Author’s response to reviews

Title: Intramuscular injection, intravenous infusion, and intravenous bolus of oxytocin in the third stage of labor for prevention of postpartum hemorrhage: a three-arm randomized control trial

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Author’s response to reviews:

Dear Dr. Nabhan:

Thank you for your comments. Please find below our responses to editor and reviewer comments on the manuscript entitled “Intramuscular injection, intravenous infusion, and intravenous bolus of oxytocin in the third stage of labor for prevention of postpartum hemorrhage: a three-arm randomized control trial”. The revised manuscript has also been uploaded to the BMC online portal.

The recently published updated 2018 Oladapo et al. Cochrane review concludes that the three studies included for analysis contain very low-quality evidence and appropriately designed
randomized trials with adequate sample sizes are still needed to address the research question of importance of route of prophylactic oxytocin after vaginal birth. We believe our study helps address this gap, and hope you approve this paper for publication in BMC Pregnancy & Childbirth.

Author responses:

Editor Comments

1. A total of 4983 women who were included in the study after found eligible of the total women delivered vaginally at El Galaa=15,143 and Shatby=8,353. This is 21%. This proportion raises 2 issues.

A. When active management of labor is the standard of care in both hospitals, it would be critical to understand how 21% of women did not receive the standard of care.

After communicating again with our colleagues regarding augmentation practices at the two hospitals, the response in the prior set of queries proved incomplete. The approach described of augmentation at 4 to 6 cm dilation is often practiced at Shatby hospital. Even so, there is still a great deal of variability in clinical care and the study enrollment period coincided with a reported decrease in the overall rates of augmentation. At El Galaa hospital, there is not a guideline, clinicians use their clinical judgment, and augmentation rates are lower. At both hospitals, women were enrolled during 3 of the 6 obstetrical shifts, thus approximately half of eligible women would not have been approached for study participation, but we see no concern for systematic bias.

B. It would be critical to explain if every women who has not received any uterotonic in the first or second stage agreed to participate and consented.

As mentioned for point A, at both hospitals, women were enrolled during 3 of the 6 obstetrical shifts, thus approximately half of eligible women would not have been approached for study participation.

2. Explain the absence of Any VBAC in this large number of women delivered vaginally.
We did not document VBAC in our study, though in these hospitals, previous CS is nearly always an indication for CS, so the number is likely very low. As cases were randomized, any VBAC cases should have been evenly distributed.

3. Explain the lack of Any traumatic PPH among this large number of women delivered vaginally in 2 teaching facilities.

We did have a small number of traumatic PPH cases reported; however, the PPH rate was very low and trauma was quite low, though within the range reported elsewhere. Overall, the primary PPH cause was documented as 92.5% atony (n=37), 5% trauma (n=2) and 2.5% retained placenta (n=1). Only the presumed primary cause of PPH was captured for this study, so additional traumatic PPH cases, where trauma was considered secondary to atony, would be underrepresented.

4. Referred cases (which is the rule in these 2 large tertiary facilities) might have received induction or augmentation. Was there any verification that they have not received any uterotonics.

For referred cases at both hospitals, women generally arrived to the hospital with a report logging all medications they received at the lower level. These reports were the primary verification. The primary investigator at El Galaa hospital mentioned that as a secondary verification, they also noted if women had a cannula in place at arrival and that women themselves occasionally reported their medications.

5. Sample size based on a personal communication while there is a high quality systematic review in this topic.

The reference cited for the Dzuba 2-arm RCT used to calculate the sample size for the IV infusion vs IM injection comparison has been updated in the manuscript reference list to better identify the source (page 15). At the time of the protocol writing in 2013, the 2012 Oladalpo Cochrane review on IV vs IM prophylactic oxytocin in the third stage of labor identified no trials
for consideration on the topic. The updated Oladalpo Cochrane review from September of this year, did not yet exist for reference, but identified no high-quality studies. Reference to the Oladalpo Cochrane review was updated to 2018 version in the manuscript (page 14). Citation of Sangkomkamhang 2015 article was also added to manuscript (page 4).

6. In these busy crowded hospital (as described in your reply), any proof of intact cold chain for oxytocin used in the study.

Although, on monitoring visits, the oxytocin stock was always inspected, it is difficult to comment on this on the whole as maintaining the cold chain is a widespread issue, including transport. With the high delivery volume at these facilities, the stock turns over at such a rapid rate that it is unlikely oxytocin was out for long enough to degrade as it should be stable at room temperature for several days. Further, as any issue would have been distributed across study arms, it should not have introduced any internal bias.

7. Are women who did not receive pre-delivery uterotonics to induce or augment labor any different in their response to prophylactic uterotonics for preventing PPH.

Since studies show pre-delivery oxytocin can desensitize the uterus to the effect of subsequent doses (cited in the manuscript as Balki et al., 2014), we wanted to eliminate the potential effect with an exclusion criterion for women with pre-delivery exposure to oxytocin. This does limit the generalizability of the study results to those women who did receive uterotonics for induction/augmentation. This caveat has been added to the manuscript (page 11).

Reviewer reports

Melania Amorim, MD, PhD (Reviewer 1):

No comments noted.

Ioannis Gallos (Reviewer 2): This is a high quality trial answering a key question on the prevention of PPH. It will be a great addition to the literature and with a potential to influence existing recommendations.
Have no major points to make.

Some minor points to consider.

1. Have noted a small imbalance in the baseline characteristics - was there any minimisation variables included in the randomisation algorithm? If not please describe the randomisation method as "simple randomisation". This works in favour of IM route so it does not explain the differences in effects. However, the authors could consider reporting also an adjusted analysis.

“Simple” has been added to the description of the randomization method (page 7). As suggested, we conducted an adjusted analysis for the baseline characteristics that could be seen as unbalanced in the model (episiotomy, epidural, multiple birth). It did not significantly change our results or estimates, so we feel it unnecessary to add to the manuscript.

2. Could the authors please provide details about the IV oxytocin infusion and report over how many minutes or hours was infused? Even as an estimate with a reasonable range. For the injection they state this was injected over one minute.

The infusion rate is reported in the results section of the manuscript. In the methods section, where the reviewer noted the approximate bolus injection time, the injection instructions given to the study staff are defined. Study staff did actually measure and document infusion time, so this is listed as a result (page 8), "the mean time to completion of the 500ml infusion for women randomized to the IV infusion arm was 28 minutes (SD=6.4)." This organization in the manuscript still makes most sense to me, but it can be easily changed upon request.

3. Following the publication of the core outcome set for prevention of PPH, the authors can consider reporting additional outcomes such as
   A. Severe maternal morbidity: Intensive care admissions
   B. Severe maternal morbidity: Shock.
   C. Death
We received no reports of any of the above outcomes in our study population. This detail is now added to the manuscript (page 9).

4. In terms of side effects I can see the authors are reporting the mean blood pressures with the three arms. Perhaps they could consider reporting hypotension also as a binary outcome. The same perhaps for tachycardia if available. Oxytocin does not cause many side effects but were there any other collected? If so please report all in a separate table.

Detail on proportion of hypotension in each group is now added to the manuscript (page 9). We did not collect pulse, so tachycardia is not possible to report. Side effects following administration of oxytocin prophylaxis were collected with an open-ended question. We also asked about adverse and serious adverse events on the study form. As reported in the results section (page 9), no issues were reported on any of the three questions on the form.

Thank you again for your consideration. We look forward to hearing from you soon.

Sincerely,

Dyanna Charles, MPH