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Clinical Research

Early Pleurodesis for Postoperative Air Leak with Autologous Blood and 50% Glucose Solution

Jeong In Hong, M.D., Jun Hee Lee, M.D., Hyun Koo Kim, M.D., Ph.D.

Department of Thoracic and Cardiovascular Surgery, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea

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Corresponding author
Hyun Koo Kim
Tel 82-2-2626-3106
Fax 82-2-866-6377
E-mail kimhyunkoo@korea.ac.kr
ORCID
https://orcid.org/0000-0001-7604-4729

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Background: Postoperative air leaks after pulmonary resection prolong the duration of chest drainage and the length of hospital stay. One of the many treatment options is bedside pleurodesis using various agents. This study evaluated the feasibility of an early intervention to stop postoperative air leaks with either autologous blood or a 50% glucose solution.
Methods: We retrospectively reviewed 323 patients who underwent bedside pleurodesis between January 2017 and March 2022. Sixty-four patients received autologous blood patch pleurodesis, and 36 were treated with a 50% glucose solution after pulmonary resection. The primary endpoints were the total postoperative tube indwelling time, post-pleurodesis tube indwelling time, and hospital stay. A propensity score-matched analysis was performed.
Results: In the autologous blood patch pleurodesis and 50% glucose solution groups, the mean initiation timing of postoperative pleurodesis were 2.06±1.62 and 3.28±1.56 days, the mean duration of the tube indwelling time after surgery was 6.58±3.02 and 6.42±4.92 days, and the mean duration of the tube indwelling time after pleurodesis, it was 4.53±3.10 and 3.11±4.80 days, respectively. In addition, the total length of hospital stay was 9.11±5.42 and 7.83±4.75 days in the autologous blood patch pleurodesis and 50% glucose solution groups, respectively.
Conclusion: Early postoperative air leak cessation with autologous blood patch pleurodesis or 50% glucose solution pleurodesis is a feasible procedure with acceptable outcomes that effectively shortens the hospital stay.

Keywords: Complication, Pleurodesis, Length of stay, Autologous blood transfusion, Glucose

Introduction

Bedside pleurodesis is a commonly performed procedure, but it lacks evidence and consensus and is implemented mainly based on the clinician's judgment. Indications include postoperative air leaks, apical residual spaces or chylothorax after thoracic surgery, and persistent air leaks in patients with pneumothorax who are unsuitable for surgical treatment [1-5]. Pleurodesis agents vary widely, from autologous blood patches and 50% glucose solution to chemical agents such as talc, antibiotics, chemotherapy agents, *Viscum album* extract, iodopovidone, and OK-432 [2,4,6-11].

The presence of a postoperative air leak itself, regardless of its duration, is considered a risk factor for worse outcomes and a prolonged hospital stay after lobectomy [12]. The recent development of minimally invasive surgery and enhanced recovery after surgery (ERAS) programs have reduced the length of hospital stay (LOS); however, chest drains remain a hindrance in this process [13]. Thus, an early intervention to discontinue postoperative air leakage is important.

Autologous blood and a 50% glucose solution are considered relatively safe pleurodesis agents compared to chemical agents, although their mechanisms of action are still unclear. Furthermore, both agents are simple to use, inexpensive, and effective in air leak cessation [1,4]. Numerous observational and prospective randomized studies on autologous blood patch pleurodesis (ABPP) have been published, the majority reporting the benefits of early

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chest drain removal and discharge [1,3,14,15]. However, the literature on pleurodesis using a 50% glucose solution is limited. Fujino et al. [2] and Tsukioka et al. [4] reported the application of this method for postoperative air leaks and pneumothorax.

This study evaluated the efficacy and safety of ABPP and 50% glucose solution for achieving pleurodesis in patients with postoperative air leakage after pulmonary resection. We also compared the outcomes of both agents using propensity score matching (PSM).

