Lung Cancer (2008) **62**, 139–144

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journal homepage: www.elsevier.com/locate/lungcan

Predictors of talc pleurodesis outcome in patients with malignant pleural effusions☆

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Received 17 December 2007; received in revised form 18 February 2008; accepted 24 February 2008

KEYWORDS
Malignant pleural effusions;
Talc;
Pleurodesis;
pH;
ADA

Summary
Objective: Chemical pleurodesis is an accepted palliative therapy for patients with recurrent, symptomatic, malignant pleural effusions (MPE). The purpose of the study was to determine the factors that have an effect on successful pleurodesis for MPE.
Patients and interventions: Eighty-four consecutive patients with biopsy-proven malignant pleural disease and recurrent, symptomatic MPE were eligible to participate in this study. Five grams of talc mixed in 150 ml of normal saline were administered via tube thoracostomy or small-bore catheters after complete drainage of the pleural effusion.
Results: Seven patients did not return for their 30-day follow-up visit and were excluded from further analysis. Successful pleurodesis was achieved in 63 of 77 eligible patients (81.8%) with MPE. In the univariate analysis, female gender, Karnofsky performance status, pleural fluid pH, cholesterol, and adenosine deaminase level showed a significant association with the probability of success. Multivariate logistic regression analysis showed that pleural fluid pH and ADA levels were independent predictors of talc pleurodesis outcome.
Conclusion: Our results show that pleurodesis using talc as the sclerosing agent is a simple and acceptable procedure with high efficacy for controlling MPE, especially when used in appropriate patients.

1. Introduction

Malignant pleural effusions (MPE) are a commonly encountered clinical problem in patients with neoplastic disease, contributing to a poor quality of life in this group of patients. In most studies, carcinoma of the lung, metastatic breast carcinoma, and lymphoma are responsible for approximately 75% of all MPE [1]. The treatment of recurrent MPE is known

☆ This study has been presented as a thematic poster at the 14th Annual Congress of European Respiratory Society.

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doi:10.1016/j.lungcan.2008.02.017

to be difficult, and several methods have been used to control recurrent, symptomatic MPE; however, the treatment is often palliative. Chemical pleurodesis using various sclerosing agents is an accepted palliative therapy for patients with recurrent, symptomatic MPE [1—3].

Pleurodesis is defined as the symphysis between the visceral and parietal pleural surfaces, the function of which is to prevent accumulation of either air or fluid into the pleural space. Effusions of malignant origin are by far the most common indication for pleurodesis. The principal mechanism of generation of pleurodesis involves an inflammatory process by a sclerosing agent within the pleural space [4,5]. The utility of various clinical and biochemical parameters in predicting pleurodesis outcome is still controversial.

A better definition of the various characteristics of the patient would help to identify more precisely the population most likely to benefit from pleurodesis. These factors may allow clinicians to make better the treatment decisions in a patient with recurrent MPE. In the present study, we aimed to determine the effects of various clinical and laboratory characteristics on talc pleurodesis outcome for MPE.

2. Materials and methods

2.1. Study population

Over the period from May 2004 to July 2007, 84 consecutive patients with biopsy-proven malignancy and recurrent symptomatic MPE were eligible to participate in this study. Informed consent was obtained from all the patients enrolled in the study.

Inclusion in the study required documentation of a MPE, complete lung expansion on chest radiography after drainage, symptoms due to the presence of fluid, improvement of symptoms after drainage, suitability of the patient's general condition for pleurodesis, and expected survival of more than 1 month. No patient received systemic corticosteroids or a non-steroid anti-inflammatory drug including pure analgesic medication during the study.

The following data were collected from all the patients: age, gender, duration of symptoms, primary malignancies, appearance of pleural fluid (serous, sero-hemorrhagic, or hemorrhagic), serum and pleural fluid biochemical parameters, pleural fluid adenosine deaminase level (Pf-ADA), Karnofsky performance status (KPS), amount of drainage, mean drainage time, and size of drainage tube.

Total protein, glucose, lactate dehydrogenase (LDH), protein, albumin, and cholesterol levels in the pleural fluid were routinely measured. A 2-ml pleural fluid sample was collected in a heparinized syringe and the pleural fluid pH was measured within 30 min after thoracentesis. The blood pH/gas analyzer, Rapidlab 1265 (Bayer, USA), was used for these measurements. ADA activity was determined in all pleural specimens, according to the method described by Giusti and Galanti [6].

