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Original Article

A Comparison of the Efficacies of OK-432 and Talc Slurry for Pleurodesis in Patients with Prolonged Air Leak after Pulmonary Resection

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Purpose: A prolonged air leak (PAL) is one of the common postoperative complications of pulmonary resection. The aim of this study was to evaluate the efficacy and safety of pleurodesis with sterile talc or OK-432 for postoperative air leak.
Methods: Patients with postoperative air leak who received chemical pleurodesis using sterile talc or OK-432 were retrospectively identified from medical records data. For pleurodesis with either agent, prior assessment and approval by the hospital safety department were carried out for each case, in addition to individual consent.
Results: Between February 2016 and June 2022, 39 patients had PALs and underwent chemical pleurodesis. Among them, 24 patients received pleurodesis with talc (Talc group) and 15 with OK-432 (OK-432 group). The leak resolved after less than two pleurodesis treatments in 22 patients (91.7%) in the Talc group compared with 14 patients (93.3%) in the OK-432 group. Pleurodesis significantly increased white blood cell counts, C-reactive protein concentration, and body temperature in the OK-432 group compared with that in the Talc group ($p < 0.001$, $p = 0.003$, and $p < 0.001$, respectively).
Conclusions: Pleurodesis with talc may be an effective treatment option for postoperative air leak. Our findings suggest that talc was as effective as OK-432 and resulted in a milder systemic inflammatory response.

Keywords: postoperative air leak, pleurodesis, talc, OK-432

Introduction

Postoperative air leakage from the lung parenchyma is known to be one of the most common complications following lung surgery.[1] However, even if air leaks are observed postoperatively, they often resolve spontaneously within the first 24 hours; Between 10% and 20% of patients, however, continue to have air leaks afterward.[2] Air leaks usually resolve within the first 5 days postoperatively with conservative chest drainage. In contrast, prolonged air leaks (PALs), usually defined as air leaks of ≥5 days, can lead to prolonged chest tube management, delayed effective physiotherapy and rehabilitation, longer hospital stay, increased morbidity, higher healthcare costs, and patient mortality.[3–5]

Several treatment options have been proposed for PAL. PAL is usually first managed conservatively with a water-sealed chest drain. When PAL persists, chemical pleurodesis is one of the main treatment options, together with the insertion of endobronchial valves and/or surgical intervention, as previously described.[6–8]

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In the more than 100-year history of pleurodesis, various methods have been proposed and tested to achieve effective pleurodesis. As pleurodesis is frequently used in malignant pleural effusion, many studies have been performed in this patient population. These methods include mechanical abrasion[9] and the installation of various chemicals. In particular, the following agents have been reported in pleurodesis for PAL: 50% glucose,[10] tetracycline,[11] minocycline,[12] autologous blood,[13] OK-432, and talc.

While talc was often used for pleurodesis in Europe and the United States in previous reports and in accordance with clinical practice guidelines,[14,15] OK-432 was often used for pleurodesis in Japan because talc has not been approved for some time. In Japan, OK-432 is considered highly effective and safe as a pleurodesis agent and is widely used in pleurodesis, although OK-432 has been approved only for the prevention of re-accumulation of malignant pleural effusion in Japan. The efficacy of OK-432 for pleurodesis was evaluated in prospective comparative studies involving East Asian patients with malignant pleural effusion, and higher success rates with OK-432 are reported compared with mitomycin C or cisplatin plus etoposide.[16,17] OK-432 has been used frequently because of these highly credible studies, although OK-432 has not been approved for PAL.

In postoperative management, treatment that induces a systemic inflammatory reaction should be avoided. Additionally, because systemic inflammatory reactions that induce fever make it difficult to distinguish fever owing to a surgical site infection, the choice of an agent should be based on its efficacy as well as the chance of inducing a systemic inflammatory reaction. To the best of our knowledge, no previous studies have directly compared OK-432 and talc as agents for pleurodesis in postoperative PAL patients. Therefore, the present study aimed to evaluate the efficacy and safety of these agents in patients with postoperative PAL.

Materials and Methods

Patients and ethical issue

Our institutional ethical committee approved this retrospective study (approval number: 22-118; approval date: 11 November 2022). The need to obtain informed consent from each patient was waived because of its retrospective setting; however, patients were given the opportunity to object to taking part in the study by providing research information on the webpage of our institution.

