Effects of OK-432 Chemical Pleurodesis for Primary Spontaneous Pneumothorax: A Case-Control Study

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Abstract

Background

Ipsilateral recurrence rate of primary spontaneous pneumothorax after video-assisted thoracoscopic surgery is higher than that after open surgery. This study aimed to evaluate the safety and efficacy of additional OK-432 pleurodesis after pleural abrasion for primary spontaneous pneumothorax patients.

Methods

This is a case-control study enrolling a total of 254 patients with primary spontaneous pneumothorax. 130 patients underwent blebs resection and pleural abrasion in the control group. 124 patients were enrolled in the OK-432 group, in which 1 Klinische Einheit of OK-432 was injected into thoracic cavity after surgery.

Results

: Patients demonstrated a trend of decreased rate of prolonged air leak in the OK-432 group (2.42% vs 19.23%, $p < 0.001$). After a median follow-up of 36 months (range, 2–69 months), the rate of ipsilateral pneumothorax recurrence was lower in the OK-432 group than it in control group ($p = 0.023$). OK-432 pleurodesis is the most important factor reducing the risk of recurrence (relative risk: 0.13, 95% confidence interval (CI): 0.02 to 1.03), and prolonged air leak patients had an increased risk of recurrence (relative risk: 11.69; 95% CI: 3.41 to 40.04).

Conclusion

OK-432 pleurodesis after pleural abrasion can reduce the risk of recurrence. OK-432 pleurodesis is a safe and effective method for reducing the rate of postoperative air leak and ipsilateral recurrence after thoracoscopic surgery.

Introduction

Primary spontaneous pneumothorax (PSP) commonly occurs in young, lean, tall males[1]. *Devilliers* was the first person to regard the rupture of subpleural blebs as a cause for spontaneous pneumothorax and *Hewson* described thoracocentesis for its relief [2]. The estimated rate of recurrence is 23–50% after the first episode, and then rises to 60% after the second episode [3]. Surgical intervention is suggested as the best option for pneumothorax in patients with a persistent air leak [4]. Thoracoscopic bullectomy with pleural abrasion provides a preferred intervention for dealing with primary spontaneous pneumothorax[5].

A few literature reports showed that the recurrence rate of pneumothorax after video-assisted thoracoscopic surgery (VATS) was higher than it after open thoracotomy [6–8]. As a consequence, the efficacy of VATS was questioned and other aggressive procedures, such as limited thoracotomy with pleurectomy, were carried out to enhance the effects of pleural symphysis[9]. Chemical pleurodesis, namely intrapleural instillation of a chemical irritant, is often employed as an alternative to shorten the duration of air leak and prevent the recurrence rate of pneumothorax in nonsurgical patients. Chemical pleurodesis using talc or minocycline in patients with PSP demonstrated a recurrence rate of 1.9% – 5% [10–13].

OK-432 is a kind of preparation of streptococcus pyogenes, type A3, which was well developed in Japan as an immunotherapeutic agent for tumor [14]. Chemical pleurodesis using both OK-432 and doxorubicin can control malignant pleural effusions caused by lung cancer [15]. It has been suggested that OK-432 chemical pleurodesis is an effective treatment for pneumothorax associated with interstitial pneumonia [16]. However, the safety and efficacy on preventing recurrence of primary spontaneous pneumothorax remains unclear. In this retrospective study, we aimed to evaluate the safety and efficacy of OK-432 pleurodesis in PSP patients.

Patients And Methods

Study population

The study was carried out at the Department of Thoracic Surgery of Third Affiliated Hospital of Sun Yat-Sen University (Guangzhou, China). A comprehensive computerized cases search was performed in our hospital database, and we retrieved the latest records of 285 patients with PSP who underwent thoracoscopic bullectomy and pleural abrasion at our institution from March 2013 and September 2018. The clinical data, operative findings, air leak status, operation time, duration of postoperative drainage, length of hospital stay, postoperative chest pain and complication were collected from medical records in our hospital.

All included patients caused by ipsilateral recurrence, persistent air leak more than 3 days, presence of hemo-pneumothorax were eligible for this study. Exclusion criteria were as follows: age > 40 years old, underlying pulmonary disease, secondary pulmonary pneumothorax, treated with other chemical irritants and previous ipsilateral thoracoscopic surgery. A flow chart illustrating the inclusion process is shown in FIGURE 1.

