Thoracoscopic tetracycline poudrage for pleurodesis in malignant pleural effusion

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Introduction Malignant pleural effusion (MPE) is a common problem and a real challenge to pulmonologists and oncologists. The optimum management of MPE depends on several factors, including patient's symptoms and primary tumor status. Complete drainage and pleurodesis to prevent recurrence is usually needed. Tetracycline, talc, and bleomycin are considered the primary sclerosing agents.

Aim of the study The aim of the study was to investigate the feasibility, effectiveness, and safety of thoracoscopically insufflated tetracycline powder to achieve pleurodesis in patients with MPE.

Patients and methods Twenty patients with recurrent pleural effusion that proved to be malignant, or showing a picture highly suggestive of pleural malignancy at thoracoscopy, were included in the study. They were subjected to tetracycline poudrage (35 mg/kg) through medical thoracoscopy. Following discharge, patients were followed up at 3 and 6 months; the primary outcome was the measure of pleurodesis failure, defined as the reaccumulation of pleural fluid requiring further pleural intervention.

Results Of the 20 patients included in this study, five were excluded from evaluation (two because of failure of lung re-expansion and three because of death within 2 months of the procedure). The overall success rate of thoracoscopic tetracycline poudrage pleurodesis in the 15 patients with MPE who completed the study was 86.6%. There was no recorded mortality or significant complications.

Conclusion From this pilot study, we can conclude that thoracoscopy with tetracycline poudrage is an easy, safe, and effective method for performing pleurodesis in MPE.

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Introduction

The discovery of malignant cells in pleural fluid and/or parietal pleura usually indicates disseminated or advanced disease and a reduced life expectancy in patients with cancer [1]. The majority of patients who present with an malignant pleural effusion (MPE) are symptomatic, although up to 25% are asymptomatic, with an incidental finding of effusion on physical examination or on chest radiography [2]. Dyspnea is the most common presenting symptom, reflecting reduced compliance of the chest wall, depression of the ipsilateral diaphragm, mediastinal shift, and reduction in lung volume [3]. Currently, lung cancer is the most common metastatic tumor to the pleura in men, and breast cancer is the most common form of cancer in women. Together, both malignancies account for ~50–65% of all malignant effusions. Lymphomas, and tumors of the genitourinary tract and gastrointestinal tract account for a further 25%. Pleural effusions from an unknown primary are responsible for 7–15% of all MPEs [1]. Treatment options for MPE are determined by several factors: symptoms and performance status of the patient; the primary tumor type and its response to systemic therapy; and lung re-expansion following pleural fluid evacuation. Although small cell lung cancer, lymphoma, and breast cancer usually respond to chemotherapy, associated secondary pleural effusions may require interventions during the course of treatment [4]. MPEs are often most effectively managed through complete drainage of the effusion and instillation of a sclerosant to promote pleurodesis and prevent recurrence of the effusion. Options for management include observation, therapeutic pleural aspiration, intercostal tube drainage and instillation of sclerosant, thoracoscopy, and pleurodesis or placement of an indwelling pleural catheter [5]. Pleurodesis is thought to occur through a diffuse inflammatory reaction and local activation of the coagulation system with fibrin deposition. The most important requirement for successful pleurodesis is satisfactory apposition of the parietal and visceral pleura, confirmed radiologically. Incomplete lung re-expansion may be due to a thick visceral peel (trapped lung), pleural loculations, proximal large airway obstruction or a persistent air leak [6]. An ideal sclerosing agent must possess several essential qualities: a high molecular weight and chemical polarity, low regional clearance, rapid systemic

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clearance, a steep dose–response curve, and ability to be well tolerated with minimal or no side effects. The choice of a sclerosing agent will be determined by the efficacy or success rate of the agent, accessibility, safety, ease of administration, number of administrations to achieve a complete response, and cost. Despite the evaluation of a wide variety of agents, to date no ideal sclerosing agent exists [1]. Tetracycline, talc, and bleomycin are considered the primary sclerosing agents [7].

Aim of the study

The aim of the study was to assess the feasibility, efficacy, and safety of thoracoscopically insufflated tetracycline powder to achieve pleurodesis in patients with MPE.

