Talc poudrage versus talc slurry in the treatment of malignant pleural effusion. 
A prospective comparative study

Alessandro Stefani, Pamela Natali, Christian Casali, Uliano Morandi*
Division of Thoracic Surgery, Department of General Surgery and Surgical Specialties, University of Modena and Reggio Emilia, Italy

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Abstract

Objective: The aim of this study was to investigate the effectiveness, safety and appropriate mode of administration of intrapleural talc for pleurodesis, in the treatment of malignant pleural effusion (MPE). Methods: Prospective not randomized trial was conducted to compare thoracoscopic talc poudrage (TP) with tube thoracostomy and talc slurry (TS) for the local control of malignant pleural effusion. Both procedures were previously standardized; 6 g of talc was administered for each procedure. Only the patients with lung re-expansion after drainage entered the study. Patients at high risk for general anaesthesia, poor general conditions and short life-expectancy received talc slurry through a chest tube, at the bedside. All the other patients underwent videothoracoscopic talc poudrage, with a pneumatic atomizer, under general anaesthesia.

Morbidity, 30-day freedom from recurrence and long-term results were assessed and the two groups were compared. Results: One hundred and nine patients entered the study (72 TP, 37 TS). Sixty-three patients in the TP group (87.5%) and 27 in the TS group (73%) had an immediate successful pleurodesis ($p = 0.049$); 53 patients (88.3%) and 16 patients (69.6%) had a successful pleurodesis 90 days after the procedure; 59 patients (81.9%) and 23 patients (62.2%), respectively, had a life-long pleural symphysis ($p = 0.023$). Adverse effects were generally mild: chest pain (36.1% in TP patients, 48.6% in TS patients) and fever (38.8% and 35.1%, respectively) were the more common but the difference was not significant between the two groups. We observed neither acute respiratory failure nor mortality due to the procedure. Conclusions: Our study confirms that intrapleural talc carries good results in the treatment of malignant pleural effusion. TP was significantly more effective than TS; both methods were safe but TS had a higher incidence of thoracic pain during the procedure. Talc pleurodesis should be offered to every patient with MPE, apart from terminally ill ones, provided that a satisfying lung re-expansion has been achieved. TP should be performed whenever possible; otherwise, a slurry bedside procedure will be worthwhile, even in patients with low performance status (PS), though poorer results have to be expected. A careful selection is essential to define the proper technique.

Keywords: Pleural effusion; Cancer; Talc

1. Introduction

Malignant pleural effusion (MPE) is a common complication of advanced cancer. It is disabling for the patient and often represents a terminal condition, with short survival, in terms of months. Dyspnoea, repeated thoracenteses and the resulting depletion in proteins, electrolytes and fluid contribute to the progressive deterioration in the patient’s condition.

Therapy of MPE can be very difficult; the goal is palliation. Systemic chemotherapy is occasionally effective for ovarian, breast and small cell lung cancers but local treatment remains the mainstay of therapy. It is widely accepted that a satisfying local palliation can be achieved with chemical pleurodesis [1], and the low morbidity and mortality of this method justifies it as a palliative procedure, compared with pleurectomy or pleural abrasion. Many intrapleural sclerosing agents have been tested and are available, such as bleomycin, corticosteroids, corynebacterium parvum, quinacrine, tetracycline, iodopovidone and talc [2—5]. A significant number of clinical studies have been published, supporting the superior effectiveness of talc upon other sclerosing agents in the treatment of MPE [6—9], and talc is now generally accepted as the agent of choice [10,11]. Nevertheless, the optimal route of talc administration is still debated, and its safety remains unclear. Chest pain and fever are commonly observed, but serious respiratory complications have also been reported [11—16]. Thoracoscopically insufflated talc (‘talc poudrage’, TP) is the preferred method in the opinion of many Authors [13,17—19], but others advocate talc instillation through a chest tube (‘talc slurry’,...
TS) as a simpler and equally effective technique [7,8,20,21]. In a recent phase III study, no difference was found in efficacy comparing TS and TP in the overall population, but when patients with lung or breast cancer were separately analysed, TP showed superior to TS [11].

We designed a prospective, non-randomized study to compare thoracoscopy and talc insufflation with tube thoracostomy and talc slurry, investigating their effectiveness and safety in the treatment of MPE.

