Efficacy and safety of whole-lung lavage for pulmonary alveolar proteinosis: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Pulmonary alveolar proteinosis (PAP) is an ultrarare disorder characterised by the accumulation of alveolar surfactant and the dysfunction of alveolar macrophages that results in hypoxemic respiratory failure. Whole-lung lavage (WLL) is currently the primary therapy for PAP. However, systematic evaluation of the clinical efficacy of WLL is lacking. We aim to perform a systematic review and meta-analysis of existing evidence to support WLL for the clinical treatment of PAP.

Methods and analysis We will search the PubMed (MEDLINE), Cochrane Library, Embase, Web of Science and Google Scholar databases from inception to December 2021 for observational studies using WLL for the treatment of PAP. Two authors will independently screen the eligible studies, assess the quality of the included papers and extract the required information. Review Manager V.5.4 will be used to perform the meta-analysis. We will evaluate the overall quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation approach. All steps of this protocol will be performed using the Cochrane Handbook for Preferred Reporting Items for Systematic Review and Meta-analysis statement.

Ethics and dissemination This systematic review and meta-analysis will be based on published data. Therefore, ethical approval is not required. We will publish our results in a peer-reviewed journal.

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INTRODUCTION

Rationale

Pulmonary alveolar proteinosis (PAP) is an ultrarare syndrome first described by Rosen et al in 1958. A recent study reported an estimated prevalence of PAP of 6.87 per million in the general population. PAP is characterised by abnormal surfactant homeostasis and the resultant accumulation of surfactant in the pulmonary alveoli and alveolar macrophages. The typical physiological consequence of PAP is impaired gas exchange, resulting in progressive dyspnoea, hypoxemia or even respiratory failure and death. PAP can be classified into three different types based on the pathogenetic mechanism. The most frequent form is primary PAP, which includes an autoimmune disease type and is associated with elevated levels of granulocyte–macrophage colony-stimulating factor (GM-CSF) autoantibodies. Next, secondary PAP results from alveolar macrophage dysfunction due to haematopoietic disorders, immune dysregulation, environmental exposure and pharmaceutical agents. Finally, congenital PAP affects almost exclusively children. Autoimmune PAP comprises the most significant proportion (90%–95%) of adult patients, whereas secondary PAP accounts for 5%–10% of adult cases. Despite increased understanding of PAP in recent decades, limited treatment options are available for this disease. Traditionally, whole-lung lavage (WLL) is the gold standard of care for primary PAP and some causes of secondary PAP, but not congenital PAP. Many improvements have been made since its initial...
introduction in the 1960s, WLL is an invasive procedure, requiring general anaesthesia and isolation of the two lungs using a double-lumen endotracheal tube. One lung is mechanically ventilated while the other is repeatedly filled with saline and drained. Each lung is usually washed with 15–20 L and up to 50 L of saline. However, no randomised controlled trials have been reported on WLL, likely due to the extreme rarity of PAP. However, numerous observational studies have been published, and cumulative experience may be valuable in assessment. Although widely considered the first-line management strategy for PAP, the clinical efficacy of WLL has not been systematically evaluated. In addition, new therapeutic strategies for PAP have emerged, including inhaled or subcutaneous GM-CSF, rituximab, plasmapheresis and statins. Moreover, WLL is not without morbidity. Thus, there is a need to evaluate the efficacy and safety of WLL in this heterogeneous disease. Therefore, to appropriately apply the available evidence to the clinical practice of WLL in PAP, a systematic review and meta-analysis of reported observational studies will be performed strictly following the Cochrane Handbook for Systematic Reviews of Interventions.

Objectives
The primary aim of this systematic review is to quantify the symptomatic or functional benefits provided by WLL compared with the change from baseline. We will determine whether WLL provides quantitative improvements in lung function, radiology findings or blood gas analysis. The secondary aim is to ascertain whether WLL has an acceptable adverse event profile.

METHODS AND ANALYSIS
Study design
The protocol has been prepared according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P).

Eligibility criteria
Types of studies
Relevant observational studies, including cohort studies, case–control studies, and case series assessing the clinical efficacy and safety of WLL in PAP will be included. Case reports or case series involving <3 patients will be excluded.

Types of participants
Patients aged ≥18 years with confirmed autoimmune PAP or secondary PAP, regardless of sex or ethnicity, will be included. The diagnosis will be based on the presence of a ‘crazy-paving’ pattern on chest high-resolution CT and the ‘milky’ appearance of bronchoalveolar lavage fluid, which gives a positive periodic acid–Schiff reaction. Transbrachial, transthoracic or surgical biopsy will also confirm the presence of PAP. Patients with a positive GM-CSF autoantibody test are diagnosed with autoimmune PAP, while negative GM-CSF autoantibody and genetic test findings with a disease known to cause PAP lead to a diagnosis of secondary PAP.