2.2. Procedures

A chest drain was inserted in all cases. Fifteen patients were treated with small-bore catheters (12 F; Pleurocan, Braun, Germany) and 69 patients received conventional large-bore chest tubes (24—28 F). A large-bore tube with an underwater seal was placed in the 7th—8th intercostals space in the posterior axillary line. Pleurodesis was not applied to the patients who did not achieve complete expansion of the pleural spaces with this process. Pleural fluid volumes were recorded daily. Talc powder was gas-sterilised using ethylene oxide. After instillation of 10 ml of 1% lidocaine, 5 g of talc was mixed in 150 ml of normal saline under sterile conditions and instilled thorough the side port of the chest tube at the bedside. The tube was clamped for 2 h. All patients underwent rotational maneuvers during the time that the chest tube was clamped. After 2 h, the tube was opened. The chest tube was removed when the drainage fell below 150 ml/24 h, and a chest X-ray was obtained to confirm complete lung expansion. All complications from the pleurodesis were recorded.

Each patient had a pre-drainage baseline posteroanterior (PA) radiograph. Post-pleurodesis PA radiographs were obtained at the following time: (1) after removal of the chest tube, (2) 3 days after removal (early response), and (3) 30 days (late response) following the procedure. Assessment of the response was based on radiologic appearance. At the end of the 30 day follow-up period, the radiographic response was classified as follows: (1) complete response (CR; no re-accumulation of pleural fluid after post-pleurodesis radiography), (2) partial response (PR; re-accumulation above the post-pleurodesis level, but below the pre-pleurodesis level), and (3) no response (NR; re-accumulation or above the pre-pleurodesis level). The patients who died or who were lost to follow-up within the first month of chest tube removal were excluded from the study.

2.3. Statistical analysis

All analyses were performed using computer software (SPSS, version 10.0; SPSS; Chicago, IL, USA). The χ^2 test was used to evaluate the association between categorized variables. Differences between the two groups were tested using the non-parametric Mann—Whitney *U*-test for continuous variables. Data are reported as the median and 25—75% interquartile range (IQR), unless otherwise stated. A p-value < 0.05 was considered statistically significant. To identify the predictors for the outcome of pleurodesis, variables that were found to be associated with pleurodesis success with a value for $p < 0.10$ by univariate analysis were entered into a multivariate logistic regression model. A receiver operating characteristic (ROC) curve were generated using commercial software and the optimal cut-off point was determined for parameters.

3. Results

This series consists of 84 consecutive patients who underwent pleurodesis for recurrent symptomatic malignant pleural effusions. Seven patients were not included in the analysis because of early death or loss to follow-up. The clinical data and patient characteristics are summarized in Table 1. Forty-one patients (53.2%) had malignant mesothelioma, 21 patients (27.3%) had lung cancer, 12 patients (15.6%) had other malignancies, and 3 patients (3.9%) had

Table 1 Characteristics of the study population

Characteristics	Patients ($n = 77$)
Age (range) (years)	62.9 (28.0—83.0)
Gender	
Female	37 (48.1%)
Male	40 (51.9%)
Tumor type	
Malignant mesothelioma	41 (53.2%)
Lung cancer[a]	21 (27.3%)
Other organ metastases	12 (15.6%)
Unknown primary	3 (3.9%)
Karnofsky performance score (range)	80 (50—100)
Drainage state	
Large-bore catheter (24—28 F)	63 (81.8%)
Small-bore catheter (12 F)	14 (18.2%)
Mean drainage time (range), days	6.90 (1—22)
Drainage prior to pleurodesis, mean ± S.D. (ml)	4892 ± 2048
Drainage following pleurodesis, mean ± S.D. (ml)	847 ± 1257

[a] Breast, stomach, ovary.

primaries of unknown origin. Complete and partial responses were observed in 63 (81.8%) patients; 14 patients (18.2%) did not respond to pleurodesis.

The potential factors that may predict pleurodesis outcome were analyzed by univariate analysis. As can be seen in Tables 2 and 3, the predictor variables achieving statistical significance were female gender, KPS > 70, pleural fluid pH ≥ 7.34, pleural fluid ADA level ≥18 U/l and, pleural fluid cholesterol ≤82 mg/dl. However, there was no association between age ($p = 0.289$), choice of tube size ($p = 0.270$), appearance of pleural fluid ($p = 0.431$), the presence of malignant cells in the effusions ($p = 0.601$), duration of chest tube ($p = 0.764$), drainage prior to pleurodesis ($p = 0.215$), drainage following pleurodesis ($p = 0.127$), tumor type ($p = 0.586$), and other biochemical parameters of pleural fluids (except pH, cholesterol and ADA levels), and talc pleurodesis outcome.

