

# Comparison of efficacy of autologous blood patch pleurodesis *versus* doxycycline pleurodesis in the management of persistent air leak in patients with secondary spontaneous pneumothorax. A randomized control trial

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Ethics approval: The study was performed after clearance from the Institute Scientific Committee and Ethics Board. The study was conducted within the boundaries of Helsinki declaration. Informed consent was obtained from participants aged  $\geq 18$  years, privacy and confidentiality of data was ensured.

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## Abstract

Secondary spontaneous pneumothorax (SSP) patients sometimes have a persistent air leak (PAL) that leads to increased morbidity and increased hospital stay. Further, these patients also need pleurodesis to prevent a recurrence. Autologous blood patch pleurodesis (ABPP) has been successfully tried in post lobectomy air leak cases. However, its utility in SSP patients with PAL has not been widely established. In this context, we performed a non-blinded randomized control study to compare the efficacy of ABPP *vs* doxycycline pleurodesis in the closure of air leak in SSP patients. This study was a non-blinded randomized control study done in 38 SSP patients with PAL. They were randomized into doxycycline arm and ABPP arm. Post pleurodesis air leak was assessed every 12 h for cessation. Success was considered when there was a complete cessation of air leak. Post-procedural complications were noted and patients were followed up for 28 days to look for recurrence. The median time for closure was 24 h [interquartile range (12.24)] for ABPP and 36 h [interquartile range (24.72)] for doxycycline pleurodesis. Success rate of ABPP *vs* doxycycline pleurodesis is 94.7% *vs* 84.2% ( $p=0.6$ ). Post-procedure pain was more in doxycycline group (15% *vs* 73%) ( $p<0.01$ ). On visual analogue scale, ABPP had a lesser pain as compared to doxycycline pleurodesis (average visual analogue scale value of 2 *vs* scale of 7). The recurrence rate was equal in both groups (5%). Though ABPP and doxycycline have similar success rates, ABPP has an early closure of air leak and greater patient tolerability. ABPP can be tried as an alternative to doxycycline pleurodesis in SSP patients with persistent air leak.

## Introduction

Spontaneous pneumothorax, the presence of air in the pleural space without a preceding trauma, can be classified as primary or secondary based on the lung parenchymal involvement. Secondary spontaneous pneumothorax (SSP) presents as a complication of underlying lung disease [1]. One of the most common

problems encountered in patients with SSP is a persistent air leak which leads to significant morbidity, increased hospital stay and also lengthens the time to Intercostal drainage tube (ICD) removal [2]. Most of the patients with SSP also have a recurrence and hence require pleurodesis.

Pleurodesis can be achieved through chemical or mechanical methods. Autologous blood patch pleurodesis (ABPP) is a type of pleurodesis in which the patient's blood is introduced through the ICD tube to achieve pleurodesis. The mechanism behind the closure of the air leak with ABPP is probably due to the patch seal mechanism followed by the inflammatory response [3]. ABPP has been successfully tried in post pneumonectomy air leak [4]. However, the literature on the use of ABPP in closure of air leak in primary and secondary spontaneous pneumothorax is relatively sparse [5-9].

In this background we performed this study to compare the success of ABPP *versus* doxycycline pleurodesis in patients of SSP with persistent air leak and to assess the time to closure, complication rate and 28 days recurrence.

## Methods

The study was a prospective non blinded randomized control study done in the department of pulmonary medicine in a tertiary care institute. The study was performed after clearance from the Institute Scientific Committee and Ethics Board and was registered with the clinical trials registry of India (CTRI/2020/09/027984). The study period was from September 2020 to May 2021. The outcome assessed include successful closure of air leak at 7 days, time for closure of air leak, duration of chest tube *in situ*, complications like fever, empyema, pain, recurrence of pneumothorax within 28 days and need for surgical intervention.

## Sample size calculation

Using nMasters software version 2.0, taking the success rate of doxycycline pleurodesis as 60% and Autologous blood patch pleurodesis as 78% with a power of 80%, and alpha error of 0.05, a sample size of 38(19 in each arm) was calculated [7,10].

## Inclusion criteria

- Age >18;
- Patients with secondary spontaneous pneumothorax and persistent air leak grade 1-2.