Patients and methods

After receiving ethical committee approval, patients with primary or secondary MPE will be enrolled in the present study.

Inclusion criteria

Patients with moderate to massive MPE, recurrent after thoracentesis and requiring pleurodesis, or patients with recurrent pleural effusion with a thoracoscopic picture highly suggestive of pleural malignancy were included in the study.

Exclusion criteria

Patients at high risk for general anesthesia, those with poor general condition, short life expectancy, or with contraindications for medical thoracoscopy or with a history of allergy to tetracycline were excluded from the study. Patients were also excluded if there was evidence of empyema, failure of lung re-expansion after pleural fluid evacuation, failure of follow-up for at least 6 months, or if they refused to participate in the study or to sign a written informed consent form.

All patients were subjected to full medical history, complete general and local examination, routine laboratory investigations, plain chest radiography, and computed tomography of the chest without contrast.

Medical thoracoscopy in accordance with a standard technique, under general anesthesia, was performed [8]. All patients underwent pleurodesis with tetracycline powder (35 mg/kg). The powder from the evacuated oral capsules was insufflated using a powder blower at the end of the medical thoracoscopy after complete evacuation of the pleural fluid. A chest tube (size 24 Fr–28 Fr) was inserted and connected to an underwater sealed chamber to allow drainage of the effusion. When the amount of pleural fluid was less than 100 ml/24 h and chest radiography showed complete lung expansion, the chest tube was removed.

Following discharge, the patients were followed up at 3 and 6 months. The primary outcome was the measure of pleurodesis failure, which was defined as the reaccumulation of pleural fluid requiring further pleural intervention.

Written informed consent was obtained from all patients.

Medical thoracoscopy procedure

All patients had to undergo fasting for at least 6 h. No other special preoperative preparation was required. The patients were monitored before and during the whole procedure (blood pressure, pulse, ECG, and pulse oximetry). The procedure was performed with patient in the lateral decubitus position, with the affected side facing upwards, under general analgesia using a combination of inhalation anesthetic (isofluorane) and intravenous anesthetic (propofol). Skin sterilization was carried out, followed by incision and blunt dissection in the appropriate intercostal space to enter the pleural space. A 7 mm trocar was then inserted, and a 0° telescope was inserted through it and connected to a video camera. The pleural space was carefully inspected through the thoracoscope (Richard Wolf rigid thoracoscopy; Richard Wolf GmbH, Knittlingen, Germany). Abnormal (suspicious) areas were biopsied. Tetracycline powder (35 mg/kg) was then insufflated. Following the procedure, a chest tube (24 Fr–28 Fr) was inserted through the same incision and was connected to an underwater sealed chamber. After recovery a control chest radiography was performed. The chest tube was left in place until less than 100 ml of fluid was drained in 24 h, following which it was removed.

Statistical analysis

Quantitative data were presented as mean (±SD) and qualitative data as number and percentage. Data entry and statistical analysis were performed using SPSS for Windows, version 20.0 (SPSS Inc., Chicago, Illinois, USA).

Results

This nonrandomized interventional study was performed to evaluate the efficacy and safety of thoracoscopic tetracycline poudrage to achieve pleurodesis in MPE.

Twenty patients with MPE were included in the present study. All patients were suffering from dyspnea. Five patients were excluded from the evaluation, two patients because the lung did not expand at the time of the procedure and three patients because they died within 2 months of the thoracoscopy.

The mean age of the studied patients was 59.73±8.27. Nine patients were female (60%) and six were male (40%). All patients were suffering from shortness of breath. Demographic data of the included patients are presented in Table 1.

Among the 15 patients who completed the study, the etiology of MPE proved to be primary in 10 patients (mesothelioma) and metastatic in five. The different primary sites of malignancy in metastatic cases were lung cancer in three patients, breast cancer in one patient, and renal cell carcinoma in one patient. The different causes of MPE are shown in Table 2.

Medical thoracoscopy with tetracycline powder insufflation (Fig. 1) at a dose of 35 mg/kg was performed in all patients, followed by chest tube insertion through the same incision at the end of the procedure. The average duration of postoperative drainage was 4.73±0.3 days. Follow-up chest radiographs at 3 and 6 months following pleurodesis with tetracycline poudrage were completed in 15 patients.

