Author’s response to reviews

Title: Different dose regimes and administration methods of tranexamic acid in cardiac surgery: a meta-analysis of randomized trials

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Author’s response to reviews:

Dear reviewers and editors:

We really appreciate your kind and detailed suggestions to our article. We’ve made changes in the revised version according to your comments.

Reviewer 1

Major comments:

1. Comment: I believe that the major limitation of this very interesting work is including trials published only from 2011. In my opinion, including all published trials on tranexamic acid would boost the relevance of this meta-analysis. The Authors could then perform a specific sub-analysis for the most relevant outcomes (e.g. mortality and seizures) including only the most recent trials.

Revision: In the revised version, we included trials published before 2011 into analysis.
2. Comment: A useful additional subgroup analysis could be inclusion of low risk-of-bias trials only

Revision: In the revised version, we did a subgroup analysis on transfusion rate for studies with low and unclear risk of bias only [Page 8]. Since the result was largely the same with results including all studies, we present the forest plot in supplement figure 4.

3. Comments: Methods/Types of studies section: it is unclear to me the difference between RCTs and randomized head-to-head comparison. Do the Authors mean placebo-controlled vs drug-vs-drug trials? If this is the case, I believe that this distinction is somewhat confusing, and leaving RCTs is sufficient and improves clarity.

Revision: In the revised version, we only included studies comparing TXA and control groups into meta-analysis. We excluded studies which compared intravenous and intravenous plus topical delivery, as well as studies which compared high and low dose regimen.

4. Comment: Methods section: Rather than reporting several paragraphs describing characteristics of included studies, I believe that a single paragraph reporting a PICO framework and a list of inclusion and exclusion criteria would improve clarity. Of note, the Authors report no exclusion criteria in the current manuscript version.

Revision: In the revised version, we adopted the PICO framework and added exclusion criteria (Trials on urgent cases or on children were excluded, head to head trials comparing TXA with other fibrinolytic medications were excluded) [Page 3-4].

5. Comment: Methods/Types of participants section: please add "WHO" between "adults" and "underwent"

Revision: We added who between adults and underwent in the revised version [Page 3].

6. Comment: please specify whether the analysis method (fixed- vs random-effects) was changed depending on the degree of heterogeneity.

Revision: In the revised version, fixed-effects model was used when no heterogeneity was detected($I^2=0\%$), random-effect model was used if there was heterogeneity($I^2>0\%$) [Page 4-5].
7. Comment: please provide one or two tables summarizing trial characteristics (e.g. type of procedure, mode of administration of TXA, investigated dose and "standardized" dose as per Author correction, control treatment)

Revision: A table including basic characteristics (year, country, type of procedure, mode of TXA administration, TXA dosage, and main outcomes) of included studies were provided in appendix 3.

8. Comment: please move from the Results/Included studies section to the Methods section the description of how the Authors "standardized" the dose of TXA in mg/kg. Of note, although I understand that this operation is necessary to compare low vs high doses both in case of bolus or continuous infusion administration, I am not sure whether this is methodologically correct. The effect of the drugs may actually be different when a single loading dose is rapidly administered (e.g. before CPB) as compared with a continuous infusion throughout the operation, even when the overall TXA dose is the same. Accordingly, please report in the limitation.

Revision: In the revised version, we abandoned the idea of standardizing the dose of TXA in all studies into mg/kg. Instead, we classified studies into two groups according to delivery methods - bolus injection alone or bolus plus continuous infusion, and defined the cutoff value for these two groups separately. For bolus injection, we defined ≥50mg/kg as high dose regimen, given the fact that the study conducted by Myles et al. proved that 50mg/kg of TXA was associated with a significant increase in seizure. For bolus plus continuous infusion, we defined 10mg/kg+1mg/kg/h as cutoff value, since this dosage was widely used in the identified studies and was proved in pharmacokinetics studies to be enough to inhibit fibrinolytic process to a large extent [Page 5].

