Egyptian Journal of Chest Diseases and Tuberculosis (2013) **62**, 617–620

The Egyptian Society of Chest Diseases and Tuberculosis

Egyptian Journal of Chest Diseases and Tuberculosis

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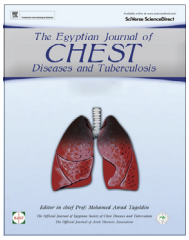

ORIGINAL ARTICLE

A new look at an old agent for pleurodesis

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Received 9 November 2012; accepted 5 August 2013
Available online 9 October 2013

KEYWORDS

Doxycycline pleurodesis;
Malignant pleural effusion

Abstract *Background and objective:* Malignant pleural effusion (MPE) is a common problem in patients with malignancies. Chemical pleurodesis is the most commonly used palliative option. Parenteral tetracycline (TET) and doxycycline (DOX) are cost-effective and safe in producing pleurodesis but mostly unavailable currently. We investigated whether oral doxycycline could produce an efficient and safe pleurodesis as does parenteral doxycycline, which is currently unavailable in many countries.

Methods: A prospective study of 24 pleurodesis procedures in 22 patients with malignant pleural effusions were conducted over a 3-year period. All pleurodesis was performed with oral forms of doxycycline as the sclerosing agent, where about 1000 mg of doxycycline was taken and prepared from the oral preparation (vibramycin 100 mg/capsule) and mixed in 50 ml. Physiological saline was then administered via tube thoracostomy. We assessed the success or failure of pleurodesis in addition to the frequency of complications and survival. Post-pleurodesis postero-anterior (PA) radiographs were obtained after tube removal and 30 days following the procedure.

Results: Twenty-two patients were included (6 women, 16 men), the mean age was (62.5 years). Origins of MPE were: lung and pleura 8 (36.4%), breast 2 (9.1%), ovarian 2 (9.1%), digestive 3 (13.6%), lymphoma 3 (13.6%) and unknown 4 (18.2%). No immediate perioperative complications were noted. Chest tube duration averaged 4.2 ± 2.6 days. Immediate postoperative events included chest pain in 10 patients (45.5%), fever in 2 (9.1%) patients, pain and fever in 5 patients (22.7%). Sixteen patients (72.7%) had successful pleurodesis and 6 patients (27.3%) had failed pleurodesis at 1 month.

Conclusions: Pleurodesis with oral forms of doxycycline dissolved in sterile saline solution have a high success rate with a low incidence of complications and could be a good option as palliative therapy in patients with symptomatic malignant pleural effusions.

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Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.

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Introduction

Malignant pleural effusions (MPEs) affect approximately 150,000 patients each year in the United States [1]. Lung and breast cancer account for 50–65% of all MPEs, with lymphomas, cancers of the genitourinary and GI tract, and cancers with unknown primaries accounting for the majority of the remaining causes of MPE [2]. Although up to 25% of patients are initially asymptomatic from the effusion, nearly 100% of patients will experience debilitating dyspnea [3]. Despite management of the underlying malignancy with chemotherapy and/or radiation therapy, MPEs tend to persist or recur and require local palliative procedures to control symptoms. Currently available techniques for palliating the dyspnea that is associated with MPE include (1) repeated thoracentesis, (2) pleurodesis, and (3) insertion of tunneled pleural catheters (TPCs) [4].

Pleurodesis is the obliteration of the pleural space by fusion of the visceral and parietal pleurae with fibrous tissue. Recurrent and symptomatic effusions and pneumothoraces are indications for pleurodesis. Most of the agents used for pleurodesis injure the pleura and cause an inflammatory reaction together with a pleural effusion. Subsequently, the local activation of the coagulation system and the production of fibrogenic cytokines such as trans-forming growth factor β lead to the production of collagen that can result in a pleurodesis [5].