## Exclusion criteria

- Previous history of pleurodesis;
- Traumatic spontaneous pneumothorax;
- Patients with underlying hematological disorders- coagulopathies;
- Patients with hypotension and other cardiopulmonary diseases;
- Known case of allergy to doxycycline;
- Patients with active pulmonary infection.

## Patient screening and recruitment

Consecutive patients with clinical and X-ray features of pneumothorax were considered for the study. After ruling out traumatic pneumothorax, the selected patients underwent intercostal tube drainage followed by chest-CT. Following CT these patients were categorized as primary and secondary spontaneous pneumothorax. After the exclusion criteria, a total of 84 spontaneous pneumothorax patients underwent thorax-CT which was reviewed by consultant radiologist and ten cases were diagnosed as primary spontaneous pneumothorax (PSP) and excluded from the study and standard care of treatment was given (Figure 1).

Seventy-four patients with secondary spontaneous pneumothorax were included in the study and after 72 h of intercostal tube drainage, a chest X-ray was taken. If there was a complete expansion of the lung but with persistent air leak, these patients were randomized to autologous blood patch pleurodesis and doxycycline pleurodesis. A total of 38 patients had persistent air leak after 72 h and they were subjected to randomization to doxycycline pleurodesis and autologous blood patch pleurodesis arms. Randomization was done *via* computer generated, sequentially numbered, opaque, sealed envelopes (SNOSE) technique. The standard of care for pleurodesis in our institute is doxycycline and hence it was used. After pleurodesis, all the patients were reviewed every 12 h till 7<sup>th</sup> day of procedure to look for cessation of air leak. Air leak was graded based on Cerfolio classification of air leaks

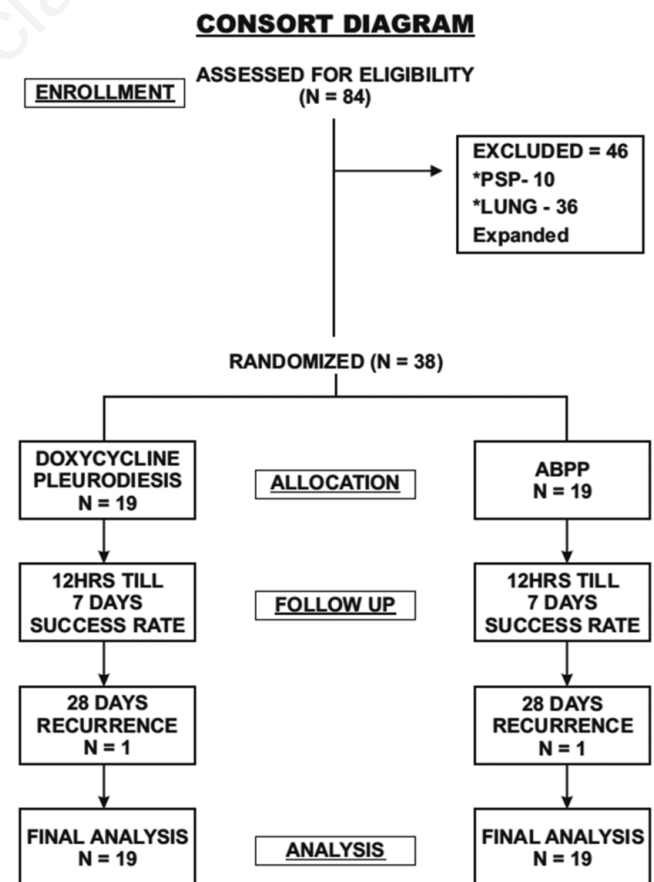


Figure 1. CONSORT diagram representing the study flow.

[11] (Table 1). The outcome was assessed by another pulmonary medicine resident doctor to avoid bias. Complete cessation of air leak at the seventh day of procedure was considered as success. The drain was not connected to negative suction. If the air leak persisted after seven days, the patients were referred to the Cardiothoracic Surgical Department for surgical management. All the patients of pleurodesis were followed up till 28 days of post procedure to look for recurrence. As per BTS guidelines for management of pneumothorax, surgical referral can be made when air leak persists for 5-7 days post tube thoracostomy (though there is no study as when to do a surgical intervention). As we allocated patients after 72 h post tube thoracostomy, we assessed for 7 days for cessation of air leak before surgical referral [12].

