

Peer Review File

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Reviewer A

Comment 1: Authors developed novel method of the bronchial occlusion using customized endobronchial plugs. It is effective and economic method for PAL patients. However, the method for impacting into the bronchus need to be described more in detail. Especially when the bronchus is angulated like RUL, the skill should be more than usual.

Reply 1: *We thank the reviewer to raise this critical point. Impacting the plugs into the target bronchus is a key step for the completion of the procedure, especially in the angulated bronchi such as RUL. We have added the details of the plug placement in the Methods session following the reviewer's advices.*

After identifying the responsible bronchus, a grasping forceps was passed through the working channel of a flexible bronchoscope to grasp the knot at the tip of the plug. Subsequently, guided by the bronchoscope, the grasping forceps held the plug to reach the target bronchus by adjusting the angle and direction. While maintaining the bronchoscope at the bronchial opening, the plug was inserted into the target bronchus with the assistance of the forceps. Once the plug blocked the target bronchus, the bronchoscope was used to press the back end of the plug further into the bronchus while simultaneously retracting the forceps. Finally, the forceps were reintroduced to impact against the back end of the plug to ensure a tight seal.

Changes in the text: *We have added the details as mentioned above (see Page 5, line113-121).*

Comment 2: The good candidate and relative contraindication should be also described.

Reply 2: *Many thanks for the reviewer's suggestion. In the study, the candidates were the patients with persistent air leakage from intercostal drainage for more than 7 days, who were unsuitable for surgical management. The exclusion criteria: (1) Patients are allergic to silicone material. (2) Patients have uncontrolled acute lung infection or severe chronic infection at the target bronchi. (3) Patients with compromised cardiopulmonary function unable to tolerate the bronchoscopic procedure.*

Changes in the text: *We have added the details in the Methods session following the reviewer's advices (see Page 4, line89-92).*

Reviewer B

Comment 1: One limitation to that others will consider: How do you ensure that the plugs don't migrate or become expectorated?

Reply 1: *We thank the reviewer to raise this critical point. (1) The rough surface of the plug after trimming facilitated it firmly into the bronchial tree. (2) The size of the plug was designed to be slightly larger than the diameter of the airway. This design took advantage of the elasticity of both the bronchial wall and the silicone material, ensuring a snug fit when it was inserted into the target bronchus. (3) Following plug insertion, the forceps were employed to impact against the back end of the plug to ensure a tight occlusion. (4) In cases where local anesthesia was administered, patients were instructed to cough after the plug placement to ensure its stability and prevent potential migration. (5) After the procedure, oral codeine was prescribed for the first 3 days to suppress coughing and prevent expectoration. Through these measures mentioned above, we aimed to minimize the risk of the plug displacement or expectorated.*

Changes in the text: *We have revised the manuscript to clarify this point (see Page 4, line 96, line 98; Page 5, line 120-126)*

Comment 2: The size of some of these plugs are large enough to obstruct larger bronchi which could present as a foreign body obstruction. Do you feel confident in the safety profile of this approach?

Reply 2: *We thank the reviewer to raise this critical point. Indeed, while the plug is generally seen as a foreign object in the bronchi, it's worth highlighting that these silicone plugs are derived from mandibular prostheses, and their biocompatibility and safety have been validated through long-term clinical experience in implant surgery. Additionally, the endobronchial Watanabe spigot (EWS) which is also made of silicone material has been used widely as an endobronchial blocker for the treatment of persistent air leakage. It was reported that the EWS could be placed in the airway for more than 3 years without obvious complications.¹ Given the good biocompatibility and tolerance of the silicone material, we consider that it is acceptable to maintain the plugs in the bronchi without severe complications. However, a close follow-up is essential to confirm the safety of the silicone plugs.*

Changes in the text: *No change was made.*

Comment 3: Another limitation is that all patients were male.

Reply 3: *We thank the reviewer to raise this critical point. The incidence ratio of pneumothorax between males and females ranged from 2:1 to 6:1.²⁻³ This gender-related difference may be attributed to the higher rate of tobacco consumption in men compared to women. Therefore, the incidence rate of pneumothorax is higher in males than in females. Our research was a retrospective study carried out at a single center,*

and due to the limited number of cases, it was possible that the study cohort consisted entirely of males. Multicenter and prospective clinical trials involving a larger sample size will be required.

Changes in the text: *We have added this limitation in the revised manuscript following the reviewer's advices (see Page 9, line228).*

Comment 4: Success of the conical plug alone was 57.7%. Line 126 is misleading as it doesn't clearly state that pleurodesis was also performed.

Reply 4: *Many thanks for the reviewer's suggestion. We apologize for the confusion. In our study, after using bronchial occlusion alone, 13 patients observed complete cessation of air leakage without the need for pleurodesis, while 7 patients experienced a reduction in bubbles in the water-sealed chamber and required additional pleurodesis as a combined therapy to achieve complete resolution of pneumothorax. Therefore, the success rate of using the plug alone was 56.5%, while the success rate of combined therapy with the plugs and pleurodesis was 30.4% (These changes in the data were made based on the comments from other reviewers, and we made corresponding revisions).*

Changes in the text: *We have revised the manuscript to clarify this point (see Page 6, line156-159).*

Comment 5: Line 153, please clarify currency/cost (US? China?)

