Author's response to reviews

Title: Anti-fibrinolytic agents in bleeding during pregnancy, delivery and puerperium: A systematic review

Authors:

Pili Ferrer (piliferrer@eresmas.com)
Ian Roberts (ian.roberts@lshtm.ac.uk)
Emma Sydenham (emma.sydenham@lshtm.ac.uk)
Karen Blackhall (karen.blackhall@lshtm.ac.uk)
Haleema Shakur (haleema.shakur@lshtm.ac.uk)

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Author's response to reviews: see over
Dear Editor

Thank you for reviewing our paper and for the very constructive comments of the referees. We have now revised the paper to respond to each of the reviewers’ suggestions. Specifically, we have responded to the comments as follows:

1. We agree that a better title would be: “ANTI-FIBRINOLYTIC AGENTS IN OBSTETRIC HAEMORRHAGE: A SYSTEMATIC REVIEW” and have changed the title accordingly. We have explained in the background section that obstetric haemorrhage can occur before, during or after delivery but that post partum haemorrhage accounts for the majority of maternal deaths. However, the last line of the background section states clearly that we reviewed randomised controlled trials of antifibrinolytics in the prevention and treatment of bleeding whether before, during and after delivery.

2. As requested we have included details of the definitions used.

3. As requested we have presented the methods and results in accordance with the Quorom guideline and have provided the flow diagram requested.

4. Our search strategy did not include terms to identify participants (such as pregnancy or postpartum) since we wanted to find out about all randomised controlled trials of the use of antifibrinolytic agents and then later classify them by participants, thus ensuring maximal sensitivity. We have included a sentence to this effect in the methods section.

5. The reviewer states that “the criteria for excluding studies due to inadequate study design were not stated.” This is not the case. We state clearly in the first paragraph of the methods section that only randomised controlled trials will be included. However, we have clarified this further by including the definition of randomised controlled trials that was used in this systematic review, specifically that “a randomised controlled trial was defined as a trial in which the individuals followed were assigned to one of two (or more) interventions using random allocation, or some quasi-random method of allocation.” The inclusion of this definition also addresses the reviewer’s concern about the inclusion of the trial by Gobel in which allocation was quasi-random.
6. We did not include PPH as an outcome since we were primarily interested in the treatment of obstetric bleeding, rather than its prevention. However, we think that the reviewer’s point is a good one and have therefore included PPH as a secondary outcome. We did not include the other suggested outcomes since very few of these were reported in the included studies.

7. Information on the interventions is given in table 3. This table includes information on when the intervention was given.

8. The table has been rearranged as suggested.

9. Despite the large number of citations screened we did not find any potentially eligible excluded trials.

10. A Quorom flow chart has been included.

11. The reviewer points out that the data may be skewed and that because of this, the mean blood loss may not convey all of the relevant information. We agree but are constrained by the data that are presented in the included trials.

12. The reviewer asks that we consider whether a mean reduction of 92 ml of blood loss would be clinically significant and suggests that a more cautious conclusion about further trials is warranted. In view of the poor quality of the included trials we are reluctant to put too much weight on the point estimates from this systematic review. We believe that the main conclusion that should be drawn is that the results are consistent with the results from the use of antifibrinolytic agents in surgical bleeding. We feel that the strongest argument for the conduct of a randomised controlled trial of TXA in post partum haemorrhage is that TXA is currently being recommended for use in this situation. We have made this point clearly in the penultimate paragraph of the discussion section.

13. We cannot include more data on side effects of tranexamic acid since none were mentioned in the included trials.
14. We have not included a discussion of the role of recombinant VIIa since this treatment does not fall within the scope of the review.

15. We would have included all data published or unpublished in the review but did not find any unpublished data. Our statement that only published data were sought was an error and this has been corrected.

16. We have corrected the spelling error.

Thank you again for reviewing our paper.

Yours sincerely

Dr Ian Roberts