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Chemical Pleurodesis Using Doxycycline and *Viscum album* Extract

Kyung Sub Song, M.D., DongYoon Keum, M.D., Jae Bum Kim, M.D.

Department of Thoracic and Cardiovascular Surgery, Keimyung University Dongsan Medical Center, Keimyung University School of Medicine

Background: In chemical pleurodesis for managing pulmonary air leak, tetracycline derivatives are commonly used, and their effectiveness has been established in many studies. Recently, a *Viscum album* extract was used in chemical pleurodesis. We compared the effects of *V. album* with those of a tetracycline derivative (doxycycline) to demonstrate the therapeutic effectiveness of the *V. album* extract in chemical pleurodesis for managing pulmonary air leak. **Methods:** Between October 2010 and October 2016, chemical pleurodesis was performed using doxycycline in 40 patients and the *V. album* extract in 37 patients. Thirty-three patients were in the postoperative state after pulmonary resection, and 44 patients suffered from spontaneous pneumothorax. **Results:** No statistically significant difference in the success rate was observed between the 2 groups (*V. album* extract and doxycycline). In both groups, chest pain was the most common complication. More patients in the doxycycline group complained of severe chest pain (42.1% vs. 13.5%, p=0.006). In the *V. album* extract group, 24.3% of the patients required a chest tube to drain the pleural effusion after cessation of the air leak (doxycycline group: 5%, p=0.022). Further, the amount of pleural effusion drained on the day after the last chemical pleurodesis in the *V. album* extract group was greater than that in the doxycycline group (162.2±170.2 mL vs. 97.0±77.2 mL, p=0.032). All patients were discharged from the hospital without complications after pleural effusion drainage. **Conclusion:** Considering that treatment using the *V. album* extract was less painful, *V. album* might be a feasible option for chemical pleurodesis. However, pleural effusion should be monitored carefully when using *V. album* extract for treating patients suffering from air leak.

Key words: 1. Pneumothorax
2. Pleurodesis
3. Viscum album
4. Doxycycline

Introduction

Chemical pleurodesis is an important treatment modality in the management of pulmonary air leak. Tetracycline derivatives are commonly used for chemical pleurodesis, and their effectiveness has been demonstrated by many researchers [1,2]. Recently, a *Viscum album* extract from European mistletoe has been used for chemical pleurodesis. However, the outcomes of using it in pulmonary air leak management have not been reported yet. In this study, to demonstrate the therapeutic effectiveness of the *V. album* extract, we compared the effects of the *V. album* extract with those of a tetracycline derivative

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Corresponding author: DongYoon Keum, Department of Thoracic and Cardiovascular Surgery, Keimyung University Dongsan Medical Center, Keimyung University School of Medicine, 56 Dalseong-ro, Jung-gu, Daegu 41931, Korea
(Tel) 82-53-250-7307 (Fax) 82-53-250-7307 (E-mail) dongyoonkeum@gmail.com

(the oral form of doxycycline).

Methods

1) Study design and patients

A retrospective study was carried out to evaluate the results of chemical pleurodesis conducted for the management of pulmonary air leak. Between October 2010 and October 2016, chemical pleurodesis was performed in 77 patients. The causes of the continuous air leak were spontaneous pneumothorax in 44 patients, lobectomy in 23 patients, and bullectomy in 10 patients. Between October 2010 and November 2014, doxycycline (Vibramycin-N; Pfizer Inc., New York, NY, USA) was used in chemical pleurodesis. Thereafter, chemical pleurodesis was performed using a *V. album* extract (Abnobaviscum F; Abnoba Heilmittel GmbH, Pforzheim, Germany).

The success of chemical pleurodesis was defined as the cessation of the air leak after pleurodesis without additional intervention. Patients requiring additional surgery to cease the air leak after pleurodesis or those who were discharged from the hospital with a 1-way valve chest tube (Heimlich chest tube) were defined as exhibiting failure of chemical pleurodesis.

2) Chemical pleurodesis with doxycycline and Viscum album extract

Typically, 20 mL of 2% lidocaine hydrochloride (400 mg) was instilled into the pleural cavity through the chest tube followed by infusion of a solution of 1,000 mg of doxycycline or 100 mg of *V. album* extract in 50 mL of normal saline. The rubber tube connecting the chest tube and the chest bottle was raised 60–80 cm above the patient to trap the sclerosing agent in the thoracic cage while allowing air to pass under pressure. In both groups, patients were rotated every 30 minutes and the fluid in the thoracic cavity was drained after 4 hours. If the air leak did not decrease the next day, chemical pleurodesis was repeated. We performed chemical pleurodesis up to 3 times.