Methods

Patients and study design

This study was a single-center retrospective observational analysis approved by the institutional review board of Korea University Guro Hospital (IRB no., 2022GR0353), and the requirement for informed consent was waived. Data were collected from the electronic medical records of patients over 18 years of age who received bedside pleurodesis using either autologous blood or 50% glucose solution from January 2017 to March 2022 at a single institution. Among these patients, only those who underwent pulmonary resection were included. To assess the safety and efficacy of these agents of interest, the following exclusion criteria were applied: (1) autologous blood or the 50% glucose solution was not used as a primary agent for the first instillation, (2) the agent was changed to a chemical agent (e.g., talc, Helixor, or minocycline) only after the first attempt, or (3) the autologous blood or the 50% glucose solution was mixed with other chemical agents during administration.

Data were collected on patients' baseline characteristics (age and sex), perioperative data (operative diagnoses, laterality of disease, surgical modality, and the extent of adhesion), and comorbidities (chronic obstructive pulmonary disease [COPD] and diabetes mellitus). The primary endpoints were the total postoperative tube indwelling time, days until chest tube removal after pleurodesis, and the total length of hospital stay. The secondary endpoints were the time to the first pleurodesis after surgery; the response rate at the first, second, and third attempts; post-procedural complications (graded by the Clavien-Dindo classification); and readmission due to recurrent pneumothorax or pleural effusion.

Bedside pleurodesis protocol

The indications for bedside pleurodesis at our institution are non-operable cases of secondary spontaneous pneumothorax, postoperative air leak with or without full lung expansion, postoperative apical residual spaces, and recurrent pneumothorax after removal of postoperative chest drains. In this study, we confined the role of autologous blood and 50% glucose solution pleurodesis to the treatment of postoperative air leaks and residual apical spaces to evaluate their role in aiding early drainage removal and shortening the LOS for patients who undergo surgery.

Our institution utilizes an electronic drainage device (Thopaz; Medela AG, Baar, Switzerland) instead of a traditional drainage system. The amount of air leakage is displayed digitally, and the leakage trend is recorded over time, so that the observer can determine the quality of the pneumostatic response. The indications for bedside pleurodesis are as follows: (1) a large amount of postoperative air leak (not protocolized, depending on the clinician's judgment); (2) an air leak trend showing the fluctuation of air leaks up to 20 mL/min beyond postoperative day 1, where the decision to remove chest drainage is not definite. We did not set the time window for a watchful wait in these situations, and the procedure was performed if indicated as early as postoperative day 1. For ABPP, 50 mL of peripheral venous blood was drawn from the patient and immediately administered through the chest tube without premedication. The electronic drainage device was then set in gravity mode, equivalent to a conventional water seal system, and placed higher than the level of the patient to prevent backflow of the agent. The patient was instructed to change positions every 15 minutes for an hour with the ward nurse's assistance to distribute the injected blood inside the pleural cavity. The drainage device suction was reapplied 90 minutes after agent administration. The 50% glucose solution pleurodesis was initiated by first injecting 20 mL of 2% lidocaine, followed by 200 mL of 50% glucose solution into the pleural cavity. The next steps were performed in the same manner as in ABPP. The decision to remove the chest tube was made at least 24 hours after pleurodesis. The indications for chest tube removal were full lung expansion on plain chest radiography and an air leakage trend of 0–10 mL/min overnight. Our institution's protocol for the threshold of pleural drainage was <180 mL/day in those with body weight <60 kg or 3 mL/kg/day in those with body weight >60 kg [16]. Upon confirmation with chest radiography, the patient was discharged the day after chest tube removal.

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Statistical analysis

Categorical variables are expressed as counts and percentages, and the chi-square test or Fisher exact test was used for comparison. Continuous variables are expressed as median and range or mean and standard deviation. The Student t-test or Mann-Whitney U test was used to compare continuous variables. PSM was performed for confounding adjustment, with covariates including age, sex, and operative diagnoses. Matching was performed in a 1:1 ratio, using a caliper width of 0.04 with the nearest neighbor. Results were considered statistically significant if the p-value was <0.05. IBM SPSS ver. 23.0 (IBM Corp., Armonk, NY, USA) was used for data analysis.

