

Phase II Study of Pleurodesis using Sterile Graded Talc in Patients with Secondary Intractable Pneumothorax: Protocol for a Multicentre, Open-label Single-arm Trial

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ABSTRACT

A pneumothorax can be primary or secondary. A high proportion of patients with secondary spontaneous pneumothorax are the elderly who are in poor general condition due to their impaired cardiac and pulmonary functions as well as due to other complications. Therefore, it may be difficult for these patients to undergo surgical procedures; in addition, the elderly may be at high risk for postoperative pulmonary fistula due to severe adhesions and emphysema complications. These non-operative and high-risk cases may be treated with pleurodesis (a procedure that involves instillation of a chemical or irritant into the thoracic cavity through an injection), bronchoscopic bronchial embolisation, or other procedures. In Japan, no device is currently approved for performing pleurodesis, but an approval of one device is expected soon. This will be an open-label, single-arm multicentre study conducted among 30 patients with secondary intractable pneumothorax who are not indicated to undergo surgery. The primary endpoint will be presence or absence of chest tube removal. The secondary endpoints will be the disappearance/decrease of air leakage, grade of dyspnoea, and duration of drainage. This study will assess the safety and efficacy of sterile graded talc pleurodesis in patients with secondary intractable pneumothorax.

Key words: secondary pneumothorax, talc, pleurodesis

Pneumothorax is defined as the leakage of air into the pleural cavity through a hole in the visceral pleura. It is classified as spontaneous, traumatic, or iatrogenic pneumothorax according to the cause. There are two types of spontaneous pneumothorax: primary and secondary.

Secondary spontaneous pneumothorax is caused by underlying pulmonary diseases, such as chronic obstructive pulmonary disease (COPD), lung cancer, and interstitial pneumonia. Therefore, unlike primary spon-

aneous pneumothorax, in secondary pneumothorax, the respiratory reserve capacity is often decreased. In addition, secondary pneumothorax is usually more severe than primary spontaneous pneumothorax; this is because the secondary pneumothorax itself causes an additional decline of the pulmonary function.

The proportion of the elderly among patients with secondary spontaneous pneumothorax is high. These elderly patients are usually in a poor general condition due

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their low cardiac and pulmonary functions as well as due to other complications. Therefore, it may be difficult for these patients to undergo surgical procedures, and they may be at a higher risk for postoperative pulmonary fistula due to severe adhesions and emphysema complications. These patients, who cannot undergo surgical procedures, are diagnosed to have intractable pneumothorax⁵⁾. Such non-operative and high-risk cases are the targets for pleurodesis (which involves instillation of a chemical or irritant into the thoracic cavity through an injection), bronchoscopic bronchial embolisation, or other procedures²⁾.

In Japan, a bronchial blocker made of silicone, the Endobronchial Watanabe Spigot (EWS), was approved in January 2013 to be manufactured and marketed as a medical device for the treatment of secondary intractable pneumothorax in patients not indicated for surgery. Some patients cannot tolerate insertion of an EWS through bronchoscopy; these patients should be treated with pleurodesis. However, no device is currently approved for performing pleurodesis, and an approval of one device is expected soon.

Talc, a pleurodesis agent, has been approved to be manufactured and marketed as a medical device in Europe. It is indicated for the treatment of chronic pleurisy (mainly malignant), spontaneous pneumothorax, and a few other diseases. However, in Japan, talc (Unitalc[®], Nobelpharma, Nihonbashi-kobunacho, Tokyo, Japan) has been approved only for the prevention of the re-accumulation of malignant pleural effusion³⁾; treatment of spontaneous pneumothorax with talc has not been approved.

Treatment of spontaneous pneumothorax with talc is recommended in Europe and the United States. The guideline of the British Thoracic Society (BTS)⁴⁾ states that pleurodesis by administration of talc using the slurry method is the desired treatment for patients who do not want to undergo video-assisted thoracic surgery (VATS); however, administration of talc (using the spraying method) with VATS is the optimal treatment method for spontaneous pneumothorax. The American College of Chest Physicians (ACCP) guideline¹⁾ recommends injection of talc slurry through a chest tube as the preferred method of pleurodesis; however, the spray method is an acceptable treatment in the prevention of recurrent secondary spontaneous pneumothorax. According to these guidelines, pleurodesis with talc is an internationally established treatment for spontaneous pneumothorax (including secondary pneumothorax). Therefore, we planned an investigator-initiated study of talc in patients with secondary intractable pneumothorax who have no indications for surgery. We aim to determine the efficacy of talc, obtain approval, and develop its use in patients with spontaneous pneumothorax in Japan. The estimated total number of patients with secondary intractable pneumothorax in Japan is 2,000; therefore, this treatment will be applied to a rare disease (RD).

