

# Talc Pleurodesis: Systemic Inflammatory Response

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## Abstract

**Study Objectives:** The aim of the study was to investigate the degree of systemic inflammation occurring with talc pleurodesis by determining serum C-reactive protein (CRP) levels, and to evaluate whether this could help to predict the success rate and/or side effects. **Materials and Methods:** In a prospective trial, 43 consecutive patients with recurrent and biopsy-proven malignant effusions were included. Five grams of talc mixed in 150 ml of normal saline were administered via tube thoracostomy. Serial determinations of CRP were made in serum at the beginning of pleurodesis (baseline), and 24 h and 72 h after the procedure. Successful therapy was defined as a complete absence or minor re-accumulation of pleural effusion one month after pleurodesis. **Results:** Three patients did not return for their 30-day follow-up visit and were excluded from further analysis. Pleurodesis was successful in 33 of 40 patients (82.5%). The patients had significantly higher serum CRP levels at 24 h and 72 h than at baseline. Mean serum CRP levels at baseline, 24<sup>th</sup> h and 72<sup>nd</sup> h were 5.5 mg·dL<sup>-1</sup>, 12.6 mg·dL<sup>-1</sup> and 26.2 mg·dL<sup>-1</sup>, respectively. Although mean serum CRP levels were higher in patients with successful pleurodesis compared with unsuccessful patients (baseline: 5.76±5.75 mg·dL<sup>-1</sup> & 4.42±2.96 mg·dL<sup>-1</sup>; at 24h: 13.41±10.40 mg·dL<sup>-1</sup> & 8.54±4.97 mg·dL<sup>-1</sup>; at 72h: 27.97±12.01 mg·dL<sup>-1</sup> & 18.07±8.95 mg·dL<sup>-1</sup>, respectively), there was no statistical significance (p=0.199). In the ROC analysis, from the standpoint of 72<sup>nd</sup> h serum CRP level, 21 mg·dL<sup>-1</sup> was the most relevant threshold to determine whether pleurodesis was successful. Sensitivity, specificity, and positive- and negative predictive value of this value were 66.7%, 71.4%, 91.7%, and 31.3%, respectively. Complications were not serious, and the most common side effects included fever (47.5%) and chest pain (17.5%). Patients with complications had a tendency to higher serum CRP levels at the 72<sup>nd</sup> h (27.5±13.3 mg·dL<sup>-1</sup> & 24.7±10.4 mg·dL<sup>-1</sup>), but this was not statistically significant (p=0.142). **Conclusions:** The inflammatory response in the pleural cavity due to talc pleurodesis is reflected in the systemic circulation, and CRP can be used to predict response to pleurodesis with a moderate efficacy.

**Keywords:** malignant pleural effusion, pleurodesis, C-reactive protein, systemic inflammatory response, side effects

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## INTRODUCTION

Malignant pleural effusion (MPE) is a frequently encountered clinical problem in patients with a neoplastic condition, and usually represents an advanced disease [1]. Thus, treatment is principally palliative. The most commonly used method to prevent further fluid formation is

pleurodesis, i.e. adhesion of the parietal and visceral pleural leaves by intrapleural administration of a sclerosing agent. The most commonly used and also the most effective sclerosing agent is talc [2-4]. The mechanism of pleurodesis is to induce inflammation within the pleural space causing subsequent fibrosis. In the process, a variety of inflammatory products such as cytokines and interleukins are produced in large amounts, and if a sufficiently potent inflammation within the pleural surface occurs, a systemic inflammatory reaction can also be seen [5-7]. C-reactive protein (CRP) is an acute-phase protein that has been used to monitor the course of various inflammatory diseases. Thus, we hypothesized that serum levels of CRP might mirror the potency of the pleural reaction, and might be used to make predictions regarding the effect of pleurodesis and perhaps also of side-effects.

Success of pleurodesis is decided by observing whether or not symptomatic fluid occurs one month after talc application. If it were possible to predict the success of the procedure, it might allow the re-application of talc within the first two or three days before the chest tube is withdrawn.

In the present study, we investigated serum CRP levels in MPE patients who underwent talc pleurodesis, and related this to the success rate and the side effects of the treatment.