Results

From January 2017 to March 2022, bedside pleurodesis was performed in 323 patients. Of these patients, 143 were treated with agents other than autologous blood or 50% glucose solution and were excluded. After applying the exclusion criteria, the ABPP and 50% glucose solution groups included 64 and 36 patients, respectively. After PSM, 36 patients were matched in each group (Fig. 1). The demographic data of the patients before and after PSM are presented in Table 1. The baseline characteristics of the 2 groups did not differ after 1:1 matching. Lung cancer was the most common diagnosis, and lobectomy was the most common surgical approach. An equal distribution of patients with COPD was observed after PSM.

Table 2 shows patient outcome comparisons between the 2 groups before and after PSM. The mean durations of the chest drainage tube indwelling time after surgery for the ABPP and 50% glucose solution groups were 6.58±3.02 and 6.42±4.92 days, the durations after the bedside pleurodesis were 4.53±3.10 and 3.11±4.80 days, and the total LOSs were 9.11±5.42 and 7.83±4.75 days, respectively. The mean initiation timing of the bedside pleurodesis after surgery showed a significant difference between the 2 groups (2.06±1.62 versus 3.28±1.56 days, p=0.002). The mean number of trials was 2.22±2.07 in the ABPP group and 1.69±1.31 in the 50% glucose solution group (p=0.200). According to the definitions of the Clavien-Dindo classification, patients who required antipyretics or analgesics were graded level I. Additional pharmacological treatment after the procedure for fever or pain was required by 16 of 36 patients (44.4%) in the ABPP group and 18 of 36 patients (50%) in the 50% glucose solution group. Grade V is defined as the death of a patient; the in-hospital mortality rate in this study was 2.8% (1 patient in each group). The readmission rates were 5.6% (2/36) and 8.3% (3/36) in the ABPP and the 50% glucose solution groups, respectively. The period from discharge to readmission ranged from 6 days to 2 months.

The cumulative rates of air leak resolution for each pleurodesis attempt with autologous blood and 50% glucose solution are shown in Fig. 2. In the first trial, successful tube removal was done in 52.8% and 63.9% of the patients in the ABPP and 50% glucose solution groups, respectively. Furthermore, 77.8% and 86.1% of the patients had their tubes removed successfully in the second trial, and 86.1% and 88.9% on the third attempt. The air leak resolution rates compared from the first to third attempts (p=0.671) and the total success rates were not significantly different between the 2 groups (p=1.000).

Discussion

In the era where patient care is driven toward utilizing minimally invasive surgery and ERAS programs, this retrospective PSM analysis showed the efficacy of simple, inexpensive pleurodesis agents. We also showed the out-

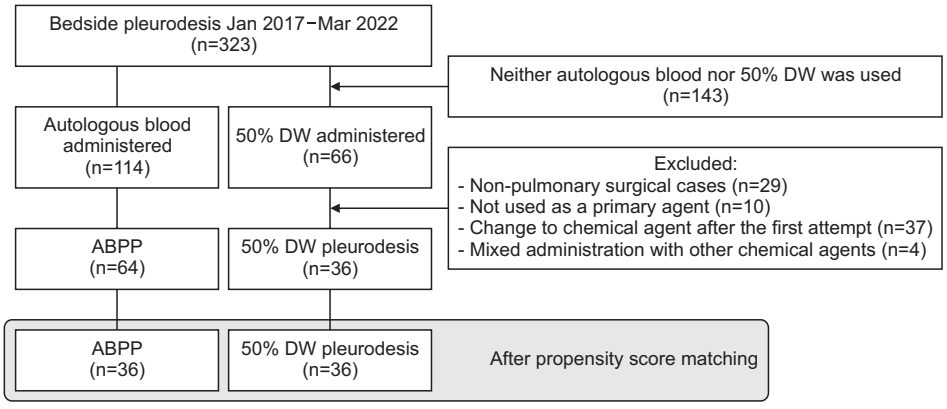

Fig. 1. Flowchart of patient recruitment. 50% DW, 50% glucose solution; ABPP, autologous blood patch pleurodesis.

