

Response to Reviewer's comments

We would like to thank the editor and reviewers for their helpful suggestions. We have already revised the manuscript and hope that the revised manuscript has met the requirements for publication. Changes were marked with yellow highlight in the revised manuscript.

Reviewer No. 02671671

This metanalysis included many limitations. The rationale of the use of metoclopramide was not fully explained.

Response: Thank you for your suggestion. Metoclopramide is initially used to treat acute migraine for decades. A few studies over the years have highlighted that metoclopramide has substantial therapeutic effectiveness in treating acute migraine episodes. The reasons behind the use of metoclopramide could be that it antagonizes the dopamine D2 receptor, which is proposed to be one of the pathogeneses of pain in migraine. A meta-analysis of pooled data illustrated that metoclopramide significantly reduced headache pain, and those patients were less likely to rescue medicines than the placebo group. However, the authors chose various inclusion and exclusion criteria for this study, which may contain data on non-migraine headaches, confounding any conclusions to be derived. Furthermore, metoclopramide also had an anti-emetic effect that ameliorates migraine patients' symptoms. Therefore, metoclopramide could be a first-line treatment for acute migraine episodes. Our findings are consistent with prior research that metoclopramide was more effective than placebo in pain reduction. In addition, metoclopramide had a higher benefit than some drugs in our analysis (subcutaneous sumatriptan, intravenous valproate, oral ibuprofen). These findings fit with the pattern described previously by Colman. However, that study selected both ED and headache clinic settings, which differed from ours. Besides, Colman and teams analyzed the pain using a complete relief of headache or significant reduction in headache pain. We have revised the manuscript to highlight the rationale of the use of metoclopramide in acute migraine headache at the ED in 'Discussion' section (Page 9 Line 7-25).

Reviewer No. 03821836

1. Did the authors register their review in a publicly available data repository?

Response: Yes. We have registered our protocol in a PROSPERO platform (CRD42022322609). We have added the data in the 'Methods' section in the revised manuscript (Page 5 Line 10-11).

2. Inclusion only of RCTs should be reflected in the title and the abstract, as well.

Response: Thank you for your suggestion. We agreed with the reviewer and revised our title to 'Pain reduction and adverse effects of intravenous metoclopramide for acute migraine attack: a systematic review and meta-analysis of randomized-controlled trial' to properly highlight the details of our article.

3. Did the authors search any grey literature source? If no, why not?

Response: We also searched any relevant grey literature at the time of searching. We used the figure template from the PRISMA flow which is not mentioned the grey literature searching. We have revised Figure 1 to add the detail about grey literature searching in the revised manuscript (**Page 5 Line 19 and Figure 1**).

4. Which adverse events were assessed? Please specify and update your analyses accordingly.

Response: The adverse events mentioned in our study were upper gastrointestinal complaints (dyspepsia, heartburn, and bloating), allergic reaction, dizziness, drowsiness, nasal congestion, dry mouth, dystonic reaction, akathisia, and significant blood pressure drop. We have revised this detail in the 'Methods' section in the revised manuscript (**Page 6 Line 8-11**).

5. RCTs only from 3 countries were included! Please comment on the generalizability of the results.

Response: Thank you for mentioning this interesting point. Despite we included up to 14 studies in our meta-analysis, there was only came from three countries: Iran, United States, and Turkey. We have added this point as one of the limitations on the generalizability in the 'Limitations' section in the revised manuscript (**Page 10 Line 7-9**).

6. Did the authors perform an Egger's test for assessment of publication bias, as stated? Please clarify.

Response: Thank you for raising this point. We have also analyzed an Egger's test for assessment of the publication bias. The regression-based Egger's test was performed using random-effect model with restricted maximum-likelihood method. P value was 0.0814 which meant that there were no small-study effects in our analyses. We revised this point in the 'Results' section in the revised manuscript (**Page 8 Line 25-26**).