Prospective Randomized Trial of Talc Slurry vs Bleomycin in Pleurodesis for Symptomatic Malignant Pleural Effusions*

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Objective: **Symptomatic malignant pleural effusions are common sequelae in patients with certain malignancies. Pleurodesis via bedside thoracostomy is the current treatment option most commonly used. To our knowledge, this is the first prospective randomized trial to examine which agent, bleomycin or talc slurry, is superior in terms of effectiveness, safety, and cost.**

Patients and Methods: **Between July 1992 and March 1995, 35 patients presenting to our medical center with symptomatic malignant pleural effusions were prospectively randomized to undergo chemical pleurodesis with either bleomycin or talc slurry via bedside thoracostomy. The conditions of patients were assessed and graded before and after treatment concerning pain, dyspnea, and chest radiographs.**

Results: **Twenty-nine patients who underwent 33 treatments (14 with bleomycin and 19 with talc) were available for follow-up. Follow-up ranged from 2 weeks to 8 months (mean, 1.7 months). Both groups demonstrated notable improvement in both pain and dyspnea following treatment, but there were no statistically significant differences between groups in the amount of improvement (two-tailed Student's *t* test). Permanent control of effusions, defined objectively on chest radiograph, was achieved with 11 bleomycin treatments (79%) and 17 talc treatments (90%) (p=0.388). The procedures were well tolerated and no significant adverse effects were observed. Talc is a much less costly agent than bleomycin ($12.36 cost to our medical center per treatment for talc vs $955.83 for bleomycin).**

Conclusion: **Given the similar efficacy and significant cost advantage, we conclude that talc is the agent of choice when utilizing pleurodesis for control of symptomatic malignant pleural effusions.**

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Key words: bleomycin; clinical trials; comparative study; human; pleural effusion, malignant; pleurodesis; prospective studies; talc

Approximately 50% of patients with malignant pulmonary disease have an associated malignant pleural effusion. These effusions most commonly occur with lung, breast, and ovarian cancer, and lymphoma, with breast and lung malignancies alone accounting for approximately 75% of these effusions.[1,2] The most common presentation of these patients involves the gradual onset of dyspnea. Cough and chest pain are also common associated symptoms, and up to one third of patients may have bilateral effusions. Diagnostic studies show this fluid most commonly to be an exudative process with pleural fluid cytologic study and/or pleural biopsy specimen giving a diagnosis in approximately 90% of cases.[3,4]

The symptomatic manifestations of these effusions can vary significantly among patients, and treatment options are often limited secondary to the prognosis and degree of medical compromise exhibited. As a result, tube thoracostomy with pleurodesis has become the most common therapeutic approach.

Tetracycline, doxycycline, talc, and bleomycin have been the agents used most commonly for pleurodesis. However, parenteral tetracycline is no longer commercially available for pleurodesis, and recent experience with doxycycline suggests it may often require several

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administrations.[5] Bleomycin and talc remain therapeutic options. However, until recent reports,[2,6-8] it was considered advisable to administer talc only in conjunction with thoracoscopy and general anesthesia. While talc poudrage given during thoracoscopy has been compared to bleomycin,[9] to our knowledge, there is no current published comparison of bleomycin vs talc slurry for pleurodesis via bedside thoracostomy. This prospective randomized trial was designed to compare the efficacy, safety, and cost-effectiveness of bleomycin vs talc slurry, given via bedside thoracostomy tube, in the treatment of symptomatic malignant pleural effusions.

Materials and Methods

Thirty-five patients with malignant pleural effusions were enrolled from July 1992 through March 1995. Four patients had bilateral effusions and one patient required retreatment due to a recurrent effusion; thus, a total of 40 procedures were done. Inclusion in the study required documentation of a malignant pleural effusion and a life expectancy of >1 month. Patients with significant loculated effusions or trapped lung after drainage were excluded from the study. The study was approved by the Investigational Review Board at Virginia Mason Medical Center, and informed consent was obtained from all eligible patients.

