Animal models of pulmonary parenchymal air leakage in the investigation of lung sealing devices: a systematic review protocol

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**Review question / Objective:** 1. What are the methodological characteristics (animal model, disease model, sealants used, experimental groups, outcome measures) of previous in-vivo models used for the testing of lung sealing devices for the treatment of pulmonary air leakage (PAL)?

2. What is the risk of bias of previous in-vivo studies used for the testing of lung sealing devices for the treatment of PAL based on the SYRCLE Risk of Bias Tool, and what is their reporting quality based on a custom reporting quality score?

3. Based on answering questions (1) and (2), can recommendations be formulated for the conduction of animal studies for the testing of lung sealing devices for the treatment of PAL?

**Information sources:** MEDLINE via Pubmed, EMBASE and Web of Science. We will attempt to retrieve all possible suitable full-texts with the help of our medical library.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 July 2022 and was last updated on 01 July 2022 (registration number INPLASY202270003).

**INTRODUCTION**

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Rationale: The current methods used for the study of lung sealing devices (i.e. sealants, staplers, sutures) as a treatment for PAL are heterogenous.[1-7] Different animal models, lesions types and outcome measures have been used. No clear review or consensus, such as the international consensus statement for anastomoses in the gastro-intestinal tract[8], exists with regard to the best methods for PAL in-vivo study designs. Homogenous methods and clearly defined recommendations for this specific topic of study could improve reproducibility of results and improve the implementation the 3R’s (reduction, refinement, replacement). The current body of literature for testing of lung sealing devices in-vivo has not previously been systematically appraised. With this systematic review, we aim to provide a comprehensive overview of the methodological characteristics of previous animal models used for the testing of lung sealing devices for the treatment of PAL and provide recommendations for future research in this field based heron. Furthermore, we will assess the internal validity and reporting quality of these studies, providing a baseline for quality improvement this field.

Condition being studied: In patients undergoing lung surgery, most surgical injuries to the lung heal without problems using conventional techniques such as sutures and staplers. However, 5.6-30% of patients undergoing pulmonary resections may develop prolonged pulmonary air leakage (generally defined as air leaks >5 days).[9] This condition necessitates protracted chest drain placement and is associated with an increase in postoperative complications (pneumonia, empyema, mortality), longer hospital stay and higher costs.[10-13] Furthermore, 4.8% of patients require additional interventions in this context.[12]

METHODS

Search strategy: A three component search strategy is deployed in MEDLINE via Pubmed, EMBASE and Web of Science. One component contains terms related to pulmonary surgery (pulmonary, lung, lobectomy, pneumonectomy, segmentectomy, pleura, lung resection) and post-operative air leakage (air leak, alveolar pleural fistula, pneumothorax, bronchial fistula, subcutaneous emphysema) and a second component contains terms related to lung sealing devices (aerostatic, seal, glue, bioglue, spray, patch, sheet, tissue adhesives, fibrin tissue adhesives, buttressing, hydrogel, mesh). Search components were combined using AND operations with the animal studies search filter designed by Hooimans et. al.[14]

Participant or population: All previous animal models used (in mammals).

Intervention: Lung sealing devices for treating PAL (i.e. lung sealing patches, gels, sprays, staplers, sutures, lasers).

Comparator: All control populations used in previous studies.

Study designs to be included: In-vivo study designs.

Eligibility criteria: Inclusion criteria are 1) in-vivo study design in mammals, 2) animal model of pulmonary parenchymal air leakage (small bronchioles within lesions may be included), 3) sealing of this air leak with a surgical lung sealing device and 4) assessing aerostatic efficacy of the lung sealing device. The following exclusion criteria were considered: 1) lung sealing device is only used to seal a large bronchus or trachea (such as large segmental or lobar bronchi), 2) lung sealing device is a non-surgical intervention (such as bronchoscopy, pleurdesis, thoracic drainage) and 3) studies only testing the hemostatic or biocompatibility
characteristics of the lung sealing device under investigation. Conference abstracts were also omitted from the final literature sample.

**Information sources:** MEDLINE via Pubmed, EMBASE and Web of Science. We will attempt to retrieve all possible suitable full-texts with the help of our medical library.

**Main outcome(s):** Outcomes will be collected and described for research question (1), regarding citation information (year of publication, country of origin), animal model used (species, weight, age, sex, number animals, disease model, experiment type [survival vs non-survival], longest survival term), defect model used (surgical approach, anatomical location, number of lesions, type of lesion, lesion dimensions, static or ventilated lung during lesion induction, hemostatic measures, baseline measurements), sealing procedures (sealing device used, static or ventilated lung during lung sealing, sealing efficacy test, experimental groups) and outcome measures (air leak, bursting pressure, macroscopy, lung physiology, histology, imaging techniques, adverse events). Quality assessment outcomes (see below) will be used to answer research question (2).

**Data management:** Citations will be managed using Endnote version 20 and extracted data will be gathered in an IBM SPSS Statistics (version 27) database.

**Quality assessment / Risk of bias analysis:** For study quality assessment, the SYRCLE Risk of bias tool will be used, which consists of bias assessment in six domains, specifically designed for use in animal systematic reviews. Items 1-8 on this tool are scored as ‘high’, ‘unclear’ or ‘low’.[15] Furthermore, an additional six questions related to internal validity are formulated (randomization, blinding, power-calculation, use of positive and negative control groups and industry funding) and answered with ‘yes’, ‘no’ or ‘unclear’. Publication bias is qualitatively (not necessarily based on statistically significant outcomes) assessed based on authors conclusions (positive/better effect, equivocal/neutral effect, worse/adverse effect, inconclusive). A reporting quality score (16 points max, based on the ARRIVE guidelines[16,17]) is calculated (1 point for each item if it is present): species specified (i.e. mongrel dogs, wistar rats), sex, age, weight, housing, anesthesia, analgesia post-operatively, antibiotic prophylaxis, sterility during surgery, type of incision to gain access to the lungs, location of defect right or left lung, location of defect lobe used, description of static lung state during defect creation, description of static lung state during sealant application, defect dimensions, ethical statement (was approval sought), data access statement, registration of protocol.

**Strategy of data synthesis:** All collected methodology and risk of bias data will be analyzed using descriptive statistics and quantitatively described. The interpretation of this data will be used to generate recommendations for future animal studies (research question 3). No meta-analysis of outcome data will be performed (unsuitel literature sample with very high heterogeneity regarding outcome measures).

**Subgroup analysis:** Analysis may be grouped per decade to observe trends in reporting quality and study methodology.

**Sensitivity analysis:** None.

**Language:** None. All non-English articles will be translated using online optical character recognition (OCR) (https://www.onlineocr.net/) and Google translate, but excluded if translation quality is unsatisfactory.

**Country(ies) involved:** The Netherlands.

**Keywords:** Lung sealant; Pulmonary air leakage; Lung resection; Animal model; In-vivo; Experimental; Tissue adhesive.

**Contributions of each author:**
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