Author’s response to reviews

Title: An improved method of delivering a sclerosing agent for the treatment of malignant pleural effusion

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Version: 1 Date: 23 Apr 2019

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Reviewer #1.

General Statement: This is a very interesting paper describing the effects of talc hydrogel foam on experimental MPE induced in mice by intrapleural injection of LLC cells. The study design, methods, and presentation convinced this reviewer. Well done.

Response: We thank the reviewer for the positive feedback and for finding our manuscript interesting.

Reviewer #2.

General Statement: The authors attempted to propose an improved method of delivering a sclerosing agent for the treatment of malignant pleural effusion in animal malignant pleural effusion models. They found the survival of mice in novel thermosensitive hydrogel talc foam
(TF) group was better than that in the talc slurry (TS) group. Effusion volume was less in the TF group, and pulmonary fibrosis was similar between the two groups.

Response: We appreciate the reviewer’s positive evaluation of our manuscript. We also thank the reviewer for pointing out key findings of the study and for raising several important points that require clarification.

Comment 1. How to measure the total effusion volume without loss in mice? In human studies, it is quite a difficulty to collect all the pleural effusion without a precise collection method especially when multiple separated pleural effusions appear after talc pleurodesis (I guess there are possible loculated effusions in TS group in figure 3B).

Response: The method we used to measure pleural effusions is based on previously published work [1, 2] and is described in detail in the “histopathological evaluation” methods section of the manuscript. In short, immediately following euthanasia, the abdominal cavity was opened, and the viscera were retracted to visualize the diaphragm, which was punctured with a 23-gauge needle to aspirate all of the pleural fluid. We were able to reposition the needle in the process to ensure complete or near complete evacuation of all of the fluid. After collection of the fluid, the thorax of each mouse was surgically explored, to collect lungs and evaluate the cavity for adhesions. No significant residual fluid was noticed in the process of exploring the thoraxes.

Comment 2. The factors of Equation 1 in the submitted manuscript were missing.

Response: We thank the reviewer for noticing this oversight, which has been corrected.

Comment 3. The survival of mice in the TS group is similar to the control group. That might imply that the conventional TS pleurodesis is not superior to controls. Please have some discussion about why TF can prolong survival, but TS cannot.

Response: To clarify, survival of mice in the talc slurry (TS) group was statistically significantly lower compared to mice in the control and in the TF groups. There was no difference in terms of survival between the control and the TF group. We have added the following to the discussion on page 9 to clarify this point: Talc foam also did not adversely affect survival compared to the control group, and demonstrated significantly better survival compared to conventional pleurodesis. The reduction in survival between the different treatment groups is likely a result of the poor distribution of the talc slurry, which may have caused cardiovascular compromise due to more focused pressure on the heart. Further studies are needed to explore these observed survival differences. However, it is unlikely that these findings would translate to the clinic, given that chemical pleurodesis has not been shown to significantly impact survival, but rather to improve quality of life.
Comment 4. Page 7, line 29-30. The abbreviation, "GLMs" and "FDR78", have not been clearly defined in the manuscript.

Response: The two abbreviations are now defined within the text and they have been added to the abbreviations list.

Comment 5. TF significantly (p < 0.05) reduced loss of right lung volume (by 30-40%) compared to the control group, which was not significantly different from TS (p > 0.05). That might be a confounding measurement to the amount of pleural effusion.

Response: The amount of pleural effusion was not significantly different between the TS and the TF groups (Figure 4), making it less likely that the effusion volume was a significant confounding factor on the loss of right lung volume. This point was added to the discussion section on page 9.

Comment 6. Foam gel form talc (TF), as described in the manuscript, means that talc was mixed in an air-liquid form. Please explain whether this is feasible/safe in cancer patients with MPE? The novelty and future application of this study will be in outpatient MPE management, in my opinion. How will the authors prevent or monitor further pneumothorax or empyema without a catheter in patients received TF pleurodesis?

Response: Administration of the novel talc foam would be similar to the current administration of other agents used for chemical pleurodesis. It would require placement of a chest tube or pleurx catheter to drain any effusion and then administer the foam. We have an ongoing project that we hope to describe in the near future, focused on efficient delivery of talc foam through a chest tube/catheter in the clinic. We feel that description of this work is beyond the scope of the work that we present here. However, in human trials, standard procedures would be employed to monitor for pneumothorax or empyema development (e.g., monitoring vital signs, chest x-ray, CT scans).

References
