Phase III Intergroup Study of Talc Poudrage vs Talc Slurry Sclerosis for Malignant Pleural Effusion

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Abstract

Study objective—To demonstrate the efficacy, safety, and appropriate mode of instillation of talc for sclerosis in treatment of malignant pleural effusions (MPEs).

Design—A prospective, randomized trial was designed to compare thoracoscopy with talc insufflation (TTI) to thoracostomy and talc slurry (TS) for patients with documented MPE.

Measurements—The primary end point was 30-day freedom from radiographic MPE recurrence among surviving patients whose lungs initially re-expanded > 90%. Morbidity, mortality, and quality of life were also assessed.

Results—Of 501 patients registered, those eligible were randomized to TTI (n = 242) or TS (n = 240). Patient demographics and primary malignancies were similar between study arms. Overall, there was no difference between study arms in the percentage of patients with successful 30-day outcomes (TTI, 78%; TS, 71%). However, the subgroup of patients with primary lung or breast cancer had higher success with TTI than with TS (82% vs 67%). Common morbidity included fever, dyspnea, and pain. Treatment-related mortality occurred in nine TTI patients and seven TS patients. Respiratory complications were more common following TTI than TS (14% vs 6%).

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Respiratory failure was observed in 4% of TS patients and 8% of TTI patients, accounting for five toxic deaths and six toxic deaths, respectively. Quality-of-life measurement demonstrated less fatigue with TTI than TS. Patient ratings of comfort and safety were also higher for TTI, but there were no differences on perceived value or convenience of the procedures.

Conclusions—Both methods of talc delivery are similar in efficacy; TTI may be better for patients with either a lung or breast primary. The etiology and incidence of respiratory complications from talc need further exploration.

Keywords

insufflation; malignant pleural effusion; slurry; talc

Malignant pleural effusion (MPE) is a common, debilitating complication of advanced cancer. Fluid accumulation resulting from tumor involvement of the pleura and lymphatics typically gives rise to dyspnea and chest pain. Although the optimal form of intrapleural therapy remains controversial, effective palliation can usually be achieved with tube thoracostomy and subsequent pleurodesis. Clinical studies[1–6] of various sclerosing agents support the superior clinical effectiveness of intrapleural talc, but its safety and appropriate mode of administration are still debated.

Talc has been commonly used for treatment of MPE due to its well-known effectiveness for producing pleural symphysis. Thoracoscopic talc poudrage was introduced by Bethune[7] in 1934 as an effective method of inducing adhesions to facilitate lobectomy. Use of talc slurry in animal models of sterile pleuritis was reported in 1940 as a more convenient variant of Bethune's method.[8] Chambers[9] first reported the successful use of talc slurry to treat MPE in 1958. Since that time, a significant number of single institution reports have been published, primarily using thorascopically insufflated talc. However, a growing number of authors have advocated talc slurry via a percutaneously placed chest tube as a simpler and equally effective method for control of MPE with minimal short-term morbidity. However, several reports[10,11] of serious respiratory complications with talc have also been published.

The objectives of the current trial Cooperative Groups Cancer and Leukemia Group B (CALGB) 9334 compare tube thoracostomy with talc slurry (TS) to surgical thoracoscopy with talc insufflation (TTI), and assesses their efficacy at 30 days, in addition to the safety and associated quality of life in a randomized multicenter trial. Portions of this work have been presented in abstract form.[12]

Materials and Methods

This was an intergroup cooperative trial led by the CALGB and monitored semiannually by its Data and Safety Monitoring Board, with participation by the Radiation Therapy Oncology Group, the Eastern Cooperative Oncology Group (ECOG), and the North Central Cooperative Oncology Group, encompassing both private and teaching hospitals. Credentialing of participating surgeons was required. Institutional review board approval and written informed patient consent were obtained.

Patients were identified either by the surgical or medical staff with eligibility criteria that included a history of a malignancy, pleural effusion requiring sclerosis, ECOG/Zubrod status 0–2, life expectancy > 2 months, and ability to undergo general anesthesia. Exclusion criteria included pregnancy, previous intrapleural therapy or radiation therapy encompassing the entire hemithorax, changes in systemic therapy within 2 weeks prior to randomization or subsequent to sclerosis (except addition of tamoxifen), and chylous or bilateral effusions requiring therapy.