Cytologic or histologic diagnosis was obtained via examination of pleural fluid after thoracentesis in 33 patients. Thoracoscopic biopsy specimens and open biopsy specimens were obtained during limited thoracotomy in two other patients. In these two patients, tube thoracostomy was placed intraoperatively, but pleurodesis was accomplished several days later in the same manner as the other patients. In the other 33 patients, tube thoracostomy (28F) was inserted at the bedside with local anesthesia, and in some cases additional IV benzodiazepines and/or narcotics. The thoracostomy tube remained on −20 cm underwater suction, and drainage and lung reexpansion were assessed with chest radiographs over the next 12 to 24 h. All patients were seen by respiratory therapists and encouraged to use incentive spirometry.

Patients eligible were then randomized by the investigational pharmacy to either talc or bleomycin pleurodesis. The preparation consisted of 20 mL of 1% lidocaine and either 60 U of bleomycin or 5 g of talc, diluted to a total of 50 mL with normal saline solution.

Pharmaceutical-grade USP-certified, asbestos-free talc (Spectrum Chemical Manufacturing Corporation; Gardena, Calif) was used. Our current method of sterilization consists of using a steam sterilizer to create a dry heat environment using a procedure obtained from the sterilizer's manufacturer (AMSCO Healthcare; Pittsburgh). Five-gram aliquots of talc are placed in glass vials, capped, and placed in sterilization pouches that are then heat sealed. The talc is then heated in the steam sterilizer for 6 h at 270°F, and verified sterile using the biological indicator *Bacillus subtilis*.

For pleurodesis, the sclerosing agent was injected into the thoracostomy tube and the tube was then flushed with 25 mL of sterile normal saline solution. Next, the tube was clamped for 2 h and the patient placed in Trendelenburg and reverse Trendelenburg positions while in the prone, supine, and left and right decubitus positions for 10 to 15-min intervals. The tube was then placed back to −20 cm underwater suction and vigorous respiratory therapy was resumed. Serial radiographs were used to ensure appropriate lung reexpansion. The thoracostomy tube was generally removed 48 h following treatment. The patients received chest radiographs immediately following tube removal, and again at follow-up. Patients were evaluated before and after treatment regarding dyspnea and pain. Pain, dyspnea, and chest radiographs were all assessed before and after treatment.

Follow-up is traditionally difficult in these patients given their underlying disease and life expectancy. Information in our study was obtained from direct patient contact and assessments from primary care, hospice, and nursing home physicians, and in all cases by follow-up chest radiographs.

Statistical analysis was as follows. Age was compared between groups using unpaired two-tailed Student's t test, and sex, side treated, and length of hospital stay with χ^2 test. Pain and dyspnea functional class scores were compared between groups with Spearman Rank test, and the change in these scores (improvement) was compared by unpaired two-tailed Student's t test. Radiograph scores were compared using χ^2 test.

Results

Thirty-five patients underwent 40 procedures. Twenty-nine patients (83%) who underwent 33 procedures (14 with bleomycin and 19 with talc) were available for follow-up after hospital discharge (Table 1). Six patients who underwent seven procedures were not available for posttreatment assessment. One of these patients underwent bilateral pleurodesis with different agents 4 days apart and died, prior to hospital discharge, of progression of disease unrelated to the pleural effusions. The additional five patients were unavailable for follow-up. Patients were deemed appropriate for assessment if they were discharged from the hospital and seen for a follow-up visit and chest radiograph a minimum of 2 weeks later. Except for the fact that none of the bleomycin group had metastatic breast cancer, the groups were similar with respect to age (p=0.544), sex (p=0.618), side of pleurodesis (p=0.094), and number of hospital days (p=0.131). Of the three patients who had bilateral effusions, one received bleomycin bilaterally while two others received dif-

Table 1—*Description of Group Data*

Variable	Bleomycin	Talc
n	14	19
Age, yr, mean, (SEM)	68 (±4.4)	65 (±3.5)
Sex, M/F	4/10	7/12
Side, L/R	4/10	11/8
Pathology		
Lung	8	5
Breast	0	5
Ovarian	2	3
Other	4	6
Hospital days		
Mean (SEM)	6.5 (±0.8)	9.2 (±1.4)
Median	5	8

ferent agents on each side. In all three of these patients, bilateral procedures were carried out a minimum of 2 days apart.

