JCS Journal of Chest Surgery
https://doi.org/10.5090/jcs.23.030
pISSN: 2765-1606 eISSN: 2765-1614
J Chest Surg. 2023;56(5):353-358

Clinical Research

Which is the More Effective Option for Pleurodesis to Prevent the Recurrence of Malignant Pleural Effusion? Large-Particle Talc or Mistletoe Extract (ABNOVA Viscum Injection)

Changsung Han, M.D., Jonggeun Lee, M.D., Jeong Su Cho, M.D., Hyo Yeong Ahn, M.D.

Department of Thoracic and Cardiovascular Surgery, Pusan National University Hospital, Pusan National University School of Medicine, Busan, Korea

ARTICLE INFO
Received March 7, 2023
Revised June 26, 2023
Accepted July 6, 2023

Corresponding author
Jonggeun Lee
Tel 82-51-240-7267
Fax 82-51-243-9389
E-mail belloot2@naver.com
ORCID
https://orcid.org/0000-0003-3797-8582

Background: Malignant pleural effusion affects many patients with advanced cancer. When chemotherapy or radiotherapy fails to relieve malignant pleural effusion and related symptoms, drainage and pleurodesis can help. Although surgical talc pleurodesis is the most widely used method, *Viscum album*, which has been recently used in surgical or bedside procedures, has demonstrated significant results and is as effective as talc. This study aimed to determine the most effective agent and procedure.
Methods: Between January 2015 and July 2022, chemical pleurodesis was performed in 137 patients with malignant pleural effusion, using a *V. album* surgical procedure in 48, a *V. album* bedside procedure in 55, and a talc surgical procedure in 34 patients. We reviewed patients' clinical responses and disease progression after chemical pleurodesis.
Results: The success rate was not significantly different among the *V. album* surgical procedures (91.7%), *V. album* bedside procedures (83.6%), and talc surgical procedures (91.2%). However, the total drainage amount and tube insertion duration in both *Viscum* groups were more effective than those in the talc group. Furthermore, the bedside *Viscum* group showed significantly lower post-pleurodesis pain scores than the other 2 groups.
Conclusion: According to our results, talc and *V. album* can be considered ideal agents for chemical pleurodesis. However, *Viscum* pleurodesis showed safer outcomes in terms of ensuring quality of life than talc. Additionally, the bedside *Viscum* group showed significantly lower pain scores than the other groups. Hence, patients for whom surgical procedures are inappropriate can undergo bedside *Viscum* pleurodesis without diminishing the therapeutic effect.

Keywords: Pleurodesis, Talc, *Viscum*, Malignant pleural effusion, Therapeutics

Introduction

Malignant pleural effusion (MPE) is a frequent complication that arises during the advanced cancer with pleural metastasis [1-3]. This complication persists in most patients who have metastasis in the pleural space. The majority of these patients experience symptoms such as dyspnea, chest pain, and recurrent, prolonged hospital stays. Consequently, physicians have been exploring various methods to alleviate these symptoms and enhance patients' quality of life [1-3].

Although chemical pleurodesis is only palliative, it remains the recommended treatment for preventing the re-accumulation of fluid and alleviating symptoms. Up until now, each institution has employed its own pleurodesis methods due to the lack of a clear consensus on the best agents or procedures to use. Despite widespread agreement on the use of chemical pleurodesis, opinions differ on the specific agent or procedure that should be employed. The criteria for selecting these agents and procedures vary among physicians, and are influenced by patient-specific factors such as the need for surgery, the formulation and cost of the agent, and the patient's overall health status.

In this study, we compared the clinical outcomes of 3 patient groups over a 4-week period. These groups were administered different chemical agents via various proce-

https://doi.org/10.5090/jcs.23.030

dures, with the aim of identifying the most effective agent and procedure. The 2 chemical agents commonly used at our institution, Pusan National University Hospital, are large-particle talc and mistletoe extract (ABNOVA viscum injection). Both agents can be administered through either surgical or bedside procedures. However, it is known that talc, when applied via a surgical procedure, can provide outcomes that are at least equivalent to, if not more effective than, those achieved with the bedside procedure in certain disease groups [4]. The findings of this study could suggest a more effective and less invasive method for achieving optimal pleurodesis.