Surgical procedure

The operation procedures were identical in two groups. In brief, 2-port VATS was performed under general anesthesia, using intubation with a single-lumen or double-lumen endotracheal tube. Patients were placed in a lateral decubitus position, and the ipsilateral lung was deflated. A 5-mm, 30° telescope (Karl Storz; Tuttlingen, Germany) was first inserted through the sixth or seventh intercostal space with a 10-mm port. The other 15-mm incision was made at the third or fourth intercostal space, anterior axillary lines.

Under thoracoscopy, pleural adhesions were freed using electrocautery. When blebs were identified clearly, they were excised with endoscopic staplers. Blind apical stapling was done at the most suspicious area if no bleb was found. Mechanical pleurodesis was performed by pleural abrasion, namely the parietal surface above sixth rib abraded by an oval forceps with a diathermy scratch pad through the port sites. After postoperative lung reinflation, normal saline solution was instilled to check for air leaks. Two chest tubes (20F and 24F) were placed in the thoracic cavity through the both insertion wounds. The surgical specimens were routinely sent for pathologic examination. The patients were extubated in the recovery room and observed for 1 to 2 hours. The chest tube was connected to a low-pressure suction system (– 10 to – 20 cm H₂O).

For OK-432 pleurodesis, 1 Klinische Einheit (KE) of OK-432 (1 KE of OK-432 contains 0.1mg of dried bacterial cells) in 100mL of normal saline was instilled into the pleural cavity after pleural abrasion and smeared the agent on pleural surfaces. Side effects and complaints of the patient were recorded.

All complications after OK-432 pleurodesis were recorded. We classified the severity of pneumothorax according to the British Thoracic Society guidelines for the management of spontaneous pneumothorax [4], which classifies a pneumothorax as “small” if the maximum distance from the collapsed lung to the thoracic wall is < 2 cm and as “large” if the maximum distance is $\geq$ 2 cm. The intensity of postoperative chest pain was evaluated by using the visual analogue scale (VAS; 0 represented no pain and 10 represented intractable pain) three times per day after the pleurodesis. When chest pain could not be relieved by oral analgesics, the VAS was > 7. Chest radiography was performed the next morning. The chest tube was removed when lung was fully expanded or the pneumothorax size less than 20%, and no air leak was noted in a 24 hours continuously.

Study endpoints and follow-up

Our primary outcome was the recurrence rate of postoperative pneumothorax, and then we analyze relative risk (RR) factors for postoperative recurrence. Secondary outcomes were as follows: postoperative duration of air leak, postoperative chest drainage (1st 24h drainage, 2nd 24h drainage, 3rd 24h drainage), length of hospital stay, postoperative chest pain, complications (postoperative air leak > 3days, pleural detachment, hemothorax, empyema, fever).

Patients were followed up during clinical visits or by telephone conversation. Content of follow-up included recurrence or not, the date of recurrence and corresponding management of recurrent pneumothorax.

Statistics Analysis

Data were analyzed using the Stata software package (version 12.0; Stata Corp LP, College Station, TX, USA). Continuous variables were expressed as the mean $\pm$ SD and analyzed by the two-sample *t* test. Categorical variables such as gender or smoking history were presented by frequency (percentage) and analyzed by the *Fisher* exact test. Freedom from recurrence was analyzed by the *Kaplan-Meier* method,

and comparisons were made by the log-rank test. To identify other factors associated with recurrence of pneumothorax, we used the Cox regression model to conduct secondary analyses for age (< 23 vs. ≥ 23 years), sex (male vs. female), BMI (< 18.5 vs. ≥ 18.5), smoking history (yes vs. no), pneumothorax site (left vs. right), pneumothorax size (< 3 vs. ≥ 3 cm), blebs number (0–2 vs. 3 or more), prolonged air leak (yes vs. no), complication (yes vs. no). A p value less than 0.05 was considered statistically significant.

Results

Patient characteristics

Between March 2013 and September 2018, a total of 254 patients enrolled in this study. 140 patients were excluded from this study because of without pleural abrasion or using other chemical pleurodesis ($n = 18$), pulmonary tuberculosis or severe pleural adhesion ($n = 8$), or loss to follow-up ($n = 5$). OK-432 pleurodesis was performed in 124 patients (48.8%) and conventional mechanical pleurodesis (control group) was performed in 130 patients (51.2%). The average age was 23 years (rang, 14–40 years). The median body mass index (BMI) was 18.5 kg/m² (range, 14.3–28.6 kg/m²). 21 patients were smokers in the OK-432 group, which was greater than the control group (16.97% vs. 7.69%, $p = 0.024$). The median operation time was 74 min (rang, 30–210 min). The two groups were evenly distributed with respect to age, sex, BMI, pneumothorax size, pneumothorax site, number of blebs. Patients' characteristics are listed in Table 1.

