



Feasibility of application of an absorbable topical collagen hemostat sheet (INTEGRAN®) for prevention of postoperative recurrence of pneumothorax in youths

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Background: Staple-line coverage is an effective method for prevention of postoperative recurrence of pneumothorax. However, the recurrence rate in young patients is still unsatisfactory using this method. Moreover, there is no consensus about the optimal material for use in this technique. To explore new material for this technique, we conducted this study to evaluate the safety of an absorbable topical collagen hemostat (INTEGRAN®) for staple-line coverage in pneumothorax surgery in young patients.

Methods: A single-arm prospective interventional study was performed in 25 patients (age <25 years old) with primary spontaneous pneumothorax (PSP) who underwent wedge resection with staple-line coverage with INTEGRAN® between 2017 and 2020. The rate of material-related adverse events (defined as a body temperature ≥ 38 °C continuing for ≥ 2 days, postoperative WBC $>18,000/\text{mm}^3$ and/or CRP >15 mg/dL, or acute empyema within 30 postoperative days) was defined as the primary endpoint. The 1-year postoperative rates of recurrence and of new bullae around the staple-line were also measured.

Results: The median age was 19 years old. None of the patients had a body temperature ≥ 38 °C continuing for ≥ 2 days, extra-abnormal examination data, and acute empyema findings. At 1-year postoperatively, the recurrence rate was 12.0%, and the rate of new bullae around the staple-line was 16.7%.

Conclusions: This study showed the safety of use of INTEGRAN® for staple-line coverage in pneumothorax surgery in young adults. The short-term recurrence rate was acceptable given the high-risk cohort examined in the study. A prospective randomized controlled study is needed for evaluation of the efficacy of INTEGRAN® for prevention of recurrence of PSP.

Trial Registration: UMIN000026530 at UMIN Clinical Trials Registry.

Keywords: Pneumothorax; primary spontaneous pneumothorax (PSP); postoperative recurrence; staple line coverage

Submitted Feb 12, 2021. Accepted for publication May 20, 2021.

doi: 10.21037/jtd-21-274

View this article at: <https://dx.doi.org/10.21037/jtd-21-274>

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Introduction

Primary spontaneous pneumothorax (PSP) is a common thoracic disease. It is not a life-threatening, but is a concern because of its high recurrence rate, which is approximately 50% after conservative therapy (1). Almost all patients with recurrent PSP need surgical intervention. However, wedge resection alone using video-assisted thoracic surgery (VATS) is associated with a high postoperative recurrence rate of 10–20% (2–4).

Due to these problems, several additional procedures are used in surgery to minimize postoperative recurrence. In Western countries, parietal pleural abrasion and pleurectomy are often used, with the intent to create adhesion of the chest wall with the lung surface and consequently prevent recurrence. However, pleural adhesion has disadvantages of reducing respiratory function and potentially interfering with future ipsilateral surgery. To address this disadvantage, staple-line coverage has been introduced, with the goal of thickening the visceral pleura and consequently preventing recurrence (5). Two materials, polyglycolic acid (PGA) and oxidized regenerated cellulose (ORC) sheets, are currently used, but both have disadvantages. A PGA sheet induces strong adhesion between the chest wall and lung surface, similarly to procedures for the parietal pleura (6,7). In contrast, an ORC sheet does not induce chest wall adhesion, but is associated with a much higher recurrence rate of 20% (8).

Recently, the efficacy of an absorbable topical collagen hemostat sheet (INTEGRAN[®], Nippon Zoki Pharmaceutical Co., Ltd., Osaka, Japan) has been shown for prevention of air leak after lobectomy for primary lung cancer (9). In addition, no intrathoracic adhesion was observed in a patient who received a second surgery after lobectomy with use of INTEGRAN[®] (10). These features suggest that INTEGRAN[®] may be an ideal clinical material for staple-line coverage in PSP surgery, especially for young adults. However, there is no report of use of INTEGRAN[®] in PSP surgery to date. In addition, all INTEGRAN[®] is left in the thoracic cavity when used in the coverage technique, whereas most is removed intraoperatively when used as a topical hemostat. Therefore, we conducted this study to evaluate the safety of this material for staple-line coverage in young adults with PSP.

