Author’s response to reviews

Title: Application of Postoperative Autotransfusion in Total Joint Arthroplasty Reduces Allogeneic Blood Requirements: A Meta-Analysis of Randomized Controlled Trials

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Author’s response to reviews:

Mar 24th, 2017

Re: Revision for “Application of Postoperative Autotransfusion in Total Joint Arthroplasty Reduces the Need for Allogenic Blood: A Meta-Analysis of Randomized Controlled Trials”, number BMSD-D-16-01052.

James Mockridge, PhD

Editor, BMC Musculoskeletal Disorders
Dear Editor:

We thank you and the reviewers for giving us the opportunity to revise our manuscript. We have carefully studied the comments raised by the reviewers and editors, and revised the paper accordingly. The following are point-by-point responses to the editors’ and reviewers’ comments. All the corresponding changes have been highlighted in the revised manuscript.

Should you have any questions, please contact us without hesitation.

We look forward to your favorable decision.

Sincerely,

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Point-by-point response

Jashvant J. Poeran (Reviewer#1):

Overall Comment:
This is a meta-analysis of randomized controlled trials comparing postoperative autotransfusion to groups without (either with or without drain) in hip and knee arthroplasty patients. The main outcome is the need for allogenic blood transfusion.
The authors extract data from 17 trials (2,314 patients) and find autotransfusion to be associated with reduced RRs for allogenic blood transfusion in hip and knee arthroplasties without subgrouping control groups based on drains vs. no drains. When comparing treatment groups to control groups with no drainage, this reduction is not maintained.

Overall, this appears to be a well performed meta-analysis providing important information on this still somewhat controversial topic. More specific comments below.

Answer: We appreciate your comment.

Comment 1: Abstract

Add some cautionary words in Conclusion on heterogeneity and what this means for reliability of summary estimates

Answer: Thank you for your comment. We have added the following information on heterogeneity in the Abstract-conclusion section:

“However, the reliability of meta-analytic results concerning TKA is limited by significant heterogeneity due to methodological factors.” (Abstract Section, line 50-51, page 2)

Comment 2: Introduction well written, nice overview, clear rationale and succinct

Answer: Thank you for your positive comment.

Comment 3: Methods

1) The section on testing for publication bias is a bit messy and not easy to understand for a clinical audience. Please revise and state first that Egger’s test and Begg’s test are used to test for publication bias and that they look at the association between intervention effects and a measure of study size. Egger by using actual standardized effect size while Begg uses ranks of effect sizes and ranks of variances. These tests should always be interpreted along with visual inspection of the funnel plot.
Please consider adding the funnel plot and also stating that you look for asymmetry, mainly due to absence of small negative trials.

Answer: Thank you for your advice. We have revised the manuscript according to your suggestions. Meanwhile, funnel plots have been added to look for asymmetry (S9 and S10). The following information is added in methods section:

“Egger's test and Begg's test are used to test for publication bias and that they look at the association between intervention effects and a measure of study size. Egger's test uses actual standardized effect size while Begg's test uses ranks of effect sizes and ranks of variances. The funnel plots are used to look for the asymmetry with visual inspection.”

(Methods Section, line 150-154, page 10)

2) Not only I2 should be used to decide on whether to use fixed or random effects; the number of studies available too is important. A small number of studies (<5-10) would be grounds to do a fixed effects approach as well. Please consider this in the 'No drain' subgroup in TKA (figure 2) and add some words to the Methods.

Answer: We quite appreciate your constructive comment. We performed a new meta-analysis for the “no drain” subgroup in TKA using fixed-effect model. The results and methods section have been revised in the manuscript accordingly. The significance of this result is not affected. The following information have been added in the statistical analysis section.

“Fixed-effect model was adopted if a small number of studies (<5) were included in meta-analysis.” (Methods Section, line 142-143, page 9)

Comment 4: Results

1) Consider adding a column to Table 1 adding information on transfusion thresholds. This is important information for your reader to assess sources of heterogeneity and in what light to interpret the results.
Answer: Thank you for your comment. We have added the information on transfusion thresholds (Table 1). The detailed transfusion trigger are provided in the supplement (S12 Table).