Types of interventions and comparators
The interventions will be WLL used alone or in combination with other therapies, such as GM-CSF. The treatment benefits will be examined and the change from baseline compared.

Types of outcomes
The primary outcomes will be alveolar oxygen partial pressure, pulmonary function tests including diffusing capacity for carbon monoxide, forced expiratory volume in 1 second and forced vital capacity; radiology measures including CT scores of lung density and lung volume; and disease severity score before and after treatment with WLL. In papers reporting on a second or multiple lavages, all non-overlapping data will be included.

The secondary outcomes will mainly include the 6-minute walk test, St. George’s Respiratory Questionnaire, Medical Research Council (MRC) dyspnoea scale before and after WLL, recurrence rate, and adverse events. Adverse events will be classified as minor (fever, headache, hypoxia, pneumonia) or major (pneumothorax, hydrothorax, acute respiratory distress syndrome and even death) complications.

Search strategy
We will systematically search the PubMed, Cochrane Library, EMBASE, Web of Science and Google Scholar databases from their inception to September 2021. We will restrict the searches to articles published in English. An example search strategy for PubMed is listed in table 1, and similar strategies will be applied to the other resources. We will also screen the reference lists of relevant articles as supplemental data sources. Furthermore,
grey literature and unpublished data from clinical trial registries will also be retrieved.

**Data collection**

**Study selection**

Relevant studies will be imported into Endnote V.20 according to the search strategy. After removing duplicates, articles will be screened by the titles and abstracts, and the full texts will be reviewed. All procedures will be conducted independently by two reviewers, with a third author reconciling any discrepancies. The selection process will follow the PRISMA 2009 flow diagram (figure 1).

**Data extraction**

The following data will be gathered by two authors independently: (a) publication details (eg, first author, year of publication, geographic location); (b) study type; (c) baseline study and participant characteristics (sample size, age, sex, classification); and (d) outcomes and adverse events. Any disagreement will be discussed and judged by a third author. We will contact the corresponding authors via email or other methods if no response is received. If there is no response, incomplete literature will be excluded.

**Quality assessments of individual studies**

Two reviewers will independently apply the Newcastle-Ottawa Scale (NOS) for non-randomised studies to assess the quality of individual studies. This scale contains eight items in three categories: the selection of study groups, the comparability of the groups and the outcome of interest for case-control or cohort studies. The star system to assess study quality in the NOS ranges from 0 to 9 stars.

**Statistical analysis**

**Meta-analysis**

This study will use RevMan V.5.4 software to perform the meta-analysis. The dichotomous variables will be expressed as ORs with 95% CIs. The continuous variable will be expressed as weighted mean difference (WMD) with 95% CIs. The WMD and 95% CI will be calculated from either the difference in mean and SD of the study outcomes, before and after the intervention in the intervention and the control group, or by the end of intervention mean and SD in both groups. When the included studies ensure comparable baseline balance, using post-intervention mean. A random effects model will be used to summarise the pooled WMD. The I² statistic will be used to estimate heterogeneity. In instances with high levels of heterogeneity (I²>50%) among the studies, a random effects model will be applied; otherwise, a fixed effects model will be employed. Since the efficacy of WLL differs in autoimmune and secondary PAP, we will perform a subgroup analysis of different PAP types. We will also conduct a sensitivity analysis to explore the effects of the studies’ bias of risk on primary outcomes, if possible. Based on sample size and insufficient data, these analyses will exclude lower-quality studies and repeat the meta-analyses to assess the quality and robustness when significant statistical heterogeneity arises.

**Publication bias**

Funnel plots will be created to assess the publication bias, in which asymmetric and symmetric plots will indicate high and low risks of reporting bias, respectively.

**Confidence in the cumulative evidence**

Two reviewers will independently grade the quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation approach. Based on the five grading factors (risk of bias, imprecision, inconsistency, indirectness and publication bias), the levels of evidence will be categorised as high, moderate, low or very low.

**Patient and public involvement**

There was no patient or public involvement in this study’s design, conduct, reporting or dissemination plans.

**Ethics and dissemination**

This systematic review and meta-analysis will be based on published data. Therefore, ethics approval is not required. The results will be disseminated through peer-reviewed publications.

**Contributors**

Conceptualisation: SL and GL. Data curation: SL and KX. Formal analysis: SL and KX. Funding acquisition: GL and XC. Methodology: SL, MX and YD. Project administration: GL and XC. Writing—original draft: SL and KX. Writing—review and editing: SL.
Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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