Answering Reviewers (Revision)

Dear *Prof.* Wang and two Reviewers,

Thank you very much for giving me an opportunity to revise my manuscript. I appreciate editor and reviewers very much for their positive and constructive comments and suggestions on the manuscript entitled *The effectiveness of intravenous tranexamic acid in total shoulder arthroplasty and reverse shoulder arthroplasty: a meta-analysis of Level 1 randomized controlled trials* (Manuscript Number: 83153). Those comments are all valuable and very helpful for revising and improving the paper, as well as the important guiding significance to my researches. I have studied comments carefully and have made correction which I hope meet with approval. Appended to this letter is my point-by-point response to the comments raised by the reviewers.

RESPONSES TO COMMENTS OF EDITOR AND REVIEWERS

Reviewer #1:

Comment 1: The title of the paper should be changed to be more appealing and in line with the purpose of the current study.

Response: Thank you for your positive comments and valuable suggestions to improve the quality of this manuscript. According to your suggestion, I have changed the title.

Revised in the manuscript (Page 1):

The efficacy and safety of intravenous tranexamic acid in total shoulder arthroplasty: a meta-analysis

Comment 2: In the results section of the study abstract, the most important findings of the current study should be highlighted without exaggeration.

Response: Thank you for your valuable suggestions to improve the quality of this manuscript. According to your suggestion, I have highlighted the most important findings of this study in the results section.

Revised in the manuscript (Page 3):

RESULTS

A total of 5 RCTs with level 1 evidence were included. There were 369 cases, with 186 in the TXA group and 183 in the placebo group. The meta-analysis showed that TXA can significantly reduce total blood loss during the perioperative period (WMD = -249.56, 95% confidence interval [CI] = -347.6 to -151.52, $P < 0.0001$), and the incidence of adverse reactions was low (OR = 0.36, 95% CI = 0.16 to 0.83, $P = 0.02$). Compared with the placebo group, the TXA group had significantly less total haemoglobin loss (WMD = -34.39, 95% CI = -50.56 to -18.22), less haemoglobin fluctuation before and after the operation (WMD = -0.6, 95% CI = -0.93 to -0.27) and less 24-hour drain output (WMD = -136.87, 95% CI =-165.87 to -106.49). There were no significant differences in the operation time (P=0.11) or hospital length of stay (P= 0.30) between the two groups.

Comment 3: Devoting the final paragraph of the study's introduction to highlighting the research problem and how to solve it within the framework of the current study's objective.

Response: Thank you for the comment. Yes, the research problem and how to solve it have been highlighted.

Revised in the manuscript (Page 5):

However, because the development and application of TSA have been slower than those of total knee and total hip arthroplasty, there is still a lack of advanced evidence-based evidence about the application of TXA in the perioperative period of TSA. Therefore, through the inclusion of high-quality randomized controlled trials (RCTs), a meta-analysis was conducted to determine the efficacy and safety of intravenous TXA in the perioperative period of TSA, thereby providing a high-quality evidence-based basis for clinical application.

Comment 4: What are the current study's future directions? I hope to work on this direction in the current study, highlighting the study's strengths as well

as the limitations mentioned in the last paragraph of the discussion section.

Response: Thank you for your profound questions which help improve the quality of this manuscript. According to your comment, I have added those content.

Revised in the manuscript (Page 13):

STRENGTHS and LIMITATIONS

The conclusions of this systematic review and meta-analysis come from only RCTs with level 1 evidence, and the heterogeneity was very low, which indicates that the above conclusions are supported by a very high level of evidence. This meta-analysis showed that TXA is efficacious and safe in TSA to a certain extent, but there are some limitations of the study. 1) Although the quality of the RCTs included in this meta-analysis was high, the total number of included studies and total sample size were relatively small; 2) data on the total haemoglobin loss and 24-hour drainage volume were retrieved from only two studies, which may have affected the reliability of the results. There is no doubt that multicentre, large-sample prospective RCTs are needed in the future to further verify the findings of this study. In TSA, the impact of intravenous TXA on medical costs and patient satisfaction in the postoperative period should also be evaluated, which will be conducive to comprehensive evaluation of the clinical value of intravenous TXA.