Patients were randomized to receive 4 to 5 g of talc, either administered as a slurry in 100-mL saline solution through a chest tube at the bedside (TS group) or insufflated during thoracoscopy in the operating room (TTI group). After drainage of the pleural fluid, lung re-expansion by > 90% as estimated by the surgeon was required to proceed on protocol. Patients randomized to TS underwent sclerosis within 24 to 36 h of chest tube placement. The chest tube was subsequently clamped for 2 h and then reattached to suction drainage. There was no requirement for the patient to rotate positions. The chest tube (possibly more than one for TTI patients) was removed once the 24-h drainage was < 150 mL, and a baseline chest radiograph (CXR) was obtained. Additional radiographs were obtained after 30 days and then monthly until death or for 6 months.

The primary objective was to determine the percentage of patients whose lung initially re-expanded > 90% and who had a successful pleurodesis at 30 days after treatment. Surgeons were to make the visual estimation during surgery following drainage of the effusion of the > 90% re-expansion prior to sclerosis. For the talc slurry study arm, the surgeon will estimate radiographically the > 90% re-expansion prior to instillation of the talc via the chest tube. Success was defined as no pleural fluid re-accumulation greater than that seen on the baseline CXR as evaluated by the surgeon. Success rates were compared using Fisher exact test. Radiologic review (E.S.) was performed by comparing 30-day CXRs with baseline CXRs. Secondary end points included time to recurrence of effusion (compared using log-rank test), frequency of complications and toxicities (Fisher exact test), and the ability to re-expand the lung as assessed by CXR (Fisher exact test). A Wilcoxon two-sample test was used to compare treatment groups with respect to the following: (1) intensity of pain as measured by a visual analog scale, and (2) satisfaction with treatment as measured by 4-point Likert scales that assessed convenience, medical safety, comfort, and cost. Change in quality of life at 30 days relative to baseline was measured using the European Organization for Research and Treatment of Cancer QLQ-C30[13] and analyzed using analysis of covariance.

Results

Between January 1995 and September 1999, 501 patients were randomized (TS, n = 250; TTI, n = 251). Nineteen patients were excluded: 13 were ineligible and 6 withdrew consent. Thus, 240 TS and 242 TTI patients remained for outcome analysis. Patient demographics (Table 1) and distribution of underlying malignancies (Table 2) were similar between study arms.

The criterion of > 90% lung re-expansion was met by 163 of 240 TS patients (68%) and 177 of 242 TTI patients (73%) [p = 0.231]. Among these, 33 of 163 TS patients (20%) and 25 of 177 TTI patients (14%) died within 30 days of the procedure. Table 3 summarizes 30-day recurrence-free survival among all eligible (both groups with either > 90% *or* < 90% re-expansion) patients, eligible patients treated with talc, all treated patients with > 90% lung re-expansion, and the subset of the patients with > 90% expansion who were alive at 30 days. There is no difference between the two treatment approaches in the rate of successful pleurodesis at 30 days among all patients treated with talc. However, the same comparison among all treated patients with > 90% lung re-expansion significantly favored TTI (67%) vs TS (56%) [p = 0.045], but successful pleurodesis among those alive at 30 days did not differ between study arms. Subgroup analyses revealed that the 30-day outcome among patients with breast or lung cancer differed between treatment arms (favoring TTI) independent of denominator (Table 3). Among TTI patients with > 90% re-expansion alive at 30 days, 82% had successful pleurodesis vs 67% of comparable TS patients (p = 0.022).

Of the 271 eligible patients who were alive at 30 days without recurrent MPE, 214 patients (79%; TS, n = 103; TTI, n = 111) had one or more subsequent follow-up assessments, and 60 late recurrences were documented (23 of 103 TS patients [22%], and 37 of 111 TTI patients [33%]). Kaplan-Meier product limit estimator was used to evaluate the distribution of time to recurrence of MPE (Fig 1). A log-rank test revealed no significant difference in time to recurrence between study arms (p = 0.622).