Follow-up ranged from 2 weeks to 8 months, with a mean (SEM) of 1.7 (±0.3) months. Subjective pain and dyspnea functional class scores were notably improved in both groups following treatment (Table 2). However, there was no statistically significant difference between the two groups with respect to degree of improvement.

Effusion control was defined objectively as a follow-up chest radiographs score of 1 or 2 (Table 3). There was no statistically significant difference between the two groups (p=0.388). Two patients in each group had a moderate effusion (radiograph score, 3) on follow-up, but their symptoms were clearly improved and did not require additional intervention. There was one significant recurrence (radiograph score, 4) in the bleomycin group, while there were none in the talc group. This recurrence was subsequently treated successfully with talc slurry.

The only significant complications observed were limited wound infections (three in the talc group and none in the bleomycin group [p=0.119]). Overall, we had very low morbidity associated with these procedures. We had no cases of respiratory failure, and no deaths directly attributable to pleurodesis.

We also undertook a cost analysis of the agents used in our study. The medication cost to our medical center for each treatment was $955.83 for bleomycin compared with $12.36 for talc.

Table 2—*Results: Pain and Dyspnea Scores Before and After Treatment*

Score	Before	After
Pain*		
Bleomycin	4.1	2.4
Talc	5.9	3.1
Dyspnea†		
Bleomycin	2.9	2.0
Talc	3.3	1.9

*0=none → 10=maximal.
†Functional class: 1=none; 2=with moderate to heavy activity; 3=with minimal activity; 4=at rest.

Table 3—*Results: Chest Radiographs**

Post-treatment Score of 1 or 2	%
Bleomycin	79
Talc	90

*Scored at follow-up with the following scale: (1) no effusion; (2) minimal effusion (<10% compared to before intervention); (3) moderate effusion (10 to 49% compared to before intervention); and (4) large effusion (50 to 99% compared to before intervention).

Discussion

Chemical pleurodesis is the treatment option used most often for the control of symptomatic malignant pleural effusions. Its efficacy is attributed to an inflammatory response resulting in decreased fibrinolytic activity as well as mesothelial cell injury and stimulation of fibroblast proliferation.[10] Adequate fluid drainage with pleural apposition is necessary prior to administration of the sclerosing agent. Incomplete lung reexpansion following drainage of the pleural fluid may indicate a multiloculated effusion, trapped lung, or bronchial obstruction. If suspected, especially if ipsilateral mediastinal shift is present, bronchoscopy should be performed. When neoplastic bronchial obstruction is present, laser therapy or bronchial stenting may facilitate pulmonary reexpansion. Once a patient is deemed appropriate for pleurodesis, an agent must be chosen. Tetracycline, the agent used most commonly in the past, is no longer commercially available. At the present time, bleomycin, doxycycline, and talc remain the agents most commonly used.

Doxycycline has been advocated as a replacement for tetracycline; however, recent reports suggest that up to two thirds of patients will require multiple treatments.[5] This is less than optimal in these patients with limited life expectancy. No recent trials comparing doxycycline are available (to our knowledge), but tetracycline has been compared with bleomycin in a recent randomized trial.[11] A statistically significant difference was noted favoring bleomycin, which was effective in 64% of patients, compared to only 33% in the tetracycline group.