The side effects of chemical pleurodesis, including fever, leukocytosis, chest pain, and pleural effusion, were then compared.

After chemical pleurodesis, we managed chest pain using intravenous injections of pethidine hydrochloride (Pethidine HCl; Jeil Pharmaceutical Co. Ltd., Seoul, Korea). To compare chest pain in both groups, the pain scale and the number of intravenous injections of pethidine hydrochloride administered on the first day of chemical pleurodesis were analyzed. The pain scale was analyzed using a numeric rating scale (NRS; 0 represented no pain, and 10 indicated intractable pain), and severe pain was defined as NRS of 7 or more [3].

The chest tube was removed when the chest drain was under 200 mL/day and the air leak stopped. After cessation of the air leak, if the chest tube was kept to drain the pleural effusion over 2 days, pleural effusion was defined as a side effect of chemical pleurodesis. Further, the amount of pleural effusion drained the day after the last chemical pleurodesis was compared.

3) Statistical analysis

Continuous variables are presented as means with standard deviation. Categorical variables are presented as frequencies with the associated percentages. For a comparative analysis between the two groups, the independent-sample t-test was used for continuous variables, while the Fisher exact test was used for categorical variables. IBM SPSS software ver. 20.0 (IBM Corp., Armonk, NY, USA) was used for the analysis. All p-values less than 0.05 were considered to indicate statistical significance.

Results

Forty patients were treated with doxycycline, while 37 patients were treated with the *V. album* extract. The mean ages of the patients in the doxycycline group and the *V. album* extract group were 57.7 years and 64.8 years, respectively. With respect to the causes of air leak, both groups showed similar distributions, and no statistically significant difference was observed. In the doxycycline group, 23 patients had chest tube insertion because of spontaneous pneumothorax, 11 were post-lobectomy patients, and 6 were post-bullectomy patients. In the *V. album* extract group, 21 were spontaneous pneumothorax patients, 12 were post-lobectomy patients, and 4 were post-bullectomy patients (Table 1).

Overall, 71 successful cases of chemical pleurodesis were observed. Among the failure cases, 3 patients needed additional surgery to manage the air leak and

Table 1. Patient characteristics

Characteristic	Doxycycline (n=40)	*Viscum album* extract (n=37)	p-value
Age (yr)	57.7±18.0 (16–86)	64.8±14.3 (21–82)	0.067
Sex (male)	37 (92.5)	32 (86.5)	0.328
Height (cm)	168.1±8.1	166.7±8.0	0.475
Weight (kg)	60±10	59±12	0.644
Body mass index (kg/m^2)	21.3±2.8	21.1±3.4	0.831
Smoking (pack-year)	25.8±22.1	33.9±25.5	0.156
Side involved (right)	25 (65.0)	20 (54.1)	0.328
Cause of air leak			0.833
Spontaneous pneumothorax	23 (57.5)	21 (56.8)	
Lobectomy	11 (27.5)	12 (32.4)	
Bullectomy	6 (15.0)	4 (10.8)	
Emphysema on computed tomography	24 (60.0)	24 (64.9)	0.706
Co-existing lung disease			
Chronic obstructive pulmonary disease	8	6	0.667
Asthma	2	3	0.667
Tuberculosis	10	3	0.068
Interstitial lung disease	1	2	0.510

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

Table 2. Results of chemical pleurodesis using doxycycline and *Viscum album* extract

Variable	Doxycycline (n=40)	*V. album* extract (n=37)	p-value
No. of times chemical pleurodesis was performed	2.5±0.8	1.4±0.6	0.000
Success of chemical pleurodesis[a)]	35 (87.5)	36 (97.3)	0.202
Duration of air leak after chemical pleurodesis[b)] (day)	6.3±4.7	5.2±5.2	0.336
Duration of hospital stay after chemical pleurodesis[b)] (day)	9.1±4.8	8.3±5.5	0.499
Fever	11 (27.5)	16 (43.2)	0.148
Leukocytosis	17 (42.5)	21 (56.8)	0.211
Pleural effusion[c)]	2 (5.0)	9 (24.3)	0.022
Amount of effusion drain[d)] (mL)	97.0±77.2	162.2±170.2	0.032
Mean NRS	6.3±1.4	3.9±2.2	0.000
Severe pain[e)]	16 (42.1)	5 (13.5)	0.006
No. of pethidine injections[f)]	1.4±0.7	0.6±0.7	0.000