Besides, as there were no drugs approved for chemical pleurodesis until 2022, the use of drugs for chemical pleurodesis was reviewed and approved by the hospital safety department for each individual case, in addition to obtaining the patient's consent for the use of the drug.

Postoperative PAL patients undergoing pleurodesis with OK-432 or sterile talc as the first treatment for PAL were retrospectively identified from electronic medical records. OK-432 was used for pleurodesis until December 2018, and talc was used in all subsequent pleurodesis procedures. We did not use any other agents for chemical pleurodesis. However, pleurodesis with autologous blood has been used in some cases and these cases were excluded in this study. Patients treated with OK-432 were defined as the "OK-432 group" and those treated with talc were defined as the "Talc group." Postoperative PAL was defined as air leak that persisted ≥5 days after surgery. The decision whether and when to perform pleurodesis was made by the medical team in charge. We have administered the same drug for the first two procedures to correctly assess the effectiveness of chemical pleurodesis. Patients who received pleurodesis within 4 days after surgery were excluded, even if the purpose of pleurodesis was to stop an air leak. This is because it cannot be ruled out that cases treated within 5 days may have spontaneously stopped air leaking within 5 days and may have been patients who did not meet the definition of PAL. Patients whose clinical course was uncertain for less than 30 days after pleurodesis were also excluded.

Pleurodesis procedure

A trocar catheter was usually inserted in the operation theater under general anesthesia; however, an additional catheter was inserted under local anesthesia, in cases in which one catheter was insufficient to drain the air properly owing to a massive air leak. Pleurodesis was performed through either catheter. In cases in which continuous suction was performed, this was discontinued during pleurodesis. OK-432 (Chugai Pharmaceutical Co., Tokyo, Japan) was prepared at a dose of 5–10 Klinische Einheit (KE) units (one unit corresponds to the extraction of 0.1 mg *Streptococcus pyogenes*), which was diluted in 10 mL of sterile saline. The trocar catheter was clamped prior to instillation of diluted adhesive agent through its lateral lumen. OK-432 was prepared at a dose of 5–10 KE units (one unit corresponds to the extraction of 0.1 mg *S. pyogenes*), which was diluted in 20 mL of sterile saline. Sterile high-grade talc (Nobelpharma Co., Ltd., Tokyo, Japan) was prepared at a dose of 4 g, which was suspended in 50 mL of sterile saline. After the agent was injected through a trocar catheter,

Table 1 Patients' characteristics in each group

Factors	Talc group (n = 24)	OK-432 group (n = 15)	p
Sex (male : female)	20:04	15:00	0.146
Age (average, range)	69.0 (47–82)	66.7 (18–82)	0.563
Comorbidities (overlap cases included)			>0.999
COPD	1	3	
Bronchial asthma	1	0	
Interstitial pneumonia	0	1	
ABPA	0	0	
Tuberculosis	0	0	
Diabetes mellitus	7	2	
Chronic renal failure	1	1	
Smoking history (pack × year, range)	55 ± 34.2 (0–120)	39.3 ± 31.8 (0–100)	0.363
Disease subject to surgery			0.5
Lung cancer	19	13	
Pneumothorax	1	2	
Others	4	0	
Surgery type			0.25
Lobectomy	15	8	
Segmentectomy	2	2	
Wedge resection	5	4	
Others	2	1	
Surgery time (min)	224 ± 95	182 ± 78	0.248
Anesthesia time (min)	286 ± 92	242 ± 81	0.306
Period from surgery to pleurodesis (day)	8.3 ± 3.4	6.4 ± 1.1	0.078

COPD: chronic obstructive pulmonary disease; ABPA: allergic bronchopulmonary aspergillosis

the trocar was clamped for 2 hours before resuming continuous suction. Antipyretics or analgesics were prepared to use when the body temperature exceeded 38.0°C or in cases of severe chest pain, respectively. Blood tests were performed immediately before chemical pleurodesis and 1–2 days after pleurodesis. When examining systemic inflammatory changes after drug administration, the pre-dose values were expressed as controls and the post-dose values as ratios to the controls.