MATERIALS AND METHODS

Ethics Committee Procedure and Consent

Study approvals will be obtained from the internal review boards of each participating institution prior to the implementation of the study.

Written informed consent will be obtained from every patient prior to the participation in the trial.

Study Design Eligibility criteria

Inclusion criteria

The inclusion criteria for this study will be as follows:

1. A diagnosis of pneumothorax by chest radiography.
2. Presence of any underlying disease that causes pneumothorax.
3. Presence of air leakage that has lasted for more than 7 days without a response to thoracic drainage at the time of case registration.
4. Not being appropriate for surgery, having a high risk for anaesthetic and surgical complications due to a low pulmonary function or other causes, or having experienced a relapse without surgery, with an expected low therapeutic benefit of a second surgery.
5. Age of 20 years or older at the time of consent.
6. Provision of free written consent for the participation in this study.

Exclusion criteria

Exclusion criteria for this study will be as follows:

1. Spontaneous, traumatic, or iatrogenic pneumothorax.
2. History of hypersensitivity to talc.
3. Presence of severe complications due to an infection.
4. Treatment for heart failure at the time of consent.
5. History of myocardial infarction within 30 days of consent.
6. Advanced blood coagulation disorders (platelet count > 50,000/ μ l)
7. Requirement for bilateral pleurodesis.
8. History of postoperative pulmonary fistula.
9. Use of systemic corticosteroids (equivalent to 10 mg/day or more of prednisolone) at the time of case registration.
10. Clinical expectation of a good response by bronchial embolisation therapy using the EWS only.
11. Pregnancy, breastfeeding, wishing to become pregnant during the observation period, or inability to control conception.
12. Participation in other trials within 6 months before consent.
13. Unsuitability for participation in this study as determined by the principal investigator or sub-investigators.

Dosage and administration

Four grams of the investigational drug will be suspended in 50 ml of physiological saline solution; the suspension will be aspirated into a syringe and slowly injected into the pleural cavity through a drug injection tube.

Then, 50 ml of physiological saline will be injected using the same method in order to ensure the suspension reaches the pleural cavity.

Negative pressure will be applied using a continuous low-pressure aspirator to prevent drainage of the suspension.

Pleurodesis and drainage of investigational drug suspension

The patient's posture will be changed after every 30 minutes (for approximately 2 hours) to ensure the suspension is sufficiently distributed throughout the pleural cavity. The range of postures will be as follows: supine position → lateral position on the unaffected side → and lateral position on the affected side + prone position. Pleurodesis will be completed 2 hours after the injection of the investigational drug suspension. A negative pressure suction of -20 cm H_2O will be applied as a guide.

Additional administration of the investigational drug

If it will be judged that the effect of pleurodesis by administration of the investigational drug is insufficient, pleurodesis will be repeated by additional administration of the drug. Additional investigational treatments will be administered only once within 30 days at intervals of 7 days or longer (treatment on the same day of the week is possible) and before the removal of the chest tube. Because the risk of acute respiratory distress syndrome (ARDS) may increase due to the additional administration of the investigational drug, the need for this additional treatment will be carefully determined according to the patient's condition.

Observation Period

The observation period will be from the date of provision of a written consent to 30 days after the pleurodesis treatment. If additional administration of the investigational drug will be performed, the observation will be extended up to 30 days after retreatment with pleurodesis (Figure 1).

Follow-up

If patients leave the hospital by 6 months after the end of the observation period, the following items will be examined on discharge date:

- Presence or absence of hospital discharge (discharge date and reason for discharge in the case of presence)
- Presence or absence of chest tube removal
- Presence or absence of continuous treatment for pneumothorax
- Others, including death

Patients who will not be discharged will be examined at 6 months.

Endpoints

Primary efficacy endpoints

1. Presence or absence of chest tube removal

This will be judged to be "present" if the chest tube is removed within 30 days after pleurodesis or retreatment

with pleurodesis. The criterion for the removal of the chest tube is the disappearance of air leakage from the chest tube, and lung re-expansion will be confirmed by chest radiography. If pleurodesis retreatment is performed due to an insufficient effect, the evaluation will be done after the retreatment. If the chest tube is placed and removed more than once during the observation period, only the first removal will be judged as "present", and no further judgment will be made. The proportion of success will be calculated as follows: the number of patients with chest tube removal divided by the number of population of efficacy.

Secondary efficacy endpoints

1. Disappearance/Decrease of air leakage

The degree of air leakage before pleurodesis (within 7 days), after pleurodesis (or after retreatment with pleurodesis), and when removing the chest tube (or at the time of discontinuation or completion) will be evaluated.

