Author’s response to reviews

Title: Efficacy of platelet-rich plasma in arthroscopic repair for discoid lateral meniscus tears

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Author’s response to reviews:

Dear Dr. James Mockridge:

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled "Efficacy of platelet-rich plasma in arthroscopic repair for discoid lateral meniscus tears".

We have revised the manuscript according to the comments and suggestions of reviewers, and responded, point by point to, the comments as listed below.

We would like to re-submit this revised manuscript to "BMC Musculoskeletal Disorders", and hope it is acceptable for publication in the journal. Looking forward to hearing from you soon.

With kindest regards,

Jian Wang

Response to Reviewer 1

1. Response to comment: 1) Please better describe the obtained PRP (leucocyte rich or leucocyte poor).
2) Also, please include a paragraph of pros and cons in the discussion.

Response: 1) Injected PRP in this study also contained leukocytes (leukocyte-rich PRP) 6.1 ± 1.5 times (range, 3.1 - 8.4) with respect to the normal blood value. This has been added into the paper on line 117-119.

2) Despite the promising preclinical findings, the use of PRP remains controversial in meniscal repair. In a study of arthroscopic meniscal repair, Griffin et al. reported that there was no difference in the proportion of patients who underwent reoperation in the PRP group (27%) compared with the non-PRP group (25%, P = 0.89). Functional outcome measures were not different between the two groups (P = 0.55). Furthermore, there was also no difference in the proportion of patients who returned to their regular sports/activities in the PRP group (71%) compared with the non-PRP group (78%, P = 0.75). Whereas in a study of open meniscal repair, Pujol et al. reported that the difference between PRP and non-PRP augment groups was significant for pain and sports activities parameters in KOOS score (P = 0.046 and 0.03, respectively). Furthermore, there was a statistically significant difference in the healing appearance of repaired menisci by MRI evaluation between the PRP and non-PRP groups (P < 0.01). These have been added into the paper on line 250-260.

2. Response to comment: Please include a sample size analyses.

Response: Thanks for your comment. For this study, the sample size calculation for patients was done according to the previous study by Pujol and colleagues. Our hypothesis was that there would be a 6% relative difference in failure rate between the PRP and non-PRP group, which meant that a sample size of 349 patients in each group was needed to get a power of 80% for a significance level of 5%. These have been added into the paper on line 166-169.

3. Response to comment: Questions regarding the method: Did you range of motion and allow 10kg weight bearing in all patients, regardless of the type of lesion?

Response: Thanks for your comment. In this study, all patients followed the same rehabilitation protocol. For the first 2 weeks, patients were allowed to bear partial body weight up to 10 kg, with range of motion from 0° to 60°. These have been added into the paper on line 143.

4. Response to comment: What kind of lesions were more frequent (describe the patterns)?

Response: Thanks for your comment. Among the patients, the most frequent lesion was longitudinal tears, which was found in 11 knees, and complex tears were found in 10 knees,
horizontal cleavage in 7 knees, and radial tears in 1 knee. These have been added into the paper on line 175 to 176.

5. Response to comment: 1) There were 3 patients lost of follow up - which group (they may all be re-ruptures).

2) How did you analyze this missing data?

Response: Thanks for your comment. 1) Despite our efforts, 3 of the selected patients were lost to follow-up due to migration (2 patients in the PRP group and 1 in the non-PRP group). This has been added into the paper on line 107.

2) In our study, the failure rate was demonstrated by intent-to-treat (ITT) and per-protocol (PP) analyses. In the ITT approach, all patients were included in the analysis in the group to which they were allocated regardless of loss to follow-up. In the PP approach, patients who completed the entire procedure were included in the analysis. There were no significant difference between PRP and non-PRP groups in the failure rate in both ITT (P = 0.63) and PP (P = 0.58) analyses. These have been added into the paper on line 159 to 162 and line 226 to 227.

6. Response to comment: How could you better access repair success (healing)?

Response: Thanks for your comment. There are some tips on DLM tears repair based on our experience. Firstly, the tear should be identified and characterized based on its size, location, and overall quality before the repair. Secondly, the tear should be anatomically reduced and the sutures should be placed perpendicularly to the lesion to restore its anatomic position. In addition, we prefer the inside-out repair because of the ability to confer greater stability to the lesion via increased number of sutures, and not having to use a large intra-articular device that allows for greater versatility. These have been added into the paper on line 270 to 274.

Response to Reviewer 2

1. Response to comment: Abstract: please provide p-value for "patient with younger age were associated". It is hard to tell if the word associated is a significant finding. Similarly, provide p-value for ...some were not associated.
Response: Thanks for your comment. In the univariate analysis of each variable, younger age (P = 0.036) and longer follow-up duration (P = 0.043) were statistically associated with a better function improvement. Whereas in multivariate analysis, only younger age (P = 0.004) was significantly associated with a better function improvement. These have been added into the paper on line 52 to 55.

2. Response to comment: Studies related to PRP should be updated and more specific to the meniscus when available. The PRP paper relating to general concepts of PRP are very outdated, and there are many more meniscus ex vivo/in vitro/animal model studies that could be tied in as opposed to a completely different system like rotator cuff.