We present the following article in accordance with the TREND reporting checklist (available at <https://dx.doi.org/10.21037/jtd-21-274>).

Methods

Study design

The single-arm prospective intervention study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Kanto Rosai Hospital on February 9, 2017 (No. 2016-19) and informed consent was taken from all the patients. Accumulation of case was started on April 1, 2017. The inclusion criteria were patients aged 16–25 years old with a surgical indication for PSP [high-risk patients for postoperative recurrence according to Sudduth *et al.* (11)], who underwent bullae resection with a surgical stapling device at Kanto Rosai Hospital, had no abnormal data in preoperative blood tests, and had an Eastern Cooperative Oncology Group performance status of 0 or 1. The exclusion criteria were secondary spontaneous pneumothorax (e.g., catamenial pneumothorax), synchronous bilateral pneumothorax, hemothorax >1,000 mL in the chest cavity or a shock vital sign (systolic blood pressure <80 mmHg and HR >100/min), history of ipsilateral thoracic surgery, hypersensitivity to bovine-derived products (e.g., insulin), and pregnancy. Written informed consent was obtained before surgery and the patient was temporarily registered. Actual registration was performed intraoperatively after confirmation of all criteria (Figure 1).

The primary endpoint of the rate of material-related adverse events (AEs) was defined as fever ≥ 38 °C continuing for ≥ 2 days; WBC $>18,000/\text{mm}^3$ and/or CRP >15 mg/dL postoperatively; or acute empyema within 30 postoperative days. To distinguish an abnormal inflammatory reaction to INTEGRAN from a normal postoperative reaction, we used relatively high cut-off values for WBC and CRP. The study protocol is registered in the UMIN Clinical Trials Registry (UMIN000026530).

Surgical procedure (protocol treatment) and follow-up

All procedures were performed by thoracic surgeons (H.A or H.K or A.K) at Kanto Rosai Hospital using a 2-port VATS approach (a 2.5-cm working window on the 3rd or 4th intercostal anterior axillary line and a 0.7-cm scope-insertion port on the 5th or 6th intercostal middle axillary line) under general anesthesia with double-lumen endotracheal tube intubation. After thorough observation of the entire visceral pleural surface, a leak test was conducted at an airway pressure of 20 cmH₂O

