

# Comparison of the efficacy of novel two covering methods for spontaneous pneumothorax: a multi-institutional study

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## ABSTRACT

**Objectives** The postoperative recurrence rate after thoracoscopic bullectomy for primary spontaneous pneumothorax (PSP) is not satisfactory. This retrospective study was conducted to elucidate an effective technique for improving the postoperative recurrence rate.

**Methods** The present study included 373 patients who underwent thoracoscopic bullectomy for PSP at three hospitals from January 2013 to May 2020. We compared the recurrence rate according to two methods that were used to cover the staple line after thoracoscopic bullectomy. Group A (146 patients) was treated with an absorbable polyglycolic acid (PGA) sheet plus fibrin glue and oxidised regenerated cellulose (ORC). Group B (227 patients) was treated with ORC alone.

**Results** There was no significant difference in preoperative characteristics of the patients. The postoperative recurrence rate of pneumothorax was 3.4% (5/146) in Group A and 17.2% (39/227) in Group B, respectively. Among 23 patients (Group A, n=3 and Group B, n=20) who received reoperation for recurrent pneumothorax, the site of recurrence was around the stapler line of the first operation in 1 of 5 (20%) patients in Group A and 28 of 39 (71.8%) patients in Group B. The 1-year recurrence-free rate was 97.4% (median follow-up period, 73 days (range, 2–3952 days)) in Group A and 80.9% (median follow-up period, 71 days (range 2–2648 days)) in Group B.

**Conclusions** Coverage with a PGA sheet may prevent the postoperative recurrence of PSP. A large-scale prospective randomised study should be conducted to clarify the most effective treatment for PSP.

## INTRODUCTION

Postoperative recurrence is a major source of concern for patients undergoing thoracoscopic bullectomy for primary spontaneous pneumothorax (PSP). In order to reduce recurrence after thoracoscopic bullectomy, many thoracic surgeons have tried to establish additional treatments, including partial pleurectomy, chemical pleurodesis, pleural abrasion and coverage with a surgical sealant.

## Key messages

### What is already known on this topic

- ▶ The most effective procedure for reducing postoperative recurrence after thoracoscopic bullectomy for primary spontaneous pneumothorax has not yet been established.

### What this study adds

- ▶ Coverage with a polyglycolic acid (PGA) sheet was a useful method for reducing postoperative recurrence after thoracoscopic bullectomy for primary spontaneous pneumothorax.

### How this study might affect research, practice and/or policy

- ▶ Some studies have reported that the use of a PGA sheet can reduce the postoperative recurrence rate, while others have reported that the use of PGA sheets was associated with serious adhesion. Combined treatment with a PGA sheet plus fibrin glue and an oxidised regenerated cellulose sheet may reduce recurrence and prevent pleural adhesion.

A prospective randomised, large-scale multi-centre and long-term follow-up study has only recently confirmed that visceral coverage was not inferior to mechanical pleurodesis in terms of postoperative recurrence.<sup>1</sup> However, the most effective procedure has not yet been established.

Since the first report on the successful application of coverage with a polyglycolic acid (PGA) sheet in the treatment of air leak in high-risk patients with secondary pneumothorax by Mukaida *et al*,<sup>2</sup> several investigators have reported that coverage with a PGA sheet along the staple line was associated with decreased postoperative recurrence after thoracoscopic bullectomy.<sup>1 3–6</sup> It is considered that PGA-induced adhesion was associated with decreased postoperative recurrence because several animal studies demonstrated



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that the use of PGA sheets was associated with an inflammatory reaction and subsequently induced the formation of adhesion.<sup>7–9</sup> However, coverage with a PGA sheet does not completely prevent postoperative recurrence and there is even a risk that the PGA-induced adhesion will interfere with reoperation for recurrent pneumothorax. To improve this problem, it is considered that additional treatments with an absorbable oxidised regenerated cellulose (ORC) sheet may reduce the risk in reoperation for recurrent pneumothorax because absorbable ORC sheets were reported to be effective for preventing postoperative adhesion in an animal study.<sup>5</sup>

To clarify the efficacy of the application of a PGA sheet plus fibrin glue, which has attracted attention in recent years, combined coverage of the staple line with a PGA sheet plus fibrin glue and an ORC sheet was compared with coverage with an ORC sheet alone in patients who underwent thoracoscopic bullectomy for PSP.

