

Doxycycline poudrage in pleurodesis of malignant pleural effusion: a novel modality for an old agent

Tamer A. Elhadidy^a, Ahmed M. Abumossalam^a, Mohamed S. Elashry^b

Context Malignant pleural effusion is a common presentation of several malignancies. Chemical pleurodesis is important in its management, but no consensus exists on the optimal agent or methods of pleurodesis.

Aim This work aimed to evaluate the outcome of oral doxycycline capsules in a poudrage form through a medical thoracoscope as a therapeutic approach for pleurodesis in patients with malignant pleural effusion.

Setting and design This study was a prospective quasiexperimental one.

Patients and methods This prospective quasiexperimental study was conducted on 70 patients with metastatic pleural effusion. They underwent pleurodesis with thoracoscopic doxycycline poudrage.

Results The success of doxycycline powder poudrage was complete in 75.7% of cases and partial in 10% of cases; however, failure was observed in 14.3%. Thus, total success rate was 85.7%. As regards complications, they were irrelevant; pain was the predominant feature in 81.4% of

Introduction

Malignant pleural effusions (MPE) are considered a frequent occurrence in many malignancies with advanced degree. They signify important reasons of morbidity and mortality. Symptoms can be debilitating to patients and mess up their life quality, especially as many patients are by now functionally disabled due to primary cancer and its treatment. In the USA, malignant effusions of the pleura affect about 150 000 patients each year [1]. Cancer of the lung and breast constitute 50–65% of all MPEs. On the other hand, lymphomas, cancers of the genitourinary and gastrointestinal tract, and cancers with unknown primaries constitute the other causes of MPEs [2]. Almost 100% of patients will experience debilitating dyspnea, whereas up to 25% of patients are initially asymptomatic from the effusion [3]. Regardless of management of the original malignancy with chemotherapy and/or radiation therapy, MPEs have a propensity to persevere or recur and necessitate local palliative methods to control symptoms. Currently available procedures for palliating dyspnea associated with MPE comprise: (a) repeated thoracentesis, (b) pleurodesis, and (c) placement of tunneled pleural catheters [4]. Pleurodesis is the obliteration of the pleural space by merging the visceral and parietal pleurae by means of fibrous tissue. Recurrent and symptomatic effusions plus pneumothoraces are essential indications for pleurodesis [5]. Pleurodesis can be carried out using surgical or chemical approaches with different chemical agents that induce adhesions between

cases, fever in 11.4% of cases, and empyema in only 4.3% of cases.

Conclusion Using oral doxycycline with thoracoscopic poudrage yielded a remarkable success rate and may alternate the need for talc powder with less complications and more safety.

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Keywords: doxycycline poudrage, malignant pleural effusion, pleurodesis, thoracoscopy

^aChest Medicine, Faculty of Medicine, Mansoura University, Mansoura,

^bChest Department, Radiotherapy, Faculty of Medicine, Mansoura University, Mansoura, Egypt

Correspondence to Tamer A. Elhadidy, MD, Chest Medicine, Faculty of Medicine, Mansoura University, Mansoura, 35116, Egypt,

Tel: 01090110110;

E-mail: hadidy1980@yahoo.com

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the two layers of pleura. More than 30 agents of pleurodesis have been projected since 1935, yet none of them is ideal. A diversity of agents could be used for pleurodesis and are typed into two broad categories according to their mechanism of action: first, cytostatic agent, which control effusion by reducing tumor volume; and second, sclerosing agents, which produce chemical pleurisy that lead to the formation of adhesions and subsequent obliteration of the pleural space [6]. Currently, talc, bleomycin, and tetracycline derivatives are the most regularly used sclerosing agents. Bleomycin is more expensive and less efficient compared with tetracycline derivatives or talc [7]. Studies have shown that the intrapleural inoculation of talc through poudrage may lead to acute respiratory distress syndrome (ARDS) [8]. The parenteral form of tetracycline is currently not available in most countries. Subsequently, parenteral doxycycline was used for pleurodesis at a dose of ~10 mg/kg and was shown to have equivalent effectiveness with tetracycline at 35 mg/kg [9]. Conversely, parenteral doxycycline is also not available currently in Egypt and many countries in the world. In contrast, doxycycline capsules are available worldwide, and hence we proceeded to investigate the safety and

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efficacy of oral doxycycline pleurodesis as does parenteral doxycycline.

Patients and methods

This prospective quasiexperimental study was carried out at the Chest Department, Mansoura University Hospital, from February 2015 to April 2016 and included 70 patients with metastatic MPE (diagnosed by means of cytology and or pleural biopsy) who were candidates for pleurodesis and for medical thoracoscopy as a therapeutic approach for pleurodesis in patients with MPE. Patients were assembled from the outpatient clinic of Mansoura University Hospitals of both the chest and the cardiothoracic department in addition to referred cases for pleurodesis from Mansoura University Oncology Center, Damietta Oncology Center, and Meet Ghamr Oncology Center (Dakhliya, Damietta, Portsaid, Kafr Elsheikh and some cases in Gharbia governates).

Patients with unilateral metastatic MPE who were candidate for medical thoracoscopy were included in the study.