2. Materials and methods

2.1. Patients

The study started in January 2000 until December 2005. We considered all patients diagnosed of MPE. From this population, only patients with lung re-expansion after drainage were selected for pleurodesis. In case of known MPE, chest tube drainage or thoracentesis led to the exclusion of the patients with trapped lung; the radiological finding of residual fluid in the costo-phrenic angle was judged as a satisfying re-expansion, and the patient was considered eligible for talc administration. Each selected patient was evaluated both by the surgical and medical staff, together with the anaesthesiologist, in order to decide the appropriate mode of talc administration: patients with acceptable performance status (PS), life expectancy >3 months and ability to undergo general anaesthesia were selected for videothoracoscopic TP, otherwise TS at the bedside was performed. However, all the patients were fully acquainted with both the procedures; in case of refusal of TP, the patient was treated with TS. Written informed consent to participate in the study was obtained from each patient, in accordance with relevant guidelines. When a diagnostic thoracoscopy was performed, frozen examination of a pleural specimen was requested, and if a tumour was found, the surgeon had to make the visual estimation of lung re-expansion prior to sclerosis.

For each patient the following clinico-pathological variables were recorded: sex, age, ECOG PS, duration of pleural effusion, type of primary malignancy, procedure-related complications. The duration of pleural effusion was assessed from presentation until pleurodesis, on the basis of chest roentgenograms.

2.2. Techniques

Both techniques were standardized before starting the study.

TP was performed by videothoracoscopy, under general anaesthesia and selective one-lung ventilation. Any residual fluid was aspirated, loculations were divided when present, pleural biopsies were taken if necessary and lung re-expansion was confirmed. Six grams of talc was insufflated and uniformly distributed onto the pleural surface, using a disposable gas-propelled atomizer, containing 3 g of sterile talc powder (Steritalc®; Novatech; La Ciotat, France). A 32-French chest drain was inserted and positioned towards the apex and a small-bore catheter (10F), with a 3-way stopcock (Pleurocath®; Plastimed; Le Plessis-Bouchard, France), was placed in the posterior costo-vertebral gutter. Both drains were connected to a 20 cm/H2O suction for 24 h. The 32F chest tube was then removed and the patient discharged, with the small-bore catheter in place, for outpatient management. To evaluate the success of pleurodesis, thoracenteses were performed, through the catheter, 3, 7, 10 and 15 days after discharge, and chest X-rays were obtained at days 7 and 15. If pleurodesis was achieved, pleural catheter was removed, usually 2 weeks after the procedure.

TS was performed through a 20F chest tube, at the bedside: 6 g of talc was instilled, as a slurry, in 200-mL saline solution, added with 20 mL of 7.5% ropivacaine. The tube was clamped for 8 h, and the patient turned in different positions. The drain was then connected to a 20 cm/H2O suction for 24 h. At the end of the procedure, if hospital discharge was possible, the chest tube was removed and a 10F Pleurocath® was inserted through the original chest tube site, prior to discharge. Outpatient management was carried on, as described for TP patients. Otherwise, the tube was left in place, until less than 100 mL of fluid were drained in 24 h.

2.3. Follow-up and assessment of the response

All the patients were prospectively followed up. They were regularly seen at ambulatory visits, and chest roentgenograms were obtained 1 month after the procedure and then monthly, for 3 months. Further follow-up was guided by the type of tumour and the onset of respiratory symptoms.

The primary objective of the study was to determine the percentage of patients who had a successful pleurodesis at 30 days from treatment, at 90 days and at the end of follow-up and to compare the two techniques. The assessment of the response was based on clinical and radiological findings. The comparison among chest roentgenograms was done by a single radiologist, doing the interpretation in a blinded fashion. Patients with normal chest X-ray were considered as having a complete response; complete success was also defined as no pleural fluid re-accumulation greater than the one observed on the baseline radiograph, taken immediately after the procedure. Patients with residual pleural fluid or re-accumulation, which did not require further thoracenteses or remained asymptomatic, were recorded as having a partial response. Failures were observed in all the other cases; they were distinguished as early and late failures, and the cut-off was 30 days from pleurodesis.

Secondary end points included procedure-related morbidity and mortality. Patients who died within 30 days from the procedure were excluded from the study; only procedure-related mortality was recorded in those cases.