## PATIENTS AND METHODS

### Patient and public involvement

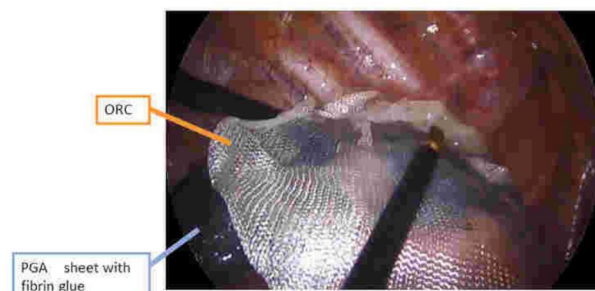
Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

### Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients who underwent bullectomy with covering sheets for spontaneous pneumothorax at three hospitals from January 2013 to May 2020 and (2) patients aged 14–30 years at the time of surgery. The exclusion criteria were as follows: (1) patients who had underlying pulmonary diseases, such as pulmonary infections, emphysema or Marfan's syndrome; (2) patients with a history of ipsilateral thoracic surgery, including pneumothorax; (3) patients who received ipsilateral mechanical or chemical pleurodesis. This study was approved by the Institutional Review Board of Nagoya City University Hospital (IRB number: 60-20-0062), Kariya Toyota General Hospital (IRB number: 617) and Suzuka General Hospital (IRB number: 268). Each patient gave their written informed consent for the use of their clinical data in this study.

### Surgical procedure

The procedures were performed under general anaesthesia with one-lung ventilation with the patient positioned in the lateral decubitus position. A three-port thoracoscopic technique was used. Bullae or blebs were excised using a linear endoscopic stapler. Group A patients underwent a procedure to widely cover the staple line with a PGA sheet (Neoveil, 10×5 cm; Gunze, Japan) plus fibrin glue and the lesion was then covered with an ORC (SURGICEL Absorbable Hemostat, 5.1×7.6 cm; Ethicon, USA) sheet (figure 1). Group B patients underwent a procedure to widely cover the staple line with an ORC



**Figure 1** Intraoperative findings. The staple line was covered with ORC and a PGA sheet with fibrin glue. ORC, oxidised regenerated cellulose; PGA, polyglycolic acid.

sheet. The decision to timing of surgery and choosing the material for coverage was dependent on each surgeon.

### Postoperative management

Negative suction (–5 cm H<sub>2</sub>O) was applied immediately after the operation and maintained until chest tube removal. The chest tube was removed without any air leakage or postoperative bleeding.

### Data collection and follow-up method

We analysed the clinical data on patient characteristics, operative details and postoperative outcomes. Complete follow-up data were obtained from the records of post-discharge visits and regular radiographic follow-up assessments. Most patients were followed up at 1 week and 1 month after discharge with chest X-ray and underwent long-term follow-up (2–3952 days). The recurrence was evaluated by chest X-ray and CT at the time of regular visit and at the time of symptom. The decision of the reoperation was decided by each surgeon and the patient's wishes.

### Statistical analysis

Fisher's exact test was used to compare the nominal variables between groups A and B. The Mann-Whitney U test was used to compare continuous variables. Recurrence-free rates after thoracoscopic bullectomy were calculated by the Kaplan-Meier method, and the log-rank test was used to assess the significance of differences between groups. Two-sided p values of <0.05 were considered to indicate statistical significance. All data were analysed using the EZR software programme.<sup>10</sup>

## RESULTS

A total of 373 patients underwent primary thoracoscopic bullectomy with covering sheets for PSP at three hospitals from January 2013 to May 2020. Coverage of the staple line after thoracoscopic bullectomy with an absorbable PGA sheet plus fibrin glue and an ORC sheet was performed for 146 patients (Group A). Coverage of the staple line after thoracoscopic bullectomy with an ORC

**Table 1** Demographic data

Variable	All (n=373)	Group A (n=146)	Group B (n=227)	P value
Age (years)				
Median (range)	20 (14–30)	19 (14–30)	20 (14–30)	0.15
Sex				
Male	344 (92.2%)	136 (93.1%)	208 (91.6%)	0.59
Female	29 (7.7%)	10 (6.9%)	19 (8.4%)	
Smoking				
Yes	37 (9.9%)	17 (11.6%)	20 (8.8%)	0.37
No	336 (90.1%)	129 (88.4%)	207 (91.2%)	
Affected side				
Right	153 (41.0%)	63 (43.2%)	90 (39.6%)	0.5
Left	220 (59.0%)	83 (56.8%)	137 (60.4%)	

sheet was performed for 227 patients (Group B). [Table 1](#) summarises the clinical characteristics of the patients in groups A and B. No significant differences were found in age, sex, smoking history or the affected side of the lung. There was no operative mortality or morbidity in either group.

