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Anesthesiology and Pain Medicine
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Peer Review Report for "A Literature Review of Intrathecal Morphine Analgesia in Patients Undergoing Major Open Hepato-Pancreatic-Biliary (HPB) Surgery"

Author(s): Jefferson Zhi Jie Tang, Laurence Weinberg

Review Timeline:

Submit Date:	25 May 2019
Revised Date:	25 Oct 2019
Accepted Date:	12 Nov 2019

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0)

16 Aug 2019

Dear AE,
I am not sure it is possible to compare the primary and secondary outcomes of published articles unless the research methodology is exactly the same.
- Page 4, Paragraph 2
1. Recently epidural analgesia has been considered the cornerstone analgesic modality for major surgeries due to its ability to provide superior postoperative pain control (as measured by visual analogue pain scores at rest and on movement) compared to intravenous opioid administration.7
**This reference does not directly refer to epidural anesthesia. This refers to ERAS
- Page 7
- Study characteristics
1. Eleven studies were included in the review27, 30-39 as shown in the PRISMA diagram (Figure 1). Six of the studies were RCTs30-32, 34, 36, 39, one study was a retrospective observational studies27, 35, one study was a prospective observational study37, and one study was a systematic review.38
**These references refer to different parameters. The methodology is not comparable

- Page 8, paragraph 4

1. Four studies assessed length of stay (LOS) and each independently found that LOS was significantly longer in patients treated with epidural analgesia.

**There could be many reasons for longer length of stay!! Can the authors confirm if LOS was directly related to epidural?

- Page 12

- Quality and methodological limitations

1. The analgesic regimens, healthcare settings and outcomes measured varied largely amongst the selected papers.

**Are authors justified in making recommendations if there are variations?

- Page 13

- Conclusion

1. Based on the limited number of trials discovered, this review suggests that single-shot intrathecal morphine may be more appropriate than epidural analgesia as a first-line analgesic technique for major open hepato-pancreatic-biliary surgery.

**How reliable is this recommendation?

Thanks.

REFEREE: Associate Editor | **Revision** (0) 16 Aug 2019

Dear EIC,

Based on reviewer comments this manuscript needs minor revision

Regards

AE

REFEREE: EIC | **Revision** (0) 16 Aug 2019

Dear Author,

Your article is reviewed by the reviewers carefully. According to their comments, this document needs minor revision. Please follow their comments as requested.

Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Prof. Farnad Imani
Anesthesiology and Pain Medicine

18th August 2019

Dear Professor Imani

Re: Manuscript ID: 94441
A literature review of intrathecal morphine analgesia in patients undergoing major open hepato-pancreatic- biliary (HPB) surgery

On behalf of my co-authors I would like to thank you and your expert Reviewer for taking the time to review our submission. We appreciate the constructive and insightful comments provided. As requested, we attach:

1. A word file including our itemised replies to the reviewers' comments
2. A highlighted manuscript word file highlighting the changes made in **red** in the word file

Expert Reviewer 1:
We thank the Reviewer for their expert comment.

Reviewer comment: *I am not sure it is possible to compare the primary and secondary outcomes of published articles unless the research methodology is exactly the same.*

Authors Response: Thank you for this very considered comment. We agree with the reviewers that it is very challenging comparing the primary and secondary outcomes of published articles unless the research methodology is exactly the same. We have also acknowledged this important comment in our discussion section by stating "*For these reasons we acknowledge that comparing the primary and secondary outcomes between different trials, each with unique and differing research methodologies, is challenging and limits the findings of our review*" .Our study objectives were to identify a wide range of international studies assessing intrathecal morphine against alternative analgesia modalities. We understood a detailed quality assessment using the Downs and Black method to assess the methodological quality of each included paper we included. With different research methodologies, we acknowledge the limitations in the study design and inconsistency and imprecision in the reporting of some of the results. Further, for transparency we have clearly provided a detailed overview of each of the studies' analgesic regimes (Table 2), pain scores at rest (Table 3) and on movement (Table 4) at 24 hours postoperatively, to clearly different the important differences between each study in our review.

Reviewer comment: *Page 4, Para 2. Recently epidural analgesia has been considered the cornerstone analgesic modality for major surgeries due to its ability to provide superior postoperative pain control (as measured by visual analogue pain scores at rest and on movement) compared to intravenous opioid administration.7 **This reference does not directly refer to epidural anaesthesia. This refers to ERAS.*

Authors Response: Thank you for pointing out this important oversight. The statement is correct the Reviewer has correctly pointed out that the reference does not refer to epidural anaesthesia. The correct reference is *"Rigg JR, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, Parsons RW, et al.; MASTER Anaethesia Trial Study Group. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet 2002 Apr;359(9314):1276-82"* .This has been corrected in our references. We have now changed the reference as per this statement.

Reviewer comment: *Reviewer: Page 7 Study characteristics. Eleven studies were included in the review[27, 30-39] as shown in the PRISMA diagram (Figure 1). Six of the studies were RCTs[30-32, 34, 36, 39] one study was a retrospective observational studies[27, 35], one study was a prospective observational study[37], and one study was a systematic review.[38] **These references refer to different parameters. The methodology is not comparable.*

Authors Response: Thank you for this very important comment. We strongly agree with the reviewer that the methodology for Reference 38 is not comparable against the other 10 studies. For this reason, we had very clearly stated in Table 1 and Table 2 that this study specifically refers to a systematic review. On reflection, we agree with the Reviewer that this study should not form part of our review and accordingly have removed this from our inclusion criteria. We have modified the Prisma Flow diagram, and all parts of the results that refer to this study. Thank you once again for this constructive comment.