Statistical analysis

SPSS version 26 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism version 9.0 (GraphPad Prism Software Inc., San Diego, CA, USA) were used for the statistical analyses and to construct the figures. The results were assessed using the Mann–Whitney test and Wilcoxon matched-pairs signed-rank test. p-Values <0.05 were considered statistically significant.

Results

Between February 2016 and June 2022, 946 patients underwent lung resection in our institution. After the operation, 39 patients (4.1%) had PALs and underwent chemical pleurodesis. Among the 39 patients, pleurodesis was performed in 24 patients using talc (talc group) and in 15 using OK-432 (OK-432 group). The mean instillation dose was 5.2 ± 2.2 g in the talc group and 5.3 ± 1.3 KE in the OK-432 group. **Table 1** shows the patients' characteristics in the two groups. The groups were comparable regarding sex, age, comorbidities, smoking history, specific lung disease, surgery type, surgery time, anesthesia time, and period from surgery to pleurodesis. Patients taking medications such as steroids or immunosuppressive drugs were not included.

Table 2 summarizes the treatment results of the patients in each group. There was no significant difference between the two groups in the number of chemical pleurodesis attempts. In the talc group, the leak stopped after one pleurodesis treatment in 18 patients (75%) vs. 13 patients (86.7%) in the OK-432 group. The leak stopped after less than or equal to two pleurodesis treatments in 22 patients (91.7%) vs. 14 patients (93.3%) in the OK-432 group. When failure cases were excluded, the duration between the first pleurodesis treatment and leak resolution was 3.8 ± 2.2 days in the talc group

Table 2 Results in patients with postoperative PAL, comparing talc or OK-432 as the chemical pleurodesis agent

Factors	Talc group (n = 24)	OK-432 group (n = 15)	p
Number of chemical pleurodesis attempts			0.585
1	18	13	
2	5	2	
3	1	0	
Cessation of air leakage after first pleurodesis	18 (75%)	13 (86.7%)	0.45
Cessation of air leakage after equals or less than two pleurodesis	22 (91.7%)	14 (93.3%)	>0.999
Duration between the first dose and leak cessation (day)*	3.8 ± 2.2	3.4 ± 3.0	0.187
Duration between the first dose and chest tube removal (day)*	5.3 ± 2.5	4.5 ± 3.1	0.205
Duration between the last dose and leak cessation (day)**	3.2 ± 1.7	2.9 ± 2.7	0.547
Duration between the last dose and chest tube removal (day)**	4.7 ± 2.3	4.1 ± 2.7	0.27
Complications (CTCAE grade >3)			
Pyothorax requiring debridement	0 (0%)	1 (6.7%)	0.2

*Failure cases excluded. **Cases with >2 attempts excluded. PAL: prolonged air leak; CTCAE: Common Terminology Criteria for Adverse Events

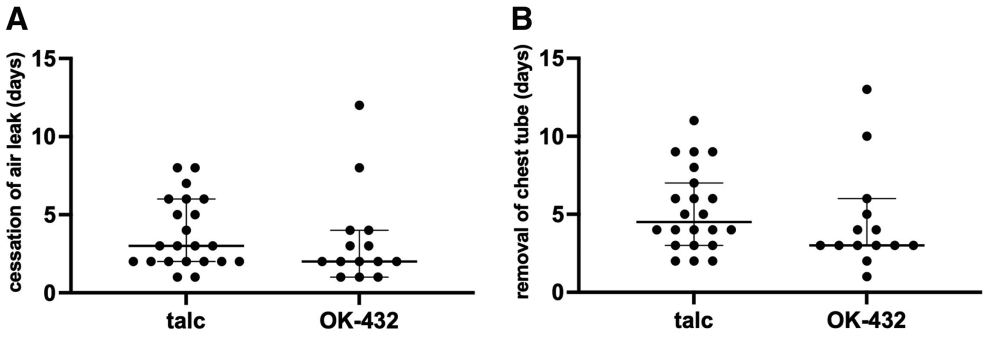

Fig. 1 Comparison of the efficacy of chemical pleurodesis between talc and OK-432. (**A**) Comparison of the time to air leak resolution after pleurodesis between the two groups. (**B**) Comparison of the time to removal of the chest tube between the two groups.