## MATERIALS AND METHODS

### Study Population

Between May 2001 and May 2003, we studied prospectively 43 consecutive patients with MPE. The following criteria had to be met for inclusion in the study: informed consent; biopsy-proven malignancy; recurrent symptomatic MPE and improvement after drainage; complete lung expansion on chest radiography after drainage, a general condition making pleurodesis possible; and expected survival of more than one month. MPE was diagnosed when malignant tissue in the pleural cavity was shown by pleural biopsy or cytopathology.

Information collected for each patient included demographics, type of malignancy, serum CRP levels, Karnofsky

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**Table 1.** Characteristics of the study population

Patient characteristics	
Number of patients	40
Sex, n (%)	
Male	22 (55)
Female	18 (45)
Age, yrs (Range)	61.7 ± 12.9 (35-80)
Primary tumor, n (%)	
Malignant mesothelioma	23 (57.5)
Lung cancer	12 (30)
Breast cancer	2 (5)
Renal cell carcinoma	1 (2.5)
Ovarian carcinoma	1 (2.5)
Unknown	1 (2.5)
Response, n (%)	
Successful pleurodesis	33 (82.5)
Unsuccessful pleurodesis	7 (17.5)
KPS, mean (Range)	80 (60-90)

KPS: Karnofsky performance status.

performance status (KPS), and side effects. Fever was defined as a temperature  $\geq 38^{\circ}\text{C}$ .

### Procedures and Assessments

A chest drain was inserted in all cases, and a large bore tube (24F to 28F) with underwater seal was placed in the seventh or eighth intercostal space at the posterior axillary line. Pleural fluid volumes were recorded daily, and a chest roentgenogram was taken daily. When the drainage fell below 150 ml/24 h and the lung had expanded completely, pleurodesis was attempted.

After instillation of 10 ml 1% lidocaine, 5 g sterilized talc was mixed in 150 ml physiological saline under sterile conditions, and instilled through the chest tube. Talc powder was gas-sterilized using ethylene oxide. The tube was clamped for 2 h and then opened. The chest tube was removed when the drainage fell below 150 ml/24 h and chest X-ray showed complete lung expansion. No patient received systemic corticosteroids or a non-steroid anti-inflammatory drug, including pure analgesic medication, during the study.

Post-pleurodesis posteroanterior (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. The

patients who died or were lost at follow-up were excluded from the study.

### CRP Assay

Serum samples of 43 patients were collected before, at 24 h and 72 h after the pleurodesis. At 24 hours the CRP levels were measured in only 25 patients for various reasons. The concentration of serum CRP was determined with an enzyme-linked immunosorbent assay (ELISA).

### Statistical Analysis

All analyses were performed using computer software (SPSS, version 10.0; SPSS, Inc; Chicago, IL). All data were expressed as mean  $\pm$  SD. A paired Student's t test was used to compare initial mean serum CRP levels at 24 h and 72 h to determine whether there was a significant increase ( $p < 0.05$ ) in the groups. Specific comparisons between two groups were performed using the Mann-Whitney *U* test or McNemar  $\chi^2$  test. Within group differences in mean values were analyzed with analysis of variance (ANOVA) for repeated measures. Furthermore, receiver operating characteristic (ROC) curves were generated using commercial software, and the optimal cut-off point was determined for mean serum CRP levels. Statistical significance was accepted for a p-value of  $< 0.05$ .

### RESULTS

Table 1 shows the characteristics of the patients and response rates of pleurodesis in this study. Three patients were not included in the analysis due to early death or because they were lost to follow-up.

The mean drainage time prior to pleurodesis was  $5.0 \pm 4.1$  days. The average time to removal of the chest tubes was  $7.6 \pm 4.6$  days (range, 1 to 22 days). Total pleural fluid drained ranged from 1.65 to 12.83 L (mean, 5.00 L).

Pleurodesis was successful in 33 of 40 patients (82.5%). As can be seen in Table 1, 23 patients (57.5%) were malignant mesothelioma, 12 patients (30%) lung cancer, and 5 patients (12.5%) other malignancies. There was no association between outcome of pleurodesis, side effects and increased CRP levels with histologic subtype (Table 2).

