Author's response to reviews

Title: Talcum Powder or Aqueous Gel to Aid External Cephalic Version: A Randomised Controlled Trial

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Author's response to reviews: see over
14 Dec 2013

The Editor
BMC Pregnancy and Childbirth

Dear Editor

Talcum Powder or Aqueous Gel to Aid External Cephalic Version: A Randomised Controlled Trial. Manuscript ID: 1416029015107488

Thank you for permitting us to revise our manuscript. We would like to express our deepest appreciation to the reviewers for their valuable input in the process of strengthening our article.

Our point by point response is as follows

1) Please include a conclusions section.
   The last paragraph concludes the article and it has now been designated as such.

2) Please ensure that your manuscript conforms to the CONSORT guidelines for the reporting of clinical trials (www.consort-statement.org).
   Consort guideline consulted – all items accounted for.

Reviewer 1
Reviewer: REMON KERIAKOS
Reviewer's report:
This is a well written article. The study has many limitations being small but the authors have acknowledges these limitations. However, the authors have not mentioned how many operators have been involved and their level of experience as this would affect the result. It might not be the gel or the talc powder which affect the result but the skills of the operator. I do not think this study as such would add much to the current practice as many obstetricians prefer gel rather than talc powder for many reasons
Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
Nothing to declare

Thank you. We accept that the trial is only powered to look at the issue of self-reported maternal procedure related pain. We have included information on operators performing the ECV. There were 37 operators– the highest number performed by an individual was 9. As the trial was randomised, provider expertise/experience could not have made a significant difference to the outcome.

Reviewer 2
Reviewer's report

Title: Talcum Powder or Aqueous Gel to Aid External Cephalic Version: A Randomised Controlled Trial

Version:1 Date:7 November 2013

Reviewer: Raed Salim

Reviewer's report:

Major Compulsory Revisions

1. In the Methods section, the authors describe that FHR tracing was performed after the attempted version. Was any period of continuous monitoring performed and for how long?

CTG monitoring was continued until a reassuring trace is obtained (i.e. at least 2 fetal heart rate accelerations of at least 15 bpm above baseline for at least 15 seconds were observed within a normal FHR trace background pattern) – this process took a variable period of time, usually 20-60 minutes. We have added to the text on this point.
2. Page 7, line 133, the authors stated that both VNRS pain score and successful ECV were considered primary outcomes. Since the sample size was too small to provide significant results regarding successful ECV it should not be listed as a primary outcome.

*We predefined both as primary outcomes at the outset before trial was started but ECV success was not powered. We have heeded this comment and that of Dr Nassar and have dropped ECV success as a primary outcome as the finding is not significant anyway. Posteriori, we have done an analysis on the power of the trial looking at ECV success and calculated the sample size required to test ECV success based on our unique trial data to provide pilot data for future powered study.*

3. It would be useful to give readers an estimate of how many women in total had a breech presentation during that time period. Additionally it would be useful to know the total numbers who underwent ECV during this time period to address issues of selection bias.

*Unfortunately, we did not keep records of other ECVs performed during the trial recruitment period. As the trial allocation was not revealed until the last moment prior to ECV and every woman had their allocated intervention performed, in our view, the risk of a systematic selection bias is small.*

4. The results between the two groups could be comparable due to different operators (either better or worse) rather than the two aids having similar or different affects. The authors need to provide information regarding the operators that performed the ECV and whether there was a different between the groups in term of their experience.

*A total of 37 operators performed the ECV. The most active operator was involved in only 9 cases (5 randomised to gel and 4 to powder). In our trial protocol, allocation was concealed until the last moment. Cross over was also permitted and we provided detailed analyses of all the ECV attempts made (including cross overs). ECV success was not significantly different. It is unlikely that operator skill level could have biased the substantive findings of the trial.*

5. How many procedures were stopped due to non reassuring FHR.
We did not have to stop any procedure due to FHR issues. CTG was not performed during ECV itself. It was performed prior to the start of ECV, after successful ECV, after a round of 2 attempts or at abandonment.

In the short gap of a few minutes between the 2 attempts within a round, we did not do a CTG; we checked fetal presentation and FHR by ultrasound (with CTG only if fetal bradycardia < 110 bpm or irregularity in FHR). There was no emergency Caesarean due to non-reassuring CTG. We recruited a total of 95 women for the trial – typically a non-reassuring CTG after ECV necessitating Caesarean delivery occurred 0.35% of cases.