2.4. Statistical analysis

The descriptive analysis was expressed in terms of the frequency, mean and standard deviation (SD). Frequencies were compared with the Chi-square test for categorical variables; Fisher’s exact test was used for small samples. t-Test and ANOVA were performed when comparing continuous variables. Survivals were calculated from the time of pleurodesis, according to the Kaplan–Meier method and
were compared using the Log-rank test. A probability value of <0.05 was considered statistically significant.

3. Results

One hundred and twenty-two patients were initially selected. Eight of these (6.5%) died within 1 month from pleurodesis and in five (4.0%) the procedure was not completed, thus, they were excluded from the study. The remaining 109 patients represented the population of the study. Clinico-pathological features are reported in Table 1. Matching all the variables, we found no association among them, except for the following: older patients had a poorer PS ($p = 0.014$), patients with a lung primary were older and had a poorer PS than those with breast metastases ($p = 0.003$ and 0.027, respectively).

Seventy-two patients underwent TP (66%) and 37 underwent TS. Table 2 summarizes the characteristics of the two groups. A significant difference was found in terms of PS and primary malignancy: TS patients had a poorer PS, and all mesotheliomas were treated with TP. However, when mesotheliomas were excluded from the analysis, no difference was found between the two groups regarding pathology. TS patients were older than TP but the difference was not statistically significant.

There was no procedure-related mortality. Of the eight early deaths (within 1 month), none was directly related to talc administration (seven TS and one TP); all of them were early deaths (within 1 month), none was directly related to talc administration (seven TS and one TP); all of them were early deaths. Complications and side effects caused by critical illness or end-stage disease that were not influenced by sex, age, PS and duration of pleural effusion (days) were compared using the Log-rank test. A probability value of <0.05 was considered statistically significant.

Table 3
TP versus TS: comparison of morbidity

<table>
<thead>
<tr>
<th>Type of complication</th>
<th>TP (n = 72)</th>
<th>TS (n = 37)</th>
<th>$p$-value</th>
</tr>
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<tbody>
<tr>
<td>Chest pain</td>
<td>26 (36.1)</td>
<td>18 (48.6)</td>
<td>0.237</td>
</tr>
<tr>
<td>Fever (&gt;37.5°)</td>
<td>28 (38.8)</td>
<td>13 (35.1)</td>
<td>0.544</td>
</tr>
<tr>
<td>Empyema</td>
<td>1 (1.4)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>2 (5.4)</td>
<td>-</td>
</tr>
<tr>
<td>Prolonged air leak</td>
<td>2 (2.7)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1 (1.4)</td>
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<tr>
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Data are presented as number (%) of patients.

patients developed talc-induced acute respiratory failure; no tumour recurrence at the port site was observed. Chest pain was more common in TS group, though the difference was not significant. Moreover, in five patients initially selected for TS, severe chest pain with acute respiratory distress developed during or shortly after talc instillation; the procedure was stopped, the talc promptly drained and the patients improved immediately and without needing ventilatory support. However, TS was no more attempted in those patients and they were not considered in the study.

Follow-up was complete for all patients within June 2006 (mean 9.4 months, median 6.0, standard deviation 9.6, range 1—55). Overall median survival was 7.7 months, 1- and 2-year survival rates were 36.5% and 12.3%, respectively. Four patients (3.6%) were alive more than 2 years after the procedure, at 30, 35 (2) and 51 months; there were 3 TP and 1 TS, and primaries were from breast, lung, ovary and mesothelioma. Survival was significantly different between TS and TP ($p = 0.006$), with a median survival of 3.9 and 11.2 months, respectively, a 6-month survival of 37% and 65% and a 1-year survival of 18% and 46%. Twenty-three patients survived more than 3 months in TS group (62.1%), 60 in TP group (83.3%). Survival was also affected by PS (median survival of 3.6 and 14.2 months for PS 2—4 and PS 0—1, respectively, $p < 0.01$), primary tumour (median survival of 5.9 and 13.6 months for lung and breast cancer, respectively, $p < 0.01$) and gender (median survival of 5.9 and 11.3 months for males and females, respectively, $p = 0.056$), though for the latter the difference was nearly significant.

Overall success rates of pleurodesis and the comparison between TS and TP groups are presented in Table 4. For the analysis of efficacy, complete and partial responses were both considered as satisfying and grouped. Effectiveness was not influenced by sex, age, PS and duration of pleural effusion (days) were compared using the Log-rank test. A probability value of <0.05 was considered statistically significant.