After talc pleurodesis, serum CRP levels showed a progressive significant rise at the 24<sup>th</sup> h and 72<sup>nd</sup> h compared to baseline. Mean serum CRP levels at baseline, 24<sup>th</sup> h and 72<sup>nd</sup> h were  $5.5 \text{ mg}\cdot\text{dL}^{-1}$ ,  $12.6 \text{ mg}\cdot\text{dL}^{-1}$  and  $26.2 \text{ mg}\cdot\text{dL}^{-1}$ , respectively. There was a statistically significant difference in the mean CRP values obtained before and at the 24<sup>th</sup> h ( $p < .001$ , 95% CI [-10.64 to -3.15]) and 72<sup>nd</sup> h after procedure ( $p < .0001$ , 95% CI [-24.90 to -16.53]) (Figure 1).

Although increases in the serum CRP levels in successful pleurodesis are greater than in unsuccessful pleurodesis (baseline:  $5.76 \pm 5.75 \text{ mg}\cdot\text{dL}^{-1}$  &  $4.42 \pm 2.96 \text{ mg}\cdot\text{dL}^{-1}$ ; at



**Table 2.** Clinical outcome in each tumor type\*

	Malignant Mesothelioma (n=23)	Lung cancer (n=12)	Other Metastases (n=5)
Pleurodesis Outcome, n(%)			
Successful	20 (87)	10 (83.3)	3 (60)
Unsuccessful	3 (13)	2 (16.7)	2 (40)
Mean serum CRP levels, mg·dL <sup>-1</sup>			
Baseline	5.2 ± 4.2	4.9 ± 3.5	8.3 ± 4.8
24 h	12 ± 6.9	11.4 ± 6.8	16.8 ± 11.1
72 h	27.5 ± 13.4	24.4 ± 11.7	24.7 ± 5.8
Side effects, n (%)			
Fever	13 (56.5)	4 (33.3)	2 (40)

\* Values given as mean ± SD. CRP: C-reactive protein.

24h: 13.41±10.40 mg·dL<sup>-1</sup> & 8.54±4.97 mg·dL<sup>-1</sup>; at 72h: 27.97±12.01 mg·dL<sup>-1</sup> & 18.07±8.95 mg·dL<sup>-1</sup>, respectively), there was no statistically significant difference in the mean CRP values obtained before and after the procedure between the groups (p=0.199) (Figure 2).

As regards the proportional increase in serum CRP value at the 24<sup>th</sup> h and 72<sup>nd</sup> h, it was found that a two-fold increase at 24 h (p=0.008) and six-fold increase at 72 h (p<0.0001) was statistically significant between the groups. The specificity and sensitivity of a two-fold increase in serum CRP levels from baseline values within the first 24 hours were 100% and 61.9%, respectively. At 72 h, the specificity and sensitivity of a six-fold increase in serum CRP levels were 85.7% and 51.5%, respectively.

In the ROC analysis, at 72<sup>nd</sup> h, serum CRP level of 21 mg·dL<sup>-1</sup> was the most relevant threshold to determine if pleurodesis was successful or not (AUC=0.706, p=0.091, 95% CI [0.525 to 0.886]) (Figure 3). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of this value were 66.7%, 71.4%, 91.7%, and 31.3%, respectively.