### Autologous blood patch pleurodesis

Using an aseptic technique 50 ml of venous blood from the cubital vein was withdrawn using a 50 ml syringe with 18-gauge needle. The withdrawn blood was immediately injected into pleural cavity through the intercostal tube without anticoagulation. The

**Table 1. Grading of air leak: Cerfolio classification of air leaks.**

Grade 1	During forced expiration only, typically when asking the patient to cough
Grade 2	Expiration only
Grade 3	Inspiration only
Grade 4	Continuous bubbling present in the air leak chamber during both inspiration and expiration

**Table 2. Baseline characteristics of study population.**

Baseline characteristics	ABPP (n=19)	Doxycycline pleurodesis (n=19)
Male	15	14
Female	4	5
Age (mean)	43.47 (18-74)	48.84 (19-75)
Smoking	7	8
History of pulmonary tuberculosis	3	1
Biomass fuel exposure	2	3
<b>Symptomatology</b>		
Chest pain	17	19
Dyspnea	17	16
Cough	9	12
<b>Underlying lung condition</b>		
COPD	8	12
Malignancy	3	7
COPD with malignancy	2	4
Interstitial lung disease	1	6
Bulla	4	2
Cyst	1	1
Air leak grade (median)	2	1

ABPP, autologous blood patch pleurodesis; COPD, chronic obstructive pulmonary disease.

chest tube was kept elevated at about 80 cm above the patient's body level to prevent the intrapleural blood from escaping into the chest but to allow continuous drainage of air. The patient remained in bed changing the position every 15 min for 2 h in an attempt to distribute the blood evenly throughout the pleural cavity.

### Doxycycline pleurodesis

Under strict aseptic precautions, 200 mg of 2% lignocaine (after checking sensitivity) was instilled in pleural cavity on affected side to reduce the pain perception. After 15 min, doxycycline 500 mg mixed with 50 ml normal saline solution was instilled through the chest tube slowly. The chest tube was clamped, and the patient remained in bed changing position every 15 min for 2 h in an attempt to distribute the drug evenly throughout the pleural cavity. The standard of care in our institute for pleurodesis was doxycycline pleurodesis. As talc was not used previously in our institute, we wanted to compare a new procedure with an established standard care.

### Statistical tests used for data analysis

Data was entered in MS Excel and analyzed using SPSS version 19.0. Continuous variables such as age and time for closure of air leak were expressed as mean (SD) or median depending upon the normality of distribution. Categorical variables such as gender, the success of the procedure and the presence of complications were expressed as proportion. The success rate and complication rate between the two intervention arms were analyzed using chi-square/Fischer's exact test. Time for closure of air leak was compared between the two groups by Mann Whitney test and a p-value less than 0.05 was considered statistically significant.

### Results

There were 29 males and 9 females, with almost equal distribution in both arms. The mean age of the study population was 47.7 years (range 18-80). The baseline characteristics of the study subjects are mentioned in Table 2. In our study population, the most common cause for SSP was COPD, contributing to more than half of the patients (n=20, 52%). Among them, eighty percent of the patients had emphysema predominance. Malignancy was the 2<sup>nd</sup> most common cause of secondary spontaneous pneumothorax. Interstitial lung diseases (ILD) were seen in 7 (18%) of the patients. Idiopathic pulmonary fibrosis accounted for four, idiopathic non-specific interstitial pneumonia (NSIP) two and connective disease-associated ILD one case. In our study, 2 cases were lymphangiomyomatosis associated with tuberous sclerosis. There was considerable overlap among etiology in our study population.

### Success rate and median time to closure

Post pleurodesis cessation of air leak was observed every 12 h till seven days post procedure. The median time for closure was 24 h [interquartile range (12,24)] for Autologous blood patch pleurodesis and 36 h [interquartile range (24,72)] for doxycycline pleurodesis.

rodesis. The success rate of blood patch pleurodesis and doxycycline pleurodesis was assessed at the end of 7 days and was noted to be 94.7% and 84.2%, respectively. The difference was not statistically significant ( $p=0.6$ ) (Table 3).