Reply 5: *Many thanks for the reviewer's suggestion. We apologize for the confusion. Original line 153, this currency was the United States Dollar (USD).*

Changes in the text: *We have revised the manuscript to clarify this point (see Page 7, line188).*

Reference

1. Kaneda H, Minami K, Nakano T, et al. Efficacy and long-term clinical outcome of bronchial occlusion with endobronchial Watanabe spigots for persistent air leaks. *Respir Investig* 2015;53:30-6.
2. Bobbio A, Dechartres A, Bouam S, et al. Epidemiology of spontaneous pneumothorax: gender-related differences. *Thorax* 2015;70:653-8.
3. Schnell J, Koryllos A, Lopez-Pastorini A, et al. Spontaneous Pneumothorax. *Dtsch Arztebl Int* 2017;114:739-44.

Reviewer C

This article presents a novel method for bronchial occlusion using customized endobronchial plugs as a treatment for refractory pneumothorax. The authors compare this technique to other treatments for prolonged air leakage, such as chemical pleurodesis and surgical intervention, and discuss the potential advantages of their approach.

However, we ask that you reconsider the following points.

Comment 1: Define refractory pneumothorax.

Reply 1: *We thank the reviewer to raise this critical point. Refractory pneumothorax includes recurrent pneumothorax (unilateral pneumothorax occurring ≥ 2 times or bilateral pneumothorax occurring ≥ 3 times) and persistent air leakage (PAL).¹ The definition of PAL has been described as an air leak that persists for more than 5 to 7 days.²⁻⁴ In our study, we used a seven-day threshold due to data obtained from the*

'programme for medicalisation of information systems' database from the French healthcare system, representing 59,637 institutions where the median duration of hospital stay was 7 days.⁵ Therefore, our study utilized a 7-day cutoff to define prolonged air leakage, based on the expected length of stay for further treatment other than pleural drainage.

Changes in the text: *We have defined refractory pneumothorax in Introduction session (see Page 3, line55).*

Comment 2: the article does not mention any additional treatment modalities for prolonged air leakage other than bronchial occlusion using customized endobronchial plugs. If pleurodesis was performed, what drugs were used? Please describe any additional treatment, e.g., 13th coagulation factor infusion, etc.

Reply 2: *We thank the reviewer to raise this critical point. We apologize for the confusion. When air leakage was not completely resolved after bronchial occlusion, we implemented additional treatment by performing chemical pleurodesis with interleukin-2 infusion.*

Changes in the text: *We have revised the manuscript to clarify this point (see Page 6, line134-135).*

Comment 3: The site of bronchial embolization should be described in detail, even down to the subareolar branches. For example, whether all bronchi in the upper lobe were embolized or whether a sublobar bronchus was selected should be described.

Reply 3: *We thank the reviewer for this suggestion and have created a Supplementary Table 1 that includes the location of bronchial occlusion for each patient.*

Changes in the text: *We have added the information on Supplementary Table 1.*

Comment 4: It is difficult to successfully embolize in a single procedure. The number of times the procedure is performed should also be described.

Reply 4: *We are grateful to the reviewer for requesting these additional details, which enhance the clarity of our patient data. We have incorporated this information into Table 2 and presented the individual case data in a new Supplementary Table 1.*

Changes in the text: *We have incorporated this information into Table 2 and presented the individual case data in a new Supplementary Table 1.*

Comment 5: Are there differences in treatment results depending on the pathological condition, such as cases of emphysema or postoperative tracheobronchial fistula? We also believe that postoperative bronchial fistula, lung cancer, and refractory pneumothorax due to tuberculosis should be omitted from this paper due to the jumble of pathological conditions.

Reply 5: *We thank the reviewer to raise this critical point. Our four participants had a history of inactive tuberculosis, indicating they had a medical history of tuberculosis that is currently inactive and characterized by old pathological lesions. Furthermore, among these four patients with old pulmonary tuberculosis, we consider their concurrent condition of COPD to be the primary cause of their pneumothorax. Therefore, the presence of old pulmonary tuberculosis in our study should not impact the treatment outcomes. However, as suggested by the reviewer, the varying pathological conditions of the lungs may potentially influence the treatment outcomes. Consequently, we have excluded data related to postoperative bronchial fistula (1 case) and lung cancer (2 cases).*

Changes in the text: *We have deleted the data related to postoperative bronchial fistula*

(1 case) and lung cancer (2 cases) in Table 1 and Table 2, and we have also made revisions to the data presented in the article.

Comment 6: In cases where pneumothorax was cured, there is no mention of recurrence. The presence or absence of recurrence should be mentioned.