Independent radiologic review (TS, n = 102; TTI, n = 102) of patients alive at 30 days corroborated the results of the clinical evaluation. Seventy percent of patients with TS had stable or improved radiologic status at 30 days compared to 76% of TTI patients.

Table 4 summarizes surgical complications experienced by at least two patients. The most common adverse event following either procedure was fever (> 38.5°C). Respiratory complications (atelectasis, pneumonia, or respiratory failure) were experienced by significantly more TTI patients (13.5%) than TS patients (5.6%) [p = 0.007; χ^2 with 80% power for a two-tailed test conducted at the 0.05 level of significance].

Adverse events were also graded according to National Cancer Institute common toxicity criteria.[14] Toxicity of at least grade 3 was experienced by 26% of patients in the TS study arm and 32% in the TTI study arm. Dyspnea (TS, 16%; TTI, 16%) and pain (TS, 10%; TTI, 5%) were the most common toxicities. Seven treatment-related deaths were reported for TS (respiratory failure [n = 5], cardiac [n = 2]), and nine treatment-related deaths were reported for TTI (respiratory [n = 6], cardiac [n = 1], infection [n = 2]).

TTI was perceived to provide more comfort (p = 0.019) and medical safety (p = 0.013) than TS, and patient perceptions of pain control tended in the same direction (p = 0.07). Similar differences were observed in the subgroup of patients whose lungs expanded > 90% (p = 0.006, p = 0.007, and p = 0.028, respectively), but not in the < 90% expansion subgroup. There was no difference between the TS and TTI study arms in patients' perception of convenience or cost of the procedure, or the degree to which it was worthwhile to their

overall care. There was no difference between study arms in the patients' daily indication of pain using a visual analog scale.

Fourteen subscales of the quality-of-life questionnaire were performed at baseline and at each subsequent follow-up for 133 TS patients (55%) and 131 TTI patients (54%). Only fatigue was significantly different between the two study arms, with patients in the TTI arm demonstrating a decrease in fatigue, compared to increased fatigue for TS patients (p = 0.016).

Discussion

The current finding of no difference in the ability of talc, whether insufflated or placed as slurry, to prevent recurrence of MPE at 30 days is not surprising. An equivalence design was used because there was no *a priori* reason to expect that efficacy would differ between the study arms. Although there is considerable variability in reported "success" rates among published studies, a review[15] of MPE studies published through 1994 reveals identical overall success rates of 91% for slurry (n = 166) and poudrage (n = 461). A small, randomized trial[16] published during the current study also demonstrated no difference between the two modes of application. Further, an animal study[17] demonstrate a similar density and distribution of adhesions following slurry vs poudrage delivery of intrapleural talc.

The observed efficacy rates in both arms of this study are, however, lower than those reported in previous trials and case series, most of which were single institution studies with small enrollment. Reports in the literature vary between 68% and 97% "success" for poudrage[4,18] and from 72 to 94% for slurry.[19,20] Varying definitions of recurrence (radiologic, symptomatic, requiring treatment) and choice of denominator may account for some of the discrepancy among studies.

A significant 30-day mortality rate was observed for MPE patients in both study arms. Reported 30-day mortality in previous studies varies considerably, from 0 to 32% for TS[19,21] and from 3 to 24% for TTI.[22,23] In some studies, lower mortality corresponds to a high percentage of breast cancer and higher mortality to a preponderance of lung cancer in the case mix. However, Kennedy and colleagues[24] reported 24% (14 of 58 patients) 30-day mortality despite a large percentage of patients with breast cancer. The results of a multivariate analysis of 85 patients with MPE[25] suggest that performance status may be the only clinical variable related to survival. The present finding of 20% mortality among TS patients and 14% among TTI patients (despite entry criteria of good performance status and life expectancy of 2 months) underscores the difficulty in predicting life expectancy in this patient population.