9. Comment: please report follow-up time for mortality assessment (in-hospital? 30-days? longest follow-up available?) in the Table describing trial characteristics

Revision: In the revised version, we included the item follow-up time for mortality assessment in the table describing trial characteristics (appendix 3).

10. Comment: it is unclear to me whether studies directly comparing a bolus versus a continuous infusion are available. I understand that no such trial was retrieved by Authors. Otherwise, it could have been a very interesting analysis.

Revision: We searched for trials that directly compared bolus with continuous infusion and found one such article. We analyzed the result of this trial in the discussion part [Page 10].
11. Comment: The Authors frequently mention patients "at high risk of bleeding". As far as the Author know, has a definition of high bleeding risk patients been provided by included trials or available in literature? This could be very useful for the reader.

Revision: Quote From Sigaut study (Reference 59): “Patients were considered at high risk for transfusion if they were receiving a dual anti-platelet at any time within 5 days of surgery, or in the following cases: repeat coronary artery bypass graft, repeat valve surgery (replacement or repair), combined coronary artery bypass graft and valve surgery, multiple valve surgery, surgery of the aorta, intracardiac tumor ablation, and surgery for endocarditis. All other cardiac surgery procedures were considered low risk.” We included this part into discussion in the revised version [Page 11].

Minor comments:

12. Comment: Please open "TXA" abbreviation the first time it is mentioned in the Background section (is currently opened the first time on page 6)

Revision: In the revised version, we opened TXA on the first line of background [Page 3].

13. Comment: I believe that initials of Authors names are not necessary when citing Authors of various trials, and can be deleted (e.g. "Myles, P. S., et al." could simply become "Myles et al.")

Revision: In the revised version, we deleted all the initials of Author names.

14. Comment: Page 23, Discussion/Adverse effects section: "TXA did not show any trend to increase the risk of thrombolytic events except for seizure.". It is unclear to me what does "thrombolytic events (I assume the Authors mean thrombotic) and how should seizures be considered a thrombotic event.

Revision: In the revise version, we replaced this sentence with "TXA did not show any trend to increase the risk of thrombolytic events including myocardial infarction, stroke and pulmonary embolism" [Page 9].

15. Comment: Page 25, Discussion/Agreements and disagreements with other studies or reviews section: what does the sentence "In a RCT studying high-dose and low-dose regimen on fibrinolysis..." mean? I think there are missing words (e.g. the effect of...)

Revision: [No revision needed for this comment]
Revision: In the revised version, this sentence was deleted.

16. Comment: The number of figures is very high. I suggest to move some figures to a Supplementary Appendix

Revision: In the revised version, we reduced the number of Figures from 32 to 13. We summarize outcomes of adverse events into Table 1 (mortality, MI, stroke, PE, renal dysfunction), and proved these figures in supplement material (supplement figure 5-9). We deleted three forest plots in subgroup analysis including on and off-pump, CABG and other kinds of surgeries, and intravenous or topical application of TXA. These three figures can be found in supplement figure 1-3.

17. Comment: The figures on risk of bias lack yellow color for "unclear risk of bias" items

Revision: We added yellow colour to the unclear risk of bias items in the revised version.

Reviewer 2

ABSTRACT

1. Comment: Please rewrite the conclusions

Revision: In the revised version, we rewrote the conclusions [Page 2].

METHODS

1. Comment: The decision to analyses only 2011-2018 is odd and questionable. I understand it, but I'm not sure it is the best solution or that it will be appreciated by readers

Revision: We searched for all relevant studies before 2011 and included them into meta analysis.

2. Comment: This sentence might be removed "Coronary artery bypass surgery, valve replacement surgery and other kinds of heart surgeries predominantly carried out in adult patients were all included."

Revision: This sentence has been deleted [Page 3].