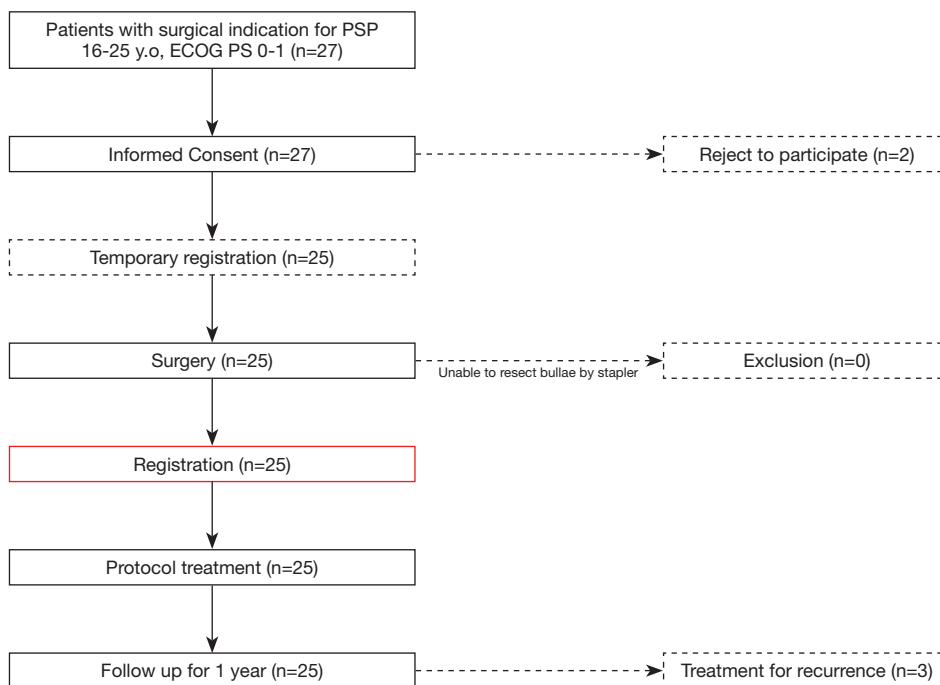


Figure 1 Scheme of this single-arm prospective intervention study. y.o, years old; ECOG, Eastern Cooperative Oncology Group.

to check for air leak. Then, bullae were resected using a surgical stapling device (Endo GIA Universal, Medtronic, Minneapolis, MN, USA or Powered ECHELON FLEX, Johnson & Johnson, New Brunswick, NJ, USA). After resection, a sealing test was performed at an airway pressure of 20 cmH₂O to confirm no air leak from the resected site. Then, both edges of the staple-line were ligated with a pre-tied loop ligature (ENDOLOOP, Johnson & Johnson). An INTEGRAN[®] sheet (0.2 g in weight and 10.0 cm × 5.0 cm in size) was then placed on the staple-line through the guide of the ENDOLOOP for both edges, and knotted with the ENDOLOOP to fix the INTEGRAN[®] sheet (Figure 2). Surgery was finished with insertion of a chest tube. This tube was removed when air leak was absent after postoperative day (POD) 1 and patients was discharged on the day after removal of the chest tube. Preventive administration of antibiotics was only performed at the start of surgery and no additional antibiotics were administered.

Patients were followed as outpatients for at least for 1 year after surgery. Chest X-ray was performed routinely just after surgery, on POD 1, on the day after chest tube removal, on POD 14, after postoperative month (POM) 1 and 6, and when recurrence was suspected. Blood tests were performed on POD 1 and 14 and in POM 1, 6,

and 12. Computed tomography (CT) with a lung field setting (window level -550 HU, window width 1,600 HU) and 1-mm slice thickness was performed in POM 12 to evaluate the formation of new bullae around the staple-line, which Choi *et al.* found to be a significant risk factor for recurrence (12). CT was also performed when postoperative recurrence was suspected.

Sample size and statistical analysis

Drug information for INTEGRAN[®] indicates that AEs (mainly fever and inflammatory reactions) occur in 2.5% of patients if INTEGRAN[®] is used as an absorbable topical hemostat. When used as a topical hemostat, most INTEGRAN[®] is removed intraoperatively after confirmation of hemostasis. However, all INTEGRAN[®] remains in the thoracic cavity when used for staple-line coverage. Thus, we estimated a threshold rate of material-related AEs of 20% and an expected rate of 4%. With 80% power and an alpha value of 0.05 (one-sided), the required sample size was calculated to be 23 patients using a binomial test. In anticipation of some censored cases, 25 patients were enrolled in the study.

