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【 ORIGINAL ARTICLE 】

Risk Factors for Chest Pain and Fever in Patients Undergoing Pleurodesis with OK-432

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Abstract:

Objective In Japan, pleurodesis is often performed using OK-432. However, OK-432 may cause severe chest pain and fever. The risk factors for these complications are unclear. The aim of this study was to identify the risk factors for chest pain and fever caused by pleurodesis with OK-432.

Methods The clinical data of 94 patients who underwent pleurodesis with OK-432 were retrospectively analyzed. Patients who developed chest pain (indicated by a record of rescue pain medication) and/or fever (a recorded temperature of >38℃) were identified. A logistic regression analysis was performed to determine the risk factors for these complications.

Results Rescue medication for chest pain was required by 43.6% of the patients and 40.4% developed pyrexia after pleurodesis with OK-432. The univariate analysis showed that the likelihood of requiring rescue medication for chest pain was significantly increased in patients of <70 years of age (p=0.028) and in those who were not premedicated with a nonsteroidal anti-inflammatory drug (NSAID; p=0.003). Age <70 years (adjusted odds ratio 2.97, 95% confidence interval 1.10-8.00, p=0.031) and a lack of premedication with an NSAID (adjusted odds ratio 4.21, 95% confidence interval 1.47-12.04, p=0.007) remained significant factors in a multivariate analysis. The absence of NSAID premedication was the only statistically significant risk factor for fever in the univariate analysis (p=0.034). The multivariate analysis revealed no significant risk factors for fever.

Conclusion The results of the present study suggest that premedication with an NSAID might be useful for preventing the chest pain caused by pleurodesis with OK-432. Furthermore, caution is advised when managing chest pain in adults of <70 years of age. Prospective studies should be performed to further investigate this issue.

Key words: OK-432, pleurodesis, chest pain, fever, risk factors

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Introduction

Pleurodesis is commonly performed in the treatment of patients with malignant pleural effusion, complications after lung surgery, and pneumothorax. The procedure entails the introduction of a sclerosing agent into the pleural space to cause inflammation and the obliteration of the space between the visceral and parietal pleura. OK-432 (a purified preparation derived from *Streptococcus pyogenes*) is commonly used as a sclerosing agent in Japan. Several studies have shown that OK-432 is useful for pleurodesis (1-3). In Western countries, talc has been the gold standard sclerosing agent for pleurodesis for many years. Talc was approved for pleurodesis in Japan in December 2013, but only for patients with malignant pleural effusion. Thus, OK-432 is a

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well-established agent that has been conventionally used for patients with malignant pleural effusion, postoperative complications, and pneumothorax. However, pleurodesis using OK-432 is associated with complications, particularly chest pain and fever (1, 4), the reasons for which have not been clarified. The aim of this study was to identify the risk factors for complications in patients undergoing pleurodesis with OK-432.

Materials and Methods

Patients

We retrospectively reviewed the medical records in the Department of General Thoracic Surgery, Kyorin University Hospital, and identified 97 potential study participants who had undergone pleurodesis with OK-432 between February 2013 and July 2016. Three patients were excluded (the volume of OK-432 was unclear in two patients and the body height was not measured in 1 patient); thus, the data of 94 patients were available for the analysis. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee of Kyorin University Hospital (approval number: 776).

Procedure

In all cases, OK-432 (Picibanil, Chugai Pharmaceutical, Tokyo, Japan) was injected into the pleural space via a 16-24 Fr chest tube connected to a water-sealed drainage system. OK-432 was administered at a dose of 5 KE or 10 KE (Klinische Einbeit; 1 KE contains 0.1 mg of dried cocci). Two hundred milligrams of minocycline and lidocaine 1% could also be administered at the discretion of the attending physician. These drugs were suspended in 20-100 mL of saline or autologous blood. Lidocaine (1%) was administered at the same time or just prior to the administration of OK-432. The physician also determined the position of the patient in bed. The analgesic agents used before pleurodesis varied from patient to patient.

Evaluation

Chest pain was defined as the need for rescue pain medication and fever was defined as a body temperature of >38℃ after pleurodesis. Fever was evaluated in accordance with the National Cancer Institute Common Terminology Criteria version 4.0.

The risk factors for chest pain and fever

The following demographic and clinical variables were investigated to determine their relationship with chest pain and fever after pleurodesis with OK-432. The variables were divided into two groups based on the approximate median values: age (<70 or ≥70 years), sex (male or female), body height (≥160 or <160 cm), body weight (≥55 or <55 kg), body surface area (≥1.6 or <1.6 m^2), disease (malignant pleural effusion or not), albumin (≥3.2 or <3.2 g/dL), C-reactive protein (≥3.0 or <3.0 mg/dL), 24-h drainage volume on the day before pleurodesis (≥150 or <150 mL), dose of OK-432 (10 or 5 KE), administration of minocycline (yes/no), administration of autologous blood (yes/no), volume of solution (100 or ≤50 mL), administration of lidocaine (1%; yes/no), and premedication with an NSAID, acetaminophen, and/or opioid (yes/no).

