Peer Review File

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Reviewer A

Comment 1: Well written. Would suggest discussing about endobronchial valves as an adjunct treat for PAL post-surgery.

Reply 1: The reviewer suggests discussing endobronchial valves as an adjunct to treat PAL post-surgery. While this emerging therapy is promising, we want to keep the current manuscript focused on the intra-operative treatment of air leak using sealants, as it's not meant to be a comprehensive review discussing all possible treatments of post-operative air leakage, but rather focusing on a single gap in evidence.

Changes in text 1: None

Reviewer B

Comment 1: I would like to thank the editors and authors for providing me such an interesting article. This article focused on off-label use of lung sealants and discussed the need to establish the guideline. Although the concept of this article was interesting, availability of sealants would depend on the country and the social system. In my country, Tachoseal, Bolheal and Beriplast are available and can be used on-label. However, this article never discussed Bolheal and Beriplast. This review paper can be unattractive and useless to some readers.

Reply 1: Indeed, the availability of sealants and precise indications for use can vary per region of the world. We based the table on the sealants that were investigated in the included systematic reviews / meta-analyses, that are available in the EU. Upon double-checking the included fibrin sealant trials, we note that the trial by Mouritzen et. al. investigated Beriplast®.(1) We have therefore included Beriplast® in the table, thereby increasing the relevance to more readers worldwide. We did not find the brand name of Bolheal in the RCTs that tested homologous fibrin sealants.

Changes in text 1: In table 2 Beriplast® was added.

Reviewer C

Comment 1: The author raises concerns regarding the use of sealants other than TachoSil—specifically Coseal, Progel, and Hemopatch—for managing air leaks during lung surgery, citing the limited clinical evidence and the issue of off-label use.

This is an incredibly important point, and the need for future clinical trials as well as ex vivo experiments, which the author emphasizes, should be widely recognized.

Reply 1: We thank the reviewer for assessing our manuscript and the recognition of the importance of discussing the off-label use of various sealants. This is precisely the reason we wrote the manuscript and why we believe this should be disseminated amongst the broader community of thoracic surgeons.

Changes in text 1: None

Reviewer D

Comment 1: Thank you for the opportunity to review this manuscript. I commend the authors for their effort in compiling the article. However, the manuscript lacks originality and does not contribute novel insights to the existing literature. It is neither a comprehensive review nor a meta-analysis. The current format reads more like a descriptive catalog of commercially available sealants rather than a critical or systematic evaluation. I recommend that the authors consider restructuring the manuscript into a systematic review with a clearer methodology and analytical depth.
Reply 1: The reviewer comments on the format of the manuscript, pointing out the lack of systematic evaluation. We agree with the reviewer on this point and see how the manuscript can benefit from a more structured methodology. We have performed an additional structured literature search (will be referred to in supplement 1) and detailed mini-review methodology in a separate paragraph. We identified two additional review articles, which are referred to in table 1, but these were smaller and less comprehensive papers that did not change the conclusions of our manuscript.
Regarding the comment that the manuscript lacks originality or does not contribute novel insights to literature, we believe that the topic of off-label use amongst lung sealants and the gaps in evidence are underreported in literature, and believe disseminating the work is relevant. This is also supported by the other reviewers.

Changes in text 1:

- Added a methods paragraph (line 55-67).
- Referred to an additional review in line 96.
- Added two additional reviews found during the structured search in table 1.
- Added a supplement with structured search methodology.

Comment 2: Line 20: You mention "prolonged air leak" — please provide a clear definition of this term.
Reply 2: Air leak lasting >5 days.
Changes in text 2:

- Line 45-46: Thoracic surgeons are often faced with the consequences of prolonged air leakage (PAL, defined as air leak >5 days).

Comment 3: Line 23: Similarly, define "intraoperative air leak" and describe how it is measured, particularly in relation to PEEP (positive end-expiratory pressure).
Reply 3: We define intra-operative leak as any leak that is identified during surgery by a water submersion test or mechanical ventilator test. In this definition, we do not include any relation to PEEP. However, we do recognize that more standardized definitions are required in this regard, as is discussed in line 82-83.
Changes in text 3:

- Line 49-51: Pre-emptive treatment of intra-operative air leaks (IAL, defined as any air leak during surgery as diagnosed by water submersion test or mechanical ventilator test) with lung sealants offers a conceptually…

Comment 4: Line 28: You refer to previous consensus papers that have not been introduced earlier. It would be helpful to briefly summarize these papers to provide context.
Reply 4: Indeed, a more extensive discussion of these papers can help the reader. We have elaborated on these papers.
Changes in text 4:

- Revised the paragraph from line 68-82.

Comment 5: Line 35: You state that no standardized mechanical ventilation parameters exist for testing intraoperative air leaks. Consider suggesting which parameters could potentially be standardized.
Reply 5: Based on the current data, it is impossible to make definitive recommendations regarding the values of various parameters for optimal leak testing. This remains to be tested, to identify which values have the best predictive value for predicting prolonged leaks. We have added this in the text, and also describing which parameters / measures should be looked into further.
Changes in text 5:

- Line 83-88: It is worth noting that no standardized mechanical ventilator parameters are defined for testing IAL size, while these can have a profound impact. It remains to be investigated which type of standardization (positive end-expiratory pressure, volume versus pressure control, respiratory rate, inspiratory: expiratory ratio) and measurements (absolute air leak values versus proportion of tidal volume) has the best predictive value of post-operative air leak.

Comment 6: Line 84: You attempt to outline principles for designing high-quality clinical trials, but these are not clearly articulated. Please elaborate, for example, on the differences in air leak outcomes between VATS and open surgery, and clarify what you mean by "standardization of chest tube removal."
Reply 6: We have further elaborated om these points in the text.
Changes in text 6:

- Line 147-153: Minimally invasive procedures should be included to reflect clinical practice, since application of sealants requires a different technique for open versus video-assisted procedures which can influence outcomes. Blinding should be applied to post-operative follow-up, and chest tube removal should be standardized using digital systems by using quantitative cut-off points for drain removal. These quantitative cut-off points can also be used in the analysis to verify the drain removal protocol was adhered to in a similar fashion in both intervention and control groups.

Comment 7: Language and Grammar: There are several grammatical and stylistic issues throughout the manuscript. A thorough language revision is recommended to improve clarity and readability.
Reply 7: We have revised the manuscript for language.

Changes in text 7: Various minor changes throughout.