Intrapleural Administration of a Large Amount of Diluted Fibrin Glue for Intractable Pneumothorax*

Takahiro Kinoshita, MD; Shinichiro Miyoshi, MD; Motokazu Katoh, MD; Tatsuya Yoshimasu, MD; Masanobu Juri, MD; Shinzi Maebeya, MD; and Yasuaki Naito, MD

Objective: Pleurodesis using chemical agents has been applied to high-risk patients with pneumothorax. This treatment, however, is sometimes unsuccessful in patients with intractable pneumothorax or intrapleural dead space. We developed a technique for the intrapleural administration of diluted fibrin glue as a treatment for such patients.

Methods: Fibrin glue was diluted fourfold with saline solution and/or contrast medium. Pleurodesis with a large amount of the diluted fibrin glue was performed in 40 high-risk patients with intractable pneumothorax and in 13 postthoracotomy patients with persistent air leakage associated with an intrapleural dead space.

Results: The air leaks were stopped by administration of the glue in all patients of both groups. During the follow-up period, a recurrence rate of 12.5% was observed in the former group. These recurrent pneumothoraces also were successfully treated by glue administration with no further recurrence. In the 13 postthoracotomy patients, there was no recurrence after the initial treatment. Pyrexia (12.5%) and chest discomfort (4.1%) were observed as side effects, but there were no findings of severe chest pain or thoracic empyema.

Conclusions: These results suggest that intrapleural administration of a large amount of diluted fibrin glue is a useful treatment for intractable pneumothoraces in high-risk or postthoracotomy patients who have an intrapleural dead space.

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Key words: dead space; dilution; fibrin glue; intractable pneumothorax; pleurodesis

Abbreviations: FGI = fibrin glue infusion

Pleurodesis by the infusion of chemical agents via a chest tube is preferable to surgery for the treatment of pneumothorax when patients are in a poor condition due to chronic pulmonary disease or some other underlying disease. Agents used for pleurodesis include talc, bacterial preparations, autologous blood, and antibiotics. The success rate of these agents ranges from 60 to 94%, and talc appears to be the most effective. The mechanism of pleurodesis with these agents is considered to be accomplished by a chemically induced fibrous pleuritis, which leads to adhesion between the visceral and parietal pleura. As a result, pleurodesis seems to be contraindicated in a pneumothorax patient who has an unexpanded lung and is often ineffective if lung inflation is insufficient.

Recently, chest surgeons often have applied fibrin glue to stop air leakage from a resected lung surface during an operation, especially for patients with an emphysematous lung. The method used in this procedure is mainly to cover the air leak site with fibrin glue. When the fibrin glue is applied to a pneumothorax patient with an unexpanded lung, it is expected that the fibrin glue will first cover the air leak, subsequently producing lung expansion that may lead to pleural adhesion. Thus, fibrin glue also has been used as a pleural sclerosing agent. However, this is often ineffective as the glue tends to clot in the chest tube and fails to reach the site of the air leak.

To overcome these problems, we devised a method of infusing diluted fibrin glue labeled with a contrast medium into the pleural cavity. This study

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TABLE 2—History of Pneumothorax*  

<table>
<thead>
<tr>
<th>Data</th>
<th>Group A (n = 40)</th>
<th>Group B (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency, (time)</td>
<td>1.9 ± 1.1 (0–5)</td>
<td>—</td>
</tr>
<tr>
<td>Previous pleurodesis cases</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>No. of infusions</td>
<td>2.0 ± 1.1 (1–5)</td>
<td>1.9 ± 1.0 (1–4)</td>
</tr>
<tr>
<td>Days before FGI</td>
<td>20.1 ± 2.7 (14–25)</td>
<td>15.2 ± 3.8 (12–22)</td>
</tr>
<tr>
<td>No previous pleurodesis cases</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Days before FGI</td>
<td>10.3 ± 1.7 (7–13)</td>
<td>6.5 ± 1.4 (5–9)</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD (range).

with prolonged air leaks after lung resection in association with an intrapleural dead space.