2) How many studies did report use of tranexamic acid?
Answer: Thank you for your comment. We carefully checked the included studies and found none of the studies reported the use of tranexamic acid.

3) S3 and S4 Figures: should you do a meta-analysis with results from only 4 or 3 studies? Please comment and mention this limitation and rationale if you choose to include it.
Answer: Thank you for your critical comment. We performed these meta-analyses to evaluate the safety of autotransfusion. Given the small heterogeneities of studies, it was reasonable to pool their results. Furthermore, previous studies also included small numbers of studies to evaluate secondary outcomes 1,2. Notably, the results were limited due to few studies included in the meta-analysis. We have mentioned these limitations in the results section and conclusion section.

“The reliability of these results were limited by small number of studies (<5).”

“Small number of studies (<5) limited the reliability of these results.” (Results Section, line 178-179, page 11; Conclusion Section, line 285-286, page 17)


4) Same issue for figures in S6 and S7.

Answer: Thank you for your critical comment. We have mentioned these limitations in the results section and conclusion section.

“Small number of studies (<5) limited the reliability of these results.” (Results Section, line 193, page 12)

5) The reason why I mentioned considering adding a funnel plot is because of the fact that the number of studies included here is not large and thus may hamper the reliability of Begg's and Egger's tests. The second sentence in the 'publication bias' section should be removed, that is not what Egger's and Begg's tests can infer.

Answer: We appreciate your critical comment. We have added the funnel plots (S9 and S10) and revised the manuscript according to your suggestions in the corresponding sites.

“Egger's test and Begg's test are used to test for publication bias and that they look at the association between intervention effects and a measure of study size. Egger's test uses actual standardized effect size while Begg's test uses ranks of effect sizes and ranks of variances. The funnel plots are used to look for the asymmetry with visual inspection.”

(Methods Section, line 150-154, page 10)

Comment 5:Discussion

1) I am concerned about the adverse reactions that you state were not significant between groups. These are rare and the number of studies reporting on them was smaller. Please Discuss this limitation in more detail as it is important to mention in light of the recommendation to use autotransfusion.

Answer: Thank you for your constructive and critical comment. We have added the following information in the corresponding sites in the discussion section:

“Notably, the numbers of included studies were small, which limited the reliability of these results. Further studies with sufficient data are required to evaluate the safety of autotransfusion systems.” (Discussion Section, line 264-266, page 16)
2) As a strength of the current study you state that strict inclusion and exclusion criteria were observed; however, this still resulted in including a group of studies that were very heterogeneous in nature. The quality of a meta-analysis is as good as the underlying studies and their comparability which in this case I feel is severely lacking. I would consider adding explicit wording on this in the Discussion to caution your readers. The heterogeneity in my eyes is the most important finding of this meta-analysis and the Discussion would greatly benefit if you would add recommendations on ways to reduce this heterogeneity for future trials, e.g. type of system used, Hb triggers, comparison groups, etc.

Answer: Thank you for your critical comment. We have elaborated the manuscript in the discussion as follows:

“Thus the reliability of meta-analytic estimates concerning TKA is questionable by significant heterogeneity due to methodological factors. To reduce the heterogeneity for future trials, factors such as types of system used, Hb triggers, comparison groups and anesthesia method should be taken into account.” (Discussion Section, line 211-214, page 13)

3) In the Conclusion you mention the results from the meta-analyses where only a few studies were involved. Please consider either removing these results here or add a word of caution that only 3 or 4 studies were included in those meta-analyses.

Answer: Thank you for your constructive comment. We have added the following information in the Conclusion section:

“However, the the reliability of secondary outcomes were limited by small number of studies.” (Conclusion Section, line 285-286, page 17)

4) Conclusion: financial comparison is not necessarily a result from your study, but more something for in the Discussion. Consider removing from the conclusion and just add in Discussion.

Answer: We appreciate your critical comment. This section is deleted and moved to Discussion. (Discussion Section, line 278-279, page 16)
5) Limitations: very short section while there are severe limitations; most important the heterogeneity and number of studies included for secondary outcomes. More studies and more information is needed on safety outcomes.

Answer: Thank you for your comment. We have revised the limitation section according to your suggestions.