Statistical analysis

Potential risk factors for chest pain and fever caused by pleurodesis with OK-432 were tested by a logistic regression analysis. Factors with an odds ratio <0.5 or >2.0 in the univariate analysis were included in a multivariate analysis. All of the statistical analyses were performed using the StatView software program (version 5 for Windows, SAS Institute, Cary, USA). p values of <0.05 were considered to indicate statistical significance.

Results

Patients

The clinical and demographic characteristics of the 94 patients (male, n=63; female, n=31) who underwent pleurodesis with OK-432 are shown in Table 1. Forty-five of these patients had malignant pleural effusion, 27 had postoperative complications, and 22 had pneumothorax. All 27 postoperative patients had undergone pulmonary tumor resection by video-assisted thoracic surgery. Eighty-four patients (89.4%) received OK-432 at a dose of 10 KE, and 10 (10.6%) received OK-432 at a dose of 5 KE. Eleven patients (11.7%) also received minocycline (200 mg). Forty-eight patients (51.1%) received lidocaine (1%), the volume of which was 10 mL in 41 patients, 20 mL in 5 patients, and unknown in 2 patients. For pain relief, 66 patients (70.2%) were premedicated with an NSAID, 22 with acetaminophen (23.4%) and 29 with an opioid (30.9%). The NSAIDs included loxoprofen (60 mg, orally, thrice daily; n=61, 92.4%) or celecoxib (200 mg or 400 mg, orally, once daily; n=5, 7.6%). Various acetaminophen and opioid regimens were used. Acetaminophen was administered orally at a dose of 325-1,600 mg per day. The daily acetaminophen doses were 1,600 mg for 2 patients; 1,300 mg for 13 patients; 1,200, 975, and 650 mg for 1 patient each; 325 mg for 2 patients; and unknown for 2 patients. The opioids prescribed included tramadol, oxycodone, morphine, and fentanyl. The most commonly used opioid was tramadol (150 mg, daily), which was administered to 19 patients.

The complications of pleurodesis

The complications of pleurodesis with OK-432 are shown in Table 2. Forty-one patients (43.6%) required rescue medication for chest pain, which was usually an NSAID (in 58.5% of cases), and which was most often diclofenac (50 mg, by suppository). Thirty-eight patients (40.4%) developed fever, which was graded as <3 in all cases.

Table 1. Patient Clinical and Demographic Characteristics (n=94).

	Patients (n)
Median age, years (range)	68.5 (23-91)
Sex, Male/Female	63/31
Median body height, cm (range)	161.2 (143.3-175.8)
Median body weight, kg (range)	54 (32.3-89.9)
Median body surface area m^2 (range)	1.56 (1.172-1.984)
Disease	
Malignant pleural effusion	45
Complication of lung surgery	27
Pneumothorax	22
Median albumin, g/dL (range)	3.2 (1.5-4.7)
Median C-reactive protein, mg/dL (range)	3.1 (0.1-21.6)
Median 24-h drainage volume on the day before pleurodesis, mL (range)	155 (0-2,300)
Dose of OK-432	
10 KE/5 KE	84/10
Administration of minocycline	
Yes/No	11/83
Administration of lidocaine 1%	
Yes/No	48/46
Administration of autologous blood	
Yes/No	13/81
Volume of solution	
≤50 mL/100 mL	43/51
Analgesic premedication	
NSAID	
Yes/No	66/28
Acetaminophen	
Yes/No	22/72
Opioid	
Yes/No	29/65

KE: Klinische Einbeit, NSAID: nonsteroidal anti-inflammatory drug

The risk factors for needing rescue medication to treat OK-432-related chest pain and fever

Among the clinical factors that were entered in the univariate analysis, age <70 years and no premedication with an NSAID were statistically significant predictors of the need for rescue medication to manage pleurodesis-related chest pain (p=0.028 and p=0.003, respectively; Table 3). No use of lidocaine (1%) and no premedication with acetaminophen or an opioid were not significant risk factors.