The postoperative recurrence-free period was defined

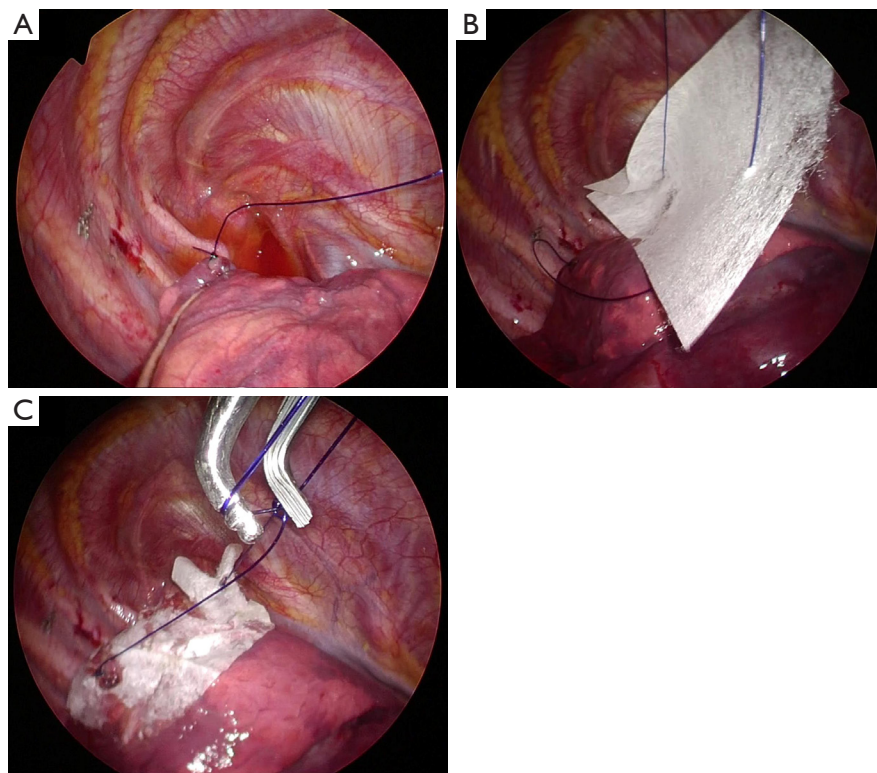


Figure 2 Surgical procedure for coverage of the staple-line with INTEGRAN®. (A) Ligate both edges of the staple-line with ENDOLOOP. (B) Place INTEGRAN sheet on the staple-line through the guide of the ENDOLOOP of both edges. (C) Knot both ENDOLOOP to fix the INTEGRAN sheet.

as the period between the date of surgery and the date of recurrence confirmed by chest X-ray or CT, or the date of the last outpatient follow-up. A recurrence-free survival curve was estimated using the Kaplan-Meier method. All statistical analyses were performed with IBM SPSS statistics 26 (IBM Corp., New York, NY, USA).

Results

Participant flow was shown in *Figure 1*. The 25 subjects (21 men and 4 women) had a median age of 19 years old (range, 16 to 25 years old). The surgical indication for PSP was prolonged air leak (n=10), recurrence after conservative therapy (n=10), metachronous bilateral pneumothorax (n=2), and patient request (n=3). Cessation of the air leak was monitored for about 1 week after chest tube insertion in patients with PSP for the first time. Surgery was performed if the air leak continued beyond one week. The characteristics of the patients and operative data are shown in *Table 1*. In almost all patients, the resected bulla was in

one region only, and only one INTEGRAN® sheet was used in staple-line covering.

Regarding postoperative body temperatures (*Figure 3*), two patients had fever ≥ 38 °C: one had fever ≥ 38 °C on POD 1, but this decreased to < 38 °C on the next day, while the other patient had fever ≥ 38 °C only on POD 2. In postoperative blood tests (*Figures 4, 5*), the maximum WBC and CRP levels were $17,900/\text{mm}^3$ and 5.58 mg/dL, respectively, and no patients had abnormal WBC ($> 18,000/\text{mm}^3$) or CRP (> 15 mg/dL) in POM 1. Acute empyema did not occur in any patients. Thus, the overall rate of material-related AEs was 0/25 (0.0%) in this study.