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effusion. The highest success rate was obtained in breast cancer patients (85.6% at 30 days and 82.1% at the end of follow-up), the poorest one in mesothelioma (70% at both times from pleurodesis); intermediate results were achieved in lung cancer (81.6% at 30 days and 71.4% at the end of follow-up) but the difference was not significant. A significant difference was found between the two techniques, at any time from pleurodesis. Of the 27 ineffective procedures, 19 (70%) were early failures (immediate or within 30 days) and 8 were distant recurrences. Mean time to recurrence was 3.3 months (SD 1.79, range 1.6–6.5 months); no difference was found between TS and TP. Responders to pleurodesis had a higher survival with respect to non-responders, at any time from the procedure, though a statistical difference could be demonstrated only at the end of follow-up: median survival time of 9.4 and 5.8 months for responders and non-responders at 30 days, respectively ($p = 0.119$), 11.7 and 6.7 at 90 days ($p = 0.221$), 9.4 and 5.8 at the end of follow-up ($p = 0.048$).

4. Discussion

Talc pleurodesis is now well recognized as the procedure of choice for the treatment of MPE, but the appropriate mode of talc administration is still debated. Several studies have reported satisfying results both with slurry and poudrage [17–21], but most of them are single institution studies, investigating only one technique, with small enrollment. Comparison within the studies is difficult, because of the differences in indications, definition of recurrence, subset of malignancies and patients. Trapped lung leads to poorer results; recurrence may be considered as radiological, symptomatic or requiring treatment; breast cancer seems to correlate with better results [15], mesothelioma and lung cancer with poorer ones [17,19,22]; performance status affects survival [15,23]. A review of talc pleurodesis studies, published in 1994 [20], found identical success rates of 91% for poudrage ($n = 461$) and slurry ($n = 166$). Yim and colleagues [21], in a small randomized trial, also demonstrated no difference between the two techniques. In 2004, the Cochrane Database Review on pleurodesis for MPE reported that available evidence suggests thoracoscopic talc pleurodesis as the preferred technique, based on efficacy [10]. A phase III intergroup study on 482 patients with MPE, published in 2005, revealed no difference in efficacy between the two modes of delivery, in the overall population; however, subset analysis suggested that TP may be more advantageous for patients with breast or lung cancer [11].

In general, the selection criteria for pleurodesis are based on lung re-expansion, PS and pleural fluid pH, although the latter is controversial [19,24]. For this reason we decided to exclude pH quantification from our evaluation and to consider only lung re-expansion. Regarding PS, it was taken into account to select the mode of talc administration; however, terminally ill patients and those with a very limited life expectancy (<1 month) were not considered for pleurodesis.

Generally, we are not favourable to the slurry procedure because it does not allow the talc to be thoroughly distributed over the whole pleural surface. Moreover, we prefer general anaesthesia to spontaneous ventilation in performing TP because it appears safer and more comfortable for the patient and it makes the procedure easier and more complete. Thus, in our study, TP was performed whenever possible and TS was reserved only for patients in whom general anaesthesia and surgical procedure were not advisable.

We have shown a significant superiority of TP versus TS in terms of efficacy. We acknowledge that our sample size is small and that the criteria we followed to propose a patient for TP or TS may lead to a selection bias. PS is obviously different, because it is the main criterion for selection. One may speculate that the lower the PS, the more advanced the disease is: because an advanced pleural disease may lead to poorer results, and a low PS could affect the efficacy of pleurodesis. We believe that a suitable method to investigate the severity of pleural disease is to evaluate the duration of pleural effusion. In our series, there is no difference in the duration of MPE, before pleurodesis, between TS and TP patients; moreover, PS does not correlate with the duration of MPE. Thus, we do not believe that the difference in PS affects the results of pleurodesis.

It is difficult to predict which patients will have successful pleurodesis. It is widely accepted that the more advanced the pleural disease, the lower the success probability will be [17]. This is mainly related to the condition of ‘trapped lung’ or to the presence of massive cancerous invasion of the pleura, with huge nodules, detected with videothoracoscopy. In our series, there are no cases of ‘trapped lungs’, and videothoracoscopic features are not available in TS patients. Thus, we investigated the duration of the pleural effusion before pleurodesis, interestingly, this correlated neither with the likelihood of success nor with the survival. Patients with lung carcinoma have been reported to have lower rates of success [23] and this was partly confirmed in our study, in

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Table 4
Results of pleurodesis (109 patients, 72 TP and 37 TS)

<table>
<thead>
<tr>
<th>Time from pleurodesis</th>
<th>Overall results</th>
<th>Technique-related results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR</td>
<td>PR</td>
</tr>
<tr>
<td>30 days</td>
<td>77</td>
<td>13</td>
</tr>
<tr>
<td>90 days*</td>
<td>60</td>
<td>9</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>67</td>
<td>15</td>
</tr>
</tbody>
</table>

Data are presented as number (%) of patients. CR: complete response; PR: partial response; F: failure; SR: satisfying response.