3. Comment: Rephrase the proportion of patients underwent blood transfusion during hospital stay, the amounts of blood transfused during hospital stay
Revision: It has been revised into “transfusion rate (the proportion of patients underwent blood transfusion during hospital stay) and transfusion volume (the amounts of blood transfused during hospital stay).”[Page 4]

4. Comment: the management of statistical heterogeneity is doubtful (both in methods and in the results). I would suggest to recheck definition (methods) and how did you apply it in the results

Revision: We rewrote this part in the statistical analysis, and it has been revised into”The fixed-effect model was used for analysis with no heterogeneity(I2=0), and random-effect model was used for analysis with heterogeneity (I2 > 0%). For outcomes with heterogeneity, an effort was made to identify its source, mainly through subgroup analysis. A P-value less than or equal to 0.05 for the Q statistic was used to define statistically significant heterogeneity. Statistical heterogeneity was also assessed using the I² test. I²=0%-40%: heterogeneity might not be important; I²=30%-60%: may represent moderate heterogeneity; I²=50% to 90%: may represent substantial heterogeneity; I²=75% to 100%: considerable heterogeneity”. [Page 4-5]

We thus used the fixed-effect model for mortality, stroke, myocardial infarction, pulmonary embolism and renal dysfunction, all of which had I²=0%. We used the random effect model for transfusion rate, transfusion volume, re-operation, postoperative blood loss, all of which had I² > 0. We also included a part entitled source of heterogeneity in the discussion section, where we analyzed the source of heterogeneity from subgroup analysis, and other clinical reasons.[Page 11]

5. Comment: it is not clear if corresponding authors of RCT were contacted for missing data. Please write it.

Revision: We admitted that Missing data was a problem that we ignored until receiving this comment. There were mainly two kinds of missing data in this meta-analysis. First of all, some studies failed to report standard deviation and only reported mean value for transfusion volume and postoperative blood loss. Fortunately, this only happened in two studies, and we were able to calculate the SD from mean, sample size and P value. Another main source of missing data was selective reporting, in that some studies only provided transfusion volume without providing the number of patients transfused (transfusion rate not reported). After receiving this comment, we sent emails to corresponding authors of 9 studies(1-9) to ask for data concerning transfusion rate. So far, we received no response from these authors. We would be willing to update results after receiving reply. We also noticed this limitation at the end of the discussion part.[Page 11-12]

RESULTS

6. Comment: All verbs should be in simple past

Revision: In the revised version, all verbs were in simple past in the result section.
7. Comment: 10340 might become 10,340
Revision: We wrote 10,591 instead of 10591 [Page 5].

8. Comment: do not start sentences with numbers
Revision: We corrected all sentences which was started with numbers.

9. Comment: it is strange to have the transfusion volume for all patients in units and the transfusion volume for transfused patients in ml
Revision: In the revised version, we used units for both results [Page 6].

10. Comment: TXA was not associated with an increased risk of death I would suggest to write Mortality between groups was not different.
Revision: In the revised version, we wrote “there was no significant difference between TXA and control group in mortality” [Page 7].

11. Comment: TXA was not associated with an increased risk of seizure I would write TXA was not associated with a statistically significant increase in risk of seizure
Revision: We included more trials into analysis in the revised version (studies before 2011), and difference in seizure became significant in TXA and control group. We thus wrote in the new version “The use of TXA was associated with a 3.21 folds increase in the risk of seizure (RR 3.21, 95% CI 1.04 to 9.90, P=0.04).” [Page 6]

12. Comment: Results are too long (for most journals) The authors should find the way to summarize them (e.g. simple tables for all non primary outcomes or subgroup analyses or non significant values. All subgroup analyses to be put in supplemental only. Keep one line for bolus+/- continuous and one line for high vs low dose and one line for seizure and one line for high vs low dose
Revision: We made several efforts to make this section shorter. (1) In the old version, we included three comparison: TXA vs Control, High-dose vs low-dose TXA, Topical+intravenous vs intravenous alone. In the revised version, we presented only one comparison, which was TXA vs Control. This made the result more concise. (2) In the revised version, we summarized results for adverse events (MI, stroke, PE, renal dysfunction) in table 1, and provided detailed results in supplement figures 5-9. (3) For subgroup analysis, we kept online only for bolus+/-continuous and high vs low dose, and provided results of other subgroup analysis in supplement figure 1-3.