**Materials and Methods**

**Subjects**

The subjects in the study were 40 patients with pneumothoraces in whom thoracotomy was thought to be contraindicated because of severe underlying disease (group A) and 13 patients with prolonged air leaks after lung resection in association with an intrapleural dead space (group B). Each patient underwent a large-volume diluted fibrin glue infusion (FGI) between March 1990 and December 1995. The patient demographics and histories of pneumothorax are shown in Tables 1 and 2, respectively.

Although strict criteria were not used to define thoracotomy as contraindicated, patients were assigned to group A if clinically they were considered to be at high risk for perioperative morbidity and mortality because of severe pulmonary disease and/or associated nonpulmonary disease. The mean age of group A was 72 years, and the group comprised 39 men and 1 woman. The left side was affected in 17 patients and the right side in 23. The pulmonary diseases that caused pneumothorax were severe emphysema in 19 patients (who were all on home oxygen therapy), bullae or blebs in 10 patients, pulmonary fibrosis in 6 patients, pneumoconiosis in 3 patients, and giant bullae in 2 patients. The associated nonpulmonary diseases were old myocardial infarction in 10 patients, severe diabetes mellitus in 9 patients, liver cirrhosis in 7 patients, renal failure in 3 patients (all were on hemodialysis), terminal cancer in 3 patients, apoplexy in 2 patients, amyotrophic lateral sclerosis in 2 patients, sarcoidosis in 1 patient, amyloidosis in 1 patient, and systemic lupus erythematosus in 1 patient. Almost all of the patients had some degree of unexpanded lung as seen on a chest radiograph. Five patients were receiving mechanical ventilation because of acute worsening of the pulmonary disease (Table 1). Pneumothoraces occurred in these five patients during treatment with mechanical ventilation, probably due to a high positive airway pressure. Pneumothoraces in all patients, excluding the present study's episode, had occurred a mean of 1.9 times before FGI. Twenty-five patients (62.5%) had undergone pleurodesis with minocycline hydrochloride, autologous blood, OK-432, or doxorubicin hydrochloride, with a mean of 2.0 infusions of those substances for the current incident of pneumothorax. Fifteen patients (37.5%) had not received pleurodesis for their pneumothorax prior to FGI. The time between the onset of pneumothorax and FGI was 20.1 days in those patients who had previously undergone pleurodesis and 10.3 days in the untreated patients.

The mean age of group B was 60 years. All the subjects were men. The left side was affected in four patients, and the right side was affected in nine patients. A lobectomy was performed in nine patients with lung cancer (all of whom had the complication of emphysematous lung), and a bullectomy was performed in three patients with giant bullae and one patient with a spontaneous pneumothorax. Eight patients had undergone previous pleurodesis with minocycline hydrochloride, autologous blood, OK-432, or doxorubicin hydrochloride, with a mean of 1.9 infusions, while five patients had not received pleurodesis prior to FGI. The time between the onset of pneumothorax and FGI was 15.2 days in the patients who had previously undergone pleurodesis and 6.5 days in the untreated patients.

**Tensile Strength Measurement of Diluted Fibrin Glue**

Before clinical application of the diluted fibrin glue as a sclerosing agent, a preliminary experiment was conducted to measure the tensile strength of the original and diluted fibrin glues. Briefly, the fibrin glue was diluted two- to sixfold with saline solution in group 1, and with saline solution and contrast medium (ioipamidol) in group 2. The contrast medium was added to determine how well the surface of the lung would be covered with the fibrin glue in clinical application. Two small plastic caps were adhered to each other by the fibrin glue at each dilution.
(n = 5), and the breaking strength was measured by a tensile strength testing scale 10 min after adhesion.21

Clinical Application of Fourfold Diluted Fibrin Glue

In the clinical application, the glue was initially diluted two- or threefold, but that was insufficient to allow a good spread over the entire lung. As a result, a fourfold dilution was finally adopted.