* Twenty-six patients in the overall population, 12 in TP group and 14 in TS died within 3 months and were not considered in these rates.
which breast cancer had the best results but mesothelioma had the poorest ones.

According to other Authors [17], we observed that, when a positive response (whether complete or partial) was achieved immediately after the procedure, it often lasted until the patient’s death. Nineteen out of 27 failures (70%) developed within 30 days, while only 8 were distant recurrences, with a time to recurrence quite short (mean 3.3 months). This is true both for TP and TS. The improvement in the response at 90 days with respect to 30 days is only apparent, and it is explained by the high incidence of failure in patients dead between 1 and 3 months (8/26 patients, 30%); this masks the real deterioration of the results, due to 4 recurrences, at 1.6, 2.0, 2.2 and 2.6 months.

As previously reported [11,17], in our series morbidity predominantly included chest pain and fever. Pain was slightly more common in TS, and in five patients the procedure was stopped because of severe pain and respiratory distress. It has to be pointed out that operated patients had pain management by anaesthesiologists, whereas no protocol for pain control was adopted for TS patients, apart from adding local anaesthetic to the slurry, as recommended to lessen postcortisone pain [21]; systemic narcotics were administered to these latter patients in case of post-procedure pain. However, in most patients, pain was slight, short lasting and easy to manage and so was fever.

There are reports of respiratory failure, Adult Respiratory Distress Syndrome (ARDS) and death, maybe related to large doses of talc [12,20], although this hypothesis is questioned [13,15]. An experimental study in rats suggested that there is a rapid absorption of talc powder through the pleural surface and demonstrated its systemic distribution, not dose related [25]. With a standard dose of 6 g we observed neither acute respiratory failure nor mortality. The respiratory distress developed during slurry procedure was related to severe chest pain. Deaths within 1 month from pleurodesis occurred in eight severely ill patients and were not due to the procedure; in such patients pleurodesis was attempted because they were considered to have a life-expectancy >1 month. A re-expansion of pulmonary oedema may be observed after rapid evacuation of large pleural effusions [15,21]. In our series three patients developed an ipsilateral pulmonary oedema after thoracoscopic evacuation of more than 2000 ml of fluid; they all recovered without the need of ventilatory support. In patients with large pleural effusions, we recommend to perform a therapeutic thoracentesis prior to thoracoscopy, with the drainage of 1000—1500 ml. Our protocol initially provided a big bore chest tube (32F) for TP to avoid the risk of drain occlusion by talc; though this never happened throughout the development of the study, we did not modify the protocol. However, at present, we acknowledge that a smaller tube may be suitable as well. In our patients, the placement of a small-bore pleural catheter (10F) allowed early discharge and outpatient control of pleurodesis results, provided that the patients were regularly seen at ambulatory visits. In case of failure of pleurodesis, pleurocath® remained as the ultimate treatment of MPE.

In our series overall survival was quite poor, with a median survival of 7.7 months and 26 patients dead within 3 months from the procedure (36.1%); this reflects our policy to attempt pleurodesis even in patients with advanced disease and low PS.

In conclusion, both techniques are safe; side effects are minor, transient and easy to manage. We believe that talc pleurodesis must be offered to every patient with MPE, apart from terminally ill ones, provided that a satisfying lung re-expansion has been achieved. We should be aware that the primary goal of pleurodesis in MPE is not survival but the control of the effusion, with the resulting improvement in the quality of life. Because TP leads to higher success rates than TS, it should be performed whenever possible. Otherwise, a slurry bedside procedure will be worthwhile, even in patients with low PS, though poorer results have to be expected. Thus, when referring a patient with MPE for talc pleurodesis, the assessment of lung re-expansion is mandatory. Then, a careful selection is essential to define the proper technique: selection criteria are based mainly on PS, general and respiratory conditions, comorbidities and life-expectancy.

References