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SHORT COMMUNICATION

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Rapid pleurodesis with doxycycline through a small-bore catheter for the treatment of metastatic malignant effusions

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Abstract *Goals of work:* The goal of the study was to evaluate the safety and efficacy of bedside pleurodesis with doxycycline using a short-term indwelling chest catheter for the palliative treatment of malignant effusions. *Materials and methods:* A prospective study of 36 rapid pleurodesis procedures in 34 patients with malignant pleural effusions was conducted over a 5-year period in a university hospital. A 12F chest catheter placement was facilitated utilizing the Seldinger percutaneous entry technique. Patients received 500 mg of intrapleural doxycycline combined in half of the cases with mepivacaine. We assessed success or failure of pleurodesis in addition to the frequency of complications and survival. *Main results:* Chest tubes were removed within 24 h in 69% and within 48 h in 94% of the patients. Complete success of pleurodesis was achieved in 17 (55%), partial success in eight (26%), and failure in six (19%) out of 31 evaluative procedures. Thus, the overall success rate of pleurodesis was 81%. Toxicity was mild and included pain (36%), fever (8%), and pneumothorax (6%). The median survival was 105 days. There was no relationship between instillation of intrapleural anesthetics and development of pain. *Conclusions:* Rapid pleurodesis with doxycycline, which can be accomplished within 24 to 48 h, is a valid option for the symptomatic treatment of malignant effusions. This technique can be used as a first-line procedure in the majority of cases, particularly if thoracoscopic facilities are not available.

Keywords Malignant pleural effusion · Pleurodesis · Doxycycline · Chest tube

Introduction

Effective palliation of malignant pleural effusion (MPE) can usually be achieved with tube thoracostomy and subsequent pleurodesis. Clinical studies of various sclerosing agents support the superior clinical effectiveness of intrapleural talc, but concern exists regarding its potential serious respiratory complications. A variety of other agents including doxycycline, tetracycline, and bleomycin are considered valid alternatives [2].

The technique used for chemical pleurodesis is critical for a good result. Large-bore chest tubes (24 French or more) were employed traditionally to drain pleural fluid and to instill sclerosing agents. The relatively long duration of chest tube drainage both prior to and after the administration of the pleurodesis agent explains the

completeness of the standard procedure in 5 to 7 days [7, 8]. Because the life expectancy of patients with MPE is short, efforts should be made to minimize the duration of their hospitalization. A few reports have advocated shortening the time of drain removal ("rapid" procedure) as a simpler and equally effective method for pleurodesis [3, 5–8].

This prospective study presents our experience with a rapid pleurodesis procedure using doxycycline as the sclerosing agent for controlling MPE.

Materials and methods

Between March 2001 and January 2005, 36 rapid pleurodesis procedures in 34 patients with MPE were performed at the Arnau de Vilanova University Hospital (Lleida, Spain) by one of the authors (José Manuel Porcel). Patients eligible for the study met the following criteria: (1) cytologically or histologically proven MPE, (2) symptomatic MPE of moderate to large size ($\geq 1/2$ hemithorax), (3) satisfactory performance status (Karnofsky score >50), and (4) radiographic demonstration of adequate pulmonary reexpansion after pleural drainage (i.e., the absence of proximal endobronchial obstruction or trapped lung).

In all patients, a 12 French thoracic catheter (Portex Seldinger Chest Drainage Kit, SIMS Portex, Hythe, United Kingdom) was placed at the bedside into the pleural space in the midaxillary line. Chest catheter placement was facilitated utilizing standard percutaneous entry (Seldinger) technique. The catheter was connected to a 3-chamber drainage unit (Argyle Aquaseal, Sherwood Medical, Tullamore, Ireland). After radiographic demonstration of lung reexpansion, usually 2 to 8 h after chest catheter placement, 500 mg of doxycycline in 100 ml of normal saline combined with 20 ml of 2% mepivacaine only in those procedures performed until June 2003, was instilled into the pleural space via the small-bore chest tube. The three-way stopcock from the kit was then closed for 2 h and then reopened to suction drainage. There was no requirement for the patient to rotate positions. The chest catheter was removed 12 to 24 h after the administration of the sclerosing agent, regardless of the residual fluid output. Patients were followed-up for fluid recurrence with clinical and radiographic examination of the chest until death.

According to the American Thoracic Society and European Respiratory Society consensus [1], complete response was defined as:

1. Long-term relief of symptoms related to the effusion with absence of fluid reaccumulation on chest radiographs until death;
2. Partial response, as diminution of dyspnea related to the effusion with only partial reaccumulation of fluid (less than 50% of the initial radiographic evidence of fluid) and no further therapeutic thoracenteses required for the remainder of the patient's life; and
3. No response or failed pleurodesis as lack of success as defined above.

Global response was defined as complete response plus partial response. Complications such as fever (temperature >37.6°C), pain, dyspnea, or pneumothorax were recorded. The local ethical committee approved the study and written informed consent was obtained from all patients. All statistical data are presented descriptively.

Results

The series consisted of 34 patients with a median age of 72 years (quartiles, 59–78 years), 17 (50%) of them were men and 17 were women. Two patients underwent a double sequential pleurodesis procedure. The underlying primary tumors were lung (11, 32%), breast (8, 23%), ovary (4, 12%), and miscellaneous areas (stomach: 2, adenocarcinoma of unknown origin: 2, endometrium: 2, esophagus: 1, oropharynx: 1, kidney: 1, melanoma: 1, and non-Hodgkin's lymphoma 1; 32%).

