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

Risa Oda,1 Katsuhiro Okuda,1 Takeshi Yamada,2 Haruhiro Yukiue,2 Ichiro Fukai,3 Osamu Kawano,3 Takuya Matsui,1 Tsutomu Tatematsu,1 Keisuke Yokota,1 Ryoichi Nakanishi1

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 staple 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. A prospective randomised, large-scale multicentre and long-term follow-up study has only recently confirmed that visceral coverage was not inferior to mechanical pleurodesis in terms of postoperative recurrence.1 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.,2 several investigators have reported that coverage with a PGA sheet along the staple line was associated with decreased postoperative recurrence after thoracoscopic bullectomy.1 3–6 It is considered that PGA-induced adhesion was associated with decreased postoperative recurrence because several animal studies demonstrated...
that the use of PGA sheets was associated with an inflammatory reaction and subsequently induced the formation of adhesion.\(^7\)\(^9\) 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.\(^8\)

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: 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 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\(_2\)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.\(^10\)

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%)|         |

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 1990,11 video-assisted thoracoscopic surgery has become widespread as 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.3 12 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.13 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.8 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.1 PGA metabolised into water and carbon.
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. 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, 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, 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

| 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

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.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

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 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.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD Ryoichi Nakanishi http://orcid.org/0000-0003-2259-5941

REFERENCES

1. Mao Y, Zhang Z, Zeng W, et al. A clinical study of efficacy of polyglycolic acid patch in surgery for pneumothorax: a systematic review and meta-analysis. J Cardiothorac Surg 2020;15:117.

2. Mukaida T, Andou A, Date H, et al. Thoracoscopic operation for secondary pneumothorax under local and epidural anesthesia in high-risk patients. Ann Thorac Surg 1998;65:924–6.

3. Lee S, Park SY, Bae MK, et al. Efficacy of polyglycolic acid sheet after thoracoscopic bullectomy for spontaneous pneumothorax. Ann Thorac Surg 2013;95:1919–23.

4. Lee S, Kim HR, Cho S, et al. Staple line coverage after bullectomy for primary spontaneous pneumothorax: a randomized trial. Ann Thorac Surg 2014;98:2005–11.

5. Bicer M, Bayram AS, Gurbuz O, et al. Assessment of the efficacy of bio-absorbable oxidized regenerated cellulose for prevention of post-operative pericardial adhesion in the rabbit model. J Int Med Res 2008;36:1311–8.

6. Kim KS. Polyglycolic acid sheet with fibrin glue technique without pleural abrasion in uniportal VATS for primary spontaneous pneumothorax. J Thorac Dis 2020;12:690–5.

7. Kurihara M, Takeno Y. Thoracoscopic surgery for pneumothorax and its recurrence after thoracoscopic surgery. Asian J Surg 1999;22:9–14.

8. Nakamura T, Shimizu Y, Watanabe S, et al. New bioabsorbable pledge and non-woven fabrics made from polyglycolide (PGA) for pulmonary surgery: clinical experience. Thorac Cardiovasc Surg 1990;38:81–5.

9. Hong KP, Kim DK, Kang KH. Staple line coverage with a polyglycolic acid patch and fibrin glue without pleural abrasion after thoracoscopic Bullectomy for primary spontaneous pneumothorax. Korean J Thorac Cardiovasc Surg 2016;49:85–91.

10. Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant 2013;48:452–8.

11. Levi JF, Kleinnmann P, Riquet M, et al. Percutaneous parietal pleurectomy for recurrent spontaneous pneumothorax. Lancet 1990;336:1577–8.

12. Sakamoto K, Takei H, Nishii T, et al. Staple line coverage with absorbable mesh after thoracoscopic bullectomy for spontaneous pneumothorax. Surg Endosc 2004;18:478–81.

13. Kawai N, Kawaguchi T, Suzuki S, et al. Low-Voltage coagulation, polyglycolic acid sheets, and fibrin glue to control air leaks in lung surgery. Gen Thorac Cardiovasc Surg 2017;65:705–9.