Response: The various cytokines in PRP are known to positively affect fibrochondrocyte migration and extracellular matrix production in vitro. Ishida et al. compared the effect of PRP with platelet poor plasma on meniscal tissue and found significant positive effects of PRP on cell viability/proliferation and matrix production. Furthermore, Howard et al. found PRP was able to increase meniscal cell number above peripheral whole blood and up-regulated gene expression of Aggrecan, Collagen type I, and Elastin. However, Freymann et al. evaluate the migratory, proliferating, and extracellular matrix forming effect of PRP on meniscus cells and found PRP showed no inducing effect on aggrecan and cartilage oligomeric matrix protein. These have been added into the paper on line 77 to 84.

3. Response to comment: You hypothesized that PRP would be beneficial...but beneficial for repair, but that doesn't really tell the ready what you mean...please expand on what you mean.

Response: Thanks for your comment. We have revised the hypothesis as "We hypothesized that arthroscopic repair for DLM tears with PRP would lead to improvements in function and pain outcomes due to the release of bioactive molecules that would possibly affect the DLM healing" on line 94 to 96.

4. Response to comment: For the PRP preparation, it is very good that you measured both platelets and leukocytes. please report the range and std dev to go along with the mean.

Response: Thanks for your comment. We have revised this sentence as "The preparation method used allowed the number of platelets per milliliter to increase by a mean of 6.4 ± 1.6 times (range, 3.5 - 8.7) with respect to baseline blood values. Injected PRP in this study also contained leukocytes (leukocyte-rich PRP) 6.1 ± 1.5 times (range, 3.1 - 8.4) with respect to the normal blood value." on line 116 to 119.
5. Response to comment: 1) What volume of PRP did you deliver?

2) in your figure, it looked like the clot was proud to the meniscal surface. What was your operative technique with filling the clot?

Response: 1) PRP (4 ml) and 500IU thrombin (1 ml) were injected simultaneously on the repaired site. This has been added into the paper on line 134.

2) We use two injectors (one 5-ml for PRP and the other 1-ml for thrombin) and a cannula needle 2.5mm in diameter to inject the PRP and thrombin into the repaired site under arthroscopic vision. The meniscal sutures previously placed were loosened so that the PRP can have the best contact area with the lesion. After the PRP gel clot was formed on the lesion, the knee was taken to 90° of flexion and the sutures were fastened down and then tied. Finally, the arthroscope was pulled out, and the portals were then sutured. These have been added into the paper on line 135-139.

6. Response to comment: 1) The statistical method is questionable. You have two time frames and performing multiple t tests instead of including time as a variable in something like a GLM increases the chance for a type I error.

2) Further, please add what data were considered continuous and what data were considered categorical.

3) Finally, in the results, a multivariate analysis is mentioned, but this is not mentioned in the statistical methods section.

Response: 1) We are very sorry for this error. We have revised the results (Lysholm score, and Ikeuchi grade, VAS for pain) with use of one time frame (duration of follow-up ≥ 12 months), and the duration of follow-up has been included as a variable in the univariate analyses. We have corrected this error in the Results (line 183-223), Table 1, Table 2 and Table 3.

2) Student’s t-tests were used for continuous variables (age, symptom duration, duration of follow-up, Lysholm score and VAS for pain) and Fisher exact test was used to analyze the
categorical variables (gender, type of DLM, repaired meniscal zone, Ikeuchi grade and failure rate). This has been added into the paper on line 157 to 159.

3) We conducted univariate linear regression analysis to identify variables associated with pain relief and function improvement. Then we performed multivariate linear regression analysis including variables with a P value < 0.05 defined by univariate analysis. These have been added into the paper on line 163 to 165.

7. Response to comment: 1) Paragraph 2 information would be better placed in the introduction.

2) The discussion would be more meaningful if the authors focused on comparing and contrasting their results with meniscus papers, even if not DLM, focusing again on PRP papers related to the meniscus would be more meaningful than trying to relate your findings to other musculoskeletal systems.

Response: 1) Thanks for your comment. Paragraph 2 information in the Discussion has been placed in the Introduction on line 72 to 74.

2) Despite the promising preclinical findings, the use of PRP remains controversial in meniscal repair. In study of arthroscopic meniscal repair, Griffin et al. reported that there was no difference in the proportion of patients who underwent reoperation in the PRP group (27%) compared with the non-PRP group (25%, P = 0.89). Functional outcome measures were not different between the two groups (P = 0.55). There was also no difference in the proportion of patients who returned to their regular sports/activities in the PRP group (71%) compared with the non-PRP group (78%, P = 0.75). Whereas in a study of open meniscal repair, Pujol et al. reported that the difference between PRP and non-PRP augment groups was significant for pain and sports activities parameters in KOOS score (P = 0.046 and 0.03, respectively). Furthermore, there was a statistically significant difference in the healing appearance of repaired menisci by MRI evaluation between the PRP and non-PRP groups (P < 0.01). These have been added into the paper on line 250-260.