Preparation of Fourfold Diluted Fibrin Glue: A fourfold diluted fibrin glue was prepared by adding 30 mL saline solution and 15 mL iopamidol (Iopamiron300; Schering; Berlin, Germany) to 15 mL (1,200 mg) fibrinogen solution containing factor XIII (fibrin glue, solution A) to give a total volume of 60 mL (solution 1). In addition, 45 mL saline solution was added to 15 mL thrombin solution (fibrin glue, solution B) to give a total volume of 60 mL (solution 2). Disposable syringes then were filled with 30 mL of each solution (solutions 1 and 2).

Intrapleural FGI: The pleural cavity with pneumothorax was drained with a double-lumen chest tube (Trocar Catheter, Two Lumens A; Sumitomo Bakelite Co; Tokyo, Japan) under x-ray fluoroscopy. The double-lumen chest tube has a small lumen used only for infusion and a larger lumen for aspiration. Fifteen milliliters of the contrast medium and 15 mL saline solution were infused through the smaller lumen of the chest tube to determine the site of the air leak. If the site of the air leak was confirmed to be bubbling from the lung surface, the tube either was moved to the site of the leak or another tube was inserted there. If the site of the leak could not be confirmed, the end of the chest tube was moved to the apex of the lung. The fibrin glue then was infused through the smaller lumen by the following method. The tube was clamped, and the fluoroscopy table was adjusted so that the upper half of the patient’s body was 30° to 50° below horizontal. A volume of 60 mL of solution 1 was infused, and the tube then was flushed with 10 mL saline solution. The patient was moved to the right decubitus position and then to the left decubitus position. Next, the fluoroscopy table was adjusted so that the upper half of the patient’s body was 30° to 50° higher than horizontal. The patient was placed in the right decubitus position and then in the left decubitus position. The patient was returned to the supine position, the upper half of the body was lowered, and 60 mL of solution 2 was infused rapidly, after which the tube was flushed with 10 mL saline solution. The patient’s body position then was changed according to the procedure for solution 1, and the fluoroscopy table finally was returned to the horizontal position. The clamp was removed 5 min later, and continuous low-pressure suction was performed at −5 cm H2O.

Evaluation of Efficacy: The chest tube was clamped on the third day after air leak termination. If no lung collapse was evident on chest radiographs, the chest tube was removed and the therapy was considered successful. If the air leak had not stopped within 3 days after FGI, the therapy was considered unsuccessful and the procedure was repeated.

RESULTS

Tensile Strength Measurement of Diluted Fibrin Glue

The tensile strength of the diluted fibrin glue in group 1 was $550 \pm 40\; \text{g/cm}^2$ at the original concentration, $551 \pm 41\; \text{g/cm}^2$ at the twofold dilution, $473 \pm 45\; \text{g/cm}^2$ at the threefold dilution, $421 \pm 51\; \text{g/cm}^2$ at the fourfold dilution, $279 \pm 60\; \text{g/cm}^2$ at the fivefold dilution, and $209 \pm 38\; \text{g/cm}^2$ at the sixfold dilution. The tensile strength in group 2 (iopamidol contrast medium) was $588 \pm 45\; \text{g/cm}^2$ at the original concentration, $540 \pm 35\; \text{g/cm}^2$ at the twofold dilution, $496 \pm 29\; \text{g/cm}^2$ at the threefold dilution, $419 \pm 46\; \text{g/cm}^2$ at the fourfold dilution, $280 \pm 58\; \text{g/cm}^2$ at the fivefold dilution, and $201 \pm 31\; \text{g/cm}^2$ at the sixfold dilution. The tensile strength at each dilution was not different between groups 1 and 2 (unpaired Student’s t test).