Methods

We retrospectively collected and analyzed data from 137 patients who underwent pleurodesis at Pusan National University Hospital between January 2015 and July 2022. Pleurodesis was carried out when chest tube drainage fell below 100 mL per day. Depending on each patient's condition and circumstances, we applied suitable chemical agents and procedures. For talc pleurodesis, we exclusively used large-particle talc via a surgical procedure. For mistletoe extraction pleurodesis, we employed ABNOVA viscum injection, which was administered through both surgical and bedside procedures. We examined the patients' medical and clinical records before and after pleurodesis, including response results, X-rays, and computed tomography scans. We recorded basic information such as age, height, weight, and any malignancies diagnosed using pleural effusion cytology, as well as any underlying cancer, prior to pleurodesis. We collected pre-pleurodesis data, including white blood cell (WBC) count and C-reactive protein (CRP) levels, at 7 AM on the day of the procedure. We then gathered post-pleurodesis data at 7 AM the following day. We assessed the patient's pain score and body temperature 4 hours after the procedure. We considered pleurodesis to be effective if pleural effusion did not recur within 4 weeks [4]. We removed the chest tube when the drainage fell below 200 mL per day.

This study was carried out in an ethical manner, adhering to the protocol approved by the Institutional Review Board (IRB) of Pusan National University Hospital (IRB no., 2211-006-120). The requirement for informed consent from individual patients was omitted because of the retrospective design of this study.

Inclusion criteria

Patients with MPE (initial or recurrent) whose lungs were fully re-inflated after chest tube insertion and fluid drainage were included in this study.

Exclusion criteria

Patients in whom lung re-inflation was not completed, as well as those who had other comorbidities that could affect pleural effusion re-accumulation, who died within 4 weeks after the pleurodesis, and who were lost to follow-up because of death, transfer to other hospitals, or other reasons were excluded from the study (Fig. 1).

Management

Talc (large-particle) pleurodesis

In the operating room, under general anesthesia, 2 g of talc powder was administered via a catheter from the talc set during video-assisted thoracic surgery (VATS). Typically, a 20F chest tube was inserted, although the tube size could vary based on the patient's condition. The chest tube was clamped for a period of 4 hours, and then unclamped for the subsequent 4 hours. As talc is a powder formulation, it cannot be effectively administered in a bedside procedure. Consequently, a statistical comparison between

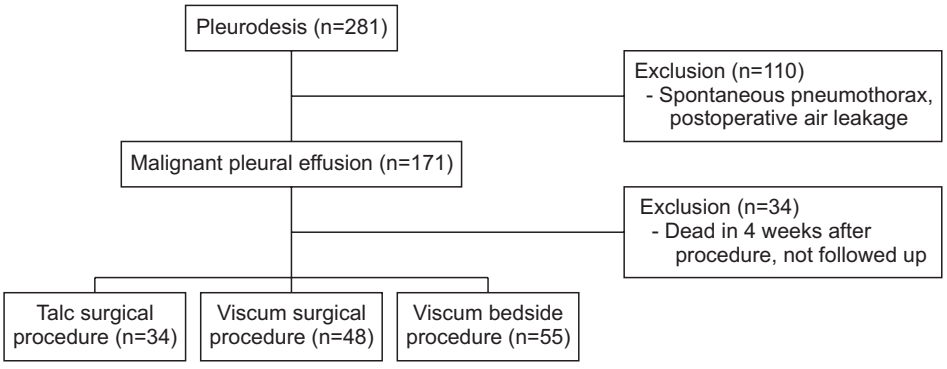

Fig. 1. Flow chart for patient group by inclusion criteria.

surgical VATS pleurodesis group and bedside pleurodesis group was not feasible.

Mistletoe extraction (ABNOVA viscum injection) pleurodesis

In the operating room, under general anesthesia, a VATS procedure was performed. During this procedure, three 20-mg ampules of *Viscum* were mixed with 50 mL of normal saline and administered through the catheter included in the *Viscum* set. Typically, a 20F chest tube was inserted, although the size of the tube could vary depending on the patient's condition. The chest tube was then clamped for a period of 4 hours, after which it was unclamped for the subsequent 4 hours.

For the bedside procedure, 400 mg of lidocaine was combined with 30 mL of normal saline and administered over a period of 30 minutes. Three 20-mg ampules of *Viscum* were then mixed with 50 mL of normal saline and introduced into the pleural space via a chest tube, which was subsequently clamped for 4 hours. The chest tube typically used for this procedure was a 12F tube. The patient's position was alternated between right and left every 20–30 minutes. After 4 hours, the chest tube was unclamped.

Classification for response

The response rate was classified as follows: (1) Successful response: no need for tube reinsertion or repeated pleurodesis, and no pleural effusion for 4 weeks. (2) Partially successful response: no need for tube insertion or additional pleurodesis but with pleural effusion in 4 weeks. (3) Failed response: with pleural effusion requiring tube re-insertion or additional pleurodesis in 4 weeks.