In Group A, five patients (3.4%) had postoperative recurrent pneumothorax, three of whom underwent a secondary operation. There was no adhesion between the pleural layers in the three patients of Group A ([figure 2A and B](#)). In Group B, 39 patients (17.2%) had a postoperative recurrent pneumothorax. Twenty of the 39 patients underwent a secondary operation for the treatment of recurrent pneumothorax. There were 12 patients with mild adhesion between the pleural layers among the 20 patients of Group B who received a secondary operation. The rate of recurrence around the staple line (28/39, 71.8%) in Group B was higher than that (1/5, 20%) in Group A. Other recurrence site was two patients at segment 1+2 and a patient at segment 6 in Group A and three patients at segment 6 in Group B. Radiologically and surgically, no recurrence site could be found in several patients (Group A, n=2 and Group B, n=21). There was no difference in the median time to recurrence between

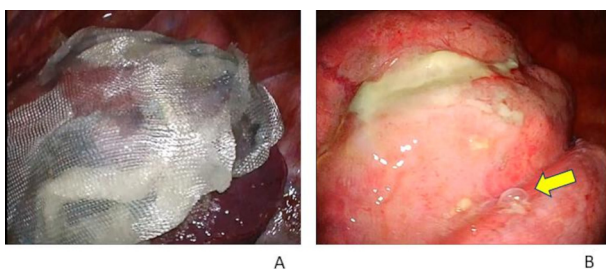
the two groups (Group A, 422 days; Group B, 364 days; [table 2](#)).

The recurrence-free curves for each group are shown in [figure 3](#). After a median follow-up period of 72 days (range: Group A, 2–3952 days; Group B, 2–2648 days), the 1-year recurrence-free rates in Groups A and B were 97.4% and 80.9%, respectively ( $p < 0.01$ ).

## DISCUSSION

In the past, bullectomy through a thoracotomy approach was the gold standard for surgical treatment of PSP. Since bullectomy through a thoracoscopic approach for the surgical treatment of PSP was first reported in 1990,<sup>11</sup> video-assisted thoracoscopic surgery has become widespread as a less-invasive procedure for PSP. However, thoracoscopic bullectomy without additional procedures is associated with a higher postoperative recurrence rate of pneumothorax in comparison to open thoracotomy. One of the mechanisms of recurrence after thoracoscopic bullectomy has been reported to be the formation of new bullae around the staple line. Additionally, incomplete resection of bullae or emphysematous changes around the staple line was found to be a risk factor for postoperative air leak.<sup>3, 12</sup> Therefore, a procedure to cover the staple line, which reinforces the visceral pleura, seems to be a reasonable approach to prevent postoperative air leaks and the recurrence of pneumothorax.

PGA sheet was introduced in the early 1970s as a new suture material and has been combined with other biodegradable polymers for use in various medical fields.<sup>13</sup> The advantages of PGA are significant, namely, it is non-toxic, biocompatible and absorbable. Some surgeons think that PGA can reduce the postoperative recurrence rate of pneumothorax. PGA sheet has been reported to thicken the visceral pleura during absorption and to promote adhesion.<sup>8</sup> Furthermore, PGA sheet can reduce the rate of postoperative pulmonary fistula in the pleura and can avoid new bullous formation and inhibit the rupture of new bullae.<sup>1</sup> PGA metabolised into water and carbon



**Figure 2** The image (A) shows the findings from the first operation and the image (B) shows the findings from the second operation because of recurrent pneumothorax in Group A. The new bulla is observed at the apex of S6 (arrow).

**Table 2** Postoperative recurrence

Variable	All (n=373)	Group A (n=146)	Group B (n=227)	P value
Postoperative recurrence	44 (11.8%)	5 (3.4%)	39 (17.2%)	<0.01
Treatment of recurrence				
Observation	15 (34.1%)	0	15 (38.4%)	0.09
Chest tube management	6 (13.6%)	2 (40.0%)	4 (10.3%)	0.07
Reoperation	23 (52.3%)	3 (60.0%)	20 (51.3%)	1.00
Site of recurrence				
Prestaple line	29 (65.9%)	1 (20.0%)	28 (71.8%)	0.01
Other (S1+2, S6)	6 (13.6%)	3 (60.0%)	3 (17.7%)	<0.01
Unknown	9 (20.5%)	1 (20.0%)	8 (20.5%)	0.66
Time to recurrence (day)				
Median (range)	376 (8–1762)	422 (26–750)	364 (8–1762)	0.77

