Peer Review File

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<mark>Reviewer A</mark>

Congratulations to the authors on your novel pleural treatment after the VATS bullectomy in order to reduce the recurrence rate of PSP. However there are some questions needed to be addressed before the consideration of acceptance for publication.

Reply: Thank you very much for your comments and thorough analysis of our paper.

Comment 1: the article title: Additional pleural painting with iodopovidone vs. talc.... That means iodopovidone plus talc vs talc only. But in your 'Abstract, method', the comparison is beween iodopovidone and talc. Can you clarify?

Reply 1: As correctly pointed out, the title contains a misprint from the previous version. We modified it, pointing out the attention to the iodopovidone pleural painting.

We carried out a study comparing pleurodesis with iodopovidone and pleurodesis with talc during thoracoscopic bullectomy in patients with spontaneous pneumothorax.

Changes in the text: the resulting title is "Additional pleural painting with iodopovidone during video-assisted thoracoscopic bullectomy for primary spontaneous pneumothorax: an observational, single-center retrospective analysis" Page 1, Lines 4-5.

Comment 2: It doesn't make sense that the drainage output after iodopovidone was larger, but the drainage period was shorter. Can you explain?

Reply 2: Thanks for pointing out this issue. We have been pondering why patients treated with iodopovidone had reduced drainage stay despite increased leakage from the drain. As described more clearly in the "Discussion" section we modified, the radiologic findings of the chest in patients treated with talc were not as satisfactory as in patients treated with iodopovidone. The residual pleural space from incomplete lung expansion induced us to maintain the drainage for a longer time while waiting for a more valid expansion of the lung parenchyma to ensure the pleurodesis effect.

Changes in the text: "The irritative process seemed to be highly associated with increased exudative production in iodopovidone pleurodesis. On the other hand, talc seemed to give the pulmonary visceral pleura an inelastic effect, reducing its reactive effusion." Page 10, Lines 234-236. "...unsatisfactory post-surgical CR images motivated the longer duration of drainage when talc poudrage was performed." Page 10, Lines 238-239.

Comment 3: Please do not write the definition, etiology and surgical indications of PSP in the text again. They are the common knowledge for thoracic surgeons.

Please start straightly towards what are the current pleural procedures or methods to prevent the recurrence of PSP. And how are their effects? What makes you think of the usage of iodopovidone?

Reply 3: We followed your advice and revised the manuscript's introduction, reducing the unnecessary information. We also included brief comments on talc and its use to clarify why we used iodopovidone as a sclerosing substance.

Changes in the text: "Primary spontaneous pneumothorax (PSP) is a relatively frequent clinical entity with a high incidence in the young population, generally accompanied by typical symptoms and well-known predisposing factors (1,2,3). Following the rupture of subpleural blebs or bullae, located primarily in the upper lobes and apex (4), the management of PSP focuses on cessation of air leak (AL) and prevention of recurrences." Page 3, Lines 68-72; "Surgical or chemical pleurodesis may be used as adjunctive therapy..." Page 4, Line 78; "Performing talc pleurodesis instead of surgical pleurodesis (e.g., pleural abrasion, pleurectomy, pleural tenting) has shown several short-term complications and long-term consequences, such as respiratory function and oncological problems, especially in the young population. However, it is less painful in the postoperative course and reduces bleeding risk compared to the surgical options. In terms of prevention of recurrence, the two procedures showed equivalent outcomes. Talc pleurodesis offers excellent results (although data from adequate comparative studies are lacking), but it should be avoided in a young population (12,13)." Page 4, Lines 81-87; "However, there is a lack of studies that firmly assessed the concentration of iodopovidone or specific instructions for its use within the pleural cavity. Primarily, the authors report its injection into the pleural space without mentioning the technic of its distribution during VATS lung resection (17)." Page 4, Lines 90-92.

Comment 4: Did you apply any synthetic materials or glue on the staple lines? **Reply 4**: No glue, reinforced reloads for stapling, or other kinds of stapling line reinforcement were used in our series.

Comment 5: How long was the follow-up period?

Reply 5: The duration of the follow-up after-surgery was 1-year. We reported this information in the M&M paragraph. Page 6, Lines 145-147.

Comment 6: Please do not write 'chest x-ray'. 'Chest radiography' is the correct term.

Reply 6: As you suggested, we replaced "chest x-ray" with "chest radiography", as well as the abbreviation "CXR" with "CR".

<mark>Reviewer B</mark>

I have read your article with interest.

Although I have never personally used talc or iodopovidone for spontaneous pneumothorax in young patients, they are inexpensive and would help reduce

medical costs. I think that is quite acceptable, since different countries have different ideas about medical costs.

However, I am very interested in the results that iodopovidone is an effective and safe chemical agent for pleurodesis.

Actually, I am not able to agree with the use of talc especially for young patients. So, it may be a good suggestion that iodopovidone would be comparable as a pleurodesis agent.