Early and Long-term Outcomes of FGI for Intractable Pneumothorax

The early and long-term outcomes of FGI for intractable pneumothorax are shown in Tables 3 and 4.

Outcome of FGI in Group A: After confirming the site of the air leak, 10 patients in group A needed a second chest tube for pleurodesis. For 35 patients (87.5%), the therapy was successful (ie, the air leak disappeared) after the first infusion. Another five patients required further infusions: four required a second infusion, and one required a third infusion. The time to disappearance of the air leak in the patients successfully treated with a single infusion was 0 to 3 h for 8 patients, 3 to 6 h for 20 patients, and 6 to 12 h for 7 patients. For all of the patients who required a second or third infusion, the air leak disappeared within 1 h. Five patients in group A were receiving mechanical ventilation. The air leak disappeared after the first infusion in four of these patients, but one patient required three infusions. We were able to wean all five of the patients from mechanical ventilation after improvements in their pulmonary disease and disappearance of the air leaks. The side effects of the therapy were fever (temperature, 37 to 38°C) in six patients (12.5%) and chest discomfort in two patients (4.1%). None of the

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Table 3—Early Outcome of FGI

<table>
<thead>
<tr>
<th>Data</th>
<th>Group A (n = 40)</th>
<th>Group B (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of infusions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>35</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Time to disappearance of air leak after first FGI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2 h</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>3–6 h</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>6–12 h</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>After second or third FGI</td>
<td>all within 1 h</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
patients died of pneumothorax or treatment-associated complications (Table 3). During follow-up over a period of 0.5 to 6.8 years (mean, 4.6 years), pneumothorax recurred in 5 of the 40 patients (12.5%) at 2 months to 2 years after FGI. The pneumothorax healed in all five of the patients in whom FGI was repeated with no further recurrences during the ensuing follow-up for 2.5 to 6.5 years (mean, 3.8 years) (Table 4).

**Outcome of FGI in Group B:** FGI was successful in all of the group B patients, with disappearance of the air leak after a single infusion. The time between FGI and the disappearance of the air leak was 0 to 12 h in three patients, 3 to 6 h in four patients, and 6 to 12 h in six patients. In other words, the air leak disappeared within 12 h in all of the patients. Fever to 12 h in six patients. In other words, the air leak disappeared within 12 h in all of the patients. Fever in two patients and chest discomfort in another two patients occurred as side effects after a single infusion (16.7%) (Table 3). The follow-up period ranged from 1.0 to 6.5 years (mean, 3.8 years), and there was no recurrence of pneumothorax observed (Table 4).

**DISCUSSION**

Pleurodesis achieved by an intrapleural infusion of chemical agents is preferred to surgery for patients with intractable pneumothorax, in whom thoracotomy is contraindicated and, occasionally, for patients with a prolonged air leak after pulmonary resection in association with an intrapleural dead space. Pleurodesis has been performed to promote pleural adhesion using t alc,1–7 bacterial components (such as OK-4328 or C parvum18), antibiotics (such as tetracycline,11,12 doxycycline13,14 or minocycline hydrochloride15–17), autologous blood,9,10 and anticancer agents (such as mitomycin C8 or adriamycin18). These techniques all achieve adhesion by triggering an inflammatory response through irritation of the pleura, thus causing severe chest pain and fever. Although the success rate of t alc has been as high as 94% and appears to be the most effective,18 Lineau et al24 and Milanez et al25 reported pulmonary infiltration and respiratory distress syndrome in patients undergoing talc pleurodesis. In addition, these agents are often ineffective if adequate lung inflation cannot be obtained, despite pleural drainage, and if dead space is present.18

Fibrin glue, made from a combination of fibrinogen and thrombin, is safe, has few side effects,19–22 and is widely used in various fields including pulmonary surgery,26,27 plastic surgery,26 GI surgery,29 liver surgery,29 and cardiovascular surgery.30,31 Scheele et al22 used intrapleural FGI to achieve pleurodesis in patients with pneumothorax. However, the treatment often failed because the fibrin often clotted inside the drain and the air leak occlusion was attempted blindly. In other studies, fibrin glue was applied after confirming the site of the air leak by thoracoscopy under local anesthesia,32–34 although it should be noted that the patients in those cases had only a limited number of bullae and blebs. This technique is probably unsuitable for patients whose lung function is very poor and where adhesions to the thoracic wall are present, as was the case for the patients in the present study.