“This meta-analysis has some limitations. Firstly, the reliability of pooled results concerning TKA is limited by significant heterogeneity due to methodological factors.

Secondly, the number of studies included for secondary outcomes are small, which requires more studies and more information on safety outcomes in future. Thirdly, the results were based on many unadjusted factors; a more precise analysis should be conducted, allowing time of randomization, drain insertion time, the timing of drain opening and closing and financial comparison. Finally, the protocol is not registered in Cochrane.” (Discussion Section, line 273-279, page 16)

Comment : Discretionary Changes: -

Tables are: sufficient.

Figures are: Sufficient, add funnel plot

Manuscript size is: Sufficient, elaborate more on limitations and heterogeneity in Discussion

Recommendation: Major Revisions

Justine Naylor (Reviewer 2): Please see comments attached to the pdf document. I was not sure why there were segments in yellow.

Answer: The segments in yellow was highlighted for the last revision.

Main issues:

Comment : 1) Protocol not registered - this should be stated as a limitation in Discussion. Not sure what the Journal policy is on SRs which have not been prospectively registered.
Answer: We appreciate your comment. The journal policy encourages authors to register their systematic reviews in a suitable registry. We will register as soon as possible. We have added this limitation in our manuscript as follows:

“Finally, the protocol is not registered.” (Discussion Section, line 279, page 16)

Comment :2) Why are there 2 Table 1s and Table 2s? -same headings but different number of studies.

Answer: Thank you for your comment. The first Table 1 and Table 2 are cited in the manuscript. We have uploaded only one Table 1 and Table 2.

Comment :3) The authors say that some studies (in TKA) had 2 controls included. How did they analyse such studies. If there was a comparisons b/w re-infusion drain and no drain, and re-infusion and regular drain in the same study, the intervention arm needs to be split.

Answer: Thank you for your constructive comment. First, we compare the intervention arm to both controls. Afterwards, we perform subgroup analyses to spilt the intervention and compare half to one control (regular drain) and the other half to the other control (no drain).

Comment :4) Should specify in the figures which direction favours the intervention. Assume RR > 1 favours the intervention?

Answer: We quite appreciate your positive suggestion. We have added “favours autotransfusion” and “favours control” in all figures. RR<1 favours the intervention in this study.

Comment :5) for the sensitivity analysis, what criteria did you use for removing 1 study?

Answer: We quite appreciate your critical comment. Every single study will be omitted and the RRs of remaining studies is calculated. The result of sensitivity analysis consists of all RR values (only one study is omitted for one RR value). We could consider the results were stable if all the RRs (calculated by the rest studies) were not significantly changed.

Reply to suggestions_queries

Note 1: Include date of search and type of studies (ie RCTs)
Answer: Thank you for your suggestion. The date of search and types of studies are included in the abstract. (Abstract Section, line 35-16, page 3)

Note 2: provides some of these factors

Answer: Thank you for your comment. We have provided these factors in the corresponding sites as follows:

“such as bleeding disorders and comorbidities” (Background Section, line 57-58, page 5)

Note 3: specify - donor transfusions?

Answer: Thank you for your comment. We have revised this sentence to specify the “transfusion”. (Background Section, line 59, page 5)

Note 4: Re-word this sentence - 'Not only may these conditions undermine the success of the surgery, but they may also result in death.'

Answer: We quite appreciate your comment. This sentence has been reworded according to your suggestion.

“Not only may these conditions undermine the success of the surgery, but they may also result in death.” (Background Section, line 63-64, page 5)

Note 5: 'to donor transfusion' c

Answer: Thank you for your suggestion. We have added “to donor transfusion” in the manuscript according to your suggestion. (Background Section, line 67, page 5)

Note 6: This section needs rewording - lack of formal power analysis in what? The literature?

Answer: Thank you for your critical comment. The “lack of formal power analysis” means “lack of formal power analysis in study size and significance level”. We have reworded this section as follows:
“Recent studies have reported that transfusion of autologous blood had no effect on the proportion of transfused patients, but some studies support autologous transfusion. Furthermore, the usefulness of autotransfusion drainage is uncertain due to methodological difficulties such as no formal power analysis in study size and significance level, different transfusion triggers, and different autotransfusion devices.”