6. Data regarding gravidity in table 1 is of limited value and should be deleted.
   Deleted.

7. Please provide the number of women with a transverse lie in both groups?
   None was in transverse presentation at recruitment.

8. Did the gestational age at the time of the ECV differ between the groups?
   No.

   Table 1.

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Median [Interquartile Range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder</td>
<td>37.5 [37.4-7.9]</td>
</tr>
<tr>
<td>Gel</td>
<td>37.8 [37.4-38.2]</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = 0.22</td>
</tr>
</tbody>
</table>

9. The results section (page 11, line 207-211) contains issues that belong to the discussion section.
   We have moved to discussion section.

10. Table 2 is very long and crowded with information. Additionally the reader may get lost due to repeated issues. The authors should try to shorten (probably 2 tables instead of 1) and report the bottom line.
We have split Table 2 into two tables. Table 2 deals with primary outcomes and secondary outcomes related to each ECV attempt including after cross-over. Table 3 deals with all other reported secondary outcomes based on intention to treat.

11. Explain why 8.3% of the neonates in the powder group had a neonatal admission though all were term neonates.

Of the four neonatal admissions for the powder arm (two was for transient tachypnoea of the newborn, one for a suspected cephalhaematoma following vacuum delivery and another for further observation following 1 minute Apgar of 5 with umbilical arterial cord pH of 6.99 and a base deficit of 15. A. Of the two neonatal admissions for the gel arm, one was for transient tachypnoea of the newborn and another for neonatal jaundice.
We have added the above to the foot notes of Table 3.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: I declare that I have no competing interests

Reviewer 3
Reviewer: Natasha Nassar
Reviewer’s report:
This is a useful study comparing use of talcum powder versus aqueous gel to help facilitate external cephalic version (ECV). The primary outcome was maternal self-reported procedure-related pain and success rate. However, the study was powered on the former outcome and there was insufficient power to conclusively determine success rate.
There are no major issues with this study, but further details regarding rationale for analyses and approaches need to be provided.
Thank you.

1. Line 94-99: can authors provide more detail about who conducted the randomisation—was this done remotely from the person undertaking ECV

“The randomisation envelopes were prepared by an author (NV who was not involved in recruitment)... The numbered envelopes were prepared en-bloc at the beginning of the study and arranged in sequence in a small box in the Delivery Suite for providers to extract and open to reveal the allocated intervention.”

2. Line 133: is the primary outcome measure of VRNS been validated? Has it been used in previous studies? How reproducible and repeatable are results?

The visual numerical rating scale (VNRS) was not specifically validated in our patients as we felt that its use in a 1-dimensional assessment of procedure related pain is well supported by available general data on the VNRS as a valid and reliable pain score scale.

In a 1986 study on “The measurement of clinical pain intensity: a comparison of six methods” by Jensen et al. Pain. 1986 Oct;27(1):117-26, evaluating the most precise, replicable, and predictively valid measure of clinical pain comparing 6 commonly used scales, all scales yield similar results in terms of the number of subjects who respond correctly to them and their predictive validity but when considering the remaining 3 criteria, the numerical rating scale appears to be the most practical index.

In a more recent study comparing the “Validity of four pain intensity rating scales” by Ferreira-Valente et al. Pain. 2011 Oct;152(10):2399-404, evaluating experimentally induced pain using a cold probe (a situation close to our scenario of pain during ECV), the order of responsivity was as follows: NRS, VAS, VRS, and FPS-R with relatively small differences in the responsivity between scales. The most support emerged for the NRS as being both (1) most responsive and (2) able to detect sex differences in pain intensity.
3. Line 146-155: given there were 2 primary outcomes why wasn’t study also powered for ECV success rate; and then higher estimate of sample size chosen?

*Our trial was a non-inferiority design (as we expect no major difference) comparing two relatively simple interventions where it is easy to establish a clinically non-significant difference to test the hypothesis on procedure related pain. It is more difficult to suggest a clinically non-significant on ECV success. In response to Dr Raed Salim’s suggestion, we have dropped ECV success as primary outcome.*

4. Line 158: need to define ‘per protocol’ analysis.

*We had intended to analyse per protocol due to our non-inferiority design/hypothesis to ensure a more robust defense of the null hypothesis. The null hypothesis in a non-inferiority trial is of a significant difference, so to ensure that the null hypothesis is not wrongly rejected, a per-protocol analysis is more appropriate as protocol violations (particularly cross-overs) would tend to cause treatment effect to converge, systematically providing support to a no difference/non-inferior finding.*

*However as all women received the intervention as originally allocated, intention to treat and per protocol analysis was actually the same. We have added this to the text.*

5. Line 158: why wasn’t intention to treat analysis performed?

*All participants received their allocated intervention, so intention to treat vs. per protocol analyses yielded identical results. We have explained this in the result section.*

6. Line 158-164: there is insufficient detail related to the various analyses conducted. More information about each component of the analysis needs to be provided. For example, how and what associations were assessed, and why (what outcomes and what predictors) and how was the multivariable analysis conducted?