## Complication rates

Patients were assessed for complication post pleurodesis till discharge. Fifteen patients of doxycycline pleurodesis group had pain whereas two had pain in autologous blood patch pleurodesis with a  $p$ -value of 0.01 (statistically significant). On visual analogue scale, ABPP had a lesser pain as compared to doxycycline pleurodesis (average visual analogue scale value of 2 versus scale of 7). Eight patients of doxycycline pleurodesis had a fever and in blood patch pleurodesis only one patient had fever ( $p=0.019$ ).

## Recurrence rate

Patients were followed up for a period of 28 days after the closure of air leak (post pleurodesis) to assess for the recurrence of pneumothorax. The recurrence rate was same in both the groups (5%) and  $p=0.7$ . One patient in each arm had a recurrence and they were referred to cardiothoracic surgery for surgical management. The subject in ABPP group had underlying COPD with more than 40-pack years of smoking. He had air leak of grade 1. His air leak resolved within 24 h of ABPP but recurred after 12 days of post pleurodesis.

The subject in doxycycline group was a 38-year-old non-smoker who worked as a cook with exposure to biomass fuel. He had post ICD grade 2 air leak and his air leak resolved more than 72 h post pleurodesis.

## Discussion

Persistent air leak leads to significant morbidity which leads to considerable delay in the removal of ICD tubes. One of the important nonsurgical treatments for an air leak is pleurodesis. In the past, many pleurodesis techniques have been tried but none had proved superior to surgery. Though surgeries have a higher success rate, the complication rates are also higher [2].

Our study population has a male predominance. Studies by Onuki *et al.* and Hobbs *et al.* also had a male predominance.

Smoking is more common in males and there is an increased risk of pneumothorax with male sex and emphysema [13,14]. The mean age of our study population is 47 years which is similar to other studies [8,13].

One of the most important causes of secondary spontaneous pneumothorax is COPD [15]. In our study, 52% of patients had underlying COPD and a majority of them had an emphysematous phenotype. The risk of recurrence of spontaneous pneumothorax secondary to COPD is high and incidence varies from 20-60% [14,15]. Malignancies were the next common cause in our study, of which primary squamous cell carcinoma of the lung was the commonest. Abu Arab and Ramadan had similar findings [16]. In contrast, Grosu *et al.* had a low incidence of malignancies in their study on SSP [17]. However, they included all cases of pneumothorax including iatrogenic pneumothorax and this may be the reason for a smaller number of malignancy cases (114 out of 2532). The incidence of ILD noted in our studies is similar to other studies [18,19].

In our study, we reviewed the patients on the 7<sup>th</sup> day of the procedure for the cessation of air leak. The success rate at 7<sup>th</sup> day in our study was 94.7% in ABPP and 84.2% in doxycycline pleurodesis. However, the difference was not statistically significant ( $p=0.6$ ). Literature review reveals a varying success rate (80-90%) of ABPP. A study by Ozpolat *et al.* found a success rate of 87.5% in 24 patients in the Autologous blood patch group [20]. A study by Chambers *et al.* found that the success rate in the blood patch pleurodesis group is around 91.7% [21]. Cagirici *et al.* [6] demonstrated that the success rate was 84% which is less as compared to our study. A possible reason is that in the former the success was assessed earlier at three days of post pleurodesis as compared to seven days in our study. A comparative result of various studies are given in Table 4.

The median time for closure was 24 h for Autologous blood patch pleurodesis and 36 h in doxycycline pleurodesis in our study. The range of closure of air leak varied between as early as 24 h to 72 h at a maximum. Most of the cases included in our study trial had air leak of grade 1 and 2. Cobanoglu *et al.* showed that 72.7% of patients had cessation of air leak within 12 h of blood injection and 100 % by 48 h [8]. Studies by Dumire *et al.* [3] and de Andrés *et al.* [22], the air leaks were sealed within 24 h of blood injection.