Nineteen (53%) pleural effusions were left-sided, 15 (42%) right-sided, and two (5%) bilateral. Pleural effusion occupied half of the hemithorax in 11 (30%), two-thirds in 15 (42%), and the entire hemithorax in ten (28%) instances.

Chest tubes were removed within 24 h in 25 (69%) and within 48 h in 34 (94%) procedures. The length of time that the chest tube remained in place was 72 h in two patients. Total pleural fluid drained ranged from 2,000 to 3,275 ml (mean, 2,675 ml). Twenty-one (62%) patients received systemic analgesics prior to pleurodesis while we instilled intrapleural anesthetics in 19 (53%) procedures. Two patients required a second injection of doxycycline during the same procedure to optimize results.

Complications after the intracavitary injection of doxycycline included pain requiring analgesics (13 cases, 36%), self-limiting fever (3 cases, 8%), and small secondary pneumothorax (2 cases, 6%). The appearance of pain did not differ between those patients with and those without the concomitant instillation of intrapleural anesthetics (9/19, 47% vs 4/17, 23%; P=0.18 by Fisher's exact test).

The global response rate of pleurodesis was 81% with 17 (55%) complete responses, eight (26%) partial responses, and six (19%) no responses among 31 procedures from patients who survived for more than 30 days. These percentages changed to 60, 37, and 3%, respectively when the 30-day outcome rather than long-term success was assessed. Of the five patients who died before 30 days (range: 3 to 23 days), none had reaccumulation of fluid. The median survival of the study group was 105 days (quartiles, 46 to 240 days; range: 3 to 610 days).

Discussion

The current study demonstrates that pleurodesis can be accomplished within 1 o 2 days with similar results to those reported with traditional techniques, which require about 1 week of indwelling chest tubes. Easy to perform and a minimally invasive procedure, rapid pleurodesis with doxycycline had a success rate of 81%, a figure that compares with the reported success rates in other trials (Table 1).

There is a wide variation in practice regarding the optimal way to achieve pleurodesis with the ongoing search for better sclerosing agents. Although talc is currently regarded as being the most efficacious, it is preferably insufflated down the channel of a thoracoscope (talc poudrage) rather than instilled down an intercostal tube (talc slurry). Whatever sclerosing agent is used, complete drainage of the pleural effusion is considered crucial for successful pleurodesis because it minimizes the dilution of the instilled drug and maximizes the pleural surface area exposed to its action. However, draining the pleural cavity with a small-bore chest catheter can be completed within a few hours. Moreover, no data support the practice of leaving a chest tube on until pleural drain loss is less than 100 ml per day once the sclerosing agent were instilled. Instead, the feasibility of complete lung reexpansion after pleurodesis procedure is most important. Thus, reducing the time of pre- and postpleurodesis drainage substantially shortens the procedure.

As shown in Table 1, a few studies have reported on the feasibility of rapid pleurodesis with agents other than doxycycline with global efficacy rates ranging from 77 to 100% in 1 month. Doxycycline induces more pain (about 40% in this study) than bleomycin, but it is significantly less expensive. It should be noted that the use of intrapleural anesthetics did not reduce the incidence of local pain of postpleurodesis. Contrary to some reports [4], we found that a single dose rather than multiple administrations of

Table 1 Published series on rapid pleurodesis procedures for the treatment of malignant pleural effusions

Study, year	No. of procedures	Size of chest tube	Duration of chest tube drainage	Pleurodesis agent	Response rate (%) at 30 days[a]	Complications (%)	Comments
Villanueva et al. 1994 [7]	9	28F	2 days (median)	Tetracycline	CR+PR: 78 NR: 22	NA	Two patients required a relatively long period of drainage
Hsu et al. 1998 [3]	22	12F	<24 h in 45% <48 h in 68%	Bleomycin	CR: 41 PR: 36 NR: 23	Fever: 77 Vomiting: 14 Hiccups: 5	Chest tube was inserted under ultrasound guidance
Spiegler et al. 2003 [6]	29	14F	<24 h <12 h in 38%	Bleomycin Talc slurry (n=11)	CR: 48 PR: 31 NR: 21	Pain: 10 Fever: 7 Pneumothorax: 3	In two patients, pleurodesis was performed as an ambulatory procedure
Sartori et al. 2004 [5]	50	9F	<48 h <24 h in 58%	Bleomycin	CR: 37.5 PR: 50 NR: 12.5	Fever: 48 Pain: 16 Vomiting: 12	Chest tube placement and complete evacuation of residual loculations under sonographic guidance. Forty-two percent of patients received two doses of bleomycin
Yildirim et al. 2005 [8]	15	12F	<48 h	Tetracyline	CR: 66 PR: 33 NR: 0	NA	Tetracycline was instilled in a fractioned-dose manner after aspirations of the effusion at 6-h intervals
Current series	36	12F	<24 h in 69% <48 h in 94%	Doxycycline	CR: 60 PR: 37 NR: 3	Pain: 36 Fever Pneumothorax: 6	Pain was not reduced by the prior installation of local anesthetics

CR Complete response, *PR* partial response, *NR* no response, and *NA* not available
[a]Long-term responses from the current series are referred in text

intrapleural doxycycline was enough to produce significant results.

In conclusion, rapid pleurodesis with doxycycline may be recommended as a first-line medical sclerosant therapy on the wards when bedside pleurodesis is considered. The advantages of this procedure are that the success rate is high, the associated complications, for the most part, are minor, it results in a better patient comfort, and it reduces the number of hospitalization days.

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