Exclusion criteria

- (1) Bilateral MPE.
- (2) Contraindication, being unfit, or refusal to undergo medical thoracoscopy.
- (3) Noncandidate for pleurodesis (central mediastinum, nonimprovement after therapeutic aspiration).

All patients after local anesthesia with lidocaine 0.5% and conscious sedation with midazolam 0.02–0.2 mg/kg underwent medical thoracoscopy using 11 mm Karl Storz medical thoracoscopy. A trocar was introduced in the midaxillary line in the fifth to seventh intercostal space, and then complete aspiration of pleural fluid and introduction of air to prevent reexpansion pulmonary edema were carried out. Subsequently, a volume of 10 ml of lidocaine 2% was instilled through a thoroscopic channel to reduce local pain. Thereafter, insufflations of 1000 mg of oral doxycycline capsules (10 capsules of vibramycine, Pfizer Inc., Germany) was carried out using a powder insufflators, with uniform distribution of all particles all over the costal pleural surface and subsequent placement of 28–32 intercostal tube in the pleural space until tube drainage stopped (duration ranged from 3 to 7 days). Thereafter, the tube was taken away with suturing the ostium. Postprocedure pain was managed with potent nonsteroidal anti-inflammatory drugs that were sufficient in our cases. Follow-up and assessment for

response after 1 month were carried out. Patients were divided into three groups based on response, both clinical and radiological evaluation (computed tomography of the chest) [6].

- (1) Complete response: complete success, no recurrence of fluid or symptoms after 1 month.
- (2) Partial response: partial success, recurrence of fluid but less than prepleurodesis level with no recurrence of symptoms.
- (3) Failure recurrence: partial success, both fluid and symptoms to the same before pleurodesis.

Our study was approved by our departmental ethical consideration and ethical consideration in our institution, Mansoura Faculty of Medicine.

Statistical analysis

Data were analyzed using statistical package for social sciences, version 21 (SPSS Inc., Chicago, Illinois, USA). Qualitative data were presented as number and percentage. Quantitative data were presented for normality using the Kolmogorov–Smirnov test. Normally distributed data were presented as mean and SD.

Results

Our study was conducted on 70 patients (Table 1) with a mean age of 48.4 ± 7.62 . An overall 51.4% were male and the others were female. According to the primary site of malignancy, bronchial carcinoma represented 44.35, breast carcinoma represented 40%, ovarian carcinoma 8.6%, and non-Hodgkin's lymphoma

Table 1 Demographic, clinical, outcome data in studied cases and procedure complications

Age	
Mean \pm SD	48.4 \pm 7.62
Range	29–65
Sex [n (%)]	
Male	36 (51.4)
Female	34 (48.6)
Primary site of malignancy [n (%)]	
Breast carcinoma	28 (40)
Ovarian carcinoma	6 (8.6)
Bronchogenic carcinoma	31 (44.3)
Non-Hodgkin lymphoma	5 (7.1)
Success [n (%)]	
Failure	10 (14.3)
Partial success	7 (10)
Complete success	53 (75.7)
Complications [n (%)]	
Pain	57 (81.4)
Fever	8 (11.4)
Empyema	3 (4.3)

represented 7.1% of cases. Success was complete in 75.7% of cases and partial in 10% of cases; however, failure was observed in 14.3% of cases, and hence total success rate was 85.7%. As regards complications, they were irrelevant; pain was the predominant feature in 81.4% of cases, fever in 11.4% of cases, and empyema in only 4.3% of cases (Fig. 1).

Discussion

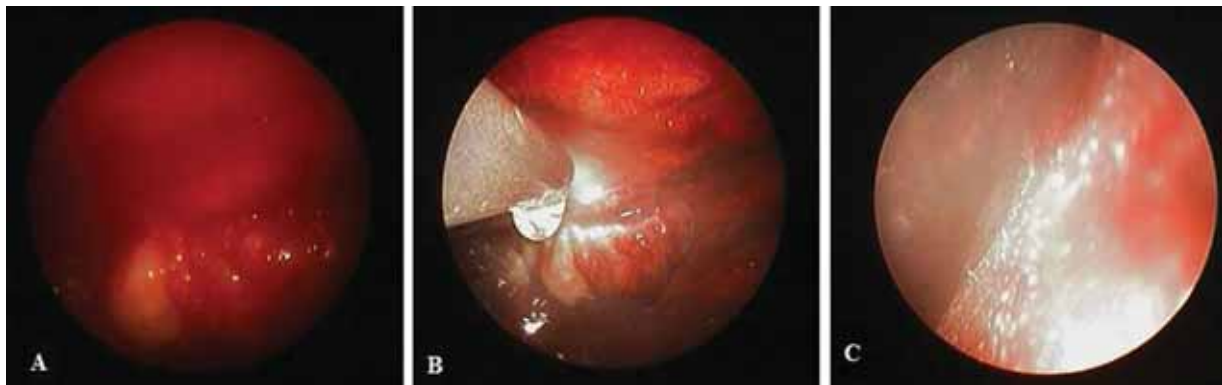
Although pleurodesis has been considered as an essential line of management of MPE, no ideal sclerosing agent or method of application is considered ideal. However, talc powder is one of the most accepted agents, but it is not commercially available in our era. Doxycycline, in addition to other agents, has been used before, but in an infusion form for pleurodesis; however, this is not available for use as well. Hence, in our study, we attempted to handle an old agent using a new technique. We found that the usage of an oral form of doxycycline with the poudrage insufflation technique may produce our target in getting rid out of this predicament and obtaining a high success rate. In our study, we used 1000 mg of oral doxycycline that was subsequently inoculated by means of medical thoracoscopy with a powder blower, and then observed for success rate and complication for 1 month.