Morbidity predominantly included postprocedure fever, dyspnea, and pain. Incidence of these complications did not differ between the two study arms. Pain—either from the chest tube or the sclerosing agent—and fever are well-recognized adverse effects of talc pleurodesis. Although self-reports of daily pain were similar between the study arms, reported satisfaction with pain control favored the TTI study arm. However, TTI patients

had pain management by anesthesiologists, whereas no pain management protocol was specified for TS patients. It has been reported that postsclerosis pain may be lessened for TS patients by adding local anesthetic to the slurry.[20] Increased respiratory complications experienced by TTI patients may have been related to atelectasis from the general anesthetic and/or single-lung ventilation.

Respiratory failure was observed in 4% of TS cases and 8% of TTI cases, accounting for five toxic deaths and six toxic deaths, respectively. These observations are consistent with some previous reports (although others report no acute respiratory failure in large series[26,27]). Using 10 g of talc in a slurry, Rinaldo et al[10] reported three cases of ARDS with bilateral infiltrates apparently precipitated by talc. Kennedy et al[24] reported that 5 of 58 patients (9%) treated with 10 g of slurry had respiratory failure, with 3 patients requiring intubation. The high incidence of respiratory complications in these series may be related to the large dose.[27] However, Marom et al[19] found no difference in complication rates among 60 patients treated with 5 g vs 10 g of TS. Rehse and colleagues[11] described the development of ARDS in 7 of 78 patients (9%) after 5 g of talc by poudrage (n = 3) and slurry (n = 4). Also, several reports[28,29] describe acute pulmonary distress of patients who received only 2 g of talc as a poudrage. Inconsistent incidence among reported series suggests a possible relationship to the size of talc particles[30] or to specific contaminants, both of which can vary among talc sources.[31]

The etiology of acute respiratory complications is unclear. Intrapleural talc (slurry or powder) can clearly migrate or be transported into the lungs and other organs[29,32] and may directly trigger adverse consequences. Indeed, long-term talc exposure in people who mine or process the substance has been reported to reduce measures of pulmonary function.[33] However, the nature of any acute response and the factors that render specific patients susceptible are unknown. In the current study, the requirement for a performance status of 0–2 was intended to eliminate patients with inadequate respiratory reserve. However, patients with MPE may have substantial interstitial pulmonary disease with low oxygen saturation, which may not be clinically evident. Unfortunately, data were not gathered in the current study to test this hypothesis. Rapid evacuation of large pleural effusions is associated with risk of re-expansion pulmonary edema. However, in only a few of the respiratory deaths were the pleural effusions large enough for this to be of concern. Despite a thorough review of the treatment-related deaths, no consistent characteristic was evident.

Thus, it is often difficult to predict which patients will have successful and uncomplicated pleurodesis with talc. Patients with lung cancer, the largest subgroup of MPE patients, have been reported to have lower rates of success, although this trend was not substantiated in the current study. Danby et al[34] noted that all failures in their series were lung cancer patients. In some patients, the lung may become "trapped" by tumor or fibrin, a condition that commonly leads to pleurodesis failure. Effusions characterized by low pH or glucose level have been reported to correlate with treatment failure and poor survival.[35,36] However, the predictive utility of pleural fluid pH is questioned by other authors.[37] Heffner and colleagues reported that pH has only "modest" value as a predictor of pleurodesis failure[38] or survival,[39] based on a meta-analysis that included 231 patients treated with thoracoscopic talc. Clinicians should acknowledge a small but currently unpredictable risk of severe

respiratory complications including death. Future studies should evaluate the predictive value of oxygen saturation or diffusion capacity for such complications.

Given the equivalent efficacy of TS and TTI, the appropriate mode of delivery for a given patient will depend on several considerations. Thoracoscopy affords an opportunity to directly inspect the pleura and to address adhesions and loculations. This may be indicated for patients who have had prior ipsilateral surgery or attempted pleurodesis, or for whom there is a significant possibility of a trapped lung. Subset analysis in the current study suggests that TTI may be more advantageous for patients with lung or breast cancer. Other authors have expressed the opinion that thoracoscopy should be used to assess all patients with lung cancer and ipsilateral MPE.[18] TTI is perceived by patients to afford greater com fort and medical safety, as well as less fatigue relative to TS. These factors may significantly impact treatment preferences for patients who rank quality of life as a principal goal of care.