(Background Section, line 75-80, page 6)

Note 7: from conception until February 2016?

Answer: Thank you for your comment. We have revised the manuscript to clarify the description as follows:

“All holdings of PubMed, the Cochrane Library, and Embase were searched for relevant trials published to February 2016” (Methods Section, line 87-88, page 6)

Note 8: change 'was' to 'is'

Answer: Thank you for your comment. We have changed “was” to “is”. (Methods Section, line 94, page 7)

Note 9: ‘,,key data such as transfusion rate’

Answer: Thank you for your comment. We have revised the manuscript according to your advice. (Methods Section, line 100, page 7)

Note 10: RCT should be your first criterion

Answer: Thank you for your comment. We have revised the order of criterion. (Methods Section, line 97, page 7)

Note 11: the use of tourniquet is not an issue provided within the same study, this was kept constant. You should either include them, or come up with a better reason not to include them.
Answer: Thank you for your comment. With the use of tourniquet, less blood loss was seen during surgery, but more blood was collected after surgery [1]. Thus the effectiveness of autotransfusion would be controversy due to tourniquet control and absence of blood loss during surgery [2-3]. We excluded the studies without tourniquet to control the effectiveness of autotransfusion among different studies.


Note 12: Study selection and data extraction

Answer: Thank you for your comment. We have revised the subtitle according to your suggestions. (Methods Section, line 106, page 7)

Note 13: you should note the funding source for each trial.

Answer: Thank you for your comment. We have complemented the funding information and revised the manuscript according to your suggestions (S12 Table).

(Methods Section, line 113, page 8)

Note 14: 'events'

Answer: Thank you for your comment. We have revised the manuscript according to your advice. (Methods Section, line 118, page 8)
Note 15: remove 'consisted change to 'included'

Answer: Thank you for your comment. We have revised the manuscript according to your suggestion. (Methods Section, line 118, page 8)

Note 16: change was to were

Answer: Thank you for your comment. We have revised the manuscript according to your advice. (Methods Section, line 122, page 8)

Note 17: change was to were

Answer: Thank you for your comment. We have revised the manuscript according to your suggestion. (Methods Section, line 134, page 9)

Note 18: re-word this

Answer: Thank you for your comment. We have polished the manuscript in the corresponding site.

“The I² statistic was used to evaluate heterogeneity. A random-effect model was used when significant heterogeneity was detected between studies (p<0.1, I²>50%). Otherwise, a fixed-effect model was adopted (I²<50 %, p>0.1). (Methods Section, line 140-142, page 9)

Note 19: have you got a list of excluded studies or atleast refer to them in reference list?

Answer: Thank you for your constructive comment. The list of excluded studies have been attached as a supplementary (S1).

Note 20: how have you dealt with this? Did you compare the intervention arm to both controls or did you split the intervention and compare half to one control and the other half to the other control??

Answer: Thank you for your critical comment. First, we compare the intervention arm to both controls. Afterwards, we perform subgroup analyses to spilt the intervention and compare half to one control and the other half to the other control.
Note 21: change was to were

Answer: Thank you for your comment. We have revised the manuscript according to your suggestion. (Results Section, line 161,163, page 10)

Note 22: I would replace this with actual group eg non-tranfusion/regular drain otherwise it is confusing. This comment applies to wherever you say 'control group'

Answer: We quite appreciate your positive comment. All the “control group” are replaced with “regular drain/no drain”.

(Abstract section, line 40, page 3; Methods section, line 117, page 8; Results section, line 168, page 11; Results section, line 176, page 11; Results section, line 178, page 11; Results section, line 182, page 11; Results section, line 190, page 12; Discussion section, line 208 page 13; Discussion section, line 243 page 14; Discussion section, line 263 page 16; )

Note 23: how did you determine which studies to exclude?

Answer: We quite appreciate your critical comment. Every single study will be omitted and the RRs of remaining studies is calculated. The result of sensitivity analysis consists of all RR values (only one study is omitted for calculating one RR value). We could consider the results were stable if the RRs (calculated by the rest studies) were not significantly changed.

Note 24: see previous comment re knees

Answer: Thank you for your comment. We have revised the manuscript according to your advice.