and 3.4 ± 3.0 days in the OK-432 group. The duration between the first pleurodesis treatment and chest tube removal was 5.3 ± 2.5 days in the talc group and 4.5 ± 3.1 days in the OK-432 group. The duration between the final pleurodesis treatment and leak resolution was 3.2 ± 1.7 days in the talc group and 2.9 ± 2.7 days in the OK-432 group (**Fig. 1A**). The duration between the final pleurodesis treatment and chest tube removal was 4.7 ± 2.3 days in the talc group and 4.1 ± 2.7 days in the OK-432 group (**Fig. 1B**). There was no significant difference between the groups regarding these factors (p = 0.304 and p = 0.205, respectively). Regarding severe complications, one case in the OK-432 group developed pyothorax that required debridement, with no such cases in the talc group. No case recurred after removal of the chest tube in either group. None of the cases were treated with other combination of treatments, such as Endobronchial Watanabe Spigot.

Figure 2 shows the changes in the systemic inflammatory markers in peripheral blood before and after pleurodesis in the talc group. White blood cell counts increased slightly but significantly after talc pleurodesis compared with before pleurodesis (p = 0.012). In contrast, C-reactive protein did not increase after talc pleurodesis (p = 0.270). Following pleurodesis, white blood cell counts in the peripheral blood were significantly higher in the OK-432 group vs. those in the talc group (p = 0.0003; **Fig. 3A**). Additionally, neutrophils counts increased significantly in the OK-432 group compared with those in the talc group (p = 0.0002; **Fig. 3B**), while no difference was observed for eosinophils or lymphocytes (p = 0.49 and p = 0.60; **Figs. 3C** and **3D**, respectively). C-reactive protein concentrations were also significantly higher in the OK-432 group than those in the talc group (p = 0.003; **Fig. 4A**). Body temperature also was significantly higher in the OK-432 group

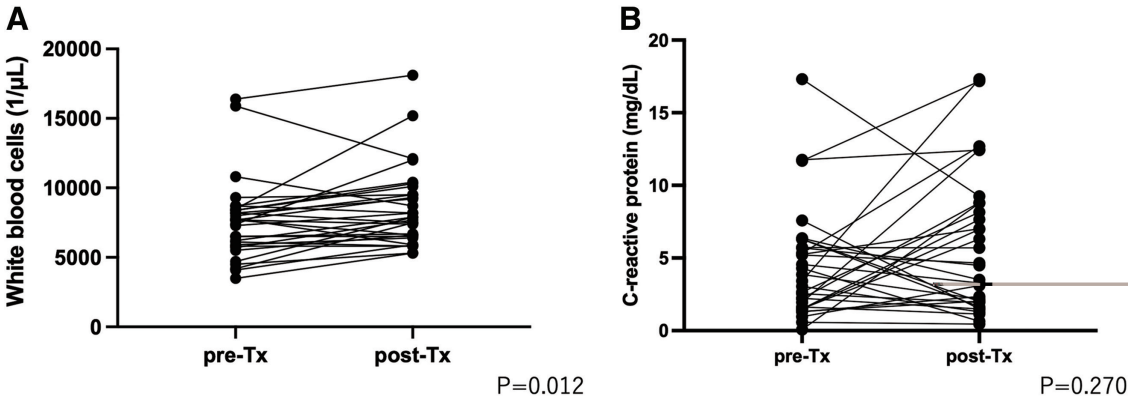

Fig. 2 Changes in inflammatory marker concentrations in the talc pleurodesis group. (**A**) Comparison of white blood cell counts pre- and post-pleurodesis. (**B**) Comparison of the C-reactive protein data pre- and post-pleurodesis.