To overcome these problems, we diluted the fibrin glue, allowing it to spread more easily from the drain tube into the pleural cavity, and also added the contrast medium to allow its spread to be checked by x-ray fluoroscopy. The glue was initially diluted two- or threefold, but this was insufficient to allow a good spread over the entire lung, as Scheele et al22 also discovered. As a result, a fourfold dilution finally was used. Dryzer et al35 reported that rotation of their patients offered no benefit to the success of pleural symphysys after intrapleural instillation of tetracycline-class agents. However, our fourfold diluted fibrin glue application needed rotational maneuvers to facilitate an adequate spreading over the entire lung area. A previous study found no significant difference in the clotting time for two- and fourfold dilutions.36 Our preliminary study showed that the tensile strength of two-, four-, and sixfold dilutions of fibrin glue, with i opanidol used as contrast medium, fell to 91.8%, 71.3%, and 34.2%, respectively, of the original fibrin glue. While dilution reduced the tensile strength, the contrast medium had no effect on the symphysys, and therefore fibrin glue application is a suitable treatment. Considering that the air leak disappeared, even in our pneumothorax patients who were receiving mechanical ventilation, the reduction in tensile strength of the fourfold dilution did not produce complications at the clinical level.

In patients with intractable pneumothoraces in whom thoracotomy was contraindicated, the efficacy rate of the first infusion was 87.5%. The five patients who required repeat infusion had air leaks at multi-

| Table 4—Long-term Outcome of FGI* |
|-----------------|-----------------|-----------------|
|                  | Group A         | Group B         |
|                  | (n = 40)        | (n = 13)        |
| Follow-up period, yr  | 4.6 ± 2.7 (0.5–6.8) | 3.8 ± 3.3 (1.0–6.5) |
| Recurrence        | 5 (12.5)        | 0 (0)           |
| Time to recurrence, mo | 10.8 ± 7.4 (2–24)  | —              |
| Follow-up period after repeated FGI, yr | 3.8 ± 1.4 (2.5–6.5) | — |
| Further recurrence after repeated FGI | 0 | — |

*Values given as mean ± SD (range) or No. (%).
ple sites. Failure of the initial infusion was attributed to inadequate coverage of the air leaks by the fibrin glue because of pleural adhesions that were present before the infusion. However, all of these patients made a successful recovery when the glue was infused again after reconfirming the sites of the air leaks.

Early intervention is desirable in lung cancer patients with an emphysematous lung, because possible prolonged air leakage from the resected lung surface may cause serious complications such as pneumonia or empyema. Conventional agents that stop air leaks by promoting adhesion between the parietal and visceral pleura are often ineffective when a large dead space occurs, such as after lung resection, preventing close contact between the two pleurases. In contrast, fibrin glue stops the air leak by reducing only slight pleural thickening and adhesions, according to animal studies. Although a large amount of fibrin glue was actually infused into the pleural cavity in our patients, no contrast medium was seen in the pleural cavity on chest radiographs taken 1 month after the therapy, and pleural thickening was absent after that time. These findings suggest that fibrin glue pleurodesis likely causes only a minimal restrictive defect.

From this study, we conclude that a large-volume intrapleural infusion of diluted fibrin glue containing contrast medium is a relatively simple and safe technique, and it is effective for high-risk patients with intractable pneumothorax as well as for patients with prolonged air leakage in association with dead space after lung resection.

References