Statistical analysis

Statistical analyses were conducted using R software ver. 4.1.3 (http://cran.r-project.org). To compare the 3 groups, we used the chi-square test or Fisher exact test for categorical variables, and 1-way analysis of variance or the Kruskal-Wallis test for continuous variables. Additionally, we employed the Bonferroni correction p-value for multiple comparisons. We set the threshold for statistical significance at $p<0.05$.

Results

Of the 137 patients enrolled in the study, 48 underwent *Viscum* surgical pleurodesis, 55 underwent *Viscum* bedside pleurodesis, and 38 underwent talc surgical pleurodesis. There were no significant differences in age, sex, height, weight, or underlying cancer types among the 3 groups (Table 1).

Mistletoe extraction (ABNOVA viscum injection) surgical pleurodesis

The total volume of drainage from pleurodesis to tube removal was 888.85±1,191.05 mL, the duration of tube insertion was 4.81±3.62 days, and the duration from tube insertion to pleurodesis was 4.88±6.72 days. After pleurodesis, the WBC count increased from 8.55±4.40 to 12.43±5.76

Table 1. Patients' baseline characteristics before pleurodesis

Characteristic	*Viscum* surgical (n=48)	*Viscum* bedside (n=55)	Talc surgical (n=34)	p-value
Age (yr)	62.79±12.60	66.51±11.27	65.24±12.41	0.292
Sex				0.571
Male	20 (41.7)	24 (43.6)	18 (52.9)	
Female	28 (58.3)	31 (56.4)	16 (47.1)	
Height (cm)	159.32±9.10	160.14±9.34	161.18±7.24	0.646
Weight (kg)	62.33±11.50	59.38±11.28	57.51±6.77	0.112
Malignancy (cytology)				0.662
No	17 (37.0)	20 (41.7)	16 (47.1)	
Yes	29 (63.0)	28 (58.3)	18 (52.9)	
Underlying cancer				0.212
Primary lung cancer	29 (60.4)	24 (43.6)	19 (55.9)	
Other cancer	19 (39.6)	31 (56.4)	15 (44.1)	
Body temperature (°C)	36.51±0.25	36.60±0.25	36.53±0.22	0.144
White blood cells (cells/mm^3)	8.55±4.40	7.28±2.88	7.11±2.58	0.096
C-reactive protein (mg/dL)	2.43±3.36	2.65±2.95	3.14±4.64	0.672

Values are presented as mean±standard deviation or number (%).

Table 2. Outcomes after pleurodesis and success rate of procedures

Outcomes	*Viscum* surgical (n=48)	*Viscum* bedside (n=55)	Talc surgical (n=34)	p-value
Total drainage amount from pleurodesis to tube removal (mL)	888.85±1,191.05	669.69±1,015.84	2,350.88±2,443.62	<0.001
Tube insertion duration (day)	4.81±3.62	6.00±6.18	9.21±4.76	<0.001
Duration from tube insertion to pleurodesis (day)	4.88±6.72	7.95±4.82	4.18±7.15	0.008
Body temperature (°C)	37.02±0.63	37.06±0.68	36.96±0.65	0.783
White blood cell (cells/mm^3)	12.43±5.76	8.76±3.89	8.54±3.07	<0.001
C-reactive protein (mg/dL)	8.50±6.52	8.08±6.66	6.74±6.83	0.488
Pain (Numerical Rating Scale)	4.38±1.83	3.29±1.95	4.06±1.78	0.012
Success outcome				0.680
Success	31 (64.6)	32 (58.2)	20 (58.8)	
Partial success	13 (27.1)	14 (25.5)	11 (32.4)	
Failed	4 (8.3)	9 (16.4)	3 (8.8)	

Values are presented as mean±standard deviation or number (%).

cells/mm^3, the CRP level increased by 6.06±6.42 mg/dL, and the body temperature increased by 0.51±0.64°C. Pain was scored using a Numerical Rating Scale (NRS), and the average score was 4.38±1.83. Regarding the final response of the patients after pleurodesis, 64.6% (n=31) demonstrated a successful response, 27.1% (n=13) demonstrated a partially successful response, and 8.3% (n=4) had a failed response (Table 2).

