Author's response to reviews

Title: Maternal adverse effects of different antenatal magnesium sulphate regimens for improving maternal and infant outcomes: a systematic review

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Author's response to reviews: see over
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The Editor
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To The Editor

Re: MS: 3245195651015314

Title: Maternal adverse effects of different antenatal magnesium sulphate regimens for improving maternal and infant outcomes: a systematic review

Authors: Bain ES, Middleton PF, Crowther CA

Please find below a detailed response to the comments from the referees which we found most helpful.

We thank you for consideration of our manuscript for publication in BMC Pregnancy and Childbirth, and we look forward to your reply.

With best wishes,

Emily Bain
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Reply to reviewers’ comments

Relevant extracts requiring responses have been extracted from the reviewers’ reports and responses made, including changes to text (where changes to text (including additions) have been made to the manuscript, we have ‘highlighted’ the alterations for easy identification within the manuscript).

Reviewer 1’s feedback and authors’ responses (Jane Norman)

We thank this reviewer for their very positive comments and valuable suggestions.

- (Discretionary revision): 1. Please clarify the use of combination therapy as an exclusion on page 6. Most women with pre-eclampsia will also be having an antihypertensive as well as MgSO4 – were they also excluded?

Thank you. We have now clarified that studies were only excluded where magnesium sulphate was given in combination with another agent for tocolysis (combination tocolysis) (page 6). We did not exclude studies...
where women with pre-eclampsia received an anti-hypertensive; indeed we have included, for example, a retrospective study by Magee et al (discussed page 20) that assessed whether the use of nifedipine (versus other antihypertensive agents) and magnesium sulphate together increased serious magnesium-related effects.

Reference

• (Discretionary revision): 2. Was there any useful information about the effect of monitoring regimes in the studies? For example it might be that an effective monitoring regimen would minimize the risk of cardiac arrest? Data analysis might be beyond the scope of this paper, but the authors thoughts on this subject could usefully be included in the discussion.

As the reviewer has noted, data analysis surrounding the effects of monitoring regimens in the studies on minimisation of adverse effects is beyond the scope of this review. However, we thank the reviewer for highlighting the importance of including further discussion regarding monitoring – we have now made further comment regarding the critical nature of monitoring during the use of this treatment on page 27.

• (Discretionary revision): 3. Please include a brief note describing the eponymous regimens (eg Prichards)

We have now ensured that the descriptions of these regimens are given each time they are named in the text, and we have provided these descriptions for these regimens in the footnotes for Table 2, page 45.

Reviewer 2’s feedback and authors’ responses (Elaine Kidney)

We thank this reviewer for their positive comments and valuable suggestions.

• (Discretionary revision): 1. Clarify whether iatrogenic overdoses were intended to be included in the review, and if so, what searches were used.

Thank you. We have clarified on page 6 in the methods that (apart from the noted exclusions) we included studies regardless of their regimen for administration of magnesium sulphate – and thus this included cases of iatrogenic overdose of magnesium sulphate. There was no search conducted specifically to identify iatrogenic overdoses; rather the search terms used were very broad (including only terms related to the concepts: magnesium sulphate and pregnancy (or the different indications for use)) to identify all studies where magnesium sulphate had been administered (including overdoses).

• (Discretionary revision): 2. Clarify methods for searching for patient safety data.

We have clarified (page 5) that any included incident reports from patient safety organisations were identified through searching Google with key word searches; only publically available reports were thus identified (as also noted on page 23).

• (Discretionary revision): 3. Acknowledge potentially missed studies from searches and limits imposed.
  o (Related comment from Reviewer’s report): A wider range of bibliographic databases (eg Lilacs, Popline may have generated a wider range of potential studies)
  o (Related comment from Reviewer’s report): Limiting studies to those written in English or with available English translations may have limited available studies.
(Related comment from Reviewer’s report): Included studies reported maternal adverse effects. Given the possibility that adverse effects may simply not have occurred in studies not mentioning them, there is a possible bias favouring selection of studies with adverse effects.

We have further addressed possible limitations associated with our searches on page 29 (including searching only those named databases, and including only English language papers / papers with English translations), which may have led to missing potentially relevant studies. We have noted the inability to include a number of studies not reporting on any adverse effects. While we agree with the reviewer that in some of these studies adverse effects may simply have not occurred, we also highlight the possibility that in many of these studies, adverse effects may have occurred, but were not reported (particularly given that the ‘minor’ side effects of magnesium sulphate are considered relatively common). Several empirical evaluations have shown that randomised trials often do not report harms or report them in a suboptimal way – for example, with tendencies to restrict reporting to only the most severe harms, or statistically significant differences (Ioannidis 2009). Thus, we do not believe that our review would favour the selection of studies with adverse effects (we were unable to include studies 1) where no adverse effects occurred and also 2) where adverse effects occurred but were not reported).

Reference

(Discretionary revision): 4. Consider a fuller description of methods for data extraction of observational studies and for collating themes and women’s experiences.

(Related comment from Reviewer’s report): Methods for assessment of quality and bias of observational studies are not explicit (“based on” recommendations of the Cochrane Handbook and the Newcastle-Ottawa Scale).

(Related comment from Reviewer’s report): There is limited information about the methods used for categorising women’s blogs into emerging themes.

We have provided further detail on the quality assessment for observational studies on page 8, and have provided further clarification regarding extraction and synthesis of text from blogs/forums on pages 7 and 9.

(Comment from Reviewer’s report): Study selection and data extraction could have been more rigorous:

a. Inclusions/exclusions were done by just one author only, with a random 10% being checked by a second author.
b. Data extraction was carried out by just one author, with the second author independently assessing a random 10%.

Complete assessment of studies and data extraction for this systematic review by two reviewers was not feasible when considering the resource and time allocations. We have commented on the potential for bias associated with the study selection and data extraction methods used on page 29.

(Comment from Reviewer’s report): Discussion and conclusion are well balanced and adequately supported by the data, although factors contributing to iatrogenic overdoses were given in the conclusion could only be found in Suppl7.

We have reported on the case studies of iatrogenic overdose in the results (pages 21-22), have referred to Table 7 and Additional file 7 (where further details can be found), and have discussed the findings (particularly from Simpson’s account of 52 errors) on page 27. We believe that this level of detail regarding the reported overdoses is sufficient given that this review covers studies of multiple other designs, and magnesium administered according to many other regimens.
Reference

- **(Comment from Reviewer’s report):** Limitations are explicit. Some mention of how their findings related to possible harms for the baby would be useful, as any harms as well as benefits for both mother and baby need to be taken into consideration.

Thank you – while the neonatal / infant adverse effects of magnesium sulphate are beyond the scope of this review, we have briefly commented on the need for a formal assessment of these possible harms on pages 28.

- **(Minor essential revision):** 1. Amend flowchart to account for removal of duplicate studies as set out in the methods section.

Thank you – we have amended the flowchart to reflect the removal of duplicate studies.