Author’s response to reviews

Title: Umbilical vein injection of misoprostol versus normal saline for the treatment of retained placenta: intrapartum placebo-controlled trial

Authors:

Sheelan S Rajab (sheelan80@yahoo.com)
Shahla K Alalaf Assistant.Prof (shahla_alaf@yahoo.com)

Version: 4
Date: 9 November 2013

Author’s response to reviews: see over
Dear Dr Norton,

Thank you very much for inviting us to submit a revised version of our manuscript entitled “Umbilical vein injection of misoprostol versus normal saline for the treatment of retained placenta: intrapartum placebo-controlled trial”. We have extensively revised our manuscript in accordance with the comments of the reviewers. Our point-by-point responses to the comments are given below.

We hope that the revisions to the manuscript and our responses are sufficient to make the manuscript suitable for publication in *BMC Pregnancy and Childbirth*.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

Shahla Alalaf, Assistant Professor
Hawler Medical University
College of Medicine, Department of Obstetrics and Gynaecology
E-mail: shahla_alaf@yahoo.com, 009647504480711
Responses to the comments of Reviewer 1:

Major Compulsory Revisions

1. The authors need to be completely clear about whether their study is randomized or not. The abstract calls it a 'randomized' clinical trial, but the manuscript talks of 'alternate allocation'. The crucial factor is whether the researcher knew what group the woman would be allocated to when she was being recruited, or whether she was allocated according to chance (e.g. by choosing allocation papers from a bag, or rolling a dice). The text and abstract needs to make this clear.

   The women were alternately allocated to the misoprostol and saline groups. The women were blinded to the group allocation, but the investigator who administered the injection was not. This is explained in the revised manuscript.

2. There is one woman excluded from the misoprostol group, but the analysis should include her under the 'intention to treat' rule. It is not clear what the authors mean by 'the cord was slipped' (did it detach from the placenta?), but once she has been included into the study and the study treatment given she need to be included. After all, the 'slipping' could be as a result of the injection. This means a re-analysis of all the data for the misoprostol group unfortunately

   The cord detached from the placenta after umbilical vein injection in one patient in the misoprostol group. Previously, this patient was excluded from the analyses, and the relevant control (saline) group patient was also excluded. Both these patients are included in the analyses presented in the revised manuscript, and the sample size has therefore increased from 44 to 46.

Minor Essential Revisions

1. In the abstract the authors should report just the results relating to the main objectives of the study.

   We have changed the results section of the abstract as suggested.

2. In the background the authors should give the Herman 1993 reference.

   The Herman (1993) reference was added to the Background section as suggested.

3. A sample size calculation should be added to the methods section.
Fifty women were diagnosed with RP during the study period, of which 46 met the criteria for inclusion. No sample size calculation was performed prior to starting the trial.

4. The measurement of blood loss section should clarify that the blood collection only started after administration of the drug (if that is true) and did not include the blood loss from the time of delivery.

The volume of vaginal blood loss was measured from the time of umbilical vein injection until delivery of the placenta. This has been clarified in the revised manuscript.

5. The gestational age was significantly different between the groups and this needs to be mentioned.

This apparent difference was an error, and has been corrected in the revised manuscript.

6. Blood loss is not usually normally distributed and so the median blood loss (and Mann-Whitney test) is the better technique for analysis.

The Mann-Whitney test was used to compare the mean rank of blood loss between the two groups.

7. In the references it would be better to use the Cochrane review (or the WHO Reproductive Health Library) instead of the unpublished thesis for the systematic review.

The Cochrane review has been cited in the revised manuscript instead of the unpublished thesis.

8. The demographic data is best reported all in the same table - I would therefore combine tables 1 and 2 (and remove the range values).

The range values have been removed from Tables 1 and 2 as suggested. However, we did not combine these tables because Table 1 compares mean values between the two groups using the T-test, and Table 2 compares proportions between the two groups using the chi-square test.

9. The outcomes are also best reported together - I would shorten table 3 to just 'need for manual removal i.e. 1 vs 6 (or probably 2 vs 6 with the 'slipped cord'
included) and add the outcomes for blood loss and time to separation beneath (but see 10 below).