Currently talc [6], tetracycline derivatives [7], and bleomycin [8] are the most frequently used sclerosing agents. Bleomycin is more expensive and less efficient than tetracycline derivatives or talc [5]. The intrapleural injection of talc can cause ARDS and death [9,10]. Tetracycline (35 mg/kg) was the most effective compound when original animal experiments on producing pleurodesis in rabbits were performed [11,12]. The parenteral form of tetracycline is currently not available in most countries. Subsequently, parenteral doxycycline was used for pleurodesis at an approximate dose of 10 mg/kg and was shown to have comparable effectiveness with tetracycline at 35 mg/kg. [7,8]. However, parenteral doxycycline is also not available currently in many parts of the world. In contrast, doxycycline capsules are available worldwide but (to our knowledge) have never been tested for their efficacy and safety in producing pleurodesis in humans when administered via tube thoracostomy. We investigated whether oral doxycycline could produce an efficient and safe pleurodesis as does parenteral doxycycline, which is currently unavailable in many countries.

Subjects and methods

Study population

A prospective study of 24 pleurodesis procedures in 22 patients with malignant pleural effusions were conducted over a 3-year period from May 2009 to June 2012 at the Dallah Hospital, Riyadh, Saudi Arabia. The cause of the malignant pleural effusions was confirmed in all patients with cancer, either by cytologic examination of pleural fluid or by needle pleural biopsy or during a previous recent thoracic evaluation. Criteria for consideration as a candidate for pleurodesis in patients with malignant pleural effusions were as follows: (1) anticipated survival longer than 1 month after performance of the pleurodesis; (2) improved respiratory symptoms after a previous therapeutic thoracentesis; (3) cytologic or histologic confirmation of the malignant nature of the pleural effusion; and (4) ability to fully re-expand the lung during drainage of pleural fluid by tube thoracostomy [7].

Procedures and assessments

A size 24F to 28F thoracostomy tube was placed through the seventh or eighth intercostal space at the posterior axillary line and was attached to a water seal with gravity drainage. Pleural fluid volumes were recorded daily, and a chest radiography was taken daily. When the drainage fell below 100 ml/24 h and the lung had expanded completely, pleurodesis was attempted. After instillation of 10 ml of 1% lidocaine, about 1000 mg of doxycycline were taken and prepared from the oral preparation (10 capsules of vibramycin 100 mg/capsule) and mixed in 50 ml physiological saline under sterile conditions then administered via a large syringe, followed by a 30–50 ml of a sterile saline flush. The tube was clamped for 2 h, then unclamped and gravity drainage resumed. The chest tube was removed when the drainage fell below 100 ml/24 h and chest X-ray showed complete lung expansion. Patients were observed for complications, were medicated for pain as needed, and were monitored with daily chest radiographs. In two patients, in whom drainage of the pleural fluid did not diminish below 100 ml/day during the 24–72 h after the initial attempt at pleurodesis, a second intrapleural instillation of doxycycline (500 mg) was used. Post-pleurodesis postero-anterior (PA) radiographs were obtained after tube removal and 30 days following the procedure. Radiographic response at day 30 was classified as successful: no or only minor re-accumulation of pleural fluid, or non-successful: re-accumulation of fluid. Minor re-accumulation refers to re-accumulation of fluid, without symptoms or not requiring repeat drainage, above the post-sclerotherapy level but below the original level [13].

Statistical analysis

The data were expressed as mean ± SD. All data were analyzed with statistical software (Sigma Stat; SPSS; Chicago, IL). A p value < 0.05 was considered significant.

Results

A total of 22 patients were included in this study, of which 16 (72.7%) were males and 6 (27.3%) were females. The mean age for the entire group was 62.5 ± 6.5 years. Pleural effusions were right sided in 10 (45.5%) cases while 12 (54.5%) cases were left sided. Origins of MPE were: lung and pleura 8 (36.4%), breast 2 (9.1%), ovarian 2 (9.1%), digestive 3 (13.6%), lymphoma 3 (13.6%) and undifferentiated carcinoma of unknown primary 4 (18.2%). (Table 1):

Sixteen patients (72.7%) had successful pleurodesis and 6 patients (27.3%) had failed pleurodesis at 1 month (Table 2).

No immediate perioperative complications were noted. Chest tube duration averaged 4.2 ± 2.6 days. Immediate postoperative events included chest pain in 10 patients (45.5%), fever in 2 (9.1%) patients, pain and fever in 5 patients (22.7%) (Table 3).