The success of tetracycline poudrage pleurodesis was defined as the absence of pleural fluid reaccumulation on follow-up chest radiographs (complete response) or the presence of residual pleural fluid (usually <500 ml) that did not require further tapping during the follow-up period (partial response). All other cases were considered failures.

Successful pleurodesis with thoracoscopic tetracycline poudrage was found in 13 patients (86.6%): 10 patients (66.6%) showed complete response, and three patients (20%) showed partial response. Failure occurred in two patients (13.4%). The outcome of tetracycline poudrage pleurodesis is shown in Table 3.

No mortality was recorded in the early postoperative period, and there was no significant morbidity observed after tetracycline powder insufflation. Two patients (13%) developed low-grade fever (<38°) that subsided spontaneously within 48 h, and four patients (26%) reported chest pain that responded well to simple analgesics (paracetamol). In two patients (13%), the drainage was prolonged for more than 6 days, and one patient (6.6%) developed empyema. The complications and morbidities related to thoracoscopic tetracycline poudrage pleurodesis are presented in Table 4.

Discussion

MPE is a common complication of end-stage malignancy. It has a significant impact on the quality of life [2]. The primary aim of management of malignant effusion is to bring relief from symptoms, and decrease the patient's discomfort. There are

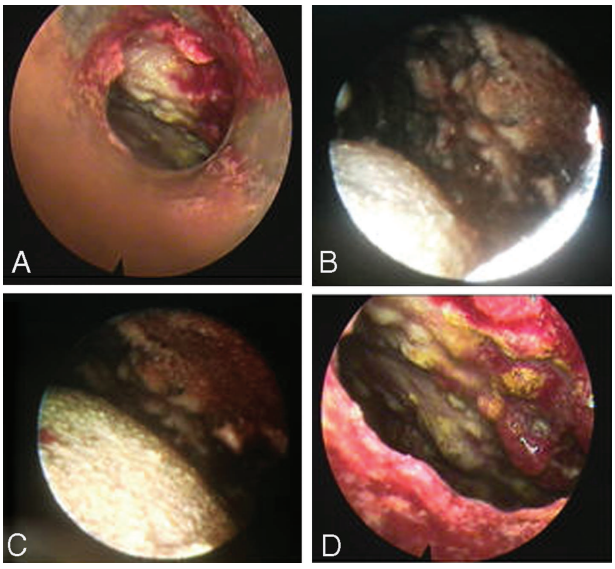
Table 1 Demographic characteristics of the studied group

Characteristics	*n* (%)
Age (years)	
Mean±SD	59.73±8.27
Range	48–74
Sex	
Female	9 (60)
Male	6 (40)

Table 2 Summary of the different etiologies of malignant pleural effusion in patients undergoing tetracycline poudrage pleurodesis

Diagnosis	Number of patients
Mesothelioma (primary)	10
Epithelial	7
Biphasic	3
Metastatic (secondary)	5
Primary lung	3
Primary breast	1
Primary kidney	1

Figure 1



(a–d) Tetracycline powder as seen on medical thoracoscopy after insufflation into the pleural space.

Table 3 Outcome of tetracycline poudrage pleurodesis in all studied patients

Pleurodesis outcome	*N*=15 [*n* (%)]
Success	13 (86.6)
Complete response	10 (66.6)
Partial response	3 (20)
Failures	2 (13.4)

Table 4 Complications and morbidities related to thoracoscopic tetracycline poudrage pleurodesis

Morbidity and complication	Number of patients (%)
Fever (low grade)	2 (13)
Chest pain	4 (26)
Prolonged drainage	2 (13)
Empyema	1 (6.6)

different treatment options for patients who suffer from MPE, including serial thoracentesis, tube thoracostomy, pleurodesis, long-term pleural catheter, pleuroperitoneal shunt, decortication, and chemotherapy and radiotherapy. The choice of therapy is determined on the basis of a patient's clinical situation as well as the underlying disease [1].

Pleurodesis offers patients MPE palliation of symptoms by draining the pleural fluid and providing a pleural symphysis that prevents the reaccumulation of malignant fluid [6].

