should describe ultrasound-guided paravertebral block as one paragraph.

**Reply 3:** We thank the reviewer for pointing this out. In paravertebral analgesia, our focus is indeed on the placement under videoscopic view, as this is easily achieved and under direct vision in esophagectomy.

**Changes manuscript** page 11

We described the ultrasound-guided paravertebral block in a separate paragraph.

Ultrasound guided technique

With ultrasound-guiding, the para-sagittal and the transversal approach are most common and described extensively elsewhere.<sup>69,70</sup> Depending on the transducer position, either the lateral rib, the tip of the transverse process or the inferior articular process needs to be identified. Cadaver studies showed that, even when the tip of the needle is correctly placed in the paravertebral space using an ultrasound guided technique, the catheter for continuous analgesia is often misplaced, being distant from the tip of the needle.<sup>71,72</sup>

**Reviewer B**

**We would like to thank the reviewer for the comments on our manuscript.**

**Comment 4** Is the rate of urinary retention the same if only local anesthetics are used?

**Reply 4:** Urinary retention during epidural analgesia can be caused both by local anesthetics and opioids. The onset and duration depends on the local anesthetic or opioid used, depending on their pharmacokinetic properties. We adjusted the manuscript to clarify this.  
DOI: 10.1097/ALN.0b013e31819f7aea

**Changes manuscript** page 7:

It can be caused by epidural local anesthetics, as well as epidural opioids.<sup>42</sup>

**Comment 5** Did you find the same results (urinary retention, hypotension, neurologicals events if only opiates are used in the epidurals?

**Reply 5:** In epidurals for esophagectomy, most commonly both an opioid and a local anesthetic are used. Literature on epidurals with only opioids in esophagectomy was not found. Neurological events (such as epidural hematoma or abscess) are not dependent on drug of choice, but are due to the catheter insertion itself.

## **Reviewer C**

**We thank this reviewer for the thorough review of our manuscript and evaluation of our study.**

This paper covers an interesting topic that is important with respect to pain management in thoracic surgery and efforts to mitigate the use of opioids and improve patient outcomes. I applaud the authors interest in the topic and efforts at detailing the current literature. However, it is not clear to me the type of manuscript being submitted. **Comment 6** Is this an invited commentary, a review of the literature such as a systematic review or meta-analysis?

**Reply 6:** This study is a narrative review, which was written on invitation. We have added a literature search as described in the author guidelines for narrative reviews. To clarify this, we adjusted the abstract.

**Changes manuscript page 2:**

In this narrative review, we provide a comprehensive overview of the available evidence for the different analgesia regimens for esophagectomy.

Page 5:

A ~~systematic~~ search was conducted in the PubMed/MEDLINE database in November 2022.

There are a few areas to address before this manuscript is suitable for publication:

Abstract:

**Comment 7** Sentences should be as concise as possible. (line 21- remove the words “however” and “more”).

**Changes manuscript page 2:**

In the last decades, ~~however~~, regional anesthesia including epidural and paravertebral analgesia is ~~more~~ frequently used. [...] In the last decades, the ~~potential~~ side-effects of epidural analgesia became more evident.

**Comment 8** The research question is not stated clearly. Are you interested in optimal pain management in preventing pneumonia or chronic pain?

**Reply 8:** To clarify the aim of the study, we adjusted the abstract.

**Changes manuscript page 2:**

In this narrative review, we provide a comprehensive overview of the available evidence for the different analgesia regimens for esophagectomy.

**Comment 9** The conclusion of your abstract is more appropriate in the conclusion of your manuscript. The conclusion in the abstract should tell the reader what you found as a result of your research- why are you suggesting that future studies should focus on more research, what was it that you found in your study that leads to this conclusion?

**Reply 9:** We agree with the reviewer that the conclusion in the abstract is not showing our reflections of the analgesia regimens and have adjusted the abstract.

**Changes manuscript page 2**

Epidural analgesia is most common, however paravertebral analgesia is a good alternative. Other techniques are also gaining ground but randomized clinical trials are lacking.

Introduction:

**Comment 10** Line 56, How do you know evidence of EA was weak- please include a reference.

**Reply 10:** In most studies the pain scores after esophagectomy are similar in TEA as compared to systemic opioids. As referenced earlier in the manuscript, the systematic review and meta-analysis by Visser et al. showed no significant differences. We have added this reference.

**Comment 11** The introduction nicely incorporates how surgical approach impacts pain but I am still left wondering what this paper is about- surgical approach or pain management. The intro should be revised to be more concise and limit the extended discussion of surgical technique.

**Reply 11:** Thank you for pointing this out. We agree with the reviewer that we should mention the pain due to surgery earlier in the introduction.

**Changes manuscript page 3**

See introduction page 3.

Methods:

**Comment 12** If this paper is a systematic review, please refer to the PRISMA guidelines regarding how to prepare your presentation. In the methods section, you need to expand your reporting to show the time frame of the research publications, not the date you pulled the papers. What article types did you review and how many of each? Were these randomized studies or case reports? How many of each? What were the specific outcomes of each? Did you discard

any publications and if so for what reason?

**Reply 12:** This is a narrative review. We have added the search according to the author guidelines. We did not perform a systematic review, and therefore, did not provide a flowchart and such.

