Author’s response to reviews

Title: Comparative evaluation of epidural bupivacaine alone and bupivacaine combined with magnesium sulfate in providing postoperative analgesia: a meta-analysis of randomized controlled trials

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Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Comparative evaluation of epidural bupivacaine alone and bupivacaine combined with magnesium sulfate in providing postoperative analgesia: a meta-analysis of randomized controlled trials (ID:BANE-D-19-00820R1). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer’s comments are as flowing:

Benjamin Aquino, MD (Reviewer 1)

1. Response to comment: I am reading the revision 1, and not the original submission. The paper is fine. It is interesting to me that the body of evidence using magnesium as an adjuvant in epidural anesthesia is so small. I had not expected that. It seems like a large scale study waiting to happen; perhaps your group will lead the way in that department. The limitations here are due largely in part to you not having enough studies to look at. For example, analysis of adverse
outcomes was underpowered because of small numbers and study heterogeneity. Overall, the paper is well organized and does what it says it will do.

Response: As Reviewer suggested that the primary limitation of our review was the small number of studies, participants, and events for most analyses. The limited data prevented us from interpreting safety data in particular with any confidence. Given adverse effects before use, further consideration and research is required before magnesium sulfate is routinely used as a intrathecal adjunct.

raffaele aspide (Reviewer 2)

1. Response to comment: Background, pag.3, line 51: DEX is badly written, correct; and a series of other opioids are not listed, perhaps it is easier to be generic.

Response: We have made correction according to the reviewer’s comments. Line 51 the statements of “Nevertheless researchers continue to find the optimum adjuvants, as the currently researched adjuvants (e.g. morphine, tramadol, fentanyl, dexmedetomidine) still have some adverse effects such as nausea and vomiting, pruritus, bradycardia, and hypotension” were corrected as “Nevertheless researchers continue to find the optimum adjuvants, as the currently researched adjuvants (e.g. opioids, tramadol, dexmedetomidine) still have some adverse effects such as nausea and vomiting, pruritus, bradycardia, and hypotension .”

2. Response to comment: Background, pag.3, line 55: “…we hypothesize that..” normally the ideas of the authors are part of the Discussion, if you really want to add it in the background, try to write better what we already know about the pathophysiology and what you don't know well

Response: Line 55 the statements of “Since magnesium ion blocks inward current flow through ion channels linked to N-methyl-D-aspartate (NMDA) receptors , we hypothesize that magnesium ion plays as a non-competitive NMDA receptor antagonist thereby exerting analgesic effect.” were corrected as “Magnesium ion (Mg2+) is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that blocks inward current flow through ion channels linked to NMDA receptors in a voltage-dependent fashion, has the potential to prevent central sensitization induced by peripheral nociceptive stimulation. ”

3. Response to comment: 2.4. Data extraction and quality assessment, pag.5, line 95: did you use EndNote X9 for data extraction or not ?

Response: We didn’t use EndNote X9 for data extraction. We just imported the studies from database into EndNote X9.
4. Response to comment: 2.5. Statistical analysis, pag.6, line 109-110: please, revise the sentence…

Response: Line 109-110 the statements of “We rated the magnitudes of SMDs as small effect (0.2–0.5), medium effect (0.5–0.8) and large effect (≥0.8).” were corrected as “We rated the effect size of SMDs as small effect (0.2–0.5), medium effect (0.5–0.8) and large effect (≥0.8).”

5. Response to comment: 2.6. Assessment of heterogeneity and subgroup analysis, pag.6, line 119: verses ?? versus….

Response: We have made correction according to the Reviewer’s comments.

6. Response to comment: 2.7. Sensitivity analysis and assessment of publication bias, pag.7, line 127: two different models…can be better understandable.

Response: We have made correction according to the Reviewer’s comments.

7. Response to comment: 3.1. Study selection and characteristics of included studies, pag.7

Response: the statements of “Study selection and characteristics of included studies.” were corrected as “Study selection and characteristics of included studies.”

8. Response to comment: 3.1. Study selection and characteristics of included studies, pag.7, line 137, "….by a continuous infusion" through which infusion route?

Response: through intravenous infusion.

9. Response to comment: 3.1. Study selection and characteristics of included studies, pag.7: I personally believe that patients subjected to a mixed anesthetic (EA / GA), in particular for thoracic surgery, in which the epidural is dorsal and not lumbar, I would say, have a different postoperative pain management, just because of the drugs given during general anesthesia, so I would exclude them from the study, but I go back to the analysis of the editor on this specific topic.

Response: This meta-analysis aimed to evaluate the effects of epidural bupivacaine alone versus bupivacaine combined with magnesium sulfate in providing postoperative analgesia. Even if the drugs given during general anesthesia have a role in the postoperative analgesia. Considering the type of study design is randomized controlled trial, we believe this will reduce the interference of general anesthetics to some extent, so we also included the studies for thoracic surgery.
10. Response to comment: 3.1. Study selection and characteristics of included studies, pag.7, line 145: placebo mean control (bupivacaine only)?

Response: Yes, placebo mean control, where administrated bupivacaine only.

11. Response to comment: 3.8. Sensitivity analysis and assessment of publication bias, pag.11, line 212: paimary…bad written

Response: We have made correction according to the Reviewer’s comments.

12. Response to comment: Discussion, pag.11, line 219: anageisa….bad written.

Response: We have made correction according to the Reviewer’s comments.

13. Response to comment: Discussion, pag.11,line 235: the doses and….. I think that the magnesium dosages used (present in the tables of the individual studies) could be a valuable piece of information to be included in the descriptive results, at least to give readers an orientation.

Response: The dosages of magnesium sulfate were presented in the intervention column of Table 1.

14. Response to comment: Discussion, pag.13, line 256-257: please, revise the sentence

Response: the statements of “our findings are similar with the findings in a recent published meta-analysis reporting a reduction of the need for postoperative rescue analgesia in pediatric after magnesium added to local anesthetics for caudal anesthesia.”were corrected as “our findings are similar with the findings in a recent published meta-analysis, where the authors reported a reduction of the need for postoperative rescue analgesics in pediatric when magnesium was added to local anesthetics for caudal anesthesia.”

15. Response to comment: Discussion, pag.13, line 259: DEX administrated by peridural route? I am not sure that this paragraph on epidural adjunct analgesic drugs is completely useful…

Response: DEX administrated by epidural route. This paragraph aimed to evaluated the effects of epidural magnesium sulfate versus other adjuvant.

16. Response to comment: Discussion, pag.13, line 267: plate… "endplate" I think is better

Response: We have made correction according to the Reviewer’s comments.
17. Response to comment: Discussion, pag.14, line 272: probably after "Firstly.." you want to say: "even if…"

Response: the statements of “However, ……” were corrected as “even if ……”.

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,

Hou-Zhong Zhang

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