Bedside TS, however, is a simpler, less invasive procedure that in this study was associated with a lower risk of respiratory complications and possibly with lower cost. Further work is still required to better define the etiology and risk of respiratory failure due to talc instillation. Other factors being equal, one should opt for the least intrusive method of palliation in this population of end-stage cancer patients. In this regard, a number of authors have reported successful control of MPE using smallbore, indwelling catheters without pleurodesis. As a follow-up to the current study, this intergroup consortium has recently undertaken a randomized trial comparing TS as the least invasive arm of the current study to small-bore catheter outpatient drainage.

ACKNOWLEDGMENT

Abbreviations

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CALGB	Cooperative Groups Cancer and Leukemia Group B
CXR	chest radiograph
ECOG	Eastern Cooperative Oncology Group
MPE	malignant pleural effusion
TS	thoracostomy and talc slurry
TTI	thoracoscopy with talc insufflation

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TIME TO RECURRENCE OF MALIGNANT PLEURAL EFFUSION
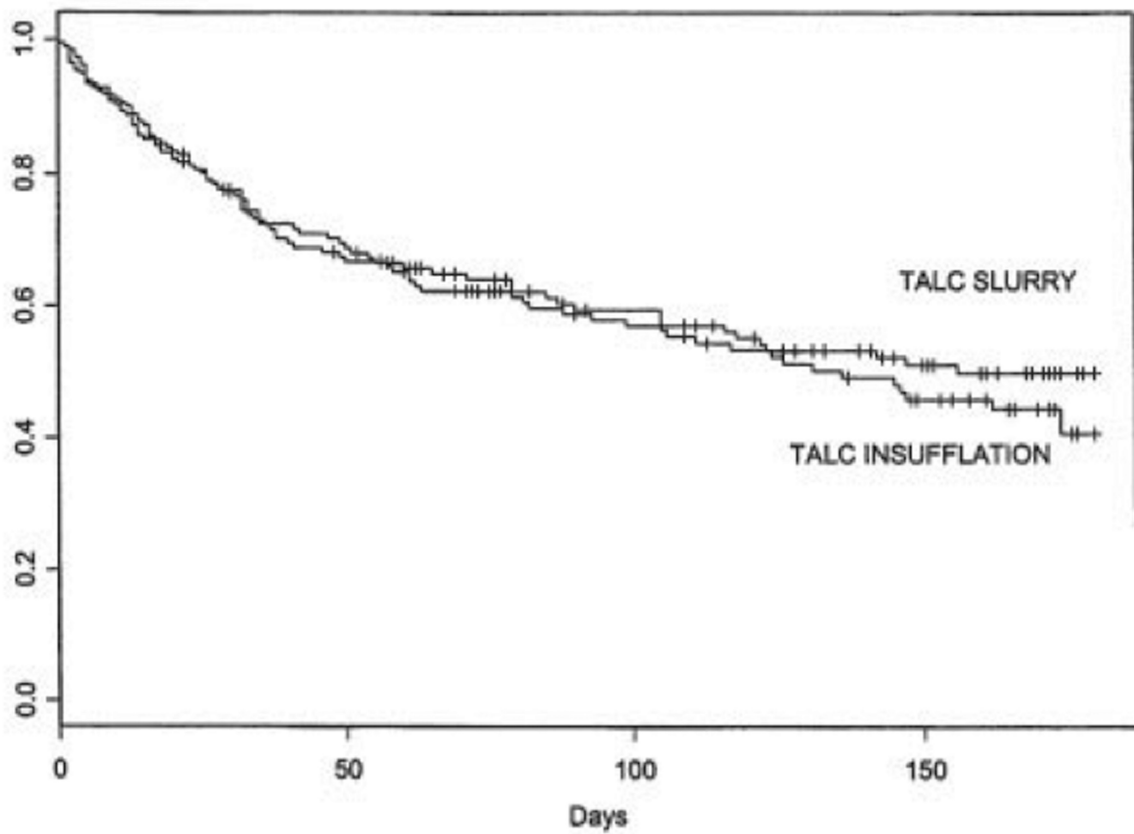
			Number of patients at risk for given time points				
Treatment	0 days	30 days	60 days	90 days	120 days	150 days	180 days
Slurry	221	135	89	66	59	44	26
Insufflation	228	144	84	61	51	38	19
Total	449	279	173	127	110	82	45

Figure 1.
Time to recurrence of MPE.

