Author’s response to reviews

Title: Comparison between minimally invasive plate osteosynthesis and open reduction–internal fixation for proximal humeral fractures: a meta-analysis based on 1050 individuals

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Responses to Editorial and Reviewers’ Comments
Editor Comments: Please address the comments from reviewer 1 and 2. In addition please consider softening your conclusion statement naming MIPO as a superior option than ORIF. While you report that some outcomes are better in some respects, the reality is that an axillary nerve injury is so significant, that that higher occurrence of this injury alone would certainly make MIPO not the "procedure of choice" for many trauma surgeons. It may be best to state the results without offering such a strong recommendation of MIPO over ORIF, and let the reader decide for themselves.
Response: Thanks for your crucial suggestion. We have revised the manuscript according to the reviewers’ comments. We have also revised our conclusion (see Conclusion section: page 12, line 252-261).

Amin Mohamadi (Reviewer 1) Comments:
1. Page 5, line 110: p-value ≤ 0.05 was considered significant; although this is not incorrect the convention is to consider p-value < 0.05 significant. The Auxiliary nerve injury will be near significant in this scenario.
Response: Thank you for your correction. We have corrected the “p-value ≤ 0.05” to “p-value < 0.05” (Statistical analysis section: page 5, line 112).
2. Page 6 literature search: the total number of studies seems too low; please provide the full search strategy for PubMed.
Response: Thank you for pointing this out. According to your suggestion, we have provided the full search strategy for PubMed (see supplementary files).

3. Since the heterogeneity is significant for many outcomes, please explore source of heterogeneity in a sensitivity analysis reporting separate results based on type of study (i.e. two separate sets of analyses for randomized trials and non-randomized trials including cohort or observational studies.
Response: Thank you for this important suggestion. The heterogeneity is significant for many outcomes. We conducted a sensitivity analysis based on type of study. After this analysis, operation time and union time became insignificant for randomized trials. This change may be due to the inclusion of only 2 randomized controlled trials. Results for all other outcomes remained unchanged. We have added this information to the text (see results of the meta-analysis section: page 9, line 197-200).

4. Page 9, line 191: "Funnel plots of the total complication rate showed no significant visual evidence of publication bias" I recommend rephrase this sentence to "Funnel plots of the total complication rate showed no substantial asymmetry indicating no significant risk for publication bias".
Response: Thank you for this correction. We have changed the sentence to "Funnel plots of the total complication rate and functional outcomes showed no substantial asymmetry, indicating no significant risk for publication bias" (see Results of the meta-analysis section: page 9, line 193-196).

5. The funnel plot should be drawn for main outcomes (clinical outcome); this can be done so using SMD.
Response: Thank you once again. We have drawn Funnel plots of the total complication rate and functional outcomes (see Figure 10).

6. The conclusion is similar previous network meta-analysis Orman S, Mohamadi A, Serino J, Murphy J, Hanna P, Weaver MJ, Dyer G, Nazarian A, Keudell AV. Comparison of surgical and non-surgical treatments for 3-and 4-part proximal humerus fractures: A network meta-analysis. Shoulder & Elbow. 2019 Feb 28:1758573219831506. I think it would be worthwhile to address this publication as well since it is the most meta-analysis on this topic to my knowledge.
Response: Thank you very much for this suggestion. The network meta-analysis by Orman et al. demonstrated that non-surgical treatment (NST) was associated lower adverse event rates compared to open reduction–internal fixation (ORIF) for 3- and 4-part proximal humerus fractures. In our meta-analysis, we found that MIPO had advantages in operation time, blood loss, postoperative pain, fracture union time, and constant score compared to ORIF. We recommend that future studies should not only compare MIPO to ORIF but also to NST to obtain
thorough evidence-based treatment guidelines. We have cited this network meta-analysis in the paper (see Conclusion section: page 12, line 258-262; Reference section: page 19, line 405-408).

Zhenzhong Zhu (Reviewer 2) Comments:

1. MIPO minimizes the damage to soft tissue, however, it is more technical demanding. Author for the first time mentioned the functional outcomes of these two methods by Neer classification, but did not addressed clearly in the study selection or data extraction part. What is the inclusion criteria of classification?

Response: Thank you for this pertinent comment. We apologize for not providing sufficient information about the inclusion criteria for the classification. Our inclusion criteria were all proximal humeral fractures (Methods section: page 4, line 86-87). We only performed a subgroup analysis based on Neer classification for the main outcomes of the constant score. Secondary outcomes were not reported separately according to Neer classification because most of the included studies did not report them separately based on Neer classification. We hope that future researches on this subject will report results separately based on Neer classification, and such results will be more accurate.

2. Base on classification, it is important to compare the fracture reduction intra-operatively by these two methods.
Response: We agree with your invaluable suggestion. It is important to compare fracture reduction intraoperatively using these two methods. However, since most of the included studies did not compare fracture reduction intraoperatively using these two methods, we were unable to perform a meta-analysis of intraoperative fracture reduction. We hope that future studies would include these important comparisons.

3. MIPO group showed the higher rate of axillary nerve injury. Did these studies include the same surgical approach? It would be more meaningful to interpret why it happens and how to avoid the injury rather simply attribute to surgical experiences.
Response: Thank you once again. Yes, these studies used the deltoid-splitting approach (see background section: page 3, line 62). Axillary nerve injury in the MIPO group may be related to the incisions in the deltoid-splitting approach extending more than 5 cm distal to the tip of the acromion. To prevent injury to the axillary nerve with the MIPO technique, incisions should not extend more than 5 cm distal to the tip of the acromion. In addition, the axillary nerve should be identified and protected by positioning the index finger on the nerve during the insertion of the plate on the proximal humerus. We have added this information to the text (see Discussion section: page 11, line 231-236).