The degree of air leakage will be determined according to the following grades:

- Disappearance - No air leakage is recognised
- Mild - Air leakage is recognised only when coughing
- Moderate - Air leakage at the time of expiration
- Severe - Sustained air leakage is recognised at the time of expiration and inspiration

2. Grade of dyspnoea according to the modified British Medical Research Council (mMRC) dyspnoea scale (Table 1)

The degree of dyspnoea according to the mMRC dyspnoea scale before pleurodesis (within 7 days), after pleurodesis (or after a retreatment with pleurodesis), and when removing the chest tube (or at the time of discontinuation or completion) will be evaluated.

3. Duration of drainage

The duration of drainage will be defined as the time (in days) from pleurodesis until the first removal of the chest tube. If the chest tube will not be removed, it will be censored at the final observation.

Safety endpoints

Adverse events

Adverse events and side effects occurring during the observation period of 30 days after the administration of the investigational drugs (in the case of addition of the investigational drug, 30 days after the additional administration) will be evaluated. The evaluation of adverse events will be performed by using the common terminology criteria for adverse events (CTCAE) v4.03; the adverse events will be listed, and the severity of each event will be graded.

Safety Considerations

During the study, the data and safety monitoring board will deliberate (and recommend on the continuation/change or termination of the study) in response to a consultation from the principal investigator in the following cases:

- Occurrence of serious adverse events
- Occurrence of problems that require an early termina-

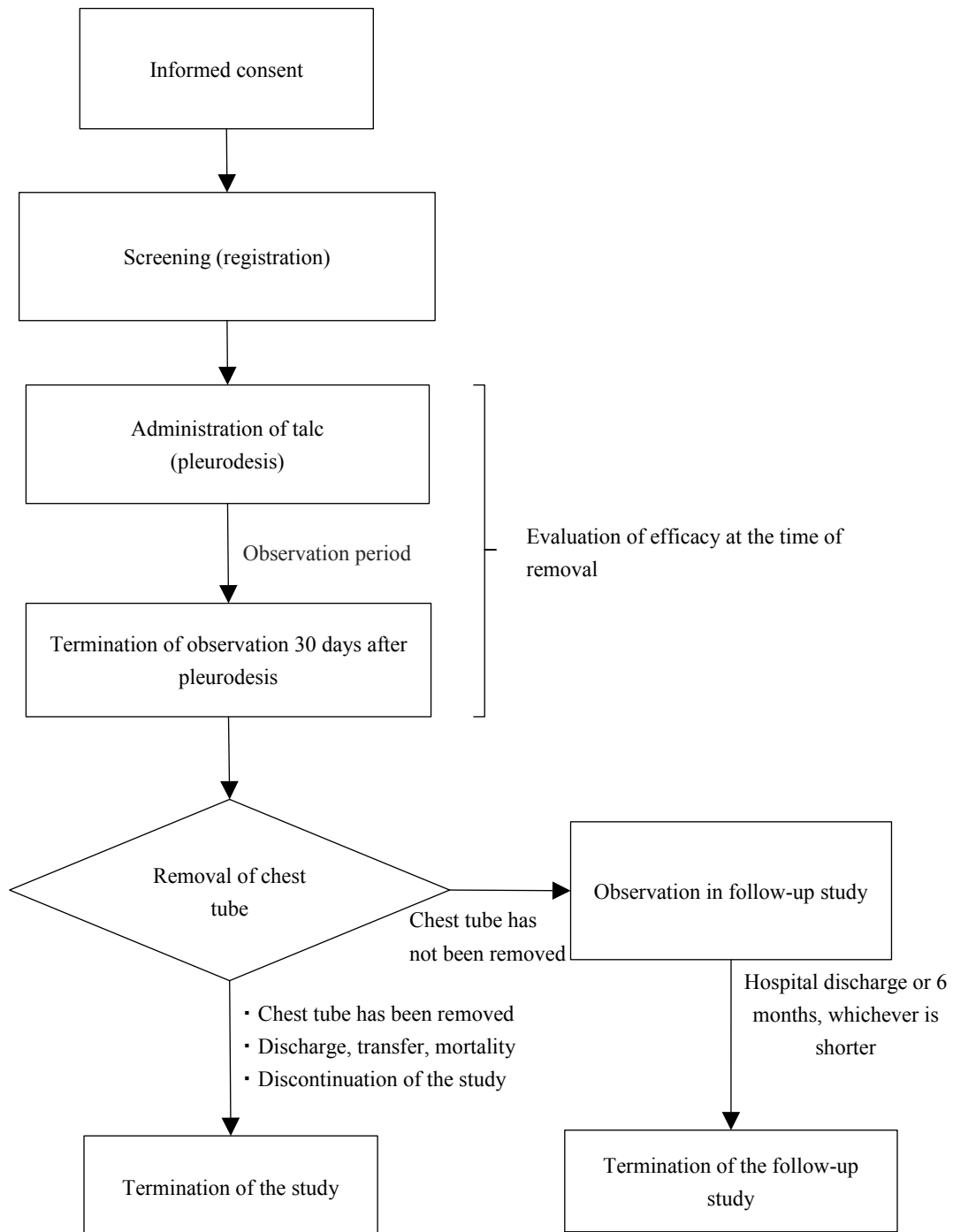


Figure 1. Study design

Table 1. mMRC dyspnoea scale

Grade	Description of Breathlessness
Grade 0	I only get breathless with strenuous exercise
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on level ground
Grade 3	I stop for breath after walking about 100 yards or after a few minutes on level ground
Grade 4	I am too breathless to leave the house or I am breathless when dressing

tion of the study

- Any other occurrence that the principal investigator requires deliberation by the data and safety monitoring board