Bleomycin is an antineoplastic antibiotic from *Streptomyces verticillus* that binds DNA producing breakage, thus inhibiting DNA synthesis. It is widely used because of its sclerosing properties for pleurodesis, and its success at controlling malignant pleural effusions has been examined in several previous publications (Table 4).[9,11-13] It has been associated with minimal toxic reactions. However, a case report does describe systemic toxicity manifested by alopecia and significant mucositis following pleurodesis in a 32-year-old woman with a malignant pleural effusion and renal failure.[14] Another report describes fatal alveolar injury attributable to intrapleural bleomycin in a 62-year-old woman with a nonmalignant pleural effusion and renal failure.[15] Bleomycin is cleared renally and should be used with caution as a sclerosing agent in patients with renal failure.

Talc ($[Mg_3Si_4]O_{10}[OH]_2$) is a trilayered magnesium sheet silicate. Preparations historically have had some minimal associated impurities, most notably

Table 4—*Past Clinical Success of Pleurodesis*

Source, yr	Agent	Dose	Success/Total (%)*	Etiology†
Ostrowski,[12] 1986	Bleomycin	60-180 U	21/26 (81)	MPEs
Kessinger and Wigton,[13] 1987	Bleomycin		8/13 (62)	MPEs
Hamed et al,[9] 1989	Bleomycin	1 mg/kg	10/15 (66)	MPEs
Moores,[11] 1991	Bleomycin	60 U	18/28 (64)	MPEs
Subtotal			**57/82 (70)**	
Weissberg and Kaufman,[19] 1986	Talc poudrage		5/5 (100)	EMPs
Daniel et al,[20] 1990	Talc poudrage	Up to 10.5 g	37/40 (93)	PEs,Pxs
Ohri et al,[21] 1992	Talc poudrage	2-5 g	50/54 (93)	PEs,Pxs
Van de Brekel et al,[22] 1993	Talc poudrage		313/356 (88)	
Weissberg and Ben-Zeev,[8] 1993	Talc poudrage or slurry	2 g	284/336 (85)	PEs,Pxs,EMPs
Hartman et al,[23] 1993	Talc poudrage	3-6 g	32/33 (97)	MPEs
Milanez et al,[24] 1994	Talc poudrage	2 g	17/18 (94)	Spontaneous Pxs
Vargas et al,[25] 1994	Talc poudrage	2 g	20/22 (91)	Benign PEs
Subtotal			**758/864 (88)**	
Chambers,[18] 1958	Talc slurry	7-14 g	19/22 (86)	MPEs
Webb et al,[2] 1992	Talc slurry	5 g	28/28 (100)	MPEs
Kennedy et al,[6] 1994	Talc slurry	10 g	31/40 (78)	MPEs
Subtotal			**78/90 (87)**	
TOTAL			**893/1,036 (86)**	

*Success defined by parameters delineated in each separate study.
†PE=pleural effusion; MPE=malignant PE; Px=pneumothorax; EMP=empyema.

asbestos. Sterile USP asbestos-free talc is currently the compound appropriate for intrapleural use, although its composition is not standardized. A recent study has shown that sterilization using either dry heat exposure, gamma irradiation, or ethylene oxide gas is simple, effective, and inexpensive.[16] We currently utilize the dry heat method. Talc can be used as a poudrage (powder or dusting) during thoracotomy or thoracoscopy, or as a slurry via thoracostomy.

Talc was first used for pleurodesis by Bethune[17] in 1935 as a poudrage during thoracoscopy preliminary to lobectomy. Chambers,[18] using a slurry in 1958, was the first to utilize talc for the treatment of malignant pleural effusions. Numerous reports have described its safe and effective use as a thoracoscopic poudrage for the treatment of pleural effusions, empyemas, and pneumothoraces (Table 4).[19-25]

Recent reports have compared talc and bleomycin when used for pleurodesis; however, in these studies, talc was given as a poudrage during thoracoscopy, thus requiring general anesthesia. One study found talc 97% effective in 33 patients compared to 64% in 28 bleomycin historical control subjects ($p<0.005$).[23] The other comparison was a randomized trial in breast cancer patients that reported a 100% success rate in 10 patients treated with thoracoscopic talc poudrage, compared to 67% in 15 bleomycin treatments ($p=0.057$).[9] This use of talc poudrage during thoracoscopy is a well-established technique. However, comparison trials utilizing the easier and potentially more cost-effective method of bedside thoracostomy and pleurodesis with talc slurry are not currently available.