Table 1
Characteristics of participants

Variables	OK-432 Group (n = 124)	Control Group (n = 130)	<i>p</i> Value
Age (yr)	22.82 ± 4.82	23.78 ± 6.13	0.083
Sex			0.156
Male	113(91.13%)	111(85.38%)	
Female	11(8.87%)	19(14.62%)	
BMI	18.9(17.8, 20.2)	18.95(17.5, 20.3)	0.177
Smoking history			0.024
Yes	21(16.94%)	10(7.69%)	
No	103(83.06%)	120(92.31%)	
Pneumothorax size (cm)			0.380
< 2	32(25.81%)	40(30.77%)	
≥ 2	92(74.19%)	90(69.23%)	
Pneumothorax site			0.616
Left	64(51.61%)	63(48.46%)	
Right	60(48.39%)	67(51.54%)	
Blebs number			0.888
< 3	59(47.58%)	63(48.46%)	
≥ 3	65(52.42%)	67(51.54%)	
Operation time (min)	70(53.5, 85)	75(65, 95)	0.009
Abbreviation: PSP, primary spontaneous pneumothorax ; BMI, body mass index.			

Surgical outcomes

Surgical outcomes are summarized in Table 2. Fever was the most common complaint after OK-432 instillation. 28 patients (11.02%) had postoperative air leak lasting longer than 3 days. 3 of them had air leak lasting more than 7 days. Patients in the OK-432 group had a trend towards a decreased rate of prolonged air leak (2.42% vs. 19.23%; $p < 0.001$). Moreover, the duration of chest drainage was shorter in OK-432 group than that in control group (3.8 ± 1.26 days vs. 4.3 ± 1.71 days, $p = 0.008$), and the mean hospital stay was also shorter in the OK-432 group (7.1 ± 2.97 days vs. 8.1 ± 2.38 days, $p = 0.003$). Pleural detachment occurred in 4 patients after removal of chest tube. Hemothorax developed in 4 patients, and

empyema occurred in 3 patients. Patients with pleural detachment or hemothorax were treated by thoracocentesis and those with empyema were managed by closed-tube thoracostomy and antibiotics. However, there was no significant differences between OK-432 group and control group in postoperative chest pain, postoperative drainage (the first 24 hr, the second 24 hr and the third 24 hr) and complication. No operative death occurred in both groups.

Table 2
Surgical outcomes of both groups

Variables	OK-432 Group [†] (n = 124)	Control Group [†] (n = 130)	p Value
Postoperative chest drainage, d	3.8 ± 1.26	4.3 ± 1.71	0.008*
Length of hospital stay, d	7.1 ± 2.97	8.1 ± 2.38	0.003*
Postoperative 1st 24h VAS score	5.4 ± 1.16	5.2 ± 0.95	0.161
Postoperative drainage			
1st 24h drainage, ml	165 (110, 210)	150 (105, 200)	0.063
2nd 24h drainage, ml	90 (52.5, 135)	90 (70, 140)	0.342
3rd 24h drainage, ml	40 (20, 70)	30 (20, 60)	0.607
Postoperative air leak > 3 days	3 (2.42%)	25 (19.23%)	< 0.001*
Complication			
Pleural detachment	1 (0.81%)	3 (2.31%)	0.356
Hemothorax	3 (2.42%)	1 (0.77%)	0.623
Empyema	1 (0.81%)	2 (1.54%)	0.610
Fever	38 (30.65%)	17 (13.08%)	0.001*
Recurrence	1 (0.81%)	10 (7.69%)	0.010*
[†] Data are presented as mean ± SD or frequency (%)			
* <i>p</i> < 0.05			
Abbreviation: VAS, visual analogue scale.			

Recurrence and risk factors

During the follow-up period (median, 36 months), ipsilateral pneumothorax recurrence occurred in 11 patients (4.33%), including 1 patients (0.81%) in the OK-432 group and 10 patients (7.69%) in the control group. There was significant difference between the OK-432 group and the control group (*p* =

0.010). For those recurrence cases, they were managed in a variety of fashions (Table 3). 4 of 10 patients were treated with thoracentesis and OK-432 pleurodesis, and the rest of those underwent a repeated VATS in the control group. In the OK-432 group, the sole recurrence case received a reoperation finally.