10. In tables 4 and 5, there are 95% CIs presented, but it is unclear what the 95% CIs are around. It would be easier if there is a continuous outcome (with statistical test) and then a single categorisation (with Relative risk and 95% CI).

The outcomes are reported together in Table 3 in the revised manuscript. The results have changed because of the increased sample size included in the analyses. Both blood loss and time to delivery of the placenta were analysed using mean values and were also categorized into two groups (<250 mL and ≥ 250 mL for blood loss; <15 minutes and ≥ 15 minutes for time to delivery of the placenta) as suggested in the Discretionary Revisions. The mean difference with the 95% CI was added both outcomes.

Discretionary Revisions
1. in the intraumbilical uterotonics section, the authors should include the Release trial (Lancet 2010), the Cochrane reviews and the WHO Recommendations on postpartum haemorrhage and retained placenta from 2012. These all show that intraumbilical oxytocin is not used because it is probably ineffective.

These references are discussed in the revised manuscript, as suggested.

2. The number of women in the study should only be written in the results and not in the methods section.

Thank you for your suggestion. However, the “Enrolment, sample size, and group allocation” part in the Methods section seems to be an appropriate place to describe the details regarding sample sizes for each intervention, and we have therefore left the information in this section.

3. Blood loss and time to separation are reported as means in the text but are categorised in the tables. It is more conventional (and easier to understand) if the data is summarised as means or medians and then a single categorical outcome used for each (for example over 250ml blood loss, and time over 15 minutes for example).

The outcomes are presented both as mean values and in dichotomized groups in the revised Table 3.

Quality of written English: Not suitable for publication unless extensively edited
The entire manuscript has been revised and corrected by a native English speaking editor.

**Responses to the comments of Reviewer 2:**

**Major Compulsory Revisions**

1. In Methods section, the authors should describe whether there was any procedure performed AFTER the umbilical vein injection (UVI), did they continue to perform the controlled cord traction?, Were the procedures performed similarly in both arms? As the physician was not blinded, this may influence the time-to-placental delivery.

The cord was occluded by finger pressure around the catheter during injection, and was clamped with the catheter still in position after injection. If spontaneous delivery of the placenta did not occur, delivery by gentle cord traction was attempted at 15 and 30 minutes after injection. The time from umbilical vein injection to delivery of the placenta was recorded. Delivery of the placenta was assessed by clinical signs of placental separation and expulsion, as described by Rogers et al. [4]. The same procedures were followed in both treatment arms. This has been clarified in the Methods section of the revised manuscript.

2. In Result section, paragraph 2, it says "There were no statistically significant differences between the two groups in terms of mean age, parity or gestational age"; however, in Table 1, the p value for gestational age is .03 (which is significantly different).

This apparent difference was an error, and has been corrected in the revised manuscript.

3. In Figure 1, there are 5 women excluded from the study, however, the reasons for exclusion were given in 4 cases, but missing in the fifth case.

The cord detached from the placenta after umbilical vein injection in one patient in the misoprostol group. Previously, this patient was excluded from the analyses, and the relevant control (saline) group patient was also excluded. Both these patients are included in the analyses presented in the revised manuscript, and the sample size has therefore increased from 44 to 46.

4. In Tables 4, it is not clear what is the meaning of 95% CI : is it the difference of amount of blood loss (in mL). The Table should show the mean blood loss in each group, and also the mean difference between groups and its 95% CI
5. In Tables 5, it is not clear what is the meaning of 95% CI: is it the time difference between groups (in minutes). The Table should show the mean time to placental separation in each group, and also the mean difference between groups and its 95% CI.

The 95% CI values shown in Tables 4 and 5 were for the mean differences between the two groups. This has been clarified in the revised manuscript (the data are now shown in the revised Table 3).

Minor Essential Revisions
1. Aims of the trial, "(2) to measure the amount of vaginal blood loss .....". "to measure" should be changed to "to compare".

This sentence has been changed as suggested.

2. Methods, Technique of UVI, "Piping’s method" should be corrected to "Pipingas' method"
3. Discussion, paragraph 1: "systemic review" should be corrected to "systematic review".
4. Acknowledgments, paragraph 1: "trail" should be corrected to "trial".

These mistakes have all been corrected.

Quality of written English: Needs some language corrections before being published

The entire manuscript has been revised and corrected by a native English speaking editor.