Postoperative outcomes are shown in *Table 2*. The median follow-up period after surgery was 367 days (range, 202 to 555 days). One patient was lost follow-up at POM 6 and was regarded as censored in the Kaplan-Meier method. There was recurrence of PSP in 3 patients, of whom one underwent a second surgery two months after the first surgery. The recurrence-free survival curve showed a 1-year recurrence-free rate of 88.0% postoperatively. In

Table 1 Characteristics of patients and surgical data

Characteristics	Value
Age (year; median)	19 [16–25]
Gender	
Male	21
Female	4
Surgical indication	
Prolonged air leakage	10
Recurrence after conservative therapy	10
Metachronous bilateral pneumothorax	2
Patient request	3
Preoperative chest drainage	
None	6
Done	19
Laterality	
Right	9
Left	16
Brinkmann Index	
0	20
≤50	3
>50	2
ECOG PS	
0	25
1	0
Used staple cartridge (n; median)	2 [1–6]
Location of responsible bulla [†]	
Apex	24
S6	2
Mediastinal side	1
Used INTEGRAN (n; median)	1 [1–2]

[†], includes overlapping locations. ECOG PS, Performance status defined by Eastern Cooperative Oncology Group.

reoperation, only mild adhesion between the lung surface and chest wall was present, and this was dissected easily by a 2-port VATS approach. Also, the responsible bulla was not around the staple-line of the first surgery, but at the top of the S6 segment in this case. New bullae had

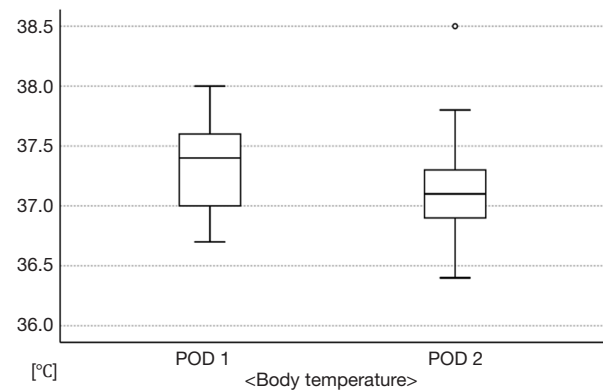


Figure 3 Box plot of body temperatures on POD 1 and POD 2. One patients had fever of ≥ 38 °C on POD 1, but had a decrease to <38 °C on the next day. The other patient had a temperature ≥ 38 °C only on POD 2. POD, postoperative day.

developed around the staple-line in 4 of 24 patients (16.7%) on CT performed in POM 12. However, all 3 patients with postoperative recurrence had no bullae around the staple-line in this CT examination.

Discussion

PSP is not life threatening, but it is problematic because of its high recurrence rate (1), which is over 25% in young patients even after surgical treatment (13). Upon PSP recurrence, patients have to restrict their social activity due to the symptoms and the need for further treatment. This is a particular concern because PSP occurs more frequently in young adults, whose quality of life may be particularly affected by this loss of social activity. Therefore, prevention of recurrence is very important in treatment of PSP, especially for young patients.

Procedures such as parietal pleural abrasion and pleurectomy have been developed to minimize postoperative recurrence of PSP. In a meta-analysis, Sudduth *et al.* showed that wedge resection + chemical pleurodesis ± pleural abrasion was the most suitable procedure, with a recurrence rate of 1.7–2.8% (11). Thus, additional intraoperative procedures for the parietal pleura that promote adhesion between the chest wall and lung surface and consequently prevent recurrence are well accepted in Western countries and recommended by some guidelines (14,15). However, pleural adhesion reduces respiratory function and may interfere with future ipsilateral thoracic surgery, which is

Table 2 Postoperative outcomes of patients

Outcome	Value
Postoperative drainage (days; median)	1 (1–7)
Postoperative hospitalization (days; median)	2 (2–8)
Follow-up period after surgery (days; median)	367 (202–555)
Occurrence of acute empyema	
None	25
Present	0
Postoperative recurrence	
None	22
Present	3
Underwent 2nd surgery	1
Conservative treatment	2
Newly occurred bullae around staple-line at POM 12	
None	20
Present	4
Unknown [†]	1

[†], lost in postoperative follow-up and not examined by CT. POM, postoperative month.

a particular concern in young patients who may eventually require a second surgery for PSP or for lung cancer.