Comment 5: Rewrite the conclusion in a more orderly and focused manner on whether or not the current study achieves its objectives.

Response: Thank you for your meticulous suggestions to improve the quality of our manuscript. According to your comments, we have rewrote the conclusion.

Revised in the manuscript (Page 13):
CONCLUSION
Our meta-analysis revealed that the application of intravenous TXA can significantly reduce total blood loss and is safe for application in TSA, so TXA is worthy of widespread clinical application. In addition, we also found that the application of TXA did not influence the operation time or length of hospital stay.

Comment 6: Some references are out of date after 2015, which necessitates updating them or excluding them and replacing them with what is new.

Response: Thank you for your valuable suggestions. According to your comment, we have updated the references that are out of the data after 2015.

Revised in the manuscript:

References Part.

Comment 7: Is the percentage of plagiarism and self citation from references within the parameters set by the journal's policy?

Response: Thank you for the comment. According to the editorial office's evaluation, this manuscript has passed the CrossCheck and Google plagiarism detection. Again, thank you for your rigor.

Comment 8: Are the statistical graphics in the current study the work of the researcher/researchers, or do they come from somewhere else? Please elaborate. If it comes from another source, the property rights and approval of the third party must be considered as much as possible before allowing use.

Response: Thank you for your rigor. All the statistical graphics in the current study are the work of the author, and according to the suggestion of the editorial office, I have attached a copyright note to each picture.

Reviewer #2

Comment 1: Specific Comments to Authors: Minor revision requirieds

Response: Thank you for your meticulous suggestions to improve the quality of our manuscript. According to your comment (mark in the attachment), we have modified this content.

Revised in the manuscript (Manuscript):

The meta-analysis showed that TXA can significantly reduce total blood loss during the perioperative period (WMD = -249.56, 95% confidence interval [CI] = -347.6 to -151.52, $P < 0.0001$), and the incidence of adverse reactions was low (OR = 0.36,

95% CI = 0.16 to 0.83, *P* = 0.02).

Studies have shown that the volume of intraoperative blood loss during total shoulder replacement can reach between 354 ml and 361 ml [9,10]. For patients undergoing primary TSA, the probability of blood transfusion is between 2.4% and 9.5% [11,12].

The common complications include angina pectoris, myocardial infarction, thrombosis, and even death [13,14].

Tranexamic acid (TXA) is a fibrinolytic inhibitor that can reversibly block the binding site of lysine, which is compatible with fibrinogen; inhibit fibrinolytic reactions; prevent blood clots from being dissolved by fibrinolytic enzymes; and reduce the extent of perioperative bleeding [15,16].

The efficacy of TXA in various surgical procedures has been confirmed, and it has higher efficacy and leads to fewer drug-related complications than other antifibrinolytic drugs [27, 28].

EDITORIAL OFFICE'S COMMENTS

Comment 1: Language Quality: Grade B (Minor language polishing).

Response: Thank you for your meticulous suggestions to improve the quality of our manuscript. In order to meet the language requirements of English papers, I have invited *American Journal Experts* to modify and polish this article.

Comment 2: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Response: Thank you for the comment. I have revised the manuscript according to the suggestions of the editorial department and reviewers.

Comment 3: . The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words).

Response: Thank you for your meticulous suggestions to improve the quality of our manuscript. According to reviewer 1's and your comments, I have changed the title.

Revised in the manuscript (Page 1):

The efficacy and safety of intravenous tranexamic acid in total shoulder arthroplasty: a meta-analysis

Comment 4: Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response: Thank you for your comment. According to your suggestion, we have provided pictures according to the requirements of the editorial office.

Comment 5: In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights.

Response: Thank you for your rigor. All the statistical graphics in the current study are the work of the author, and according to the suggestion of the editorial office, I have attached a copyright note to each picture.

I appreciate for *Professor* Wang and two Reviewers' warm work earnestly. According

to the two reviewers' suggestions and comments, I had revised the manuscript. And in order to meet the language requirements of English papers, I have invited *American Journal Experts* to modify and polish this article. If there are any other modifications I could make, I would like very much to modify them and I really appreciate your help. We hope that this manuscript could be considered for publication in your journal. Once again, thank you very much for your comments and suggestions. If this article needs further revision, please do not hesitate to contact me.