Original Article

Effects of picibanil as sclerosing agent in primary spontaneous pneumothorax patient after thoracoscopic procedures

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Background: Recurrence is one the most important issue after thoracic surgery for pneumothorax, and the choice of additional chemical pleurodesis after surgery to eliminate recurrence remained unclear. Herein, we made prudent assessment of the safety and efficacy of chemical pleurodesis with picibanil (OK-432) for reduction of recurrence of pneumothorax.

Methods: Between 1994 and 2014, 1,695 patients, who suffered from primary spontaneous pneumothorax (PSP), were treated by video-assisted thoracic surgery (VATS). After the operation, additional OK-432 was instilled into the pleural for chemical pleurodesis in 89 patients. The surgical outcome and demographic data of these patients were retrospectively reviewed.

Results: The most frequent indications of surgical intervention were ipsilateral recurrence of pneumothorax (67.4%) and prolonged air-leakage (21.3%). There was no mortality and associated complication were as following, fever, intolerable pain, and post-operative effusion, wound poor healing. Median length of post-operative stay was three days. During routine post-operative follow-up, only two patients (2.2%) suffered from recurrence of pneumothorax and no additional surgical intervention was indicated.

Conclusions: The long-term result of additional chemical pleurodesis, using OK-432 following VATS bullectomy is safe and effective with low recurrence rate (2.2%). Our experience suggested that OK-432 was a reliable sclerosing agent for chemical pleurodesis.

Keywords: Picibanil (OK-432); pleurodesis; pneumothorax; recurrence; thoracoscopy

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Introduction

Primary spontaneous pneumothorax (PSP) is defined as the presence of air into the pleural space without evident thoracic trauma or underlying pulmonary disease, which most commonly occurs in young, tall, lean males (1,2). For patients suffered from spontaneous pneumothorax, there are three clinical issues to solve. The first issue is pneumothorax caused symptoms, such as chest pain, chest tightness, dyspnea, or the worst desaturation with respiratory failure, which could be relieved by tube thoracostomy, pain killer and oxygen supply (3). The second clinical problem is associated with poor healing of lung parenchyma and persistent air-leakage after tube thoracostomy or video-assisted thoracic surgery (VATS) (4). And the last and the most important clinical issue for patient suffered from pneumothorax is recurrence of pneumothorax. Without intervention, recurrence rate was as high as 49% in 1 year (5,6). The surgical indication for PSP had been proposed as

recurrence of pneumothorax, prolonged air-leakage, complicated with hemothorax, bilateral pneumothorax and patients with specific risks of atmosphere change, such as pilots, flight attendants or deep-sea divers (3,7,8). VATS is regarded as superior to thoracotomy approach in terms of reduced pain, less invasive, shorter days of hospital stay and fewer atelectasis following the procedures (9). Unfortunately, VATS bullectomy alone was associated with higher recurrence rate between 10% and 24% and recurrence rate of open thoracotomy was around 3% (4,10,11). Although, in most practice guidelines, chemical pleurodesis is regarded as the salvage for patients who would not tolerate surgical intervention to treat pneumothorax (3,12). When VATS bullectomy combined with pleurectomy, some kind of pleurodesis, either mechanical abrasion or chemical pleurodesis, the risk of recurrence was reduced to 1–6% (13-16).

There have been a lot of sclerosants used for chemical pleurodesis, to achieve symphysis between the visceral and parietal pleura to prevent recurrent pleural effusion or recurrent pneumothorax, including talc, tetracycline and its derivatives, minocycline, bleomycin, autologous blood patch, iodopovidone, picibanil (OK-432), and silver nitrate (17). OK-432, a lyophilized preparation of heat-killed Su-strain of type 3, group A *Streptococcus pyogenes*, is a chemical irritant that has been used in sclerotherapy for postoperative air-leakage, intractable pneumothorax and malignant pleural effusions (17-20). In this study, we report our clinical experience of using OK-432 for additional chemical pleurodesis after patients received VATS bullectomy for PSP.

Methods

Study design and patients

The objective of this retrospective study was to evaluate the safety and efficacy of OK-432 as sclerosing agents in patients after VATS for PSP. We cautiously review the medical records of these patients with pneumothorax, who received VATS bullectomy in National Taiwan University Hospital between April 1994 and May 2014. Patients, who was aged over 50 years old or had underlying pulmonary diseases, were excluded from current study to avoid patients with secondary pneumothorax. This study was reviewed and approved by the Research Ethics Committee of National Taiwan University Hospital (approval number 201202011RIC).

VATS procedures

Under general anesthesia and one-lung ventilation, patient received needlescopic or conventional VATS for bullectomy with or without mechanical pleurodesis. There was no difference between needlescopic and conventional VATS in methods of anesthesia, patient preparations, procedures of operations and post-operative recurrence rate (21,22).

