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:

Reviewer 1:

1. Comment: page 10, line 1: please replace "thrombolytic" with "thrombotic", as I also suggested in my previous reviews.

Revision: In the revised version, we replaced "thrombolytic" with "thrombotic".

2. Comment: page 9, paragraph "3. Impact of trial quality": please move Authors' consideration on Myles's RCT risk of bias to the discussion.

Revision: Thank you very much for the valuable suggestion. In the revised version, we moved this part to the discussion.
Reviewer 2 (Reviewer 2):

1. Comments: They do not report n/N (%) for all the clinical outcomes; they do not report the increase of fits as absolute risk.

Revision: We really appreciate your valuable suggestion. We do realize that only reporting relative risk could lead to critical information missing. We thus reported the exact numbers, percentages and absolute risk differences for transfusion rate, re-operation rate, and seizure attack in the result section of this revised version.

ADDITIONAL REQUESTS/SUGGESTIONS:

2. Comments: TITLE Different dose regimes and administration methods of tranexamic acid in cardiac surgery: A meta-analysis suggestion

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

Revision: In the revised version, the letter “A” was changed from capital to lowercase.

3. Comments: ABSTRACT Reviewers and authors want to see number and percentages in the 2 groups Transfusion requirements (what is this? Rate?), Peri-operative blood loss n/N (%) vs n/N (%), Re-operation rate, Seizure

The same in the manuscript, for all the clinical data.

Revision: Thanks very much for your valuable comments. We realized that critical data were missing in the original version, both in the abstract and in the result section.

In the revised version, the relative risk of transfusion rate, re-operation rate and seizure was presented in the abstract, so as the mean difference of perioperative blood loss. Exact numbers, percentages and absolute risk reduction of transfusion rate, re-operation rate, and seizure attack were presented in detail in the result section.

4. Comments: ABSTRACT without increasing this risk of seizure becomes without increasing the risk of seizure

Revision: In the revised version, we changed “this” to “the”.

5. Comments: Results are still too long.

Revision: Thank you very much for the valuable comments. The results were indeed too long, even after great efforts to make it brief. We found it very hard to cut it down further, given the fact that unimportant results had already been deleted during the first revision and that we added results on exact numbers, percentages and absolute risk for some of the items during this second revision. However, we still managed to cut the results down from 2207 words (first revision) to 1971 words (second revision). The words highlighted in blue with strikethrough were deleted. Some parts highlighted in yellow has been rephrased and made briefer.

6. Comments: Figures are still too many.

Revision: Thank you very much for the valuable suggestion. We totally agree that even after great efforts to reduce the number of figures, 13 figures are still too many for a meta-analysis. The distinct feature of this meta-analysis is trying to compare different dose regimen and administration methods of TXA, and this made it hard not to include many figures. We’ve already put those figures on unimportant results into Supplement Materials in the first revision. During this second revision, we further reduced the number of figures from 13 to 11. We achieved this by moving Figure 13 (the Funnel Plot) to supplement material and combining Figure 5 (TXA vs control-transfusion volume for all) and Figure 6 (TXA vs control-transfusion volume for transfused patients) together into one.

Knowing that including 11 figures is not optimal for a meta-analysis, this is the best we can do so far. We are more than willing to further reduce the number of figures according to specific advice on how to do it.

7. Comments: In the revised version, we rated Myles et al study as having high risk of bias and explained the limitation of this specific study in the discussion part. IT IS HARD TO RATE "HIGH RISK OF BIAS" A STUDY PUBLISHED ON THE NEJM WHICH RANDOMIZED ALMOST HALF OF THE PATIENTS INCLUDED IN THE META-ANALYSIS

Revision: Thanks very much for kindly reminding us of this problem. It was indeed improper to rate this study as having high risk of bias.

In the revised version, we rated this study from Myles et al as having unclear risk of bias. As we wrote in the manuscript “We consider this article to have unclear of bias mainly for two reasons. One is that after 1392 patients had been enrolled, they reduced the TXA dosage from 100mg/kg to 50mg/kg, and the dose reduction underpowered this trial. The other reason is that the first 2127 participants had not been taking aspirin regularly before the trial or had stopped taking
aspirin at least 4 days before surgery, while participants who were subsequently enrolled may or may not have been previously exposed to aspirin therapy. ”

Since this was the study with the largest sample size included, we also did analysis on rest of the studies with low and unclear risk of bias except Myles study, and found that excluding the trial from Myles et al didn’t make a difference. This part was presented at the end of the discussion section.

8. Comments: I find it difficult to understand how is this possible: In the previous version you wrote: 23 studies with a total of 10340 participants were included. In the present version you write: 49 studies with 10,591 Did you double the n of studies and added only 200 patients?

Revision: Thanks very much for your comments. We should have explained this issue more clearly.

In the original version, we included three kinds of studies published from 2011/11/01 to 2018/02/27. The first kind of study was trial comparing TXA to control group, and we included 15 studies with 7018 patients in this category. The second kind of study was trial comparing high dose to low dose TXA, and we included 5 studies with 3101 patients in this category. The third kind of study was trial comparing topical application to topical+intravenous infusion of TXA, and we included 3 studies with 221 patients in this category. In summary, we included 23 studies with a total of 10340 (7018+3101+221) patients in the previous version.

In the revised version, in order to keep message clear and brief, we only included one kind of study which compared TXA to control group into meta-analysis. We analyzed all studies published before 2018/12/31, with a total of 49 studies including 10591 patients. Among these 49 studies, 15 studies with 7018 patients published from 2011/01/01 to 2018/02/27 were also included in the original version. We added 34 studies with 3575 patients published before 2011/01/01 and from 2018/02/27 to 2018/12/31.