By the way, you mentioned that drain output was significantly higher in the iodopovidone group. I have a question: you mentioned using 100cc of 2% iodine; is it possible to induce inflammation in a broad pleural area by diluting the iodopovidone, for example, 200cc of 1% or 400cc of 0.5%? I ask because when we perform chemical pleurodesis, we have had success in reducing the amount of drain output by diluting and injecting large volumes.

Reply: Thank you very much for your comments. We are honored to have piqued your interest into our study. You highlighted the peculiar finding of hyperproduction of pleural fluid by patients treated with iodopovidone. Honestly, we did not consider the possibility of further diluting the concentration of iodopovidone in the solution.

Based on the sparse data on the use of iodopovidone in the treatment of PNX and those from the treatment of recurrent pleural effusion, we prepared an internal protocol recommending a 2% safe dilution and a valid 100 mL volume to be easily distributed over the parietal pleural surface. A prospective study on patients undergoing surgery and pleurodesis with iodopovidone only could consider the possible cut-off of effective dilution of the sclerosant.

<mark>Reviewer C</mark>

Congratulations to your data. This is an interesting study. However, several points should be clarified. The following are my comments.

Comment 1: As you mentioned that routine negative suction is used in all patients, the retained 100 ml of 2% iodopovidone solution naturally would be evacuated instantly. What's your viewpoint on this problem?

Reply 1: Thank you for pointing out this technical detail. As per our internal protocol, every patient undergoing concomitant surgery and pleurodesis is placed under continuous aspiration of the chest drain (-40 cmH2O) following extubating the patient in the PACU room. In several cases, an immediate inflammatory response occurred with the production of clear pleural fluid collected in the drainage tube after the reposition of the patient from the lateral surgical decubitus to the supine position. The distribution of iodine on the parietal and visceral pleura through a soaked sponge should be sufficient to induce pleural inflammation. It is uncertain if a chest tube with continuous aspiration may

invalidate the intrapleural action of iodopovidone solution concerning its residence time in the pleural cavity.

Comment 2: I am wondering why the IP group which exhibited higher pleural drainage would have shorter chest tube days and length of hospital stay? In common practice, earlier tube removal is relevant to less pleural output. In the method section, you defined the identical tube removal criteria for both groups. Please explain this point.

Reply 2: Thanks for the question. The drainage removal was performed following the same criterion in both study groups. According to postoperative chest radiography, even those patients eligible for the chest tube removal (low serum production, no air leak) were kept with drain until a complete lung re-expansion. In patients treated with talc pleurodesis, the residual pleural space from incomplete lung expansion prompted us to maintain drainage longer while waiting for a more valid expansion of the lung parenchyma to ensure the pleurodesis effect, compared to the iodopovidone group.

Changes in the text: "Drain output and AL were recorded every day until ChT removal, which was performed at cessation of AL and < 3 mL/kg/2h of serous ChT output, and after radiographic evidence of a satisfactory lung re-expansion" Page 6, Lines 142-14; "Based on our experience, unsatisfactory post-surgical CR images motivated the longer duration of drainage when talc poudrage was performed." Page 10, Lines 238-239.

Comment 3: Equal number of subgroups in your retrospective across the ling timespan (8 years), any selection bias? Please provide the numbers per year in your study.

Reply 3: Thank you for your comment. The retrospective data collection started with the first patient who underwent iodopovidone pleurodeses during VATS bullectomy (July 2012).

Previously, the juvenile, spontaneous pneumothorax or recurrence was preferably treated with partial decortication or only talc poudrage following blebs exeresis, depending on surgeon preference or patient choice and consent.

We included a detailed table for in the "supplementary material", providing the numbers of patients treated with iodopovidone and talc per year. A statement expressing a possible bias was added in the "discussion" section.

Changes in the text: "The distribution of patients who underwent talc or iodopovidone pleurodesis was not uniform during the study period (as shown in Table S1 - Supplementary Appendix), representing a potential selection bias." Page 11, Lines 258-260.

Comment 4: At last, language polishment is required. The operative figure should be provided with a clear one and, a comparison of TC group is encouraged.

Reply 4: A bilingual professional English speaker has made an extensive language revision. We added a more detailed image (Figure 1) where the complete

intraoperative procedure of pleural painting with iodopovidone solution was described in the figure legend. Unfortunately, we did not acquire clear pictures or video of talc poudrage during blebs resection surgery, but it is a well-known procedure, we suppose. On the other hand, it could be more interesting to inform about the pleural painting technique as an innovative method of spreading iodopovidone in support of desert surgery for spontaneous relapse of pneumothorax.

Changes in the text: ------ "Figure 1. Intraoperative steps of a thoracoscopic iodopovidone solution painting on the parietal pleura. Division of Thoracic Surgery – "A. Businco" Oncology Hospital - Cagliari (IT). This image is published with the patient's consent. a) blebs resection with automated thoracoscopic stapling; b-c) 2% iodopovidone injection through a nasogastric tube; d) pleural cavity filled with 100 mL iodopovidone solution; e-f) pleural painting with the iodopovidone soaked sponge all over the parietal pleural." Page 15, Lines 371-375