*We have added details to this section of methodology in the text.*
7. Line 187- why weren’t final per protocol results presented, taking into account crossovers?

This data is in Table 2. We have added it to the text now. We have also highlighted the finding that cross-over rates were borderline significant between the arms, with a trend for higher cross-over of powder to gel than gel to powder after failure of ECV with the originally allocated intervention.

8. Line 197-199: Sentence related to predictors of ECV success does not belong in results and should be moved to introduction with more information provided. 

We have moved the lines to introduction and added details.

9. Line 199-203: rationale for this analysis needs to be provided in the analysis section of methods

We have added rationale to methods.

10. Line 203: Revise ‘take up’ to ‘rate’

Amended.

11. Line 206: why weren’t intention to treat results presented?

See above 4. and 5. They were the same because there were no protocol violations for the initial allocated intervention.

12. Line 207-213: this section belongs in the discussion

Moved.

13. Line 216-218: move this sentence to discussion

14. Line 218-219: what harms were assessed- need to be described in methods.

Moved to discussion. Harms defined in methods i.e. “For assessment of major harms of the study, we looked at procedure related Caesarean delivery, fetal or neonatal death, neonatal hypoxic-ischaemic encephalopathy and major abruptio placenta.”
15. Line 218-219: More information on harms should be provided in introduction

More information from the cited literature review provided.

16. Line 239: need to address imprecision of this result

We have added “However this finding is not significant and the confidence interval is wide.”

17. Line 240: need to address that in your trial all women received a beta-mimetic and what the impact of this has on your results

Beta mimetics at ECV is standard, widely used practice given to all women in both arms. We have stated this clearly in methods. We do not believe it has any impact on our results.

18. Line 251-254: rationale as to why study wasn’t powered for ECV success given it was also a primary outcome should be provided.

See response to 3 above.

19. Table 1: footnote needs to be deleted and details related to data expressed needs to be moved to column titles of table so reader understands units presented

Amended.

20. Table 1: delete footnote related to ‘Analysis….’

Deleted.

21. Table 1: footnote: delete repeated word ‘sound’

Deleted.

22. Table 2: Check numbers and percentage for caesarean delivery

Numbers correct. Error for percentage corrected.

23. Table 2: Which outcome does the RR 2.1 (95%CI 0.4-12) relate to?

Error. Deleted.
24. Table 2: delete first 4 lines of footnote; and add units expressed in titles of table.

Amended.

Editorial comments
1. Line 54: delete ‘shows that’ and replace with reported

Amended.

2. Line 64: Replace ‘latterly’ with Recently

Amended.

3. Line 79: correct consents to consent

Amended.

4. Line 102: insert ‘out’ after carried

Inserted.

5. Line 104: revise comprise to ‘comprised’

Amended.

6. Line 105: end sentence at 2-3 minutes. Delete ‘and following which’ and commence new sentence with ‘Fetal presentation…were THEN checked by….’

Amended.

7. Line 107: replace ‘could’ by ‘was’

Amended.

8. Line 139: insert ‘collected’ following ‘Secondary outcomes COLLECTED include…’

Amended.

9. Line 155: delete ‘in a single block’ as it repeats line 96

Deleted.

10. Line 182: delete ‘analyzes’

Deleted.

11. Line 259: replace find with ‘found’

Amended.

12. Line 262: delete ‘this resulted in the possibility that’ and start sentence with ‘Cross0ver…’ and change ‘might be more’ to ‘was’ and then revise end of sentence to ‘…operators MAY HAVE BEEN more confident with gel’
Amended.
13. Line 264: revise result to ‘results’ and delete like and replace with ‘such as’
Amended.
14. Line 265: replace ‘nullity’ with ‘the null’
Amended.
15. Line 274: replace ‘is’ with ‘was’
Amended.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests

We resubmit our revised manuscript for consideration of publication.

Yours sincerely

Peng Chiong Tan (Corresponding Author on behalf of all authors)