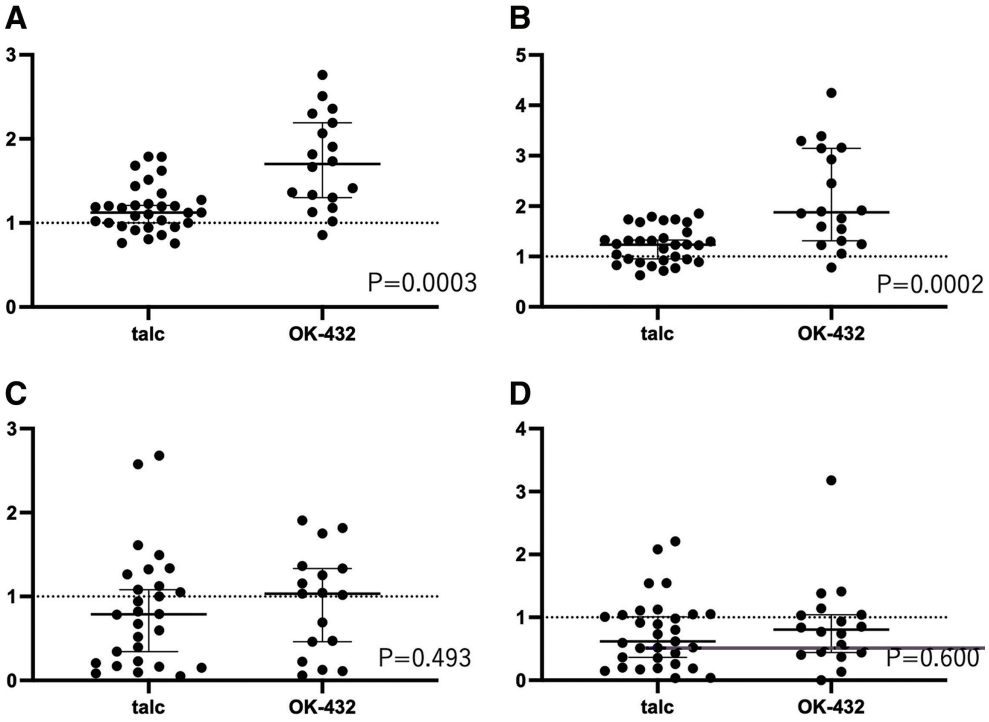

Fig. 3 Comparison of white blood cell counts in peripheral blood in patients with chemical pleurodesis between talc and OK-432. The index was the ratio of increase in posttreatment data to the pretreatment data. Comparisons of the increases in (**A**) total white blood cell count, (**B**) neutrophil count, (**C**) eosinophil count, and (**D**) lymphocyte count between the two groups.

compared with that in the talc group when the body temperature before pleurodesis and 1 day after pleurodesis were compared ($p < 0.001$; **Fig. 4B**).

Discussion

In this study, talc and OK-432 were compared as chemical pleurodesis agents for PALs after lung resection. The results showed almost equal efficacy between the agents, and that talc was characterized by a less intense systemic inflammatory response immediately after pleurodesis compared with OK-432.

Several basic studies have been performed to determine the mechanism of action of talc pleurodesis. Muta et al. examined the visceral pleura histologically and found that the pleura was significantly thicker with talc compared with OK-432 when pleurodesis was performed in a mice model.[18] Mierzejewski et al. performed in vitro

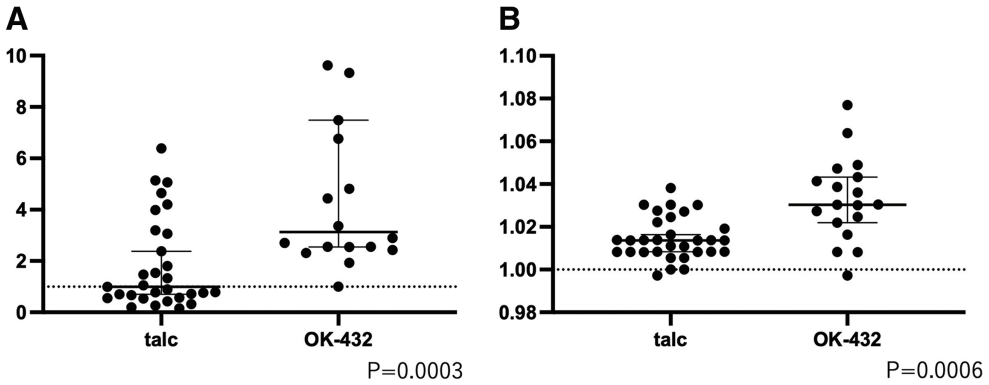

Fig. 4 Comparison of inflammatory markers other than white blood cell count in patients with chemical pleurodesis between talc and OK-432. The index was the ratio of increase in posttreatment data to the pretreatment data. Comparison of (**A**) C-reactive protein concentration in peripheral blood and (**B**) body temperature between the two groups.