The aim of the present study was to evaluate the efficacy and safety of tetracycline in its powder form in achieving pleurodesis when insufflated through medical thoracoscopy inside the pleural cavity in patients with MPE.

Dyspnea was the most common presenting symptom in patients with MPE in the present study. This is also reported in the literature and in other studies [9,10]. Dyspnea usually occurs because of a combination of reduced compliance of the chest wall, depression of the ipsilateral diaphragm, and mediastinal shift. Usually, the intensity of dyspnea depends on the volume of the effusion and the underlying condition of the lung [10].

Fifteen patients completed the present trial. The results showed that 13 out of 15 patients (86.6%) had successful pleurodesis with thoracoscopic teracycline poudrage. There was no need for further interventions during the 6-month follow-up period.

Parenteral tetracycline was used in other studies with success rates between 50 and 92%, with a mean of 65% [11–14].

Tetty *et al.* [15] studied chest tube insertion and tetracycline pleurodesis using tetracycline capsules. They achieved a success rate of 77%, which is slightly less but comparable to the results of the present study. However, there is a difference in the method adopted for pleurodesis in the study by Tetty and colleagues. Tetracycline was used after dilution, in liquid form, whereas in the present trial we used tetracycline in its powder form; insufflation of the powder into the pleural space was done through medical thoracoscopy.

Thoracoscopic instillation of parenteral tetracycline has been studied in two randomized trials on malignant effusions in breast cancer. Evans *et al.* [16] compared thoracoscopic instillation of 500 mg tetracycline with that with 1.5 g by means of a chest tube. The complete response rate at 1 month for both groups was 76%. Fentiman *et al.* [17], on the other hand, compared talc poudrage with thoracoscopically administered tetracycline (500 mg). The talc group was found to be superior with a successful palliation at 1 month of 92% compared with 48% for the tetracycline group.

In the present study, we used tetracycline powder at a dose of 35 versus 20 mg/kg or even lower doses in previous studies. The success rate achieved and maintained in our trial is significantly higher than that of previous trials that investigated the efficacy of tetracycline pleurodesis.

Tetracycline hydrochloride is a very frequently used chemical pleurodesis agent. The direct effects of this drug are similar to growth factors that are released from fibroblasts [18]. Tetracycline has an excellent safety profile, and it is relatively inexpensive. It is well tolerated and side effects are infrequent, mild, and transient [19].

In another previous randomized study, Boutin *et al.* [20] compared the results of 40 consecutive patients with MPEs in whom talc (4.5 g) and tetracycline powder (20 mg/kg) were insufflated through the thoracoscope. The long-term success rate remained at 90% in the talc group, whereas it dropped to 50% at 6 months in the tetracycline group. The authors of this study suggested that the observed differences in the results may be because tetracycline, being soluble, gradually disappears from the pleural cavity, while talc remains in place indefinitely, thus producing a permanent pleurodesis [21]. The present study showed different results, as the success rate of thoracoscopic tetracycline poudrage pleurodesis remained 86.6% after 6 months. The dose of tetracycline used in the present trial is 35 mg/

kg, versus 20 mg/kg in the study by Boutin and colleagues. This higher dose used in the present trial may have induced more important inflammation that helped in the long-term success of pleurodesis.

The average duration of postoperative drainage in the present trial was 4.73±0.3 days, and this was shorter than the previously reported drainage duration. Hartman *et al.* [22] reported a mean drainage time of 6.5±2.1 days for tetracycline, 4.0±1.2 days for talc poudrage, and 6.6±1.6 days for bleomycin.

The results of the present study showed no mortality related to the procedure, and no significant complications. Two patients (13%) developed low-grade fever (37.8°), which subsided within 48 h, and four patients (26%) had moderate chest pain, which was managed with simple analgesics (paracetamol) with good response. In two patients (13%), the drainage was prolonged for more than 7 days, and one patient (6.6%) developed empyema.

The commonly reported side effects of teracycline pleurodesis in previous studies include fever (10%) and pleuritic chest pain (30%), which are usually transient and responded readily to antipyretics and analgesia [11–15].

Conclusion

MPE is a common complication of end-stage malignancy. Management is palliative, and chemical pleurodesis using thoracoscopic tetracycline poudrage has been shown to be safe and effective in our pilot study.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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