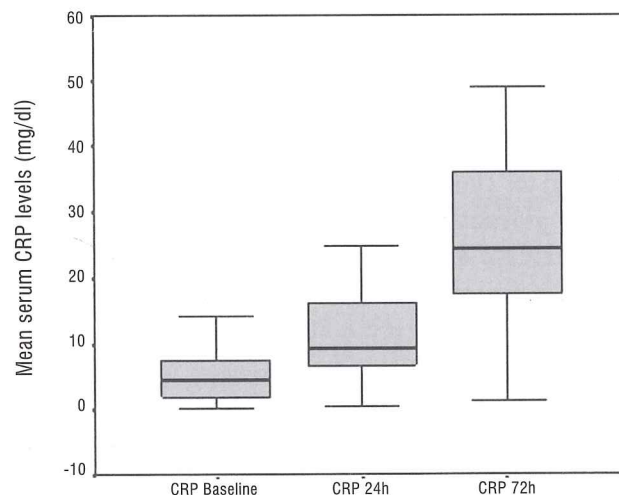
The side effects related to pleurodesis were minor. Complications included fever in 19 patients (47.5%), moderate chest pain in 7 (17.5%), transient atrial arrhythmia in 1 (2.5%) and hypotension in 1 (2.5%). The atrial arrhythmia and hypotension spontaneously resolved within 24 h after the pleurodesis and required no further therapy. There were no major complications or deaths attributable to the procedure. Patients with side effects at 72 h tended to have greater serum CRP levels (27.5±13.3 mg·dL<sup>-1</sup>) than those without (24.7±10.4 mg·dL<sup>-1</sup>), but this was not statistically significant (p=0.142) (Figure 4). The presence of fever tended to occur less frequently in patients with unsuccessful pleurodesis (2 of 7 subjects, 28.6%) than in those with

successful pleurodesis (17 of 33 subjects, 51.5%), although this relationship did not reach significance (p=0.248).

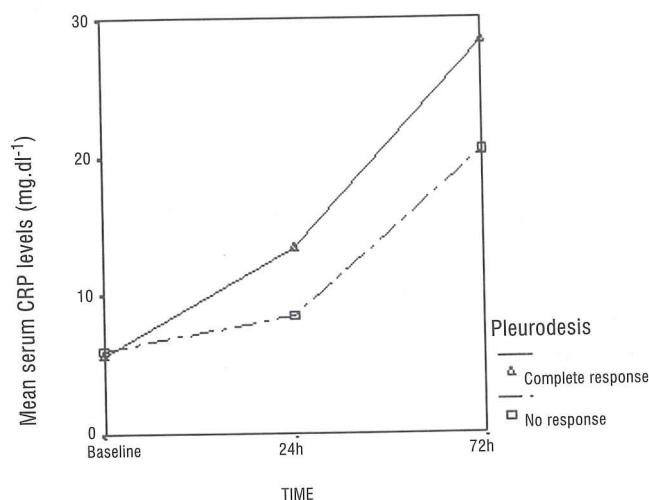
## DISCUSSION

The results of this study demonstrated that the inflammatory reaction in the pleural cavity due to talc pleurodesis is reflected within the systemic circulation. Recently, serum levels of CRP have been seen as an active biomarker of the inflammatory response. In this study, we found that the intrapleural injection of talc induced a significant increase in serum CRP levels at 24 and 72 h after pleurodesis. We also investigated whether serum CRP levels could help to identify the success of pleurodesis. Although serum CRP levels showed a trend of being higher in patients with successful pleurodesis than in those with unsuccessful pleurodesis, statistically significant differences were not reached, probably due to the small number of patients.

There is currently a suspicion of information on the systemic effects of talc pleurodesis. In recent studies, it has been demonstrated that pleurodesis causes a systemic inflammation, and there is a tendency toward a correlation between the success of pleurodesis and the degree of inflammation [7]. Marchi et al. demonstrated that the intrapleural injection of talc and silver nitrate in the rabbit could increase the concentration of various parameters such as WBC count, neutrophil percentage, lactate dehydrogenase, interleukin-8 and vascular endothelial growth factor in the serum [8]. This was confirmed in our study; serum CRP values from all patients measured at 24 and 72 h after pleurodesis showed statistically significant elevations from their values before the procedure.



**Figure 1.** Mean serum CRP levels in MPE patients related to time before and after talc pleurodesis. Mean serum CRP values were significantly higher at the 24h and 72nd h than at baseline (p<0.01, 95% CI [-10.63,-3.14]; p<0.001, 95% CI [-24.89,-16.53], respectively).

