Author's response to reviews

Title: How Effective are the Components of Active Management of the Third Stage of Labor?

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Author's response to reviews: see over
Dear Dr. Galal:

We would like to thank you and the Referees for the opportunity to revise our manuscript ID 6178361217479288 entitled “How Effective are the Components of Active Management of the Third Stage of Labor?”. Per your request, we have responded to all of the comments raised by the Referees and made corresponding changes in the manuscript.

Included below are detailed responses to the various comments provided by the Referees. The comments are copied directly from the pdf you provided, and our replies have been inserted just below each.

We thank you and the Referees for your careful review of our paper. Please feel free to contact me with any outstanding questions.

Sincerely,

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RESPONSES TO REFEREE 2:

MAJOR REVISIONS

1. The authors suggest the components of active management include PPH, prophylactic uterotonic and uterine massage, however guidelines and current practice in several countries including the UK includes controlled cord traction (either early or delayed) and it does not include uterine massage. This should be acknowledged and discussed.

We have revised the introductory paragraph to acknowledge that the variation across AMTSL guidelines. We also added one of the references suggested by the Referee to the sentence on AMTSL guidelines (RCOG guidelines on intrapartum care, 2007). Sentence three of the introductory paragraph now states:

“Although there is some variation across guidelines, the AMTSL interventions commonly include prophylactic administration of a uterotonic agent, controlled traction of the umbilical cord, and uterine massage.”

We added another of the references suggested by the Referee to the fourth paragraph of the discussion section (Farrar et al., 2010). In this paragraph we discuss the real world differences in AMTSL practices (as opposed to differences in guidelines) as both a limitation and strength of our paper. We think this fits best in the discussion section of the paper, where paragraph four states:

“Finally, there was some variation in procedures for administering AMTSL interventions, and these differences occurred both within- and between-sites. This variation is also a strength, however, since it reflects real differences in implementation of active management of the third stage of labor.”

2. The authors do not comment on the differences in timing of cord clamping and the potential to affect PPH (as well as infant wellbeing) until the discussion, although data are limited this should be mentioned in the introduction and commented on further in the discussion as there are differences between and within countries and it is topical and debated in most literature related to the third stage.

We did not mention early cord clamping at all in the discussion section of our paper. While we are aware that the timing of umbilical cord clamping (early versus delayed) has been found to have some impact on infant health and well-being, we are not aware of any evidence of a relationship between the timing of cord clamping and the incidence of post-partum hemorrhage. Our multivariate analyses supported this lack of evidence and we consistently found that inclusion of a control variable for the timing of cord clamping had no significant effect on the incidence of post-partum hemorrhage. As a result, we omitted early cord clamping from the final logistic regression model for this paper.

Since the timing of cord clamping is not relevant to the issues we explore in this paper, we prefer not to include details about differences in AMTSL guidelines relating to the timing of cord clamping – either in the introduction or discussion sections.
3. The recent Cochrane review Oladapo OT, Okusanya BO, Abalos E. Intramuscular versus intravenous prophylactic oxytocin for the third stage of labour. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD009332. DOI: 10.1002/14651858.CD009332.pub2. should be cited when referring to effectiveness of oxytocin by route of administration and also Mshweshwe N, Hofmeyr G, Gülmezoglu A. Controlled cord traction for the third stage of labour. Cochrane Database of Systematic Reviews 2009 Issue 4. Art. No.: CD008020. DOI: 10.1002/14651858.CD008020. when referring to literature on CCT.

We thank the Referee for pointing this out and have added the above article as suggested at the end of paragraph 2 in the background section.

4. In the background section third paragraph it would be preferable to clarify how ‘large’ the RCT was the WHO conducted and what is meant by ‘very little effect’.

We revised the sentence referencing the large WHO RCT on controlled cord traction to incorporate the above suggestions. The sentence now states:

“Most recently, a large randomized controlled trial involving more than 24000 participants found that provision of controlled cord traction had only a small, non-significant effect on the risk of severe hemorrhage among women who were already receiving oxytocin prophylaxis (intravenous or intramuscular).”

4 (cont.) In the fifth paragraph the authors say staff were not blinded which of course they couldn’t have been as they were providing the intervention……….. were the assessors of the outcomes blinded though?