Table 3
Treatments of recurrent postoperative pneumothorax

Treatments	Control Group (n = 130)	OK-432 Group (n = 124)
Thoracentesis and use of OK-432	4 (40%)	0 (0%)
Reoperation	6 (60%)	1 (100%)
Total	10	1

Kaplan-Meier curves for each group are shown in FIGURE 2. The two curves did not diverge immediately after surgery. No convergence was found between the both curves during the whole follow-up period. Additional OK-432 pleurodesis demonstrated a lower rate of recurrence comparing with the control group (40 months, 33.1% vs. 52.3%, log-rank $p = 0.023$). The median recurrence time was 35 months (range, 21–44 months) in the OK-432 group and 40 months (range, 21–56 months) in the control group.

As showed in Table 4, we analyzed the association between age, sex, BMI, smoking history, pneumothorax site, pneumothorax size, blebs number, prolonged air leak, complication and recurrence. 7 patients of 29 patients (24.14%) with prolonged air leak led to postoperative recurrence. Prolonged air leak (≥ 3 days) increased the risk of postoperative recurrence, with a related risk value of 11.69 (95% CI, 3.41–40.04, $p < 0.001$). OK-432 pleurodesis was a significant predictor for recurrence by the Cox regression model ($p = 0.013$). Other factors including sex, BMI, smoking history, pneumothorax site, pneumothorax size, blebs number and complication, did not significantly correlate with recurrence.

Table 4
Related risk factors of recurrence

Risk factors	Recurrence rate (%)	RR (95% CI) ^{††}	<i>p</i> value
Group			
Control	10 (7.70)	1	0.013 ^{**}
OK-432	1 (0.81)	0.13(0.02–1.03)	
Age (y)			
< 23	8 (5.33)	1	0.270
≥ 23	3 (3.13)	0.49(0.13–1.85)	
Sex			
Female	2 (6.67)	1	0.347
Male	9 (4.01)	2.24(0.48–10.38)	
BMI			
< 18.5	4 (3.74)	1	0.762
≥ 18.5	7 (4.76)	1.01(0.95–1.07)	
Pneumothorax site			
Left	7 (5.51)	1	0.373
Right	4 (3.15)	0.58(0.17–1.98)	
Pneumothorax size (cm)			
< 2	4 (5.56)	1	0.572
≥ 2	7 (3.85)	0.70(0.20–2.39)	
Blebs number			
< 3	3 (2.46)	1	0.167
≥ 3	8 (6.06)	2.43(0.64–9.15)	
Smoking history			
Yes	2 (6.45)	1	0.509
No	9 (4.02)	0.58(0.13–2.68)	

^{††}RR = relative risk; CI = confidence interval

^{**}*p* < 0.05

Risk factors	Recurrence rate (%)	RR (95% CI) ^{††}	<i>p</i> value
Prolonged air leak			
Yes	7 (24.14)	11.69(3.41–40.04)	< 0.001 ^{**}
No	4 (0.80)	1	
Complication			
Yes	6 (54.55)	1	0.408
No	5 (0.41)	0.37(0.05–2.91)	
††RR = relative risk; CI = confidence interval			
^{**} <i>p</i> < 0.05			

Discussion

Due to the possible recurrence, an adequate pleurodesis is really necessary to reduce the rate of recurrence for postoperative patients with PSP [5, 17, 18]. Combination of pleural abrasion and chemical pleurodesis has become the recommendation for PSP patients [19]. In our study, we found that OK-432 pleurodesis resulted in a significant decrease in the rate of prolonged air leak after VATS, as well as the incidence of ipsilateral recurrence. We then analyzed the role of OK-432 pleurodesis in PSP, and attempted to determine the risk factors influencing the recurrence. To our best knowledge, this is the first retrospective study to observe that prolonged air leak increases the risk of recurrence remarkably and OK-432 pleurodesis reduces the risk of recurrence.

The underlying benefits of OK-432 may be attributed to the inflammation reaction of pleural surface caused by the stimulation of OK-432. This effect reinforces the cutting edge of blebs, which are may occasionally missed during the first surgery, and may promote the pleura symphysis to prevent the recurrence of pneumothorax.

As was shown in above results, patients who received OK-432 pleurodesis had shorter duration of chest tube and hospital stays after the VATS, which were consistent with previous similar studies [13]. It may be largely due to the shorter postoperative air leak. These results indicated that OK-432 was likely to provide better quality of life after surgery compared with unique mechanical pleurodesis. In both groups, just a few patients occurred unpleasant complications, including pleural detachment, hemothorax and empyema, but these complications had been resolved by thoracocentesis or closed-tube thoracostomy combined with antibiotics. No mortality occurred in our study. Consequently, we suggest that OK-432 pleurodesis is safe for PSP patients.