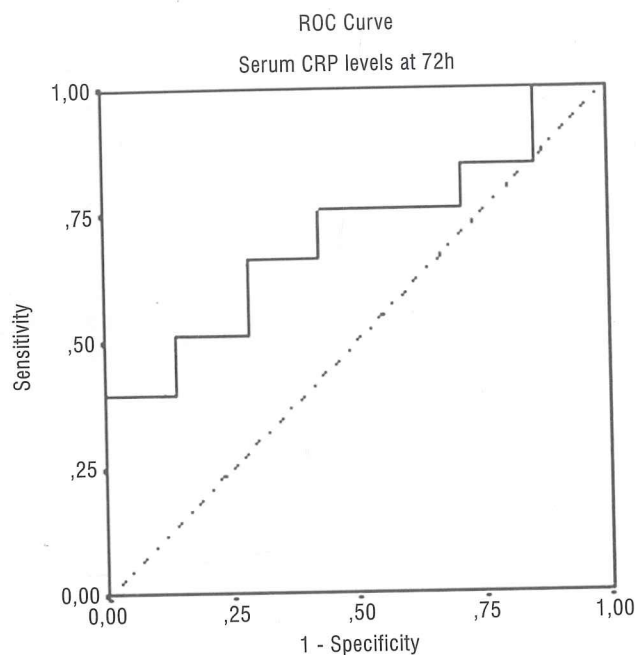


**Figure 2.** During the post-pleurodesis period, CRP values tended to increase in the successful group; however, this increase was not significantly different between the groups ( $p=0.199$ ).

It has been suggested that corticosteroids can be associated with a reduction in the success rate of pleurodesis [9]. In a recent study, Teixeira et al. aimed to determine whether the administration of anti-inflammatory drugs interferes with experimental pleurodesis induced by silver nitrate or talc [10]. They concluded that the sustained systemic administration of anti-inflammatory agents (steroidal or nonsteroidal) reduces the degree of pleural adhesions in animals with talc-induced pleurodesis but does not affect silver nitrate-induced pleurodesis. It is possible that the inflammatory process is crucial to the successful induction of pleurodesis by sclerosing agents.

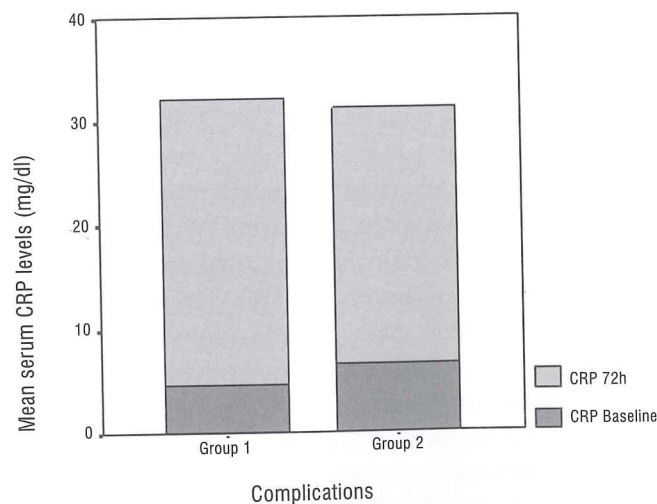
Markers of inflammation within the systemic circulation might be an indicator of the severity of inflammation in the pleural region, and thus might serve as a predictor of the success or not of pleurodesis. In our study, the best CRP threshold value was  $21 \text{ mg}\cdot\text{dL}^{-1}$  at the 72<sup>nd</sup> h. Of course, the sensitivity and specificity were not very great. However, for clinical purposes, one can assume that there is a great probability that pleurodesis will be unsuccessful if the serum CRP level is lower than  $21 \text{ mg}\cdot\text{dL}^{-1}$  at 72 h.

A more than two-fold increase in mean serum CRP levels within the first 24 h was detected in 61.9% of patients who had successful pleurodesis, whereas none of the patients with an unsuccessful pleurodesis showed this - thus the specificity of a two-fold increase in CRP levels from baseline values within the first 24 h was 100%. In the 72<sup>nd</sup> h of the procedure, six-fold or greater increment rates were obtained in 51.5% of the group with successful pleurodesis, whereas in 85.7% of the patients with an unsuccessful pleurodesis this did not occur.



**Figure 3.** ROC analysis identified a serum CRP level of  $21 \text{ mg}\cdot\text{dL}^{-1}$  as having the highest diagnostic accuracy as a threshold value for predicting successful pleurodesis (AUC=0.706,  $p=0.091$ , 95% CI= 0.525-0.886).