Under thoracoscopic surveillance, adhesions between lung surface and chest wall were freed using electrocautery directly. When blebs, most at apex of upper lobes, were identified, they were removed by wedge resection by using an endoscopic stapler. Blind stapling at apical area, the most suspicious area, was performed, if no bleb or active air-leakage could be identified. Pleural abrasion method was chosen for mechanical pleurodesis (23). Lung re-inflation method was applied to check air-leakage, when normal saline was instilled into pleural space. One chest tube (28 Fr) or pigtail (8 Fr) was inserted through the incision wounds to place at the apex area of upper lobe.

After the VATS bullectomy and pleurodesis, extubation was performed in the operating room and then the patient was observed for one to two hours in the recovery room. Chest roentgenogram was scheduled on the next coming morning. The thoracic drainage system was connected to a low-pressure suction (–10 cmH_2O), if the lung was not fully expanded on chest roentgenogram.

Chemical pleurodesis using OK-432

When postoperative air-leakage occurred or instilled for prophylactic use to reduce recurrence, OK-432 was chosen for chemical pleurodesis to achieve the adhesion between the two layers of pleura. The procedure of OK-432 pleurodesis was as following, the first step was instilled 20 mL of 2% lidocaine hydrochloride (400 mg) into the pleural space via thoracic drainage tube, and then instilled the 20 mL of normal saline solution containing 5–10 Klinische Einheit (KE) of OK-432 (1 KE equals to 0.1 mg of dried cocci; Chugai Pharmaceutical Co., Tokyo, Japan) (17). The drainage tube between the thoracic drainage tube (chest tube or pigtail) and chest bottle was raised 40 to 60 cm above the patient to indwell the sclerosing agent and allow air to pass through at the same time. Patients were ordered to change positions (left-side decubitus, supine or right-side decubitus position) every 30 minutes, in order to make the sclerosing agent contacting all over the whole pleural surfaces. Associated

Table 1 Clinical characteristics and operative findings of patients using OK-432 as sclerosing agent

Characteristics	OK-432 group (N=89)
Age, years	26.2±8.4[a]
Males, no. (%)	66 (74.2)
Body height, cm	171.9±9.0[a]
Body weight, kg	55.3±9.1
BMI, kg/m^2	18.7±2.4[a]
Smoking, no. (%)	22 (24.7)
Side involved, no. (%)	
Right	45 (50.6)
Left	47 (52.8)
Surgical indications, no. (%)	
Recurrent pneumothorax	60 (67.4)
Persistent air leaks	19 (21.3)
Bilateral pneumothorax	3 (3.4)
Hemopneumothorax	2 (2.2)
Uncomplicated first episode	5 (5.6)
Vanderschueren's stage, no. (%)	
Stage 1	4 (4.5)
Stage 2	23 (25.8)
Stage 3	48 (53.9)
Stage 4	14 (15.7)
Mechanical pleurodesis, no. (%)	
Abrasion	73 (82.0)
Mesh pleurodesis	16 (18.0)

[a], mean ± standard deviation. BMI, body mass index.

side effects and complaints of pleurodesis were documented. The rubber tube was lowered 2 hours later to drainage the effusion out.

The postoperative pain was assessed 3 times per day and the intensity of pain was recorded by the visual analogue scale (VAS; zero indicated no pain and ten indicated the most severe, intractable pain). If the post-operative pain was not relieved by oral analgesics, and VAS was greater than seven, meperidine hydrochloride (Demerol®, 50mg/ampule) would be prescribed for pain control. The thoracic drainage tube would be removed when the lung was fully expanded and no more air-leakage was noted in the past 24 hours period.

All adverse events and complains were documented. Fever was defined as body core temperature ≥38 ℃. Loculated effusion was routinely checked on chest roentgenogram (CXR) and sonography after pleurodesis.

Follow-up and pulmonary function analysis

After discharge from the hospital, all patients were scheduled to follow at the outpatient clinics, where CXR was arranged to check if recurrent pneumothorax occurred and pulmonary function tests were also performed. The latest patient followed up in May 2018. Spirometer (Microspiro HI-298; Chest Corporation, Tokyo, Japan) was used to estimate forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1.0). Three acceptable forced expiratory maneuvers were recorded, and analyzed.

Data collection and analysis

The patient demographic data and related surgical results including, operative findings, dosed and times of pleurodesis, post-operative pain scale (VAS) and doses of meperidine, complications, duration of chest tube drainage retained, and length of hospital stay were collected through retrospective chart review. Continuous variables such as age or height were expressed as mean ± standard deviation. Categorical variables such as sex or smoking status were presented by frequency (%).