The primary side effects of the pleurodesis with OK-432 were chest pain and fever, which almost could be well-relieved by nonsteroidal anti-inflammatory medications (NSAIDs) [12, 20]. 38 of 124 patients

suffered fever after OK-432 chemical pleurodesis, which was significantly higher than the control. Fever is one of the most common complication, and it was regarded as a kind of response to inflammatory reaction from chemical pleurodesis. Several studies confirmed that tetracycline pleurodesis induced 9% – 81% of fever [21, 22]. Interestingly, fever spontaneously disappeared after about 2 days by conservative measures in all these patients. As for chest pain, the majority of patients used NSAIDs to relieve postoperative chest pain, and only a little proportion of patients needed different dose of meperidine to relieve severe pain. Prolonged air leak was another complication in this study (2.45% in OK-432 group and 19.24% in control group), which was lower compared to other analogous studies [23, 24]. By means of the instillation of OK-432 or fresh frozen plasma, all air leaks could be settled successfully.

Many chemical irritants, such as minocycline, tetracycline and talc, have been used to decrease the rate of recurrence or hasten the cutting edge of air leak in spontaneous pneumothorax patients [10, 13, 25]. OK-432 was chosen for chemical pleurodesis in our study because it was easily purchased, safe, relatively low-cost, and available. The reported recurrence rate after VATS bullectomy alone was 16.0% – 23.9% [23, 26]. *Cheng-Hung How* argued that the recurrence was noted in one patient in the OK432 group and none in the minocycline group during a median follow-up of 16 months [12]. Moreover, another study showed that the rate of recurrent ipsilateral pneumothorax was 3.8% for PSP patients with high recurrence risk, who received pleural abrasion with minocycline [27]. The recurrence rate of our study was 0.81% in OK-432 group, suggesting that OK-432 pleurodesis was an effective way to prevent the recurrence of PSP. What caused the recurrence? Maybe it was attributed to the regeneration of newly-formed bulla, especially around the previous resection site. During these reoperation procedures, we found more or less bullas on the apex of lung which were newly-formed or missed in the first operation.

A variety of treatment approaches were applied to reduce the recurrence [28, 29]. The best procedure has not yet been established. Researchers have devoted themselves to analysis the risk factors for recurrent pneumothorax after VATS. Our results indicate that sex, age, BMI, smoking history, pneumothorax site, pneumothorax size, blebs number and complication did not correlate with postoperative recurrence, but prolonged air leak (> 3days) increased the risk of postoperative recurrence. However, a recent report holds that absence of smoking history, comorbidities, previous surgery for ipsilateral spontaneous pneumothorax and hand stitching increase the risk of postoperative recurrence [30]. To our best knowledge, this is the first case-control study to reveal that OK-432 after pleural abrasion reduces the rate of recurrence compared with single mechanical pleurodesis. So we carefully recommend that OK-432 chemical pleurodesis should be taken into consideration for SPS patients, especially if postoperative prolonged air leak occurred.

Limitations

Some limitations should also be acknowledged. Firstly, there were differences in both groups about smoking history and operation time, which may influence the surgical outcomes at some extent. Secondly, the median recurrence time was 40 months in the control group, so the relatively short follow-up period possibly underestimated the recurrence rate. Thirdly, the level of operation was associated with

the learning curve of VATS technique. Surgical levels vary from person to person, and the level of young surgeons is inferior to those senior in general. Moreover, 3 patients in the control group experienced persistent postoperative air leak (over 7 days) that resolved with chemical pleurodesis with OK-432, and no recurrence occurred in these patients, which may cause bias on the results. Finally, this was a retrospective, small, single-center study, and further prospective, randomized, long-term follow-up researches are needed to rigorously test the efficacy of this treatment.

Conclusion

In conclusion, OK-432 pleurodesis after pleural abrasion is a safe and effective method and it can reduce the recurrence risk in PSP patients.

Abbreviations

CI

confidence interval

PSP

primary spontaneous pneumothorax

VATS

video-assisted thoracoscopic surgery

KE

Klinische Einheit

VAS

visual analogue scale

RR

relative risk

BMI

body mass index

NSAIDs

nonsteroidal anti-inflammatory medications

Declarations

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Author information

Contributions

Zhang K and Zhang J designed the study; Wu WB, Chen HG and Wu YH collected clinical data; Li XJ performed the statistic analysis; Zhang K and Wang WB wrote the manuscript; Zhang J revised the manuscript. All authors issued final approval for the version to be submitted.

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Ethics declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of THird Affiliated Hospital of Sun Yat-sen University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Diagram illustrating the study flow.

Figure 2

Kaplan-Meier curves for each group indicating the recurrence freedom rates.