In the multivariate analysis, age <70 years, and no premedication with an NSAID were identified as significant independent predictors of the need for rescue medication to manage pleurodesis-related chest pain (adjusted odds ratio 2.97, 95% confidence interval 1.10-8.00, p=0.031, and adjusted odds ratio 4.21, 95% confidence interval 1.47-12.04, p=0.007, respectively; Table 4). A lack of premedication with an NSAID was the only statistically significant predictor of fever in the univariate analysis (p=0.034); age <70 years and a volume of OK-432 exceeding 100 mL tended to be associated with fever, but not to a statistically significant extent (Table 5). However, the multivariate analysis revealed no significant risk factors for fever (Table 6). Although it was not statistically significant, the use of NSAIDs tended to be associated with fever caused by pleurodesis with OK-432 (adjusted odds ratio 2.43, 95% confidence interval 0.95-6.22, p=0.065).

Table 2. Complications of Pleurodesis.

Rescue medication for chest pain, n (%)	41 (43.6)
Rescue medicine	
NSAID	24
Acetaminophen	6
Opioid and acetaminophen	5
Opioid	4
Pentazocine	2
Fever, n (%)	38 (40.4)
Grade 1	29
Grade 2	9
Grade 3	0

NSAID: nonsteroidal anti-inflammatory drug

Discussion

To date, there have been no reports on the risk factors for complications of pleurodesis using OK-432. In the present study, we made some important clinical observations. In particular, age <70 years and the absence of premedication with an NSAID were statistically significant predictors of the need for rescue medication to manage chest pain.

The mechanism of the therapeutic effects of OK-432 for malignant effusion is thought to involve the induction of the release of various inflammatory cytokines, such as tumor necrosis factor-α, interferon-γ, interleukin-1, and interleukin-8 (5, 6), which cause the fusion of the parietal and visceral pleurae; however, it is associated with an increased risk of adverse effects (chest pain and fever) from severe pleuritis. In this study, the rates of chest pain and fever due to pleurodesis with OK-432 were 43.6% and 40.4% respectively. This is consistent with previous reports (1, 4).

Chest pain was less common in elderly adults (≥70 years) than in their younger adult counterparts (<70 years). It is known that the immune response decreases with increasing age. Age-associated changes in the signal transduction and function of neutrophils and in the development and function of lymphocytes have been reported (7, 8). Given our finding that chest pain was less common in elderly adults, it may be that the inflammation triggered by the immune response to pleurodesis with OK-432 is milder in that age group. Fever was also less common in elderly adults; albeit, not significantly so.

The absence of premedication with an NSAID was a significant predictor of the need for rescue medication to manage chest pain. There is no consensus on the use of premedication for pleurodesis (9). Animal studies have shown that NSAIDs may impair the action of agents used for pleurodesis (10). Thus, there is a widespread belief that

Table 3. Univariate Analysis of Factors Associated with Rescue Medication for Chest Pain after Pleurodesis.

		OR	95% CI	p value
Age, years	<70/≥70	2.60	1.11-6.10	0.028
Sex	Male/Female	0.75	0.32-1.78	0.514
Body height, cm	≥160/<160	1.43	0.62-3.31	0.397
Body weight, kg	≥55/<55	0.50	0.22-1.16	0.105
Body surface area, m^2	≥1.6/<1.6	0.56	0.24-1.32	0.183
Disease	Malignant pleural effusion	1.07	0.47-2.41	0.877
Albumin, g/dL	≥3.2/<3.2	0.77	0.34-1.75	0.533
C-reactive protein, mg/dL	≥3.0/<3.0	0.87	0.38-1.97	0.736
24-h drainage volume on the day before pleurodesis, mL	≥150/<150	1.03	0.46-2.34	0.936
Dose of OK-432	10 KE/5 KE	1.93	0.47-7.97	0.365
Administration of minocycline	Yes/No	1.09	0.31-3.85	0.896
Administration of autologous blood	Yes/No	2.33	0.70-7.74	0.168
Volume of solution	100 mL/≤50 mL	0.96	0.42-2.17	0.919
Administration of lidocaine 1%	No/Yes	0.99	0.44-2.24	0.979
NSAID	No/Yes	4.22	1.64-10.85	0.003
Acetaminophen	No/Yes	0.44	0.17-1.17	0.099
Opioid	No/Yes	0.41	0.17-1.01	0.053

OR: odds ratio, CI: confidence interval, KE: Klinische Einbeit, NSAID: nonsteroidal anti-inflammatory drug

Table 4. Multivariate Analysis of Factors Associated with Rescue Medication for Chest Pain after Pleurodesis.