Table 1. Demographic data of patients

Characteristic	Before matching			After matching		
	ABPP (n=64)	50% DW (n=36)	p-value	ABPP (n=36)	50% DW (n=36)	p-value
Age (yr)	66.31±10.34	66.53±10.53	0.921	66.31±11.01	66.53±10.53	0.931
Sex			0.049			1.000
Male	46 (71.9)	32 (88.9)		32 (88.9)	32 (88.9)	
Female	18 (28.1)	4 (11.1)		4 (11.1)	4 (11.1)	
Diagnosis			0.152			0.561
Lung cancer	59 (92.2)	29 (80.6)		31 (86.1)	29 (80.6)	
Pneumothorax	5 (7.8)	6 (16.7)		5 (13.9)	6 (16.7)	
Others	0	1 (2.8)		0	1 (2.8)	
Laterality			0.586			0.147
Left	23 (35.9)	11 (30.6)		17 (47.2)	11 (30.6)	
Right	41 (64.1)	25 (69.4)		19 (52.8)	25 (69.4)	
Surgery			0.915			0.896
Wedge resection	10 (15.6)	7 (19.4)		7 (19.4)	7 (19.4)	
Segmentectomy	9 (14.1)	5 (13.9)		6 (16.7)	5 (13.9)	
Lobectomy	39 (60.9)	22 (61.1)		19 (52.8)	22 (61.1)	
Lobectomy with wedge resection	1 (1.6)	0		1 (2.8)	0	
Sleeve lobectomy	1 (1.6)	1 (2.8)		1 (2.8)	1 (2.8)	
Bilobectomy	4 (6.2)	1 (2.8)		2 (5.6)	1 (2.8)	
Pleurolysis during the operation			0.250			0.458
Yes	27 (42.2)	11 (30.6)		14 (38.9)	11 (30.6)	
No	37 (57.8)	25 (69.4)		22 (61.1)	25 (69.4)	
Chronic obstructive pulmonary disease	24 (37.5)	18 (50.0)	0.315	18 (50.0)	18 (50.0)	1.000
Diabetes mellitus	16 (25.0)	3 (8.3)	0.076	9 (25.0)	3 (8.3)	0.114

Values are presented as mean±standard deviation or number (%).
ABPP, autologous blood patch pleurodesis; 50% DW, 50% glucose solution.

Table 2. Patient outcomes after bedside pleurodesis in the ABPP and 50% DW groups

Variable	Before matching			After matching		
	ABPP (n=64)	50% DW (n=36)	p-value	ABPP (n=36)	50% DW (n=36)	p-value
Tube indwelling time, postoperative (day)	6.31±2.91	6.42±4.92	0.894	6.58±3.02	6.42±4.92	0.863
Tube indwelling time post-pleurodesis (day)	4.09±2.96	3.11±4.80	0.208	4.53±3.10	3.11±4.80	0.142
Length of hospital stay (day)	9.23±5.60	7.83±4.75	0.209	9.11±5.42	7.83±4.75	0.291
Time of first pleurodesis (postoperative day)	2.22±1.63	3.28±1.56	0.002	2.06±1.62	3.28±1.56	0.002
Clavien-Dindo classification			0.574			0.892
Grade I	26 (40.6)	18 (50)		16 (44.4)	18 (50)	
Grade II	0	0		0	0	
Grade III	0	0		0	0	
Grade IV	0	0		0	0	
Grade V	1 (1.6)	1 (2.8)		1 (2.8)	1 (2.8)	
Readmission rate due to recurrence or complications	3 (4.7)	3 (8.3)	0.664	2 (5.6)	3 (8.3)	1.000

Values are presented as mean±standard deviation or number (%).
ABPP, autologous blood patch pleurodesis; 50% DW, 50% glucose solution.

comes of earlier postoperative interventions. Unlike pneumothorax, where the parenchymal air leak is an entity of the disease, postoperative air leaks and residual apical spaces are considered complications that prevent patients from being discharged. These postoperative air leaks and residual apical spaces are associated with other pulmonary complications and predict worse outcomes [12].