Statistical Considerations

Sample size

Outcomes of treatment in patients with secondary pneumothorax who are not indicated for surgery, have not been published. Therefore, medical records of patients who were discharged from the Nagoya Medical Center between January 2010 and September 2014 after undergoing treatment with autologous blood adhesions due to a pneumothorax were analysed. The number of patients was 30, and the number of procedures was 35 because of multiple operations. The patients had undergone various treatments, such as multiple injections (median, 2 injections; range: 1–10) and EWS use (4 cases). If the number of autologous blood injections was limited to 2 in a group similar to this study group, the number of subjects required will be 14.

The proportion of catheter removal at 28 days following treatment with autologous blood alone was 43% (6/14) in patients who had received up to two injections and 43% (3/7) in subjects that had received one injection. Therefore, 43% will be considered the threshold for success. However, due to the small number of patients, the threshold was set at 36%, a mean of 43% and 30%, which was the threshold in the clinical study to obtain approval of EWS. The threshold is consistent with the proportion of success clinically experienced in the disease. The expected proportion of success was set at 63% in anticipation of an improvement of 20% or more. Accordingly, when the expected proportion is 63%, and the threshold is 36%, the calculated number of required patients is 27 based on the binomial distribution, with a one-sided significance level of 2.5%, and statistical power of 80%. In anticipation of dropouts, the sample size was set at 30.

Statistical analysis

Analysis set

All patients who will receive the investigational drug will be comprise the full-analysis set (FAS). Within the FAS, an analysis set that does not have a serious protocol violation, satisfies the protocol, and can evaluate the efficacy is defined as the per-protocol set (PPS). In this study, the FAS will be the primary analysis set for efficacy. Patients who received the investigational drug will be analysed for the safety of the drug.

Primary endpoint analysis

The proportion of success will be calculated, and its exact confidence interval will be estimated using the binomial distribution. The probability less than or equal to the threshold (36%) of the distribution will be calculated; a binomial distribution is assumed for the observed proportion of success.

Secondary endpoint analysis

Change in the degree of disappearance/decrease of air leakage from before pleurodesis to 30 days after pleurodesis will be analysed using the Wilcoxon signed-rank test. Change in the degree of dyspnoea from before pleurodesis to 30 days after pleurodesis (or the time of chest tube removal) will be analysed using the Wilcoxon signed-rank test. A Kaplan-Meier curve for the duration of drainage will be created.

Organisation Structure

This study will be conducted at 7 institutions (Appendix 1). HS, HK, NM, NT, MM, OK, and AB will supervise the work related to this study as investigators, managers and instructors. They will also serve as managers of the team of sub-investigators and study cooperators. AK will be responsible for statistical analysis in this study. AS will be responsible for case registration, data management and study monitoring.

DISCUSSION

Patients with secondary intractable pneumothorax often required chest drainage for a long time. Some of the non-operative patients cannot tolerate insertion of EWS through bronchoscopy. Approval of talc pleurodesis will benefit such patients.

Talc, which is a pleurodesis agent, has been approved in Europe and United States as a medical device for the treatment of chronic pleurisy (mainly malignant), spontaneous pneumothorax, and other conditions for which pleurodesis is indicated.

However, in Japan, talc has been approved only for the prevention of re-accumulation of malignant pleural effusion; its use in the treatment of spontaneous pneumothorax has not been approved. This study aims to expand the indications of talc in Japan by assessing its safety and efficacy in secondary intractable pneumothorax.

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This study is registered in the Center for Clinical Trials, Japan Medical Association (JMA-IIA00272).

Competing interests

The authors declare that they have no competing interests.

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Appendix 1. Participating facilities list

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- 1 National Hospital Organization Nagoya Medical Center, Aichi, Japan
 - 2 Kyorin University Hospital, Tokyo, Japan
 - 3 Teikyo University School of Medicine, Tokyo, Japan
 - 4 Nihon University Itabashi Hospital, Tokyo, Japan
 - 5 St. Marianna University Hospital, Kanagawa, Japan
 - 6 Nagoya City University Hospital, Aichi, Japan
 - 7 Japanese Red Cross Okayama Hospital, Okayama, Japan
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