The most common complication following pleurodesis was chest pain soon after the instillation of pleurodising agent. The incidence of pain in ABPP was less as compared to doxycycline group (15% vs 78%). Also on using visual analogue scale (VAS) to assess the intensity of pain, it was less intense in ABPP group (VAS of 2 vs 7). The incidence of pain reported in other studies varied from 19-55% in doxycycline pleurodesis and 1-4% in autologous blood patch pleurodesis [8,10]. The comparatively less pain in other studies following doxycycline pleurodesis is probably related to use of narcotic analgesia and higher dose of intrapleural

**Table 3. Comparative results: doxycycline pleurodesis vs autologous blood patch pleurodesis.**

Outcome parameter	ABPP (n=19)	Doxycycline pleurodesis (n=19)	p-value
Success rate (at 7 days)	18 (94.7%)	16 (84.2%)	0.6
Median time for closure (h, interquartile range)	36 h (24.72)	24 h (12.24)	
Pain	3	14	<0.01
Pain score (VAS average)	2	7	
Fever	2	7	≤0.019
Giddiness and chills	1	1	0.405
Recurrence (28 days)	1	1	

VAS, visual analogue scale.



**Table 4. Brief review of trials using autologous blood patch pleurodesis.**

Series no.	Study	Study type	Sample size (n)	Study population	Comparator arm	Results
1.	Robinson <i>et al.</i> [5] Year: 1987	Observational, single arm	25	Recurrent pneumothorax		21 out of 25 had successful closure
2.	Shackcloth [4] Year: 2006	Randomized control trial	22	Post lobectomy	Tube thoracostomy with ABPP <i>vs</i> tube thoracostomy alone with crossover to ABPP if air leak present beyond 10 days	Median length of air leak in ABPP: 5 days Only thoracostomy: 11 days (p<0.001)
3.	Cagirici <i>et al.</i> [6] Year: 1998	Observational	32	Spontaneous pneumothorax with PAL	None	Air leak cessation in 27 (84%) within 72 h No recurrence up to 2 years Three cases of empyema noted
4.	Martínez-Escobar <i>et al.</i> [7] Year: 2006	Non randomized	27	ARDS with pneumothorax	ABPP <i>vs</i> conventional drain system	Decreased ventilator weaning time in ABPP arm Mortality reduced (3.7% <i>vs</i> 29.6%)
5.	Cobanoğlu <i>et al.</i> [8] Year: 2009	Non randomized, 3 arms	50	Persistent air leak resulting from primary and secondary spontaneous pneumothorax	ABPP, talc and tetracycline pleurodesis	Success rate of ABPP-75.0% Talc: 84.2% Tetracycline: 63.6%
6.	Khan <i>et al.</i> [9] Year: 2017	Randomized control trial	30	Primary spontaneous pneumothorax with PAL	ABPP (16) <i>vs</i> bleomycin (14)	Success rate of ABPP <i>vs</i> bleomycin (100% <i>vs</i> 93.7%) p>0.5 Fever (0% <i>vs</i> 42.9%)

ABPP, autologous blood patch pleurodesis; PAL, persistent air leak; ARDS, acute respiratory distress syndrome.

lignocaine of more than 250 mg [10,22]. We have used 200mg of lignocaine. Fever was the second common complication in our study which was significantly high in doxycycline arm (38%) than in ABPP arm (10%). In several studies incidence of fever was 0-22% in doxycycline pleurodesis whereas 1-4% in autologous blood patch pleurodesis [10,21,22] Few of our patients had mild fever on presentation and this may be the cause for increased incidence of fever post pleurodesis. Other complications like chills, giddiness, syncopal attacks were similar in both groups and at par with other studies [21].

We followed up patients post pleurodesis for 28 days to look for recurrence. Two patients had recurrence, 1 in each group (5%). A review noted a varying recurrence rate of 4-29% [23]. However, many studies had a varying follow-up period ranging from 17 to 132 months which may explain the higher recurrence rate as compared to our study.

We did not notice any case of post blood patch pleurodesis developing empyema in contrast to other studies [6,24]. One possible reason is that we have excluded cases of active infection prior to ABPP.

## Limitations

- This was a single-center, tertiary hospital-based study done in a particular geographic location in India, so the results may not be generalized to all.
- Air leak was assessed by manual technique which is inherently more prone to interobserver variations.

- Cases with active infection were excluded. One of the common causes for the secondary spontaneous pneumothorax is pneumonia, which has been excluded in the study.

## Conclusions

ABPP has a better success rate in closure of air leak than doxycycline pleurodesis though the difference is not statistically significant. Also the recurrence rate is equal in both ABPP and doxycycline pleurodesis. However, ABPP has a better patient tolerability and early closure of air leak. ABPP can be tried as an alternative to doxycycline pleurodesis, however large comparison trials are recommended to establish the same.

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