Interest in this more simplified approach of utilizing talc slurry for bedside pleurodesis was regenerated by Webb and colleagues[2] who reported a 100% success rate in 28 patients with no significant complications (Table 4). Kennedy and colleagues[6] have also shown talc slurry to be a very effective agent, although they did note some concerns with respect to pain and fever at the time of administration (Table 4). There were no such problems with severe chest pain or prolonged pyrexia documented in any of our patients. The pain was easily controlled with nonsteroidal anti-inflammatory drugs or small doses of narcotics in those who needed additional relief.

More notably, one report has described three cases (one resulting in death) of ARDS attributed to pleurodesis with 12 g of talc slurry.[26] Another report described acute pneumonitis, possibly secondary to talc emboli, following a pleural biopsy in conjunction with pleurodesis using 2 g of talc slurry.[27] One other series of 40 procedures using talc slurry (10 g) noted three cases of respiratory failure attributed to the procedure.[6] One patient had undergone bilateral simultaneous pleurodesis, and none of these patients died as a result.

We experienced none of these complications in our patients. However, based on the adverse effects noted in these reports, we would make several recommendations: (1) that talc not be administered immediately following lung or pleural biopsy due to the risk of talc emboli; (2) that bilateral simultaneous pleurodesis be avoided; and (3) that no more than 5 g be administered in a single treatment.

We found both bleomycin and talc slurry to be effective in the control of malignant pleural effu-

sions, with no statistically significant difference between the two agents. We encountered no significant problems with pain control during the procedure with either group, and no major complications of pleurodesis resulting in major morbidity or mortality. The only complication occurred in three patients who developed minor wound infections at the thoracostomy site following talc pleurodesis. All three were treated successfully with a single course of oral antibiotics and local wound care.

Talc is a much less costly agent than bleomycin ($12.36 cost to our institution per treatment for talc vs $955.83 for bleomycin). A recent study has looked at the cost-effectiveness of talc, bleomycin, doxycycline, and tetracycline (as a historical agent).[28] It found bleomycin to be the most cost-effective; however, in that report, the method of talc administration was as a thoracoscopic poudrage, thus adding operating room and general anesthesia fees which boosted costs significantly.

Conclusions

Pleural effusions can have a significant impact on the quality of life in patients with end-stage malignancy. Therapy in these patients should be simple, safe, efficacious, and cost-effective, while minimizing time spent in the hospital. Chemical pleurodesis via bedside thoracostomy has been shown to be effective with a variety of agents, and has become a common therapeutic approach. Using this approach, we found both bleomycin and talc slurry to be highly effective at controlling malignant pleural effusions and decreasing the associated symptoms of dyspnea and pain. Neither group in our study experienced major side effects or complications. However, talc is notably more cost-effective. We now routinely use talc slurry pleurodesis administered via bedside thoracostomy as primary treatment in all appropriate patients with malignant pleural effusions.