The success rate of pleurodesis was significantly higher in females (91.9%; 34/37) than in males (72.5%; 29/40; $p < 0.05$).

KPS was significantly higher in patients with successful pleurodesis than in those with unsuccessful pleurodesis ($p < 0.001$). We found that the sensitivity and specificity of KPS >70 were 78.6 and 74.2%, respectively (Table 4).

ROC analysis identified a pleural fluid pH of 7.34 as having diagnostic accuracy as a threshold value for predicting pleurodesis outcome (area under the curve [AUC], 0.679; 95% CI [0.563—0.781]; Fig. 1). We calculated that the sensitivity and specificity of this value were 85.7 and 49.2%, respectively (Table 4).

The pleural fluid ADA level was significantly higher in patients with successful pleurodesis than in those with unsuccessful pleurodesis. In the ROC analysis, we calculated a pleural fluid ADA of 18 IU/l as having the highest diagnostic accuracy (AUC, 0.815, 95% CI [0.704—0.898]; Fig. 2). The sensitivity and specificity of a pleural fluid ADA level ≥18 IU/l were 84.6 and 80.7%, respectively (Table 4).

Multivariate analysis was carried out to determine the predictors associated with pleurodesis outcome. The five clinical variables were entered into the logistic regression analysis; only pleural fluid pH and ADA levels were identified as independent predictors of successful of pleurodesis (Table 5).

Table 2 Characteristics of the study population

Characteristics	Successful pleurodesis ($n = 63$)	Unsuccessful pleurodesis ($n = 14$)	p
Age (±S.D.) (years)	65.1 ± 10.2	61.2 ± 12.5	0.289
Gender			0.037
Female	34	3	
Male	29	11	
Tumor type			0.586
Malignant mesothelioma	32	9	
Lung cancer	18	3	
Other organ metastases	11	1	
Primary unknown	2	1	
Karnofsky performance score (range)	80 (60—100)	70 (60—90)	0.000
Drainage state			0.270
Large-bore catheter (24—28 F)	53	10	
Small-bore catheter (12 F)	10	4	
Mean drainage time (range), day	7.0 (1—22)	6.5 (1—12)	0.764
Mean duration of drainage after pleurodesis (range), day	3.1 (1—14)	2.8 (1—8)	0.294
Drainage prior to pleurodesis, mean ± S.D. (ml)	4695 ± 2095	5781 ± 1839	0.215
Drainage following pleurodesis, mean ± S.D. (ml)	895 ± 1461	635 ± 343	0.127

Table 3 Comparison of pleural fluid data before pleurodesis

Variables	Successful pleurodesis ($n=63$)	Unsuccessful pleurodesis ($n=14$)	p
LDH (IU/l)	733 (477—1156)	793 (561—1120)	0.729
Total protein (g/dl)	4.90 (4.40—5.45)	4.10 (3.65—5.40)	0.157
Albumin (g/dl)	2.90 (2.70—3.40)	2.50 (2.15—2.85)	0.132
Glucose (mg/dl)	67 (35—101)	82 (53—101)	0.747
Cholesterol (mg/dl)	97 (81—127)	76 (63—92)	0.048
ADA (U/l)	27 (19—44)	7 (5—17)	0.000
pH	7.33 (7.29—7.39)	7.26 (7.20—7.33)	0.037

Data are presented as median (25—75% IQR), p-values calculated with the Mann—Whitney U-test. ADA: Adenosine deaminase; LDH: lactic dehydrogenase.

Table 4 Operating characteristics of each variable

Variables	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Pleural fluid pH (≥7.34)	85.7	49.2	0.679 (0.563—0.781)
Pleural fluid ADA (≥18 IU/l)	84.6	80.7	0.815 (0.704—0.898)
Karnofsky performance score (>70)	78.6	74.2	0.798 (0.691—0.882)
Gender, female	78.6	54.0	0.663 (0.546—0.767)
Pleural fluid cholesterol (≤82 mg/dl)	69.2	64.5	0.675 (0.557—0.779)