Table 1

Characteristics of Eligible Patients[*]

Characteristics	TS	TTI
Patients, No.	240	242
Female gender	140 (58)	129 (53)
Age, yr		
Mean (SD)	61.5 (12.9)	62.5 (11.7)
Median (range)	65 (23–87)	64 (34–85)
Race		
White	198 (82)	192 (79)
Hispanic	5 (2)	7 (3)
African American	30 (13)	36 (15)
Other	7 (3)	7 (3)
Performance status		
0	28 (12)	30 (12)
1	111 (46)	88 (36)
2	95 (40)	113 (47)
0–2	6 (2)	11 (5)

[*] Data are presented as No. (%) unless otherwise indicated.

Table 2

Distribution of Primary Malignancies[*]

Primary Site	TS	TTI
Lung	93 (39)	89 (37)
Breast	56 (23)	59 (24)
GI	25 (10)	20 (8)
Gynecologic	8 (3)	12 (5)
Genitourinary	8 (3)	12 (5)
Sarcoma	6 (2)	6 (2)
Head and neck	3 (1)	9 (4)
Melanoma	1 (< 1)	4 (2)
Lymphoma	1 (< 1)	2 (1)
Mesothelioma	4 (2)	0
Other or unknown	35 (14)	29 (11)

[*] Data are presented as No. (%).

Table 3

Efficacy of Talc Slurry and Talc Insufflation[*]

	TS				TTI			
Denominator	**No.**	**Alive Without Recurrence, No.**	**%**	**CI**	**No.**	**Alive Without Recurrence, No.**	**%**	**CI**	**p Value**
All malignancies								
All eligible patients	240	126	53	46–59	242	145	60	53–66	0.119
Eligible, treated	221	126	57	50–64	228	145	64	57–70	0.177
> 90%, treated	163	92	56	50–64	177	119	67	65–77	0.045
> 90%, alive	130	92	71	62–78	152	119	78	71–85	0.169
Lung or breast cancer								
All eligible patients	149	75	50		148	96	65		0.014
Eligible, treated	136	75	55		140	96	69		0.026
> 90%, treated	98	52	53		108	78	72		0.006
> 90%, alive	78	52	67		95	78	82		0.022
Other cancers								
All eligible patients	91	51	56		94	49	51		0.659
Eligible, treated	85	51	60		88	49	56		0.645
> 90%, treated	65	40	62		69	41	59		0.861
> 90%, alive	52	40	77		57	41	72		0.662

[*] CI = confidence interval.

Table 4

Surgical Complications Among Treated Patients[*]

Toxicity	TS (n = 196)	TTI (n = 223)
RBC transfusion	5 (2.6)	10 (4.5)
Postprocedure fever	68 (34.7)	68 (30.0)
Wound infection	2 (1.0)	1 (0.4)
Empyema	2 (1.0)	1 (0.4)
Bronchopleural fistula	4 (2.0)	6 (2.7)
Atelectasis (requiring more than two bronchoscopies)	0 (0)	3 (1.3)
Pneumonia (requiring antibiotics)	7 (3.6)	21 (9.3)
Respiratory failure	8 (4.0)	18 (8.1)
Dysrhythmia (requiring treatment)	9 (4.6)	12 (5.4)
Myocardial infarction	1 (0.5)	1 (0.4)
Deep vein thrombosis	0 (0)	7 (3.1)
Pulmonary embolism	0 (0)	4 (1.8)
Postoperative death	12 (6.1)	19 (8.4)

[*] Data are presented as No. (%).