Mistletoe extraction (ABNOVA viscum injection) bedside pleurodesis

The total drainage amount from pleurodesis to tube removal was 669.69±1,015.84 mL, the duration of tube insertion was 6.00±6.18 days, and the duration from tube insertion to pleurodesis was 7.95±4.82 days. After pleurodesis, the WBC count increased from 7.28±2.88 to 8.76±3.89 cells/mm^3, the CRP level increased by 5.40±6.37 mg/dL, and the body temperature increased by 0.46±0.63°C. The average NRS pain score was 3.29±1.95. Regarding the final response of the patients after pleurodesis, 58.2% (n=32) demonstrated a successful response, 25.5% (n=14) demonstrated a partially successful response, and 16.4% (n=9) had a failed response (Table 2).

Talc (large-particle) surgical pleurodesis

The total drainage amount from pleurodesis to tube removal was 2,350.88±2,443.62 mL, the tube insertion duration was 9.21±4.76 days, and the duration from tube insertion to pleurodesis was 4.18±7.15 days. After pleurodesis, the WBC count increased from 7.11±2.58 to 8.54±3.07 cells/mm^3, the CRP level increased by 3.56±6.66 mg/dL, and the body temperature increased by 0.43±0.64°C. The average NRS score for post-pleurodesis pain was 4.06±1.78. Of the final responses, 58.8% (n=20) were successful, 32.4% (n=11) were partially successful, and 8.8% (n=3) were unsuccessful (Table 2).

The success rates among the 3 groups (VATS talc, VATS *Viscum*, bedside *Viscum*) were not significantly different, consistent with previous study findings. Similarly, there was no significant difference observed in complications across the three groups. However, significant differences were noted in the total amount of drainage from pleurodesis to tube removal, the duration from tube insertion to pleurodesis, the difference in the WBC count, and the tube insertion period, as well as the post-pleurodesis pain score. Notably, both *Viscum* groups had a significantly lower total drainage amount from pleurodesis to tube removal and a shorter duration of tube insertion than the talc group. Furthermore, the bedside *Viscum* group experienced less post-pleurodesis pain and a longer duration from tube insertion to pleurodesis, which were significantly different results compared to the *Viscum* surgical procedure and talc groups (Table 2).

Discussion

MPE is a frequent yet debilitating complication of advanced cancer. Chemical pleurodesis is commonly employed to reduce the recurrence of MPE and alleviate associated symptoms such as dyspnea and chest pain. To date, chemical pleurodesis has proven to be the most effective treatment for MPE that is resistant to other therapeutic approaches [5]. This procedure involves introducing a sclerosing agent into the pleural cavity to trigger an inflammatory response, leading to pleural adhesion and fibrosis. This process of obliterating the pleural cavity helps

prevent MPE recurrence [4]. A variety of chemical agents can be used for pleurodesis, but a definitive consensus on the best agent has yet to be reached. The effectiveness of chemical pleurodesis varies depending on the agent and procedure employed, making the selection of a safe and effective combination of agent and procedure critical [5]. Talc is the preferred agent according to international guidelines [4], and its superiority over alternative agents has been reported in multiple studies [6-8]. Additionally, previous analyses have indicated potential benefits of surgical procedures, such as a more uniform distribution of the agent [9,10]. Current evidence, therefore, suggests that administering talc through a surgical procedure is a highly effective method, potentially offering increased efficacy in certain situations [9]. Moreover, thoracoscopy allows the surgeon to examine the pleural cavity and perform a pleural biopsy or adhesiolysis, although this extends the operation time and increases the risk associated with anesthesia [10]. Consequently, for more effective pleurodesis, talc pleurodesis is typically performed surgically. However, bedside administration may be considered for patients with a low performance status despite the various advantages of surgical procedures [4]. Unlike talc, *Viscum*, is a liquid sclerosing agent that not only induces inflammation but also has an anti-tumor effect by stimulating the immune system [1]. Several studies have confirmed its efficacy as being relatively equivalent to that of talc, leading many institutions to start using *Viscum* in recent years. Its use has shown better results than talc in terms of improving patients' quality of life [1,3,4]. At Pusan National University Hospital, talc and *Viscum* are primarily used, with the choice of agent left to the physician's discretion. This study aimed to verify the efficacy of each pleurodesis agent and procedure by comparing success rates and various factors, including infection markers, tube insertion duration, and total drainage amount from pleurodesis to tube removal. Finally, we established criteria for selecting the chemical agents and administration procedures.

In this study, *Viscum* was not inferior to talc in terms of the success rate, regardless of the procedure applied. Consistent with previous studies [4,5], we identified a significant difference in pain scores among the 3 groups. Upon further comparison, the group treated with *Viscum* at the bedside exhibited lower post-pleurodesis pain scores than the other 2 groups. Additionally, both *Viscum* groups reported significantly less total drainage from pleurodesis and a shorter tube insertion period than the talc group. These factors could potentially shorten hospital stays and cause less discomfort and pain. Therefore, the use of *Viscum*, particularly in bedside procedures, may lead to better outcomes than talc in terms of improving patient quality of life and reducing the risks associated with surgery and general anesthesia. The time from chest tube insertion to pleurodesis also yielded significant results. The *Viscum* bedside group had longer procedures, but this was influenced by the physician's assessment of the patient's performance and the condition of the pleura for surgery. As a result, the *Viscum* and talc VATS groups had shorter procedures, while the bedside group had longer procedures.