The article does not say if the assessors of the outcomes were blinded, only that an objective means of measuring blood loss was used (plastic drape device). The Referee makes a good point, however, and we therefore decided to omit the sentence about the lack of blinding of study staff.

4 (cont.). At the end of the sixth paragraph the authors suggest that early clamping is no longer recommended, however this is not the case for all countries including the UK and although there is limited evidence of benefit for preterm and term infants there is also the risk of increased jaundice in term infants. There is limited evidence of benefit from delayed cord clamping because it increases placental transfusion volume, but this is not the same as harm to infants or mothers from early cord clamping, their sentence needs revising to reflect this.

We have omitted this sentence altogether since it appears to be a source of confusion and is not relevant to the issues we explore in this paper.
5. Under the methods section if the methods of the data collection have been reported elsewhere and a reference given there is no need to go on and describe it the section from ‘The trials to regimen’ should be removed.

We respectfully disagree with the Referee on this point. We think all of the information included in the methods section is essential to our article. We are not reporting on the data collection related to the PPH treatment trials, which was the focus of the original RCT papers, but are instead presenting methodological information about the collection of data relevant to the analyses reported in our paper.

6. The description of blood loss measurement needs to be moved to where it’s first described in paragraph 2 of methods also in the discussion comment should be made on the accuracy of this method of assessment.

We agree with this suggestion but felt that measurement of blood loss should be moved to the third paragraph, rather than the second, since this is where the details relating to measurement of all other variables was discussed. The revised sentence on measurement of blood loss now appears in the third sentence of paragraph three and states:

“Blood loss was measured beginning immediately after birth of the baby and continuing for the first hour post-partum using a polyurethane receptacle with calibrated funnel (Brasss-V Drapes®, Excellent Fixable Drapes, India) that was placed under the woman’s buttocks.”

7. Results section paragraph 6 I’m not sure where the OR=1.3 95, CI 0.43-2.96 came from shouldn’t it be 0.28 (0.14-0.55) ? or do they mean against IM oxytocin and CCT?

We thank the Referee for pointing out this potential source of confusion. This result (OR=1.13) came from conducting additional tests for differences between AMTSL groups in the oxytocin prophylaxis regimen, the results of which are listed at the bottom of Table 4. In order to prevent confusion, we included a footnote after the parentheses with these results that explains they were obtained through conducting additional tests, and notes they can be found at the bottom of Table 4. We inserted the same footnote after every other result that is referenced in this paragraph and the subsequent one (paragraph 7) which was obtained through these additional tests.

MINOR REVISIONS

1. It would be useful to understand what is meant by hospital practice in the different countries or is this described elsewhere

Clinicians at all study sites provided AMTSL components as per the standards of their hospital facilities. There was some minor variation in practices (such as dose of oxytocin provided, 10 IU vs. 5 IU, which we note in the methods section). We also acknowledge these differences in the discussion section by stating
“Finally, there was some variation in procedures for administering AMTSL interventions, and these differences occurred both within- and between-sites. This variation is also a strength, however, since it reflects real world differences in implementation of active management of the third stage of labor”.

**BMC REVIEWER QUESTIONS**

3. Are the data sound? Yes they seem to be, though it would be good to have a little background on the sites the studies were conducted in

In the first paragraph of the methods section we state that the study sites “involved nine secondary- and tertiary-level hospitals from five counties.” In that same paragraph we subsequently list the number of hospital sites per country and clinical regimen. We are not sure what additional information would be helpful or what specifically the Referee would like to see included.

6. Are limitations of the work clearly stated? Yes, but I think more needs to be said on the use of single centre sites that are familiar with certain practices ie active or physiological management of the 3rd stage and the generalizability of results to the general population, the authors do touch on this but it needs to be more explicit.

As noted in question 5 (above), all of the sites included in this secondary analysis were secondary- or tertiary-level hospitals and the AMTSL interventions used reflected standard practices at each site. While our results are generalizable to other hospitals facilities with clinicians who are trained in and familiar with provision of the AMTSL interventions studied in our paper, they may not be generalizable to non-hospital settings or any setting where the clinicians are not trained in provision of AMTSL. We believe, however, that the latter is a universal limitation of advocating for any new intervention and there is always a learning curve associated with the adoption of any new innovations which does not warrant specific explanation in our paper.

Furthermore we note in the final paragraph of the discussion section that “the studies were carried out in hospital facilities only, and thus may not be generalizable to other delivery settings”.