To avoid these problems, staple-line coverage was first reported by Sakamoto *et al.* in 2004 as a procedure to thicken the visceral pleura and prevent new occurrence of bullae around the staple-line in wedge resection. The recurrence rate after staple-line coverage by a PGA sheet was 2.6%, compared to 9.5% after wedge resection only, and a pathologically proven grossly thickened visceral pleura with fibrosis was present in the PGA-covered area, which may prevent occurrence of new bullae around the staple-line (16). Subsequently, Lee *et al.* showed that staple-line coverage was non-inferior to mechanical pleurodesis and superior to intraoperative pleural abrasion in terms of postoperative recurrence (17,18). However, there is strong adhesion between the lung surface covered with PGA and the chest wall, a similar disadvantage to procedures for the parietal pleura (6,7).

An ORC sheet for staple-line coverage is used mainly in Japan, and this sheet thickens the visceral pleura with minimal or no chest wall adhesion (19). However, Ozawa *et al.* found that patients with an ORC covering had a much higher recurrence rate than patients with PGA

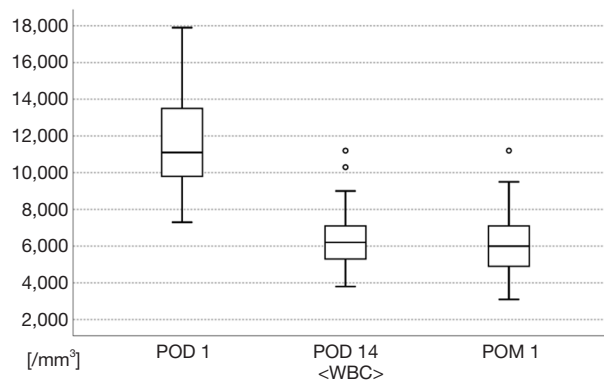


Figure 4 Box plot of postoperative WBC. No patients had WBC >18,000/mm³ on POD 1 or POD 14, or in POM 1. POD, postoperative day; POM, postoperative month.

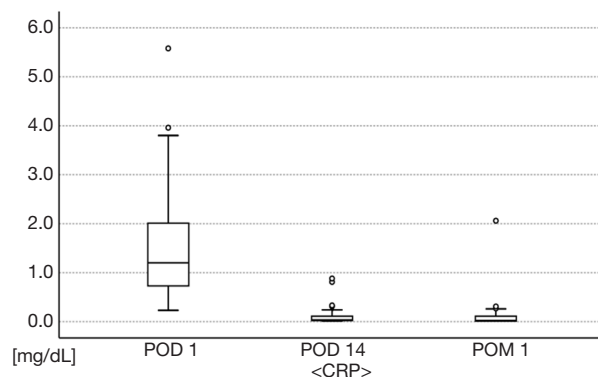


Figure 5 Box plot of postoperative CRP. No patients had CRP >15 mg/dL on POD 1 or POD 14, or at POM 1. POD, postoperative day; POM, postoperative month.

covering (22.8% *vs.* 3.6%) (8). Thus, there is no consensus on the most suitable material for staple-line coverage for prevention of recurrence of PSP.

Recently, Miyamoto *et al.* and Fujiu *et al.* found that pleural covering by INTEGRAN[®] induces visceral pleural thickening without adhesion to the chest wall (9,10), which suggests that this material could be suitable for staple-line coverage in PSP surgery for young patients. INTEGRAN[®] is widely used as an absorbable topical hemostat. Collagen derived from the dermis of Australian calves is converted to pure atelocollagen by enzyme solubilization to remove telopeptides that cause antigenicity, and is then chemically cross-linked with a polyepoxy compound to form an insoluble and stable fiber. This raw material is formed into sheets as INTEGRAN[®], which has low antigenicity because

it contains no protein components other than collagen (20). INTEGRAN[®] also contains no blood products, which suggests that it might be safe for staple-line coverage without concerns of allergic reaction and blood-borne infections.