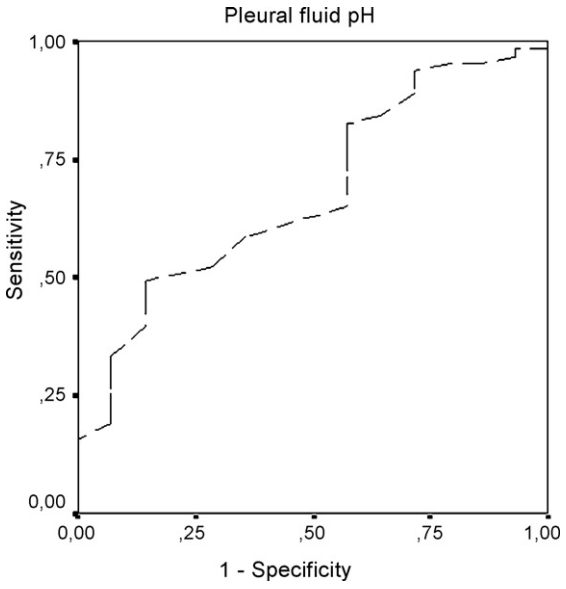

Fig. 1 Receiver operating curve for pleural fluid pH for distinguishing successful and unsuccessful pleurodesis.

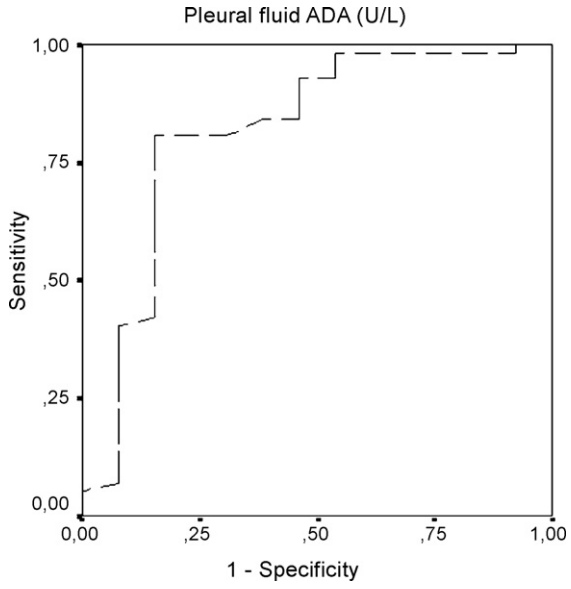

Fig. 2 ROC analysis identified a pleural fluid ADA level of >18 IU as having the highest diagnostic accuracy as a threshold value for predicting successful pleurodesis.

Table 5 Predictors of pleurodesis outcome on stepwise backward elimination regression analysis

Risk factors	Univariate analysis			Multivariate logistic regression		
	p-Value	OR	95% CI	p-Value	OR	95% CI
Gender	0.037	0.233	0.059—0.915	0.503	0.469	0.051—4.310
Pf-pH	0.033	1.061	1.016—2.201	0.023*	1.109	1.044—1.201
KPS	0.002	1.116	1.041—1.195	0.055	1.095	0.998—1.202
Pf-ADA	0.010	1.080	1.019—1.145	0.001*	1.171	1.064—1.288
Pf-cholesterol	0.065	1.021	0.999—1.043	0.096	1.026	0.995—1.058

Pf: Pleural fluid; ADA: adenosine deaminase; KPS: Karnofsky performance score.
* $p<0.05$.

4. Discussion

MPE continues to be a leading cause of a poor quality of life in patients with malignancies. Although various methods have been used in the treatment of MPE, chemical pleurodesis has emerged as the most favored method. In the current study, the success rate of talc pleurodesis was 81.8%. This result is consistent with a recent report on the outcome of talc pleurodesis [7]. In the last two decades, efforts have been made to improve pleurodesis outcome. In clinical practice, several sclerosing agents, such as doxycycline, bleomycin, *Corynebacterium parvum*, and talc have been used to achieve pleurodesis; however, there have been problems associated with all the above agents [1—4].

The purpose of this study was to determine the potential clinical and laboratory factors that may be predictive of outcome with talc pleurodesis. For this reason, we analyzed the relationship between various clinical and biochemical parameters and pleurodesis outcome. The result of the current study demonstrated that patients with symptomatic, recurrent MPE can be managed effectively with talc pleurodesis. An important clinical finding was the identification and characterization of patients who would most likely benefit from pleurodesis. To determine pleurodesis outcome, although different criteria, including pleural fluid pH and measurement of pleural pressure, have been reported by several studies, there is no method or parameter available which would allow for the pre-determination of pleurodesis success. Recently, Psathakis et al. suggested that serial pleural fluid neutrophil and D-dimer values could be used to predict the outcome of talc pleurodesis [8].

Our data demonstrate that the overall success rate of pleurodesis was significantly higher in females than in males. One possible explanation for the differences in the results as a function of gender may be that chemotherapy-sensitive tumors, such as breast cancer, are more common in females. The patients received systemic chemotherapy for underlying malignancies after pleurodesis.