Results

Between April 1994 and May 2014, the total number 1,695 patients with PSP were treated by VATS. Routine postoperative follow-up and data collection for check postoperative events and recurrence of pneumothorax were documented till 2018 May. This study enrolled 89 patients, who received chemical pleurodesis with OK-432 after VATS procedure. The result of the patient demographics, pre-operative characteristics, indications for surgery, and intra-operative finding are summarized in *Table 1*. Patients consisted of 66 male and 23 female, with a median age of 23 years. The mean body mass index of all patients was 18.7 kg/m^2. About 1 of 5 patients had smoking habit of cigarettes. The incidence of left-side pneumothorax was 52.8%, included three patients had bilateral pneumothorax. The indication for VATS bullectomy was as following recurrent pneumothorax (67.4%), persistent air-leakage

Table 2 Results in patients using OK-432 as sclerosing agent

Variables	OK-432 group (N=89)
Meperidine requested, no. (%)	13 (14.6)
Dose of meperidine, mg	59.9±79.0[a]
Postoperative pain (VAS)	
First pleurodesis day	3.6±1.9[a]
Second pleurodesis day	3.0±1.5[a]
Third pleurodesis day	2.2±0.9[a]
Complications, no. (%)	7 (7.9)
Fever	6 (6.7)
Loculated effusions	1 (1.1)
Postoperative tube stay, days	3.9±1.5[a]
Postoperative hospital stay, days	6.8±4.6[a]
Recurrence, no. (%)	2 (2.2)
Pulmonary function test (%)	
FVC	87.2±10.1[a]
FEV1.0	87.5±8.6[a]

[a], mean ± standard deviation. VAS, visual analogue scale; FVC, forced vital capacity; FEV1.0, forced expiratory volume in 1 s.

(21.3%), bilateral concurrent pneumothorax (3.4%), hemopneumothorax (2.2%) and uncomplicated first episode of pneumothorax (5.6%). On thoracoscopy, four patients had no endoscopic abnormalities (Vanderschueren's stage 1), 23 patients had pleuropulmonary adhesions (Vanderschueren's stage 2), 48 patients had blebs or bullae <2 cm in greatest diameter (Vanderschueren's stage 3), and 14 patients had bullae >2 cm in greatest diameter.

The mean dose of OK-432 instillation was 7.6±4.2 KE. The clinical characteristics and post-operative results of the patients are summarized in *Table 2*. Wound pain was the most common complaint after VATS procedure and the severity was decreased gradually. Fever was the most frequent complication after chemical pleurodesis with OK-432, and the following was loculated effusion. Fever was resolved by took acetaminophen 500 mg. One patient developed loculated effusions on CXR that resolved gradually without any invasive interventions. Thirteen patients complained severe pain that required immediate meperidine intramuscular injection and the dose of meperidine were 59.9±79.0 mg.

The durations of chest tube drainage and the post-operative stay hospitalization were 3.9±1.5 and 6.8±4.6 days separately. Until the latest post-operative follow-up in May 2018, only two patients (2.2%) suffered from ipsilateral recurrent pneumothorax. The pneumothorax resolved spontaneously without tube thoracostomy or surgical intervention. Pulmonary function was measured by Spirometer to evaluate the influence of chemical pleurodesis with Ok-432 (*Table 2*).

Discussion

This study demonstrates that chemical pleurodesis with OK-432 following VATS procedure provides a safe, and effective treatment for PSP.

The therapeutic aims of pneumothorax focused on evacuating air from the pleural space (symptoms relief), ceasing air leakage (parenchyma healing), and preventing recurrences (3). To prevent recurrence of pneumothorax is the most important therapeutic challenge in the management of PSP. Many treatments are proposed to reduce recurrence of pneumothorax included simple aspiration, tube thoracostomy with chemical pleurodesis or pulmonary resection by open thoracotomy or VATS with mechanical pleurodesis (24). The options of management may depend on the severity of clinical manifestations, the medical and social background of patients, availability of skilled physicians and facility of medical center.

Chemical pleurodesis, played a crucial role of stopping air-leak or preventing recurrent pneumothorax, which could be instilled through the thoracic drainage tube, medical thoracoscopy, or during the VATS procedure. Pleurodesis means to achieve symphysis between parietal and visceral pleura and to prevent relapse of pneumothorax (8). There have been a lot of sclerosing agents used for chemical pleurodesis, to prevent recurrent pleural effusion or pneumothorax, including talc, tetracycline, minocycline, bleomycin, autologous blood patch, iodopovidone, OK-432, silver nitrate, and quinacrine (17). Light *et al.* conducted a prospective randomized trial and showed that intrapleural instillation of tetracycline via thoracostomy tube could diminish incidence of recurrence of PSP (25).

In general practice, surgical intervention was indicated when patients faced with recurrent or complicated spontaneous pneumothorax. Chemical pleurodesis could be an adjunct after drainage or surgery. Although, VATS is regarded as better than thoracotomy approach in terms of pain relief, minimal invasive, shorter days of hospital stay and less pulmonary complications (9). The higher recurrence rate of VATS bullectomy was an unfavorable concern.

