

The Efficacy and Safety of Sterile Graded Talc in Pleurodesis for Malignant Pleural Effusion: Phase II Study

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Abstract

Objective: Introduction of NPC-05 (sterile graded talc) into Japanese clinical practice is expected to lead to persistent prevention of re-accumulation of MPE and alleviation of concomitant symptoms in patients, including dyspnea and chest pain. We conduct an investigator-initiated trial in Japan to clarify the efficacy and safety of NPC-05 for use as a pleurodesis agent.

Methods: This study is a multicenter uncontrolled open-label phase II study. An uncontrolled open-label joint clinical study is conducted in 6 institutes, involving 30 patients with MPE.

Conclusion: Sterile graded talc has been described as the most useful pleurodesis drug for treating malignant pleural effusion in many guidelines and meta-analyses; thus, it is used as a standard pleurodesis agent in Western countries. However, its efficacy and safety have not been examined in Japan.

This study assessed the efficacy and safety of NC-05, sterile graded talc, in 30 Japanese patients with malignant pleural effusion.

Keywords: Sterile graded talc; Pleurodesis; Malignant pleural effusion; Efficacy; Safety

Introduction

Malignant pleural effusion (MPE) is often observed in patients with malignant tumors, including those with lung cancer and breast cancer, and is accompanied by dyspnea, chest pain, cough, and other symptoms, and has a poor prognosis. For these patients, administration of pleurodesis drugs to obliterate the pleural space is important as palliative care, and is also clinically significant to adhere to the pleura to suppress re-accumulation of pleural effusion, and to alleviate the patient's symptoms [1-3].

In some countries, talc, tetracycline, and bleomycin are used as the main pleurodesis drugs, and the efficacy and safety of tetracycline and talc have been demonstrated in multiple randomized trials since 1970 and 1980, respectively [4,5]. As the use of these agents is recommended in treatment guidelines [2,3,6], these agents are already positioned as standard pleurodesis drugs in Western countries, and have been widely used for treatment of MPE.

Talc is hydrated magnesium silicate ($Mg_3(Si_2O_5)(OH)_2$); it occurs naturally and is mined in many parts of the world. In 1935, Bethune [7] for the first time used talc in the pleural space to achieve pleural adhesion prior to lung lobectomy. Thereafter, in 1958, Chambers [8] reported that administration of talc into the pleural space was useful for treatment of malignant pleural effusion. Since then, many researchers have reported the results of using talc in basic and clinical studies, concluding that using talc was one of the best, simplest, and most inexpensive methods for achieving pleural adhesion [9-11].

Given that talc is already frequently used as a standard pleurodesis drug in Western countries, this study investigated the introduction of talc, in particular, aseptically prepared talc with a standardized particle size (NPC-05) that is believed to result in fewer adverse reactions, such as acute respiratory distress syndrome (ARDS), into clinical practice as a pleurodesis agent in Japan.

Treatment Methods

An uncontrolled open-label joint clinical study is conducted in 6 institutes, involving 30 patients with MPE. The slurry method is employed for pleurodesis, in which 4 g of NPC-05 is suspended in 50 mL of physiological saline for injection into the pleural space.

Endpoints

Efficacy evaluation

Primary endpoint: Presence or absence of re-accumulation of MPE after 30 days of pleurodesis treatment.

Secondary endpoint: Severity of dyspnea after 30 days of pleurodesis treatment. Severity of chest pain after 30 days of pleurodesis treatment.

Safety evaluation

Adverse events and reactions (from the start of study drug administration to 30 days after the start of treatment).

Eligibility criteria

Inclusion criteria

- Patients with histologically or cytologically diagnosed definitive carcinomatous pleurisy.
- Patients who had symptoms, including dyspnea, that were due to MPE, and for whom control of those symptoms was a clinical priority.
- Patients who showed sufficient lung re-expansion after pleural effusion drainage through a chest drainage tube.
- Patients whose symptoms, including dyspnea, were alleviated after pleural effusion drainage.
- Patients expected to survive for more than 30 days after pleurodesis.
- Patients with Eastern Cooperative Oncology Group (ECOG) performance status 0-2 after drainage of MPE.s
- Patients aged 20-75 years.
- Patients who personally provided written informed consent for participation in the trial.

Exclusion criteria

- Patients with talc hypersensitivity.
- Patients with lidocaine hydrochloride hypersensitivity.
- Patients with serious infectious disease complications.
- Patients with severe emphysema or fibrosis of the lung.
- Patients who were receiving treatment for heart failure at the time of obtaining informed consent.
- Patients who had a history of myocardial infarction in the 30 days prior to obtaining informed consent
- Patients with severe coagulopathy.
- Patients with SpO₂<90% at room air after pleural effusion drainage.
- Patients with prominent pleural adhesion.
- Patients who may require pleural adhesion in both lungs.
- Patients with a history of surgical treatment in the pleural space, including pneumonectomy on the affected side and extrapleural pneumonectomy.
- Patients with a history of pleurodesis in the affected side.
- Patients who were receiving systemic administration (oral or intravenous) of corticosteroid at the time of obtaining informed consent.

- Pregnant or breastfeeding women, patients who desired to become pregnant, or who did not agree to contraception by appropriate methods during the trial.
- Patients who had already participated in other trials within 6 months prior to obtaining informed consent.
- Patients who were determined as being unsuitable for this trial by the principal investigator or sub-investigators.

Follow-up

Up to 30 days after pleurodesis.

Study Design and Statistical Analyses

This study was a multicenter uncontrolled open-label phase II study. The targeted sample size was 30 patients.

For patient background factors, frequency distribution (number/proportion of patients) and summary statistics (mean, standard deviation, median, minimum, and maximum) were obtained for each category of qualitative and quantitative data, respectively.

For the primary endpoint, the effectiveness rate, defined as the “re-accumulation of pleural effusion after 30 days of pleurodesis,” was calculated. The binomial distribution was used for precise estimation of the efficacy rate in this period. The null hypothesis, viz., the “true response rate is less than the threshold value of the effectiveness rate (40%, based on the observed effectiveness rate)”, is tested using the binomial distribution.

For the secondary endpoint, changes in severity before and after treatment were compared using the Wilcoxon signed-rank test.

Interim Analysis and Monitoring

No interim analysis is performed

Participating Institutions

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Discussion

The results of this trial will be the pivotal data for the drug approval of NPC-05 for pleurodesis for malignant pleural effusion.

Acknowledgement

Japan Medical Association

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