Values are presented as mean±standard deviation or number (%).
NRS, numeric rating scale.
[a)]Success of chemical pleurodesis was defined as cessation of the air leak after pleurodesis without additional intervention. [b)]Duration of the air leak or the hospital stay after chemical pleurodesis was calculated in patients in whom chemical pleurodesis was successful. [c)]Pleural effusion as a complication of chemical pleurodesis was defined when the patient needed an additional procedure to control the localized pleural effusion or had a chest tube maintained to drain the pleural effusion for more than 2 days after cessation of the air leak. [d)]Amount of pleural effusion drained the day after the last chemical pleurodesis. [e)]NRS $\geq$7. [f)]No. of pethidine injections administered on the first day of chemical pleurodesis.

3 patients were discharged from the hospital with a 1-way valve chest tube. With respect to the success rate of chemical pleurodesis, no statistically significant difference was observed between the doxycycline group and the *V. album* extract group (87.5% versus 97.3%, p=0.202) (Table 2). With respect to the durations of the air leak and the hospital stay after chemical pleurodesis, no statistically significant difference was observed between the groups (Table 2).

An additional analysis of 44 patients suffering from spontaneous pneumothorax showed similar results. No statistically significant difference was observed in

Table 3. Results of chemical pleurodesis using doxycycline and *Viscum album* extract in patients with spontaneous pneumothorax

Variable	Doxycycline (n=23)	*V. album* extract (n=21)	p-value
Success of chemical pleurodesis[a)]	19 (82.6)	21 (100.0)	0.109
Duration of air leak after chemical pleurodesis[b)] (day)	5.2±3.4	5.4±5.2	0.844
Duration of hospital stay after chemical pleurodesis[b)] (day)	8.2±3.8	8.9±5.5	0.645

Values are presented as number (%) or mean±standard deviation.
[a)]Success of chemical pleurodesis was defined as cessation of the air leak after pleurodesis with no additional intervention required.
[b)]Duration of the air leak or the hospital stay after chemical pleurodesis was calculated in patients in whom chemical pleurodesis was successful.

the success rate of chemical pleurodesis, duration of the air leak, or duration of hospital stay (Table 3).

When the side effect of pleural effusion was observed, 2 patients in the doxycycline group and 9 patients in the *V. album* extract group required a chest tube to drain the pleural effusion after cessation of the air leak (5% versus 24.3%, p=0.022) (Table 2). Additional thoracic catheter insertion to control localized pleural effusion was performed in 1 patient in the doxycycline group and 2 patients in the *V. album* extract group (2.5% versus 5.4%, p=0.605). The amount of pleural effusion drained on the day after the last chemical pleurodesis in the *V. album* extract group was more than that in the doxycycline group (162.2±170.2 mL versus 97.0±77.2 mL, p=0.032).

After chemical pleurodesis, patients in the doxycycline group expressed a higher NRS (6.29±1.393 versus 3.86±2.188, p=0.000) and needed a higher dose of pethidine hydrochloride injected intravenously than those in the *V. album* extract group (1.42±0.712 versus 0.62±0.681, p=0.000). Further, more patients in the doxycycline group complained of severe chest pain than those in the *V. album* extract group (42.1% versus 13.5%, p=0.006) (Table 2). Respiratory failure and pneumonitis were not observed in this study.

Discussion

Continuous air leak after pneumothorax or lung resection surgery is a common cause of prolonged hospital stays with increased expenditure. Chemical pleurodesis is an important method of continuous air leak management. In chemical pleurodesis, talc, tetracycline, minocycline, doxycycline, iodopovidone, bleomycin, erythromycin, and other drugs are used [1,4-6]. However, the most effective method of chemical pleurodesis has not been established yet.

