BMJ Open

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

Shixu Liu, Xiangning Cui, Kun Xia, Yuanyuan Duan, Mengran Xiong, Guangxi Li

To cite: Liu S, Cui X, Xia K, *et al*. Efficacy and safety of whole-lung lavage for pulmonary alveolar proteinosis: a protocol for a systematic review and meta-analysis. *BMJ Open* 2022;**12**:e057671. doi:10.1136/bmjopen-2021-057671

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-057671).

SL and XC contributed equally.

Received 27 September 2021
Accepted 03 April 2022

Guanganmen Hospital, China Academy of Traditional Chinese Medicine, Beijing, China

Correspondence to
Guangxi Li; lgx0410@163.com

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.

PROSPERO registration number CRD42022306221 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022306221).

Strengths and limitations of this study

- This is the first systematic evaluation of the clinical efficacy and safety of whole-lung lavage (WLL) for the treatment of pulmonary alveolar proteinosis (PAP).
- We will collect a broad range of outcomes to assess the potential benefits and safety of WLL in patients with PAP.
- A limitation of our study is that we will only include papers published in English owing to the authors' linguistic competence.
- Original studies will be pre–post studies because of the ultrararity of PAP. They will be influenced by natural processes and characteristics of the patients and settings, and these may not be discerned from the effects of the intervention.
- Heterogeneity due to remarkably different types of PAP may limit the strengths of the associations and conclusions.

INTRODUCTION

Rationale

Pulmonary alveolar proteinosis (PAP) is an ultrarare syndrome first described by Rosen *et al* in 1958.[1] A recent study reported an estimated prevalence of PAP of 6.87 per million in the general population.[2] PAP is characterised by abnormal surfactant homeostasis and the resultant accumulation of surfactant in the pulmonary alveoli and alveolar macrophages.[3 4] The typical physiological consequence of PAP is impaired gas exchange, resulting in progressive dyspnoea, hypoxemia or even respiratory failure and death.[5] 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.[4] Finally, congenital PAP affects almost exclusively children.[6] Autoimmune PAP comprises the most significant proportion (90%–95%) of adult patients, whereas secondary PAP accounts for 5%–10% of adult cases.[7] 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.[8] Many improvements have been made since its initial

introduction in the 1960s.[9] 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.[10 11] Each lung is usually washed with 15–20 L and up to 50 L of saline.[8 12] However, no randomised controlled trials have been reported on WLL, likely due to the extreme rarity of PAP. However, numerous observational studies[13–15] 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.[16]

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).[17]

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.[8] Transbronchial, 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,

Table 1 Search strategy applied in PubMed

Search	Query
#1	"Pulmonary alveolar proteinosis"(Mesh)
#2	"Pulmonary alveolar proteinos*"(Title/Abstract)
#3	"PAP"(Title/Abstract)
#4	#1 OR #2 OR #3
#5	"Bronchoalveolar lavage"(Mesh)
#6	(Bronchoalveolar(Title/Abstract)OR Bronchioalveolar(Title/Abstract)) AND Lavage*(Title/Abstract)
#7	"Bronchopulmonary lavage*"(Title/Abstract)
#8	"Bronchial lavage*"(Title/Abstract)
#9	Pulmonary(Title/Abstract)AND (Lavage*(Title/Abstract)OR Washing(Title/Abstract))
#10	"Whole lung lavage"(Title/Abstract)
#11	#5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	#4 AND #11

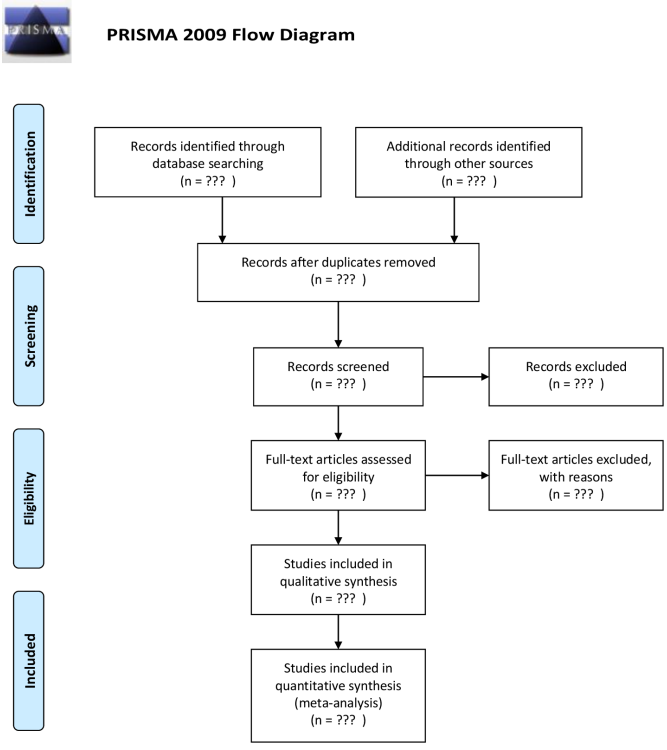

Figure 1 Flow diagram of study selection process. PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis.[24]