References

1 Lynch TJ. Management of malignant pleural effusions. Chest 1993; 103:385S-89S
2 Webb WR, Ozmen V, Moulder PV, et al. Iodized talc pleurodesis for the treatment of pleural effusions. J Thorac Cardiovasc Surg 1992; 103:881-86
3 Austin EH, Flye MW. The treatment of recurrent malignant pleural effusion. Ann Thorac Surg 1979; 28:190-203
4 Sahn SA. Malignant pleural effusions. Clin Chest Med 1985; 6:113-25
5 Mansson T. Treatment of malignant pleural effusion with doxycycline. Scand J Infect Dis Suppl 1988; 53:29-34
6 Kennedy L, Rusch VW, Strange C, et al. Pleurodesis using talc slurry. Chest 1994; 106:342-46
7 Kennedy L, Sahn S. Talc pleurodesis for the treatment of pneumothorax and pleural effusion. Chest 1994; 106:1215-22
8 Weissberg D, Ben-Zeev I. Talc pleurodesis—experience with 360 patients. J Thorac Cardiovasc Surg 1993; 106:689-95
9 Hamed H, Fentiman IS, Chaudary MA, et al. Comparison of intracavitary bleomycin and talc for control of pleural effusions secondary to carcinoma of the breast. Br J Surg 1989; 76:1266-67
10 Agrenius V, Chmielewska J, Widstrom O, et al. Pleural fibrinolytic activity is decreased in inflammation as demonstrated in quinacrine pleurodesis treatment of malignant pleural effusion. Am Rev Respir Dis 1989; 140:1381-85
11 Moores DWO. Malignant pleural effusion. Semin Oncol 1991; 18:59-61
12 Ostrowski MJ. An assessment of the long-term results of controlling the reaccumulation of malignant effusions using intracavitary bleomycin. Cancer 1986; 57:721-27
13 Kessinger A, Wigton RS. Intracavitary bleomycin and tetracycline in the management of malignant pleural effusions: a randomized study. J Surg Oncol 1987; 36:81-83
14 Siegel RD, Schiffman FJ. Systemic toxicity following intracavitary administration of bleomycin. Chest 1990; 98:507
15 Audu PBD, Sing RF, Mette SA, et al. Fatal diffuse alveolar injury following use of intrapleural bleomycin [letter]. Chest 1993; 103:1638
16 Kennedy L, Vaughan LM, Steed LL, et al. Sterilization of talc for pleurodesis: available techniques, efficacy, and cost analysis. Chest 1995; 107:1032-34
17 Bethune N. A new technic for the deliberate production of pleural adhesions as a preliminary to lobectomy. J Thorac Surg 1935; 4:251-61
18 Chambers JS. Palliative treatment of neoplastic pleural effusion with intercostal intubation and talc installation. West J Surg Obstet Gynecol 1958; 66:26-28
19 Weissberg D, Kaufman M. The use of talc for pleurodesis in the treatment of resistant empyema. Ann Thorac Surg 1986; 41:143-45
20 Daniel TM, Tribble CG, Rodgers BM. Thoracoscopy and talc poudrage for pneumothoraces and effusions. Ann Thorac Surg 1990; 50:186-89
21 Ohri SK, Oswal SK, Townsend ER, et al. Early and late outcome after diagnostic thoracoscopy and talc pleurodesis. Ann Thorac Surg 1992; 53:1038-41
22 Van de Brekel JA, Duurkens VAM, Vanderschueren RGJRA. Pneumothorax—results of thoracoscopy and pleurodesis with talc poudrage and thoracotomy. Chest 1993; 103:345-47
23 Hartman DL, Gaither JM, Kesler KA, et al. Comparison of insufflated talc under thoracoscopic guidance with standard tetracycline and bleomycin pleurodesis for control of malignant pleural effusions. J Thorac Surg 1993; 105:743-48
24 Milanez JRC, Vargas FS, Filomeno LTB, et al. Intrapleural talc for the prevention of recurrent pneumothorax. Chest 1994; 106:1162-65
25 Vargas FS, Milanez JRC, Filomeno LTB, et al. Intrapleural talc for the prevention of recurrence in benign or undiagnosed pleural effusions. Chest 1994; 106:1771-75
26 Rinaldo JE, Owens GR, Rogers RM. Adult respiratory distress syndrome following intrapleural instillation of talc. J Thorac Cardiovasc Surg 1983; 85:523-26
27 Bouchama A, Chastre J, Gaudichet A, et al. Acute pneumonitis with bilateral pleural effusion after talc pleurodesis. Chest 1984; 86:795-97
28 Belani CP, Einarson TR, Arikian SR, et al. Cost-effectiveness analysis of pleurodesis in the management of malignant pleural effusion. J Oncol Management 1995; Jan/Feb:24-34