Table 3 Clinical applications of chemical pleurodesis with Ok-432

Author, date, journal and study type	Patient groups	Case numbers	Recurrence (%)	OK-432 dose (KE)	Complications	Mortality	Comments
Kishi *et al.* (2003), *Nihon Kokyuki Gakkai Zasshi*, retrospective review (18)	Lymphangioleiomyomatosis	5	1 (20.0)	5 or 10	Nil	0	–
Taniguch *et al.* (2008), *General Thoracic Cardiovascular Surgery*, case report (27)	Lymphangioleiomyomatosis	1	0	Not mentioned	Nil	0	Recurrent pneumothorax after VATS bullectomy
Ogasawara *et al.* (2012), *International Medicine*, prospective study (28)	Pneumothorax/refractory pleural effusion	12	–	5 or 10	Fever	0	The serum levels of both PCT and CRP increased significantly two days after pleurodesis with OK-432
How *et al.* (2013), *Journal of the Formosan Medical Association*, retrospective review (20)	Post-operative air-leakage in PSP	29	1 (3.4)	5–20 (in divided 2 dose), median dose 10	Chest pain, fever and loculated effusion	0	Focused on ceasing post-operative air-leakage, duration of chest tube insertion and hospital stay
Ogawa *et al.* (2018), *Respiratory Medicine*, retrospective review (19)	Interstitial pneumonia (IP)	39	7 (18.0)	5–55 (divided in 6 doses), median dose 10	Fever, chest pain hypoxia and respiratory failure	5 death for aspiration pneumonia	–
Shinno *et al.* (2018), *Respirology*, retrospective review (29)	Old age/ interstitial abnormalities	35	0	Not mentioned	None of ARDS	0	Most cases for malignant pleural effusion and successful rate, 24/35 (68%)
How *et al.* (2019), *current study*, retrospective review	Primary spontaneous pneumothorax (PSP)	89	2 (2.2)	5–20 (in divided 2 dose), median dose 10	Fever and loculated effusion	0	–

KE, Klinische Einheit; VATS, video-assisted thoracic surgery; PCT, procalcitonin; CRP, C-reactive protein; ARDS, acute respiratory distress syndrome.

The recurrence rate of VATS bullectomy alone and open thoracotomy was 10% to 24% and 3% separately (4,10,11). Additional pleurodesis following VATS bullectomy could effectively reduce the risk of recurrence to 1–6% (13-16). There are numerous benefits of additional chemical pleurodesis after VATS for PSP. In addition to prevent recurrence of pneumothorax, it may shorten the durations of post-operative air-leakage and hospital stay (17,26).

In this study, following VATs procedure, additional pleurodesis with OK-432, a product of heat-killed *Streptococcus pyogenes*, was used to prevent recurrence. There were several study of OK-432 focused on ceasing post-operative air-leakage, diminishing recurrence of pneumothorax, malignant pleural effusion, and the safety in patients with interstitial pneumonia. These studies were summarized in *Table 3*. In this study, our data demonstrated that pleurodesis with OK-432 is also safe and effective with low recurrence rate (2.2%) after VATS for PSP. In our

hospital, OK-432 was initially used as a salvage treatment for prolonged, and intractable air-leakage after chemical pleurodesis with minocycline. In recent years, OK-432 was used as the primary treatment for additional chemical pleurodesis after VATS procedure.

Fever was the most common compliant associated with OK-432 pleurodesis (6.7%). In clinical practice, chills and fever usually developed a few hours after OK-432 instillation, but resolved within one day after took acetaminophen. The significantly increased serum level of procalcitonin (PCT) or C-reactive protein (CRP) were also reported by Ogasawara *et al.* (27). Another concern with instillation of sclerosing agents into pleural space for chemical pleurodesis is empyema. In our study population, only one patient with loculated effusions was found by CXR. Our results suggest that pleurodesis by OK-432 associated with low incidence of pleural infection.

The more intense pleurodesis may result in more restrictive pulmonary dysfunction. The results of pulmonary function tests after pleurodesis did not showed any restrictive or obstructive pattern.

There are several limitations of present study. At the first, it is a retrospective chart review study of a group of patients treated by several surgeons during a 20-year period. There was no standardized treatment policy for all patients with PSP and treatments were modified over time through. We believe that a prospective study with precise definition of variables and standardized treatment protocol will be helpful in validating our results.

In conclusion, this study demonstrates that using Ok-432 as additional chemical pleurodesis for patients with PSP after VATS procedures is safe and effective with low recurrence rate.

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Footnote

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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 study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was reviewed and approved by the Research Ethics Committee of National Taiwan University Hospital (approval number 201202011RIC). Informed consent was waived due to the retrospective nature of the study.

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