The total success rate in our work accounted for 75.7% as complete success, and on adding up partially succeeded cases it was 85.7% after 1 month of follow-up. In this study, usage of an oral form of doxycycline with poudrage yielded success rate similar to that documented in a study by Porcel *et al.* [10], who conducted a prospective study of 36 rapid pleurodesis procedures in 34 patients with MPEs. Patients received 500 mg of intrapleural doxycycline. Complete success of

pleurodesis was achieved in 17 (55%) cases, partial success in eight (26%) cases, and failure in six (19%) of 31 evaluative procedures. Thus, the overall success rate of pleurodesis was 81%. Heffner *et al.* [9] examined the outcome in 31 patients receiving doxycycline through a chest tube for MPEs or persistent bronchopleural fistulae and stated that, of the 27 patients with MPEs, 21 (77.8%) patients had successful pleurodesis at 1-month interval.

Recently, Elnady and Sakr [11] performed pleurodesis in 27 patients with MPE, using nearly the same technique [thoracoscopic doxycycline poudrage (TDP)]. In their research, at the end of thoracoscopy, a new method for doxycycline delivery to the pleura was used through a pneumatic atomizer insufflations at the end of thoracoscopy, in which about 500–1000 mg of doxycycline was taken and prepared as a powder from the oral preparation (5–10 capsules of vibramycin 100 mg/capsule). In the study by Elnady, 74.1% had successful pleurodesis, 18.5% had partial response, and 7.4% had failed pleurodesis at 1 month. Adverse effects included pain (48.1%), fever (3.7%), and pain and fever (22.2%). The mean drainage time for intercostal tube was about 1.52 days. However, the duration ranged from 3 to 7 days in our cases. Their results are in line with our study; 74.1% had a successful pleurodesis, 18.5% had partial response, and 7.4% had failed pleurodesis at 1 month, with the difference in number and our cases already diagnosed and prepared for pleurodesis. However, in their study they performed diagnostic thoracoscopy and applied TDP in the same session. As regards recorded complications, they were minimal and easily controlled in the form of pain noticed in 57 (81.4%) cases; it may be due to chest tube irritation rather than doxycycline powder alone. Simple

Figure 1



(a) Visible visceral pleural nodules with medical thoracoscopy. (b) Inserted thoracoscopic poudrage channel through thoracoscopic trocar with doxycycline spurt. (c) Spilled doxycycline on visceral pleural layers.

nonsteroidal analgesics prescribed in general for 24–48 h, easily overcame this problem. Fever greater than 38°C that lasted for about 24 h was recorded as a complication in eight (11.4%) cases and alleviated with paracetamol.

In a recent study conducted by Hatata *et al.* [12], after 90 days, 19 of 22 surviving patients (86.4%, 95% CI=59.8–94.8%) had successful pleurodesis. In their study, no procedure-related major complications were recorded. Minor adverse effects included pain (28.6%), fever (25%), and wound infection (10.7%). Survival rate at 90 days was 78.6%. The mean duration of hospitalization was 1.93±0.92 days. On comparing our results with that for talc poudrage, which is considered now as ideal pleurodesis agents, we found that the success rate for talc poudrage was 87% in the study of thoroscopic talc poudrage versus bleomycin by Diacon *et al.* [13], which is comparable to that of TDP. The reported side effects of thoroscopic talc pleurodesis included ARDS, pneumonitis, empyema, and local wound infections. Although serious respiratory complications traditionally were believed to occur very rarely with talc pleurodesis and only with larger talc doses (≥ 10 g per session), recent retrospective studies have found a higher incidence with talc doses as low as 2 g and with a range of different techniques of application [14]. Systemic distribution of talc is discussed as a possible mechanism for ARDS [15]. In future, the safety of talc for pleurodesis will need close attention and more careful manipulations. Similar to other maneuvers, doxycycline poudrage has been considered of restricted facilities owing to limitations in patients with hypersensitivity to the drug (doxycycline), unfit cases for medical thoracoscopy, and also patients with sarcomatous type of mesothelioma and synovial sarcoma. Moreover, patients with chest wall deformity and trapped lung represented an absolute contraindication from the start. Nonenrollment of a comparative arm in our study needs more research with other agents using the same technique for better evaluation.

Conclusion

By means of thoroscopic instillation of oral doxycycline using the poudrage technique it seems

to be a nonsurgical substitute with higher success rate and alternates the need for talc powder with less complications and more safety.

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Nil.

Conflicts of interest

There are no conflicts of interests.

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