Author's response to reviews

Title: The role of osmotic agents in children with acute encephalopathies: a systematic review

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Author's response to reviews: see over
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The Scientific editor,
BMC-series Journals

Dear Dr. Kou stos,

Re: MS: 7892184092925044 – The role of osmotic agents in children with acute encephalopathies: a systematic review

Thank you for the opportunity to respond to the reviewers comments and for considering this paper for publication in BMC Pediatrics. My co-authors and I have answered the points raised by the editorial team and reviewers, as outlined below and present a revised draft.

We have added more context information on the abstract as suggested. We have tried to adhere to all the requirements of the PRISMA guidelines. The protocol that guided this review is available from the ‘review protocols’ section of the Joanna Briggs Institute website and this is indicated in the manuscript. A review protocol number is not available.

We have addressed the issues raised by the reviewers below:

Comments by reviewer Malinee Laopaiboon

- The authors need to report what data, following PICOS, was collected from each study.
We have summarized the characteristics of all the included studies in additional file 1.

- The data of this review could not be combined so the sentence of ‘Quantitative studies were considered for pooling for statistical meta-analysis using the JBI-MAStARI.’ in the subheading of assessment of studies need to be skipped.

- This statement is in the methods section and shows that it was in our plan to pool the data for a meta-analysis. We have omitted the statement that follows this; ‘Heterogeneity was assessed using the standard Chi-square test’.

- Adding flow diagram of study selection as suggested in PRIMA would be good for readers to understand the review selection process.

- We have included a flow diagram to show the different phases of the search.

- Methodological validity of included studies was mentioned in the method but results of the consideration were not reported. This needs to be added.

- We have reported the results of our methodological assessment of the included studies. These are summarized in tables 2, 3 and 4.

- The authors report that 10 studies presented mortality. At most 9 of them could show results in forest plot of figure 1. But it is unclear why the figure shows only 5 lines of data. In addition each line was labeled only its comparison interventions. The figure is unclear if each line represents data of each study. Labeling study for each line is more information to readers.

- We have clarified that all the 10 studies reported on mortality; but we only analysed the trials, for which there were comparison groups. The forest plot provides a summary of mortality in three trials and each line of data represents the interventions that were compared. In the case of the study by Peltola et al., there were several intervention groups. To make this clearer, we have included the reference for the study for each line.

- The discussion is good. However, if the authors add the methodology limitation of the finding according to most included studies were observational studies, it would be better.
We have acknowledged this limitation and have added this to the discussion.

Comments by reviewer Neeraj S Naval

- The age covered is 0-16 but there is no mention made within analysis of each study of the age group encompassed or if subgroups defined by age were given within any of the studies. As there is a potentially large difference between neonates and adolescents, such data would be a valuable addition to this paper. If this was not available or no additional information was given by such subgroup analysis, this would bear mentioning if only to show it was considered.

- Although we intended to include studies that recruited children between the ages of 0 and 16, only one study included young infants. We have commented on this in the text and have indicated this on our summary of included studies in additional file 1.

- When available, the dosing of the agents used, particularly those with positive results, would be beneficial.

  - We have included the dosing of the agents used in our summary in additional file 1.

- Please provide a p value for the decreased mortality seen with hypertonic saline compared to mannitol for study Reference 32.

  - The P value provided is on examination of the 3 groups of intervention (P=0.003) and it would be inappropriate to include it since we omitted the last group of intervention in our analysis. We have indicated this in the summary (additional file 1) and have provided the relative risk.

- Page 3, PP 1: “Therefore, management of raised ICP aims to reduce ICP, …” Recommend rewording – e.g. Management of elevated intracranial pressure involves optimizing CPP and oxygen supply to the brain in addition to reduction of ICP.

  - We have re-worded this appropriately.

- Page 3, PP1: “Besides standard management such as correction of hypoglycemia and electrolyte imbalances…” This sentence implies that this is therapy for ICP management – would reword to clarify management of the critically ill.
- We have omitted this statement.

- Page 6, PP1 and Figure 1: DexGlycerol is referred to in the figure and glycerol and dexamethasone is referred to in the text – that these are the same should be stated.
  - DexGlycerol and, glycerol and dexamethasone refer to the same intervention. This has been corrected.

- Figure 1 lists heterogeneous agents and associated relative risk – listed as “rate ratio” – the assumption being that the agent listed first has the associated RR compared to the second. Based on this, there are the following concerns: Figure 1 shows glycerol had a higher mortality rate than the DexGlycerol group yet this is not referred to in the text.
  - Glycerol and Dexamethasone combination does have less mortality compared to glycerol. We have now indicated this in the text.

Comments by reviewer James Riviello

- On page 6, in the first sentence of Neurological sequelae, the words these and was, are together.
  - The whole statement reads: “Four studies reported on neurological sequelae[1, 28, 30, 33], but only one of these studies was a clinical trial[28].”
    We have added the word “studies” to clarify this sentence.

This manuscript has not been previously published in a citable format. The revised manuscript has been reviewed by all the authors. We hope that it is suitable for publication.

Thank you

Yours faithfully,

Samson Gwer