

Peer-review Comments and Authors' Responses

Reviewer 1

1) Search results in the abstract and the results section are not matching.

Authors' response:

Thank you for the meticulous review, we have identified and fixed the inconsistencies in the abstract and results section.

2) Table 1, figures 2, 3 and 4 are not cited in the text, the authors only put the names of the tables and figures in the place they are supposed to be. Please review.

Authors' response:

Thank you for the helpful review. Upon further discussion with all the authors, we have decided to include only table 1, figure 1 and figure 2 and will not include effect size calculation. This is due to erroneous assumption with the meta-analysis calculation in the studies. Since most studies that were included used median value instead of mean, we would be unable to estimate the effect size correctly using the Hedges d calculation. The assumption of the transformation from median value to mean would not be correct since it was clear that the study population was not normally distributed. Hence, we would be unable to transform the dataset. This was amended in the meta-analysis section in the manuscript.

3) Include in the flowchart the main reasons of the excluded studies

Authors' response:

The reason that we did not list the excluded studies because the population of neonates is a difficult population with limited studies being done. Therefore, with our significant inclusion criteria for the mini review we were only able to retrieve limited studies and those that did not meet the inclusion criteria was excluded but we did not specify any exclusion criteria.

4) Review the meta-analysis as a topic in the discussion section. The meta-analysis are the results

from your study (your systematic review), so it should be listed on the results section, not on the discussion. Please reorganize the document in a way that the discussion will show the interpretation of your findings as well as the context of the overall research (not only comments about the included studies).

Authors' response:

Thank you for the input and suggestion, the result section was amended as suggested.

5) The authors discussed the limitations from the included studies. Please include the limitations of the mini-review and how it can affect the results presented in the review.

Authors' response:

Thank you for the suggestion. The limitation of our mini review is the neonates from mothers with opioid use disorders, who are generally vulnerable and have many challenges to study. This limits the availability of available experimental studies due to factors like ethical reason, high risk population and social issues surrounding the population. There are also lack of complementary therapy studies in opioid use disorder in this population. All authors agreed that including only experimental studies will gather stronger evidence of effect size of treatment arms. However, what we did not foresee was the difficulty in analyzing data that were not normally distributed. The available studies also had high risk of bias. In addition, it proves to be a challenge to objectively measure results as most parameters used can be subjective and not standardized.

Reviewer 2

6) On the first page, affiliation author 17 is empty. Please complete.

Authors' response:

We have completed the missing affiliation.

7) Introduction: It is well written and the objective is well established in the last sentence. In the second paragraph, there is a square bracket instead of a parenthesis (I highlighted it in yellow).

Authors' response:

Thank you we have amended the typing.

8) *Methods:*

- Why did you not include observational studies in your review? Considering some ethical concerns (neonatal population + patients in neonatal intensive care) there are more publications of observational studies than RCTs.

- Why did you not search in other databases like Embase, and Cochrane Library in order to increase the retrieval of articles?

Authors' response:

All authors agreed that including only experimental studies will gather stronger evidence of effect size of treatment arms. However, what we did not foresee was the difficulty in analyzing data that were not normally distributed. We have thought about more databases search however, none of the authors had access to Cochrane library or Embase for us to be able to extract more articles.

9) *Results:*

Please check and correct the year of publication of your included studies. I highlighted it in yellow and with a green circle, because sometimes the year of publication is different in the text, in the forest plot, tables, and references. For example: Raith 2015 appears in the Risk of Bias Assessment and 2021 in the forest plot. In the references we have Raith 2015 and 2021 do not appear.

Authors' response:

Thank you for the input, we have corrected the publication years in the manuscript.

10) *I would like to know the limitations of your study.*

I consider your review is very important for the treatment of Neonatal Opioid Withdrawal Syndrome because it demonstrates the difficulties in getting a robust conclusion of the use of

non-pharmacological methods due to the high risk of bias in the majority of the published studies.

Authors' response:

Thank you for the kind words, we really appreciate it. Our study limitations are as follows: population of study that includes neonates from mothers with opioid use disorders, who are generally vulnerable and have many challenges to study. This limits the availability of available experimental studies due to factors like ethical reason, high risk population and social issues surrounding the population. There are also lack of complementary therapy studies in opioid use disorder in this population. Due to the nature of the complementary treatment arm, we found it difficult to analyze data that were not normally distributed. The available studies also had high risk of bias. In addition, it proves to be a challenge to objectively measure results as most parameters used can be subjective and not standardized.