Most of the patients included in this study were diagnosed with lung cancer and underwent lobectomy. At our institution, as uncomplicated lobectomy cases are dis-

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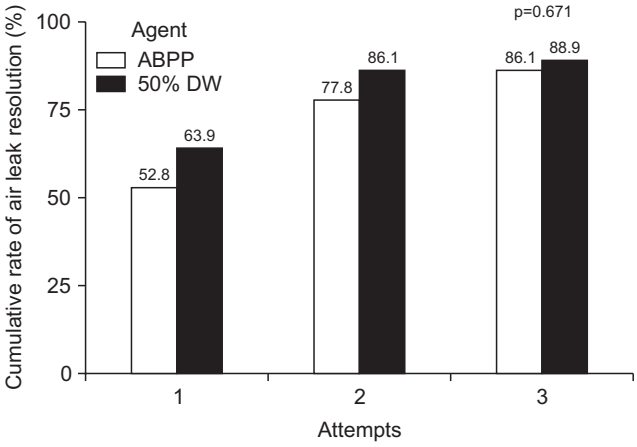

Fig. 2. Cumulative rate of air leak resolution on the first, second, and third attempts. ABPP, autologous blood patch pleurodesis; 50% DW, 50% glucose solution.

charged on an average of 3–5 days after surgery, we initiated interventions for postoperative complications as early as day 1. In this study, initial instillation was performed after a mean period of 2.06±1.62 days in the ABPP group and 3.28±1.56 days in the 50% glucose solution group, which might contradict the conventional Society of Thoracic Surgery definition of prolonged air leak (PAL; an air leak persisting beyond postoperative day 5). A recent meta-analysis on ABPP for PAL by Karampinis et al. [3] included 10 studies from 1998 to 2020 and reported that the timing of ABPP ranged from 5 days to 2 weeks after pulmonary resection. However, the authors concluded that this time point for treating PAL was too late and suggested a revision of the definition. Thus, we have used the term "postoperative" air leak instead of "prolonged" or "persistent" air leak, which are arbitrary and outdated terms [3,8,12,17].

Compared to recent retrospective matched studies of ABPP for PAL [1,18], where the classic "postoperative day 5" rule was applied, the mean period between the date of surgery and the date of chest drainage tube removal was reported to range from 8 to 11 days; however, our study showed a shorter duration (6.58±3.02 days). In a comparative study by Ibrahim et al. [19], patients received ABPP if the air leak persisted beyond postoperative day 3. The mean duration of drain placement was 7.87 days, and the LOS was 10.04 days. Few published results with 50% glucose solution are comparable to those with ABPP. Fujino et al. [2] performed pleurodesis with 50% glucose solution on postoperative day 3 for earlier chest tube removal, which resulted in a shorter mean drainage period of 6.8 days, similar to our result of 6.42±4.92 days. A significant difference was observed between the 2 groups when the first timing of pleurodesis after surgery was analyzed. This may reflect the perception that a blood draw is an invasive procedure, which may seem reasonable in the early postoperative period, when the patient is already experiencing frequent blood draws for laboratory work.

As shown in Fig. 2, the cumulative air leak resolution rates of both agents were favorable. A meta-analysis of ABPP studies in patients undergoing lung resection showed a pooled success rate of 85.7% within 48 hours after the procedure [3]. The success rate of 50% glucose solution was presented by Fujino et al. [2], with rates of 28/46 (60.9%) on the first attempt, 36/46 (78.3%) on the second attempt, and 39/46 (84.8%) on the third attempt. Our results are comparable to those of the aforementioned analyses. Additionally, both agents showed a high response rate after the second attempt. Thus, we recommend conducting pleurodesis at least twice with either ABPP or 50% glucose solution before switching to chemical agents.