This study has some limitations. First, this was a small single-center study. The talc group, in particular, had a limited number of patients, which made comparisons between subgroups challenging. Since mid-2010, the use of talc has been discontinued, and even when there are suitable patients, its usage must be restricted. Secondly, given the retrospective nature of this study, postoperative management of pleurodesis, such as pain control, could vary based on the physician and the patient's condition. Lastly, patients with MPE represent a diverse group with a range of underlying cancer types, stages, and overall health conditions, leading to varying prognoses. Future studies or evaluations should take into account the clinical status of patients to ensure the most appropriate pleurodesis is performed.

In conclusion, *Viscum* and talc demonstrated similar treatment outcomes. Considering their high success rates and controllable side effects, both chemical agents are good options for pleurodesis. Additionally, this study suggests that bedside *Viscum* may be considered as a more effective and comfortable agent for patients with advanced cancer who are not suitable candidates for surgery.

Article information

ORCID

Changsung Han: https://orcid.org/0000-0003-3665-8982
Jonggeun Lee: https://orcid.org/0000-0003-3797-8582
Jeong Su Cho: https://orcid.org/0000-0002-7422-6171
Hyo Yeong Ahn: https://orcid.org/0000-0003-3198-8237

Author contributions

Conceptualization: AHY, LJG, CJS. Data curation: LJG, HCS. Formal analysis: HCS. Methodology: LJG, CJS. Writing–original draft: HCS. Writing–review & editing: all authors. Final approval of the manuscript: all authors.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Funding

This work was supported by a clinical research grant from Pusan National University Hospital in 2023.

References

1. El-Kolaly RM, Abo-Elnasr M, El-Guindy D. Outcome of pleurodesis using different agents in management of malignant pleural effusion. Egypt J Chest Dis Tuberc 2016;65:435-40. https://doi.org/10.1016/j.ejcdt.2015.12.017
2. Eom JS, Ahn HY, Mok JH, et al. Pleurodesis using mistletoe extract delivered via a spray catheter during semirigid pleuroscopy for managing symptomatic malignant pleural effusion. Respiration 2018;95:177-81. https://doi.org/10.1159/000481869
3. Chang Y, Cho D, Cho K, Cho M. Viscum pleurodesis is as effective as talc pleurodesis and tends to have less adverse effect. Support Care Cancer 2020;28:5463-7. https://doi.org/10.1007/s00520-020-05405-0
4. Loizzi D, Sollitto F, Piazzolla M, Ardo NP. Thoracoscopic pleurodesis using talc poudrage versus cytotoxic drug in malignant pleural effusion: narrative review. J Xiangya Med 2021;6:6. https://doi.org/10.21037/jxym-20-67
5. Cho JS, Na KJ, Lee Y, et al. Chemical pleurodesis using mistletoe extraction (ABNOVAviscum(R) injection) for malignant pleural effusion. Ann Thorac Cardiovasc Surg 2016;22:20-6. https://doi.org/10.5761/atcs.oa.15-00230
6. Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ; BTS Pleural Disease Guideline Group. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. Thorax 2010;65 Suppl 2:ii32-40. https://doi.org/10.1136/thx.2010.136994
7. Tan C, Sedrakyan A, Browne J, Swift S, Treasure T. The evidence on the effectiveness of management for malignant pleural effusion: a systematic review. Eur J Cardiothorac Surg 2006;29:829-38. https://doi.org/10.1016/j.ejcts.2005.12.025
8. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database Syst Rev 2004;(1):CD002916. https://doi.org/10.1002/14651858.CD002916.pub2
9. Rahman NM, Ali NJ, Brown G, et al. Local anaesthetic thoracoscopy: British Thoracic Society Pleural Disease Guideline 2010. Thorax 2010;65 Suppl 2:ii54-60. https://doi.org/10.1136/thx.2010.137018
10. Stefani A, Natali P, Casali C, Morandi U. Talc poudrage versus talc slurry in the treatment of malignant pleural effusion: a prospective comparative study. Eur J Cardiothorac Surg 2006;30:827-32. https://doi.org/10.1016/j.ejcts.2006.10.002