S, segment

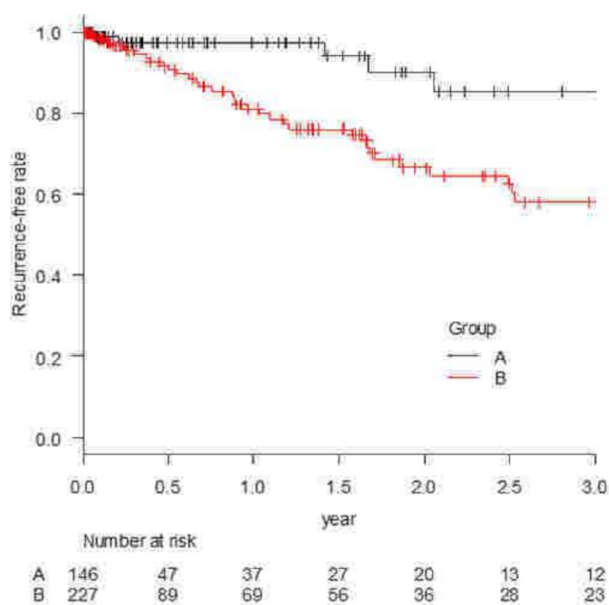
dioxide in 15 weeks according to the package insert. The application of a PGA sheet with fibrin glue after bullectomy for PSP was efficacious in reducing recurrence.<sup>6</sup> However, serious adhesion potentially makes second surgery difficult in reoperation for recurrent pneumothorax.

Since Kurihara *et al* reported that postoperative recurrence was reduced by the application of an ORC sheet with fibrin glue to the staple line,<sup>7</sup> we also started to use ORC sheets to cover the staple line. However, the reduction of postoperative recurrence was not as great as we expected. Because an animal study revealed that covering tissue with an ORC sheet prevents long-term foreign body reactions and adhesion at the surgical site,<sup>5</sup> we have continued to use ORC sheets to prevent serious pleural adhesion in order to reduce the risks of reoperation for recurrent pneumothorax. We rub fibrin

glue in PGA sheet and cover PGA sheet widely by ORC to prevent adhering the chest wall. ORC absorbed within 15 days in the body according to the package insert. Both PGA and ORC trigger inflammation due to acidification, while PGA causes more severe and a longer period of inflammatory reaction. Histologically, ORC has significantly fewer neovascularisation and sparse thickening with no difference in pleural thickness, which is thought to have a mild inflammation compared with PGA. ORC absorbed faster than PGA; however, we think that coating a PGA sheet with fibrin glue and ORC could suppress the impact of inflammation on the thoracic wall for several days during acute period.

The postoperative recurrence rate of pneumothorax was significantly lower in Group A. This indicates that staple line coverage with a PGA sheet plus fibrin glue is a useful method for reducing the postoperative recurrence of PSP without any additional postoperative morbidity. Moreover, the rate of recurrence around staple line was lower in Group A than in Group B. This might be because the presence of the PGA sheet prevents the formation of new bullae and inhibits the rupture of new bullae, probably due to the thickening of the pleura. Although PGA sheets potentially cause serious adhesion to the parietal pleura, there was no adhesion between the visceral and parietal pleurae in a recurrent case treated with a PGA sheet plus fibrin glue and an ORC sheet. In these cases, coverage with ORC sheets was considered to prevent pleural adhesion, as previously described. A study with a group in which coverage is applied with PGA sheets alone may be needed to elucidate the effect of PGA sheets.

On the other hand, the cost of PGA sheet plus fibrin glue is high (approximately US\$500). However, the total cost for the treatment of PSP in the follow-up period, including the cost for the treatment of postoperative recurrent pneumothorax, may not be significantly different. Considering the burden on the patient at the time of recurrence and the cost of treatment associated



**Figure 3** The rate of recurrence-free after bullectomy in each group.

with readmission, it is considered to be an acceptable cost.

The present study is associated with several limitations. First, this was a retrospective study, and it is difficult to accurately grasp the presence or absence of recurrence in all cases. Second, there were biases in the surgical methods (including covering methods) in each of the three institutions, and the methods of postoperative follow-up were different. Including our novel two covering methods, it may be useful for planning a large-scale prospective randomised study to clarify the most effective treatment for PSP.

In conclusion, staple line coverage with PGA sheet plus fibrin glue and ORC was a useful method for reducing the postoperative recurrence rate of PSP compared with coverage with ORC sheet alone.

**Contributors** RO, KO and RN designed the study. RO, TY, HY, IF, OK, TM, TT and KY analysed qualitative data. RO and KO produced the first draft to which all authors contributed. All authors have reviewed and approved the final version. KO is the guarantor of the study.

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**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** Consent obtained directly from patient(s)

**Ethics approval** This study was approved by the Institutional Review Board of Nagoya City University Hospital (IRB number: 60-20-0062), Kariya Toyota General Hospital (IRB number: 617) and Suzuka General Hospital (IRB number: 268). Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data are available on reasonable request.

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