Reply 6: *We are grateful to the reviewer for requesting these additional details, which enhance the clarity of our patient data. In our study, three patients experienced pneumothorax recurrence, and it is noteworthy that these three patients were those who achieved complete resolution of pneumothorax solely through bronchial occlusion without the need for combined pleurodesis procedures. This suggests that additional pleurodesis procedures may potentially reduce the risk of pneumothorax recurrence. We have incorporated this information into Table 2 and presented the individual case data in a new Supplementary Table 1.*

Changes in the text: *We have incorporated this information into Table 2 and presented the individual case data in a new Supplementary Table 1.*

Reference

1. Zhai CC, Lin XS, Yao ZH, et al. Erythromycin poudrage versus erythromycin slurry in the treatment of refractory spontaneous pneumothorax. *J Thorac Dis* 2018;10:757-65.
2. Liberman M, Muzikansky A, Wright CD, et al. Incidence and risk factors of persistent air leak after major pulmonary resection and use of chemical pleurodesis. *Ann Thorac Surg* 2010;89:891-8.
3. Lazarus DR, Casal RF. Persistent air leaks: a review with an emphasis on bronchoscopic management. *J Thorac Dis* 2017;9:4660-70.

4. Varela G, Jiménez MF, Novoa N, et al. Estimating hospital costs attributable to prolonged air leak in pulmonary lobectomy. *Eur J Cardiothorac Surg* 2005;27:329-33.
5. Bobbio A, Dechartres A, Bouam S, et al. Epidemiology of spontaneous pneumothorax: gender-related differences. *Thorax* 2015;70:653-8.

Reviewer D

This is a single-center, retrospective study on the usefulness and safety of bronchial embolization with customized endobronchial plugs for prolonged air leakage. I thought the method for the bronchial occlusion in this study is very effective.

My Comments are listed below.

Comment 1: In patients with poor overall clinical condition, pleurodesis is often performed as a treatment for prolonged air leakage except for bronchopleural fistulas. In fact, seven patients underwent both bronchial embolization and pleurodesis in this study. You should describe about the indications for pleurodesis in the introduction section.

Reply 1: *Many thanks for the reviewer's suggestion. Existing guidelines recommend medical pleurodesis as an alternative treatment in patients with prolonged air leakage who are not suitable candidates for surgery. As the reviewer's comments, the indication for pleurodesis have been clearly defined in the Introduction section.*

Changes in the text: *The indication for pleurodesis have been clearly defined in the Introduction section (see Page 3, line64-65).*

Comment 2: Please describe both the degree of collapsed lung on imaging findings

and the amount of air leakage, in each case before bronchial embolization.

Reply 2: *We are grateful to the reviewer for requesting these additional details, which enhance the clarity of our patient data. In our study, the median degree of collapsed lung on imaging findings was 20% (10%-85%). Although the U.S. Food and Drug Administration has approved the use of digital chest drainage systems such as Thopaz system, which allows for digital monitoring of the amount of air leakage, this product is currently not available in China. Therefore, in our study, we primarily relied on visual inspection to assess the air leakage and were unable to perform quantitative analysis. We have incorporated this information into Table 1 and presented the individual case data in a new Supplementary Table 1.*

Changes in the text: *We have incorporated this information into Table 1 and presented the individual case data in a new Supplementary Table 1.*

Comment 3: Patients with interstitial pneumonia are at risk of acute exacerbation of interstitial pneumonia due to pleurodesis or surgery, but were there any interstitial pneumonia patients among the cohort?

Reply 3: *We thank the reviewer to raise this critical point. In our study, only one patient had obstructive bronchitis. And this patient achieved complete resolution of pneumothorax solely through bronchial occlusion without the need for combined pleurodesis procedures. Furthermore, this patient did not experience acute exacerbations of interstitial pneumonia during the bronchoscopic procedure. It's important to note that our research was a retrospective study with a limited number of participants from a single center. To draw more comprehensive conclusions, multicenter and prospective clinical trials involving a larger sample size will be necessary.*

Changes in the text: No change was made.

Comment 4: As you know, it is advisable to mention the time taken for the procedure of bronchial embolization. Is this not noted in the nursing record during the procedure?

Reply 4: We thank the reviewer to raise this critical point. In our department, the nursing records only document the start and end times of the bronchoscopic procedure and do not include specific details, such as the placement time in each plug. Consequently, the total operation time does not accurately reflect the actual insertion time of the endobronchial plugs, and as a result, we lacked this specific data. This represents a limitation in our study, and we acknowledge the need to collect such data in the future.

Changes in the text: No change was made.

Comment 5: English editing should be performed by native English speakers.

Reply 5: Many thanks for the reviewer's suggestion. The manuscript has been edited for English language usage, grammar, punctuation and spelling by qualified native English-speaking editors at International Science Editing before submission.



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This document certifies that the manuscript titled **A novel method for the bronchial occlusion of prolonged air leakage using customized endobronchial plugs** has been edited for English language usage, grammar, punctuation and spelling by one or more native English-speaking editors at International Science Editing. Using their scientific and editing backgrounds to highlight passages that were found to be confusing or lacking in clarity, our editors have focused on correcting the language and rephrasing sentences when required. Our editors endeavour to ensure that neither the original research content nor the authors' intentions have been altered in any way during the editing of the manuscript.

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