The KPS score index allows patients to be classified according to their functional impairment. A higher score means the patient is better able to carry out daily activities. Burrows et al. reported the prognostic importance of the KPS score in patients with MPE [9]. In the present study, the KPS score was significantly higher in successful patients as compared with the unsuccessful group. In addition, the KPS score of all patients who were excluded due to death and lost to follow-up were below 70. Even though the *p*-value did not indicate a significant difference, we assumed that general health and functional status should be considered before an attempt at pleurodesis.

Several studies have reported that a low pleural fluid pH correlates with the extent of intrapleural tumor burden and that the sclerosing agent must reach a maximum surface area of normal mesothelium for best results [4,5]. On the basis of this observation, physiologic measurements, such as pleural fluid pH, may be indicative of the outcome of pleurodesis [10]. However, other investigations have not detected an association between pH and pleurodesis success [11]. Heffner et al. reported, in a recent meta-analysis, that pleural fluid pH has only modest value for predicting symptomatic failure, and should be used with caution when selecting patient for pleurodesis [12]. The present study confirms that low pleural fluid pH was associated with failure of pleurodesis. We identified that a pleural fluid pH value $\geq$7.34 to be the decision threshold with a high diagnostic accuracy for predicting talc pleurodesis outcome.

Surprisingly, one of the most interesting results of this study was the ADA level of pleural effusions that was associated with successful pleurodesis. ADA is the enzyme that catalyses the conversion of adenosine to inosine, and is present in abundance in lymphocytes. Therefore, the presence of ADA in various body fluids reflects the activity of cell-mediated immunity. Our results showed that the level of ADA was significantly higher in patients who had undergone successful pleurodesis than in those in whom pleurodesis was unsuccessful. We believe that studying higher and different patient populations will allow us to attain a more consistent value.

Lung cancer is the most common malignancy producing MPE, followed by breast cancer and lymphoma. However, malignant mesothelioma was the most common primary malignancy observed in this series. The high incidence of malignant mesothelioma in the present study can be attributed to the fact that environmental asbestos exposure due to the use of asbestos-contaminated white-soil is very widespread in our rural region. No significant differences were found among the outcome of pleurodesis and histopathologic types of malignant disease.

There is no evidence that large tubes (20—24 F) are any better than small tubes (10—14 F) in the management of MPE. Despite the small number of patients, our findings confirmed that small-bore tubes are often as effective as large-bore tubes. In addition, there was no statistical difference between the duration of drainage after pleurodesis in the successful and unsuccessful groups. The results have been confirmed by other authors and demonstrated that shorter pleurodesis regime is safe and effective compared to longer drainage [13]. Previous studies have shown that rotation does not influence the dispersion or the overall effectiveness of pleurodesis with talc suspension [14].

Our study has some limitations. First, our sample size was relatively small. We believe that studying higher and different patients populations will allow us to attain a more consistent value. Second, there was a prominent difference in the patient populations in the present study. For the above-mentioned reason, malignant mesothelioma was the most common cause for pleurodesis in our patients. Thirdly, our study was not designed to compare talc poudrage and talc slurry for patients with MPE. A recently published prospective study comparing the efficacy and safety of talc poudrage and talc slurry showed that both methods of talc delivery were equally effective [7]. Finally, we do not know the mean size of the talc particles used to produce pleurodesis.

In conclusion, talc pleurodesis can be used as an effective method in the control of MPE, especially when applied to appropriate patients. Appropriate patient selection remains challenging and perhaps the most important attribute of a successful pleurodesis. We believed that the success criteria applied in this study can be feasible introduced into clinical practice. Our findings have demonstrated that the predictive variables achieving successful pleurodesis were female gender, KPS score >70, pleural fluid pH $\geq$ 7.34, and pleural fluid ADA $\geq$ 18 IU/l, pleural fluid cholesterol $\leq$ 82 mg/dl. These

biochemical parameters are easily obtained from the pleural fluid examination. However, we do not suggest that these biochemical parameters are a contraindication to pleurodesis, but only predictor of success. Specific attention must be given to survival expectancy and performance status. The available data suggest that pleurodesis is not recommended for the palliation of symptoms for patients with limited life expectancy (<1 month) and poor performance status. Nevertheless, it is difficult to accurately determine the predictors of successful pleurodesis. Further prospective studies are required to clarify the additional patient characteristics as potential predictors of pleurodesis outcome.

Conflict of interest

We have no conflicts of interest that are directly relevant to the content of this study.

Acknowledgement

This study was supported by Research Fund of Osmangazi University, Eskisehir, Turkey.

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