experiments and reported that the use of various agents on mesothelial cells increased the concentration of interleukin-1 beta and other inflammatory markers.[19] Rivas et al. reported that talc induced a foreign body reaction as a result of peritoneal mesothelial inflammation and fibrosis associated with foreign body giant cells.[20] Kwek et al. reported that 18-fluoroxydeoxyglucose uptake was seen over a relatively long period of time after talc pleurodesis, concordant with areas of pleural thickening, but without evidence of malignancy.[21]

When carefully examining the results of the present study, the efficacy of the first pleurodesis with talc tended to be slightly lower than that with OK-432, although there was no significant difference. In comparison, the efficacy after the second pleurodesis with talc was very high and did not differ significantly from that with OK-432. The systemic inflammatory response was obviously milder in the talc group vs. that in the OK-432 group. Considering the results of previous reports, the following deductions can be made: At clinical doses, talc initially elicits a milder inflammatory response than that seen with other drugs. However, talc may elicit a concomitant localized foreign body reaction over time, resulting in further thickening of the pleura and reinforcing the effect of pleurodesis. We speculate that it is through these mechanisms that talc was equally effective as OK-432 and had fewer side effects.

Ideal pleurodesis agents are currently being sought to be identified. It is currently believed that the formation of fibrin adhesions and fibrosis is a critical process in the formation of a permanent bond between the visceral and parietal pleurae.[22] It is believed that the most important mechanism involved in the formation of pleural adhesion is inflammation, although there are a variety of pathways underlying the formation of these adhesions.[23] Essentially, all agents used in pleurodesis behave as local irritants, resulting in pleural adhesions. On the other hand, it is unfavorable that systemic inflammation is somehow involved in the formation of pleural adhesions. The ideal pleurodesis agent should produce durable adhesions with only local inflammation and without systemic inflammation, as much as possible. Although there is no ideal pleurodesis agent that is easily available and exhibits strong adhesion-promoting properties but not systemic inflammation-promoting properties, talc may be one agent that comes close to satisfying these requirements.

Some may argue that talc pleurodesis carries the risk of developing acute respiratory distress syndrome (ARDS). Indeed, in the 1980s and 1990s, several patients were reported to have developed ARDS after talc pleurodesis, which is raising safety concerns.[24] In response to these criticisms, some animal studies have shown that smaller talc particles and higher doses of talc may increase the risk of acute respiratory failure.[25,26] A prospective study was subsequently conducted and revealed that none of the 558 patients who received pleurodesis with 4 g of larger particle talc developed ARDS.[27] Similarly, no cases of ARDS were reported in more than 400 cases of pleurodesis with large-particle-size talc in patients with recurrent pneumothorax.[28] These studies suggest that a certain level of safety is expected with talc pleurodesis.

Regarding the method of talc administration, in previous reports, talc was administered by thoracoscopic poudrage[28,29]; however, we used the slurry method. No significant difference in efficacy has been reported between poudrage and the slurry method for malignant

pleural effusions.[30] Therefore, the slurry method was adopted in our institution, considering the minimal invasiveness, as poudrage requires thoracoscopy. Nevertheless, the results in the talc group in our study were similar to those reported in previous reports, and it was inferred that the efficacy of the slurry method was not significantly different from that of poudrage.

This study has some limitations. First of all, this was a retrospective study; therefore, selection bias or recall bias is possible. Additionally, we could not rule out the possibility of confounding background factors because historical controls were used as study controls, and the surgeries were not performed at the same time. Furthermore, the use of historical controls may lead to a possible evaluation bias.

Conclusion

Talc pleurodesis showed similar efficacy and safety of OK-432, and resulted in a milder systemic inflammatory response in patients with postoperative PAL compared with pleurodesis with OK-432. Pleurodesis with talc may be an effective treatment option for postoperative PAL. Prospective studies are required to investigate this issue further.

Disclosure Statement

None declared.

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