		OR	95% CI	p value
Age	<70/≥70	2.97	1.10-8.00	0.031
Administration of autologous blood	Yes/No	3.19	0.85-12.05	0.086
NSAID	No/Yes	4.21	1.47-12.04	0.007
Acetaminophen	No/Yes	0.72	0.16-3.18	0.662
Opioid	No/Yes	0.68	0.18-2.51	0.557

OR: odds ratio, CI: confidence interval, NSAID: nonsteroidal anti-inflammatory drug

NSAIDs should be avoided before the procedure. A multicenter randomized trial (TIME1) that compared the effects of opioids versus NSAIDs and larger versus smaller chest tube sizes on pain control in patients undergoing talc pleurodesis for malignant pleural effusion found that there was no significant difference in the pain scores of patients premedicated with NSAIDs or opiates and that the efficacy of pleurodesis at 3 months was not inferior in patients who were treated with NSAIDs (11). In terms of pleurodesis for spontaneous pneumothorax, it has been reported that the use of an NSAID obviates the need for narcotics without increasing the rate of recurrence (12).

The intrapleural administration of local analgesia just before the administration of the sclerosing agent has been suggested (9, 13); however, there is little evidence to support this recommendation. Furthermore, the present study shows that non-administration of lidocaine (1%) did not increase the risk of chest pain. A prospective study is needed to determine whether the administration of lidocaine (1%) has any benefit in patients undergoing pleurodesis. Pleurodesis with minocycline is reported to cause chest pain (14). However, the risk of chest pain was not increased in this study. This is thought to be due to the small number of patients who underwent pleurodesis with minocycline.

The present study is associated with several limitations, including its retrospective nature, single-center design, small study population, and a patient selection bias. In addition, this study did not review the relationship between success or failure and the complications of pleurodesis because the objective of this study was to analyze risk factors; the success of pleurodesis for malignant pleural effusion, and the incidence of complications of lung surgery and pneumothorax were not evaluated. It is necessary to investigate the association between the complications of pleurodesis and the outcomes. Furthermore, in Japan, OK-432 is the preferred sclerosing agent, whereas in Western countries talc pleurodesis has been the gold standard for the treatment of malignant pleural effusion for many years. Talc pleurodesis also causes chest pain and fever (15, 16). Further investigations are needed to identify the risk factors for complications caused

Table 5. Univariate Analysis of Factors Associated with Fever after Pleurodesis.

		OR	95% CI	p value
Age, years	<70/≥70	2.07	0.88-4.84	0.095
Sex	Male/Female	1.68	0.68-4.14	0.260
Body height, cm	≥160/<160	1.67	0.71-3.91	0.240
Body weight, kg	≥55/<55	0.90	0.39-2.07	0.801
Body surface area	≥1.6/<1.6	0.84	0.36-1.95	0.681
Disease	Malignant pleural effusion	1.38	0.60-3.15	0.447
Albumin, g/dL	≥3.2/<3.2	1.00	0.44-2.28	0.999
C-reactive protein, mg/dL	≥53.0/<3.0	1.65	0.71-3.80	0.242
24-h drainage volume on the day before pleurodesis, mL	≥150/<150	1.15	0.50-2.63	0.740
Dose of OK-432	10 KE/5 KE	3.00	0.60-14.99	0.181
Administration of minocycline	Yes/No	0.29	0.06-1.43	0.128
Administration of autologous blood	Yes/No	0.61	0.18-2.16	0.448
Volume of solution	100 mL/≤50 mL	2.22	0.95-5.20	0.067
Administration of lidocaine 1%	No/Yes	1.83	0.80-4.22	0.154
NSAID	No/Yes	2.67	1.08-6.60	0.034
Acetaminophen	No/Yes	0.60	0.23-1.57	0.298
Opioid	No/Yes	0.94	0.39-2.30	0.900

OR: odds ratio, CI: confidence interval, KE: Klinische Einbeit, NSAID: nonsteroidal anti-inflammatory drug

Table 6. Multivariate Analysis of Factors Associated with Fever after Pleurodesis.

		OR	95% CI	p value
Age	<70/≥70	1.86	0.75-4.59	0.181
Dose of OK-432	10 KE/5 KE	1.12	0.16-7.81	0.906
Administration of minocycline	Yes/No	0.37	0.06-2.48	0.305
Volume of solution	100 mL/≤50 mL	2.00	0.79-5.03	0.141
NSAID use	No/Yes	2.43	0.95-6.22	0.065

OR: odds ratio, CI: confidence interval, KE: Klinische Einbeit, NSAID: nonsteroidal anti-inflammatory drug

by pleurodesis with OK-432 and talc.

In conclusion, this study showed that age <70 years and the absence of premedication with an NSAID were risk factors for the need for rescue medication for the management chest pain. It might be better to consider premedication with an NSAID to prevent the chest pain caused by pleurodesis with OK-432. Furthermore, caution is advised in the management of chest pain in adults of <70 years of age. Prospective studies are needed to further investigate this issue.

The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee at Kyorin University Hospital (approval number: 776).

The authors state that they have no Conflict of Interest (COI).

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