There has been no previous report of use of INTEGRAN[®] for staple-line coverage in PSP surgery. INTEGRAN[®] is widely used as a topical hemostat, but almost all is removed intraoperatively after confirmation of hemostasis. In contrast, all INTEGRAN[®] is left in the thoracic cavity when used for staple-line coverage. Thus, we conducted this study to establish the safety of use of INTEGRAN[®] as a material for staple-line coverage in PSP surgery, especially for young adults.

Drug information for INTEGRAN[®] indicates main AEs of fever, local inflammation, and hematoma when used as a topical hemostat. In our study, postoperative fever occurred in 2 patients, but none had fever for >24 hours. Moreover, no patients had an abnormal inflammatory reaction and acute empyema did not occur in any cases. These results suggest that 0.2 g of INTEGRAN[®] can be safely left in the intrathoracic cavity, and we consider that INTEGRAN[®] can be safely used for staple-line coverage.

The 1-year postoperative recurrence rate was 12.0% in our study, which appears to be inferior to that in previous reports. However, we consider the recurrence rate in our study is acceptable because our study was conducted in young patients, which is a high-risk cohort. Joharifard *et al.* found a postoperative recurrence rate of 40% in young children who underwent wedge resection with intraoperative pleural abrasion (21). In a meta-analysis, Sudduth *et al.* found a postoperative recurrence rate of about 10% in patients <25 years old even after wedge resection with intraoperative pleural abrasion (11). Noh *et al.* found a postoperative recurrence rate of 17.9% in patients aged <25 years old, despite treatment with wedge resection with staple-line coverage and/or pleurodesis (13). Thus, staple-line coverage with INTEGRAN[®] appears to be equivalent to other procedures for prevention of postoperative recurrence.

Formation of new bullae around the staple-line occurred in only 4 patients on CT in POM 12, and recurrence occurred only in patients without new bullae. These results may be explained by the hypothesis that INTEGRAN[®] thickens the visceral pleura and prevents rupture, even if new bullae formation occurs. However, we note that patients who had recurrence after staple-line coverage with

INTEGRAN[®] showed mild adhesion of the INTEGRAN[®]-covered lung surface and the chest wall in second surgery, which differs from the findings in Miyamoto *et al.* and Fujii *et al.* (9,10). Although the adhesion was mild and easily dissected by a VATS approach, this suggests that chest wall adhesion may still occur in use of INTEGRAN[®] for staple-line coverage. Regardless, this study was conducted to evaluate the safety of INTEGRAN[®] for staple-line coverage, and the number of cases and follow-up period were insufficient to evaluate the efficacy. Evaluation of the efficacy of INTEGRAN[®] for prevention of recurrence of PSP will require a prospective randomized study and we are now planning such a study.

Conclusions

In conclusion, this study showed that INTEGRAN[®], a sheet-type absorbable topical collagen hemostat, can be safely used as material to cover a staple-line at the resection margin in surgery for young patients with PSP. To evaluate the efficacy of INTEGRAN[®] for prevention of recurrence of PSP, a further prospective randomized study is required.

Acknowledgments

Funding: This work was supported by research funds to promote hospital functions from the Japan Organization of Occupational Health and Safety.

Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at <https://dx.doi.org/10.21037/jtd-21-274>

Data Sharing Statement: Available at <https://dx.doi.org/10.21037/jtd-21-274>

Peer Review File: Available at <https://dx.doi.org/10.21037/jtd-21-274>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/jtd-21-274>). HA reports funding from Japan Organization of Occupational Health and Safety. HA serves as an unpaid editorial board member of Journal of Thoracic

Disease. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The single-arm prospective intervention study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Kanto Rosai Hospital on February 9, 2017 (No. 2016-19) and informed consent was taken from all the patients.

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Cite this article as: Adachi H, Kigoshi H, Kikuchi A, Ito H, Masuda M. Feasibility of application of an absorbable topical collagen hemostat sheet (INTEGRAN®) for prevention of postoperative recurrence of pneumothorax in youths. *J Thorac Dis* 2021;13(7):3979-3987. doi: 10.21037/jtd-21-274