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 in case of missing or incorrect data. 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.[18] 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.[19]

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.[20] When the included studies ensure comparable baseline balance, using postintervention mean. A random effects model will be used to summarise the pooled WMD. The I^2 statistic will be used to estimate heterogeneity. In instances with high levels of heterogeneity (I^2>50%) among the studies, a random effects model will be applied; otherwise, a fixed effects model will be employed.[21] 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.[22]

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.[23]

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, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Guangxi Li http://orcid.org/0000-0001-6100-1910

REFERENCES

1 Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. *N Engl J Med* 1958;258:1123–42.
2 McCarthy C, Avetisyan R, Carey BC, *et al*. Prevalence and healthcare burden of pulmonary alveolar proteinosis. *Orphanet J Rare Dis* 2018;13:129.
3 Iftikhar H, Nair GB, Kumar A. Update on diagnosis and treatment of adult pulmonary alveolar proteinosis. *Ther Clin Risk Manag* 2021;17:701–10.
4 Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. *Am J Respir Crit Care Med* 2002;166:215–35.
5 Kumar A, Abdelmalak B, Inoue Y, *et al*. Pulmonary alveolar proteinosis in adults: pathophysiology and clinical approach. *Lancet Respir Med* 2018;6:554–65.
6 Jouneau S, Ménard C, Lederlin M. Pulmonary alveolar proteinosis. *Respirology* 2020;25:816–26.
7 Inoue Y, Trapnell BC, Tazawa R, *et al*. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. *Am J Respir Crit Care Med* 2008;177:752–62.
8 Trapnell BC, Nakata K, Bonella F, *et al*. Pulmonary alveolar proteinosis. *Nat Rev Dis Primers* 2019;5:16.
9 Rsmirez J, Schultz RB, Dutton RE. Pulmonary alveolar proteinosis: a new technique and rationale for treatment. *Arch Intern Med* 1963;112:419–31.
10 Campo I, Luisetti M, Griese M, *et al*. Whole lung lavage therapy for pulmonary alveolar proteinosis: a global survey of current practices and procedures. *Orphanet J Rare Dis* 2016;11:1–10.
11 Michaud G, Reddy C, Ernst A. Whole-lung lavage for pulmonary alveolar proteinosis. *Chest* 2009;136:1678–81.
12 Gay P, Wallaert B, Nowak S, *et al*. Efficacy of whole-lung lavage in pulmonary alveolar proteinosis: a multicenter International study of GELF. *Respiration* 2017;93:198–206.
13 Zhou X, Lu G, Yu Z, *et al*. Long-Term follow-up of whole lung lavage in patients with pulmonary alveolar proteinosis. *Exp Ther Med* 2014;8:763–8.
14 Beccaria M, Luisetti M, Rodi G, *et al*. Long-Term durable benefit after whole lung lavage in pulmonary alveolar proteinosis. *Eur Respir J* 2004;23:526–31.
15 Byun MK, Kim DS, Kim YW, *et al*. Clinical features and outcomes of idiopathic pulmonary alveolar proteinosis in Korean population. *J Korean Med Sci* 2010;25:393–8.
16 Cumpston M, Li T, Page MJ, *et al*. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for systematic reviews of interventions. *Cochrane Database Syst Rev* 2019;10:ED000142.
17 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
18 Wells GA, Shea B, O'Connell D. *The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Oxford, 2000.
19 Wells BS, O'Connell JP. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Available from:. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp2022
20 Higgins JP, Thomas J, Chandler J. *Cochrane Handbook for systematic reviews of interventions*. John Wiley & Sons, 2019.
21 Deeks JJ, Higgins JP, Altman DG. Analysing data and undertaking meta-analyses. *Cochrane handbook for systematic reviews of interventions* 2019:241–84.
22 Guyatt G, Oxman AD, Akl EA, *et al*. Grade guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
23 Atkins D, Best D, Briss PA, *et al*. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490.
24 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.