Postprocedural complications were graded using the Clavien-Dindo classification. Almost half of the patients required supplementary medication for fever or pain (grade I). This high incidence is concordant with early postoperative pain and fever. Two patients developed pneumonia and acute respiratory distress syndrome (ARDS). One patient diagnosed with idiopathic pulmonary fibrosis and lung cancer in the ABPP group underwent bedside pleurodesis on postoperative day 5 after lobectomy. Two days later, air leak resolution was achieved and the drain was removed. However, the patient experienced an exacerbation of COPD, which progressed to respiratory failure. Another patient with underlying COPD in the 50% glucose solution group underwent lobectomy to treat lung cancer. The air leak persisted after 3 procedures with 50% glucose solution; consequently, chemical pleurodesis was attempted with talc slurry. After 2 rounds with talc, the patient developed pneumonia and ARDS. A bronchoscopic examination revealed a bronchopleural fistula; repeated doses of pleurodesis might have caused the patient's condition to deteriorate. We believe this case emphasizes the need for a careful choice of the agent for pleurodesis in postoperative air leak patients. Both patients died despite intensive care unit management.

The limitations of our study include bias due to the retrospective nature of this observational study. Furthermore, the heterogeneity of the bedside pleurodesis protocol has allowed several different regimens for pleurodesis agents, such as a mixture of 50% glucose solution and talc or autologous blood with *Viscum album* extract. Deciding on the timing and the choice of the subsequent agent after

failed air leak cessation was not protocolized. Thus, the choice varied according to clinicians' judgment based on the degree of leakage reduction and the patient's response to the previous agent (e.g., development of fever or complaining of pain). We excluded complex regimens to assess the efficacy of the individual agents using the exclusion criteria described earlier. Therefore, our findings provide limited insight into their concurrent use with other chemical agents. Next, since our study proposed an earlier intervention for postoperative air leaks, the possibility of spontaneous resolution might have been masked. However, our success rates were similar to those of previously reported studies; we also showed a shorter LOS. According to the literature, the overall pooled incidence of empyema in patients with ABPP is 1.5%–9% [1,3,18]. Infection after pleurodesis has also been acknowledged in several studies using 50% glucose solution. However, this risk is still debatable [2,4,5]. In particular, it has been argued that the risk may not be due to the choice of the solution, but due to the prolonged indwelling of the chest tube. In light of the possibility that prolonged chest tube drainage may be associated with pleural infection, our outcomes provide relevant evidence, since there were no cases of postprocedural empyema.

In conclusion, this study showed that both ABPP and 50% glucose solution are feasible pleurodesis agents for postoperative air leaks and residual apical spaces after pulmonary resection, with acceptable outcomes. However, a thorough evaluation of the presence of bronchopleural fistula would be critical before administering pleurodesis agents. A 50% glucose solution may be preferable if a patient is reluctant to undergo a blood draw. Moreover, early postoperative intervention should lead to shorter chest drainage duration and LOS and lower morbidity and mortality rates. Further prospective and randomized trials are required to improve our understanding of the usage of these agents.

Article information

ORCID

Jeong In Hong: https://orcid.org/0000-0002-9660-7063
Jun Hee Lee: https://orcid.org/0000-0002-6592-6483
Hyun Koo Kim: https://orcid.org/0000-0001-7604-4729

Author contributions

Conceptualization: JIH, HKK. Data curation: JIH. Formal analysis: JIH. Funding acquisition: JHL, HKK. Methodology: JIH, JHL, HKK. Project administration: HKK. Visualization: JIH. Writing–original draft: JIH. Writing–review & editing: JIH, JHL, HKK. Final approval of the manuscript: HKK.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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