Reviewer comment: *Reviewer: Page 8, para 4. Four studies assessed length of stay (LOS) and each independently found that LOS was significantly longer in patients treated with epidural analgesia. **There could be many reasons for longer length of stay!! Can the authors confirm if LOS was directly related to epidural?*

Authors Response: Thank you for this insightful comment. In these three studies:

1. Sakowska M, Docherty E, Linscott D, Connor S. A change in practice from epidural to intrathecal morphine analgesia for hepato-pancreato-biliary surgery. *World J Surg* 2009 Sep;33(9):1802-8. doi: 10.1007/s00268-009-0131-2. [PMID: 19548026].

2. Koea JB, Young Y, Gunn K. Fast Track Liver Resection: The Effect of a Comprehensive Care Package and Analgesia with Single Dose Intrathecal Morphine with Gabapentin or Continuous Epidural Analgesia. *HPB Surg* 2009 Dec;2009:271986. doi: 10.1155/2009/271986. [PMID: 20029637].

3. Kasivisvanathan R, Abbassi-Ghadi N, Prout J, Clevenger B, Fusai GK, Mallett SV. A prospective cohort study of intrathecal versus epidural analgesia for patients undergoing hepatic resection. *HPB (Oxford)* 2014 Aug;16(8):768-75. doi: 10.1111/hpb.12222. [PMID: 24467320].

There was a statistically significant increase in the length of stay in patients treated with epidural analgesia in comparison to patients treated with intrathecal morphine. Please see the table below, which summarised the studies that compare length of stay in patients receiving epidural analgesia to other modalities.

In terms of reasons for for reduced length of stay in patients treated with intrathecal morphine, they are likely to be multifactorial. They include increased quality of analgesia (and hence reduced pain scores at rest and movement), reduced postoperative intravenous fluid administration (hence reducing the risk of fluid overload and quicker return to oral intake of fluid), and absence of epidural motor block allowing for early mobilisation (and hence quicker return to baseline function).

TABLE 2 - LOS outcomes

First author, year of publication	Modality 1	Length of stay (days)	Modality 2	Length of stay (days)	p-value
Sakowska, 2009	ITM	7 (Range: 3-55)	Epidural	9 (Range: 3-36)	<0.01*
Roy, 2006	ITM	-	Placebo	-	-
Kasivisvanathan, 2013	ITM + PCA	11 (IQR: 9-13)	Epidural	13 (IQR: 11-15)	0.011*
Koea, 2009	ITM	4.7 ± 0.9	Epidural	6.8 ± 1.2	0.02*
De Pietri, 2006	ITM	-	Epidural	-	-
Devys, 2002	ITM + PCA	-	PCA	-	-
Ko, 2008	ITM + PCA	10.8 ± 2.8	PCA	10.7 ± 2.9	-
Lee, 2013	ITM	15.0 ± 7.2	CWI	17.9 ± 11.6	0.44
Dichtwald, 2016	ITM	11.2 ± 9.5	IVO	10.6 ± 8.0	-
Duncan, 2007	ITM	9 Range (8-14.5)	Epidural	12 Range (9-15)	-

Reviewer comment: *Reviewer: Page 12 Quality and methodological limitations*
*The analgesic regimens, healthcare settings and outcomes measured varied largely amongst the selected papers. **Are authors justified in making recommendations if there are variations?*

Authors Response: Thank you once again for this considered comment. We aimed to complete a comprehensive review of the available literature on the topic of intrathecal morphine in patients undergoing open hepato-pancreato-biliary surgery. As articulated in our manuscript, we found that analgesic regimens, healthcare settings and outcomes measured varied largely amongst the selected paper. We have discussed these limitations of the study, which we have outlined in the discussion section. Based

on our review, intrathecal morphine may be a better first-line analgesic modality than epidural analgesia in the context of major open hepato-pancreatic-biliary surgery, but high-quality evidence supporting this is limited. We have also stated in the concluding paragraph that "*to make definitive recommendations, large RCTs are required to substantiate this review's findings*".

Reviewer comment: *Reviewer: Page 13 Conclusion Based on the limited number of trials discovered, this review suggests that single-shot intrathecal morphine may be more appropriate than epidural analgesia as a first-line analgesic technique for major open hepato-pancreatic-biliary surgery. **How reliable is this recommendation?*

Authors Response: Thank you for this comment. We have completed a comprehensive review of the available literature on the topic of intrathecal morphine in patients undergoing open hepato-pancreato-biliary surgery, and we have found consistent clinically and statistically significant trends reported among the papers that have fit our inclusion criteria. Our recommendations cannot of course be weighted as heavily as that from a multi-centre, randomised controlled trial, but we acknowledge this in the paper and state clearly that to make definitive recommendations, large RCTs are required to substantiate this review's findings.

Once again, we would genuinely like to thank the Editor and expert Reviewers for taking the time to review and consider our manuscript for publication in Anesthesiology and Pain Medicine.

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) 12 Nov 2019

Dear AE,
I read the revised manuscript as titled "A literature review of intrathecal morphine analgesia in patients undergoing major open hepato-pancreatic- biliary (HPB) surgery" and the author has corrected my previous questions. Now it is ready for publishing.
Sincerely

REFEREE: Associate Editor | **Revision** (1) 12 Nov 2019

Dear EIC,
Based on reviewer comments, fortunately, the author could reply to all requested items, and the Editorial can consider this revised format for the next steps.
Final decision: Acceptance
Regards
AE

REFEREE: EIC | **Revision** (1) 12 Nov 2019

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.