**Comment 13** The first time a word is abbreviated, it must be written out. There are several areas where this is not done (line 79, 97, 162)

**Reply 13:** We agree with the reviewer and have gone over the abbreviations in the manuscript.

**Changes manuscript** page 6:

However, opioids can lead to opioid-induced hyperalgesia (OIH), chronic pain and opioid dependence and should therefore be limited where possible.<sup>26</sup>

Page 7:

A meta-analysis by Visser et al. reported, in (mostly open) esophagectomy, mean difference in Numeric Rating Scale (NRS) score 0.89 with 95%CI -0.47 – 2.24) for epidural analgesia compared to systemic analgesia and no additional beneficial effect on postoperative complications.<sup>6</sup>

Page 9:

Bupivacaine is the LA of choice in most studies on paravertebral block (PVB).<sup>49–51</sup>

Page 14:

Those patients received unfractionated heparin 300 UI/kg intraoperatively and vitamin K anticoagulants postoperatively, to achieve an International Normalized Ratio (INR) of 2 - 2.5.

**Comment 14** I am not sure of the relevance to include the statements specific to anticoagulation. This is a known contraindication in the surgical field and not to main theme of your topic (lines 110-115).

**Reply 14:** Though we agree with the reviewer that anticoagulation is usually stopped before surgery, in some cases it needs to be resumed shortly after. When an epidural is in place, the catheter still needs to be removed. This means the anticoagulation cannot be resumed until after the epidural is removed. This prevents early resumption of anticoagulation, which most often results in omitting the epidural. We therefore believe this information is very relevant.

**Comment 15** In some of the papers you discuss, you do not include the specific significant outcomes which would be meaningful to the reader. This would decrease the potential for the reader to interpret your paper with any bias.

**Reply 15:** We have added the outcomes of the papers.

**Changes manuscript page 8**

A Cochrane review by Yeung and colleagues (including mostly studies with the video assisted technique) showed that PVB leads to similar postoperative pain scores (measured with the NRS) as EA in thoracotomy (both minimally invasive and open surgery) at 24 and 48 hours after surgery (standardized mean difference of 0.16 and 0.12 respectively).<sup>41</sup> According to this review, the risk of hypotension (Risk Ratio (RR) 0.16), urinary retention (RR 0.22), itching (RR 0.29), nausea and vomiting (RR 0.48) is lower for PVB compared to EA.

Page 13

Turhan and colleagues reported lower pain scores for PVB (n=35) versus ESPB (n=35) in patients undergoing video assisted thoracoscopic lung surgery (median VAS 1 vs 3 at 12 hours and 1 vs 2 at 24 hours, respectively).<sup>80</sup>

Page 15

INB leads to similar pain scores as EA (mean difference of 0.41 at rest, 0.79 during movement at 24 hours after surgery), but at the cost of a higher opioid consumption (mean difference 3.77 MMEs at 24 h and 48.31 MMEs at 48 h postoperatively). When comparing INB with PVB, INB resulted in higher pain scores (difference of 1.29 points at 7-24 hours postoperatively) and higher opioid consumption only after 48 hours postoperatively (mean difference 3.87 MMEs).<sup>92</sup>

**Comment 16** Cryoanalgesia: the papers you reference are old and this is why it is important to document the years of publication that your search included as the most recent evidence related to cryoanalgesia shows that older studies were done with varying probe settings (temp and time) and modern research has clarified the appropriate settings to achieve promising outcomes.

**Reply 16:** The papers we referenced on cryoanalgesia are from 2001 to 2013. We added the nuance of probe settings the reviewer is mentioning.

**Changes manuscript page 18**

Studies found on cryoanalgesia are from 2001 to 2013. Most studies on cryoanalgesia use different probe settings with regard to temperature and duration, which may cause these conflicting results. With the right probe settings, further improvement may be possible.

**Comment 17** Line 259 is misleading. You do not clearly explain the two comparison groups for the reader to make an informed decision about the outcomes. This study looked at a surgical technique vs. application of cryo.

**Reply 17:** We agree with the reviewer and have specified this in the manuscript.

**Changes manuscript** page 17

A randomized study including 160 esophagectomy patients with posterolateral thoracotomy demonstrated that cryoanalgesia, freezing the fourth up to eighth intercostal nerve with  $-60^{\circ}$  Celsius, led to similar pain scores, for both acute pain during the first postoperative week and chronic pain at one year postoperatively compared to non-divided intercostal muscle flap.<sup>96</sup>

**Comment 18** Line 262 is misleading as well. You state “cryo ...increased post-operative pain” however this is only partially true. This study showed that at 6 months there were no differences between groups with respect to pain levels.

**Reply 18:** We added the nuance the reviewer is mentioning.

**Changes manuscript** page 17

Cryoanalgesia in combination with EA increased postoperative pain in comparison to EA only in the first postoperative weeks. Six months after surgery when pain scores were similar in a randomized clinical trial including 42 thoracotomy patients.<sup>97</sup>

**Comment 19** Conclusion:

You included cryoanalgesia specifically in your paper yet, did not include your opinion in this section.

**Reply 19:** We only included epidural and paravertebral blocks in the conclusion, as evidence is most clear in these subjects.