13. Comment: Not simple to understand how did you calculate this without a network meta-analysis The use of high-dose TXA did not reduce the need for allogeneic blood transfusion compared to low-dose TXA
Revision: We understand that a network meta-analysis is the most preferable way to compare high and low-dose regimen in terms of transfusion requirement, but given the limited time for revision and lack of experience in this field, we are unable to conduct a network meta-analysis in this revised version. We noticed this drawback at the end of the discussion part[Page 12].

In the revise version, we tried to compare the effect of high and low-dose TXA by comparing their RR for transfusion rate, and found that the relative risk of low-dose regimen was even lower than high-dose regimen. We thus drew the conclusion that the use of high-dose TXA may not further reduce transfusion need compared to low-dose TXA. We understand that such kind of comparison was not completely valid, but that’s what we could do within limited time and resources. We also did qualitative analysis on studies that directly compared high and low-dose regimen, and found that none of the studies showed significant decrease in transfusion.

14. Comment: Topical + intravenous versus intravenous application. Make it clear what does this mean. The use of TXA did not reduce the need for allogeneic blood transfusion (p 20 line 9)

Revision: As we’ve mentioned above, we completely deleted the comparison between Topical+intravenous and intravenous delivery alone in the revised version.

15. Comment: Supplemental results should include major exclusion with reasons for exclusion

Revision: In the revised version, we provide appendix 4 on major exclusion with reasons for exclusion. In this table, we only included studies that we had some trouble excluding them from analysis. Studies that obviously did not met with the inclusion criteria were not provided in this table.

16. Comment: A TSA analysis could be useful

Revision: We understand that in the original version, we included only 15 trials that compared TXA with control, and that the number of studies included may not be enough to get valuable results. In the revised version, we included 49 studies that compared TXA with control, and we believe that it should be enough. Our research team hasn’t done TSA analysis before and we are currently learning how to conduct such analysis. We are willing to include TSA into this meta-analysis once we’ve learned how to do it.

DISCUSSION

17. Comment: It seems too schematic and long and detailed and comprehensive

Revision: In the revised version, we made the discussion part more concise and deleted the details that we already reported in the result section. We also deleted all the subtitles which made this part too schematic[Page 9-12].
18. Comment: There were also a few studies compared becomes There were also a few studies which compared

Revision: This sentence was deleted.

19. Comment: The non-inclusion of reference 32 because it is an abstract is questionable according to methodological issue The authors should probably put it into the (supplemental) results as major exclusion and write that the exclusion reason is NON RECENT abstract publication only

Revision: We put it into supplement material-appendix major exclusions.

20. Comment: I disagree with this sentence They thus recommended that patients with a high risk of bleeding should receive high-dose TXA, while those at low risk of bleeding should receive low-dose TXA. This result was largely in accordance with our findings, in the conclusion you correctly write High-dose TXA does not further decrease transfusion rate

Revision: In the revised version, this sentence was deleted.

21. Comment: Half of the patients were randomized in the Myles et al study This should be acknowledged and a detailed comparison with this study should be performed This is also the highest study included

Revision: In the revised version, we rated this study as having high risk of bias and explained the limitation of this specific study in the discussion part. We also conducted subgroup analysis for studies with low and unclear risk of bias only, and exclude this study (with high risk of bias) from analysis. The results for transfusion rate didn’t change though[Page 8-9].

REFERENCE

22. Comment: There is no 2018 reference (we're now in 2019)

Revision: In the revised version, we updated our search until 2018/12/31, and included 3 references from 2018.

23. Comment: FIGURES Most figures should be put as supplemental material only

Revision: In the reversed version, we reduced the number of figures from 32 to 13, and put 9 figures in the supplement material.
SUPPLEMENTAL

24. Comment: I suggest to prepare a nice supplemental material were to put the search string, most of the figures. Remember to name it properly with title, authors, index…..

Revision: In the supplement material, we provided PRISMA checklist (appendix 1), details in search strategy (appendix 2), table of study characteristics (appendix 3), major exclusions (appendix 4) and 9 Supplement figures.