To our current knowledge, the pleurodesis procedure can be repeated in patients where the previous intervention fails. However, when making the decision of repeat pleurodesis, the only criterion is the continuance of fluid collection and subsequent dyspneic complaints after a certain period. Although different criteria including pleural fluid pH and measurement of pleural pressure have been reported to determine the outcome of the pleurodesis in several studies [11], there is no method or parameter available which al-



**Figure 4.** Mean serum CRP levels between group 1 (with side effect) and group 2 (without side effect) after pleurodesis. Although at the 72<sup>nd</sup> h, increase in the serum CRP levels in group 1 was greater than in group 2, these differences were not statistically significant ( $p=0.142$ ).



lows for the predetermination of whether pleurodesis will be successful or not. When initial pleurodesis for MPE fails, European Respiratory Society guidelines have proposed that several alternatives may be considered [1]. These alternatives include repeat pleurodesis, repeat thoracentesis, pleuroperitoneal shunting, and pleurectomy. Namely, the criteria of timing as well as patient profile for repeat pleurodesis are unknown at present. In the present study, we confirmed that the proportional increase in serum CRP levels was significantly higher in successful than in unsuccessful patients. The proportional increase noted in this series may be used to make the decision of repeat pleurodesis, through the already stuck tube. However, it should be noted that early repetition of talc has a systemic distribution associated with a high rate of side effects such as acute respiratory distress syndrome (ARDS), and the physician must give careful consideration when deciding on repeat pleurodesis.

A large number of studies have focused on the safety of various sclerosing agents. Recent animal studies have suggested that low-dose silver nitrate, when injected intrapleurally, produces more pleural inflammation and less systemic inflammation than low-dose talc [12]. The **same authors** also showed that the intrapleural injection of talc and silver nitrate produces a systemic inflammatory response that may have a role in the pathogenesis of fever and ARDS, which occur with pleurodesis [8]. They concluded that silver nitrate induced an earlier and more intense acute pleural inflammation than talc. In another study, Lee et al. showed that transforming growth factor-beta can produce effective pleural fibrosis without necessitating acute pleural inflammation [13]. Since there is no evidence that these agents produces serious side effects as has been reported with talc, such as ARDS, it should be considered as an alternative to talc for the production of a pleurodesis.

Chest pain and fever are the most frequently seen adverse effects of all pleurodesis agents [1,2]. In our study, none of the patients developed any of the serious complications, including respiratory failure, ARDS, or severe arrhythmia. The development of serious adverse effect has been attributed to the large dose of talc by some authors [14]. Absence of serious adverse effect in our series may be a result of the talc dose not exceeding 5 grams. Increasing doses of talc can lead to systemic inflammation, which in turn can result in ARDS or other serious adverse effects. Furthermore, previous experimental studies in animals have shown systemic distribution of talc after intrapleural administration [15]. The size of talc particles has also been implicated in side effects after talc pleurodesis [16]. In our study, although CRP values obtained from the patients who developed complications were

higher than those obtained from non-complicated patients, the difference was not statistically significant.

There are a number of limitations to our study, the most important of which was the low number of cases. Further studies on more patients will allow us to obtain a more consistent cut-off value. Secondly, the intervention itself, i.e. tube insertion, could alter CRP levels. This has already been reported in the study of Froudarakis et al. [17]. They concluded that fever and systemic inflammatory reaction are due to talc poudrage and not to thoracoscopy. Thirdly, serum CRP levels could not be measured in 15 of the 40 patients at the 24<sup>th</sup> h, mostly due to technical problems. Fourthly, the measurement of the pleural fluid CRP levels could have provided more information about the mechanism of pleurodesis. Finally, we do not know the mean size of the talc particles used to produce pleurodesis.

In conclusion, our results demonstrate that the inflammatory response in the pleural cavity due to talc pleurodesis is reflected in the systemic circulation, and this can be used to predict the response to pleurodesis. Further studies will be needed to determine additional factors associated with outcome and side effects of pleurodesis.

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**Abbreviations:** MPE = Malignant pleural effusions, CRP = C-reactive protein, h = Hour, PPV= Positive predictive value, NPV=Negative predictive value