In this study, the efficacy of doxycycline and a *V. album* extract used in chemical pleurodesis for continuous air leak management was compared. Tetracycline derivatives are commonly used in chemical pleurodesis [2], and doxycycline has been reported to be more effective than bleomycin, talc, and erythromycin for continuous air leak management [7-11].

Abnobaviscum F is an extract of *V. album* (European mistletoe), which grows on trees of the genus Fraxinus. This extract was first employed in chemical pleurodesis in 1977 [12]. Its underlying mechanism in chemical pleurodesis is the stimulation of antitumor immunity instead of mechanical sclerosis [13]. The effect of the *V. album* extract on malignant pleural effusion has been proven in some studies [12-15], but its use in continuous air leak management has not been reported.

In the present study, no statistically significant result related to the success rate of chemical pleurodesis was observed between the doxycycline group and the *V. album* extract group. The durations of air leak and hospital stay after chemical pleurodesis were also similar in both groups. In an additional analysis of patients suffering from spontaneous pneumothorax, a statistically significant result was likewise not observed.

The common adverse effects of chemical pleurodesis are pain, fever, and gastrointestinal symptoms [16]. Far less commonly, patients may experience respiratory failure and pneumonitis [17]. In this study, pain was measured using an NRS. The validity of NRS has been demonstrated in many studies [3,18]. According to the NRS data, 42.1% of the patients in the doxycycline group complained of severe pain after pleurodesis. Similar to our results, the most common complication of chemical pleurodesis using minocycline or doxycycline has been reported to be pain [19,20]. However, only 13.5% (p=0.006) of the patients in the *V. album* extract group complained of

severe pain (Table 2). The mean NRS values in the doxycycline group and the *V. album* extract group were 6.3±1.4 and 3.9±2.2, respectively (p=0.000). This result indicated that chemical pleurodesis performed using the *V. album* extract was less painful than that conducted using doxycycline. Therefore, a lower dose of pethidine was injected in the *V. album* extract group.

To compare the amount of pleural effusion after chemical pleurodesis in both groups, data on the amount of pleural effusion drained on the day after the last chemical pleurodesis were collected. In the *V. album* extract group, the amount of pleural effusion drained on the day after the last chemical pleurodesis was considerably greater than that in the doxycycline group (162.2±170.2 mL versus 97.0±77.2 mL, p=0.032). Further, 24.3% of the patients in the *V. album* extract group needed a chest tube to drain the pleural effusion for over 2 days after cessation of the air leak (versus 5.0% in the doxycycline group, p= 0.022). This indicated that more pleural effusion was formed in the *V. album* extract group than in the doxycycline group after chemical pleurodesis. The problem of pleural effusion after *V. album* treatment has previously been discussed in another report [14]. It may be related to the stimulation of an antitumor reaction via an increase in the amount of macrophages, eosinophils, and CD8+ T cells [13]. Patients who experienced the complication of pleural effusion were discharged from the hospital without further complications after effusion drainage in both groups.

This study has some limitations. First, the indications of chemical pleurodesis were indefinite. Therefore, there may have been differences in the timing of chemical pleurodesis among patients. For example, some patients underwent pleurodesis within 1 week after air leak because of a massive air leak, while the other patients underwent pleurodesis after observation for 1–2 weeks. Second, we repeated chemical pleurodesis when the air leak did not decrease after the initial chemical pleurodesis. With regard to this indication, the term 'decrease' was subjective. However, there was no suitable index to measure the amount of air leakage. Third, this study was a retrospective study based on medical records. Information about some patients could not be obtained. This might have led to information bias. Fourth, in each patient, the number of times chemical pleurodesis was performed and the duration of maintaining the chest tube were different. Therefore, the total and mean amounts of pleural effusion drained were not objective values that could be used for comparing the amount of pleural effusion formed after chemical pleurodesis. Therefore, there was no adequate value except for the amount of pleural effusion drained on the day after the last chemical pleurodesis for comparing the pleural effusion formed after chemical pleurodesis.

In conclusion, more pleural effusion was drained in the *V. album* extract group than in the doxycycline group. However, the durations of the hospital stay and keeping the chest tube in place after chemical pleurodesis were similar in the 2 groups, and chest pain after chemical pleurodesis was reported by fewer patients in the *V. album* extract group. Considering these results, *V. album* extract may be a feasible and useful option for chemical pleurodesis.

Conflict of interest

No potential conflicts of interest relevant to this article are reported.

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