Randomized Trials Describing Lung Inflammation after Pleurodesis with Talc of Varying Particle Size

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We report two trials describing whether talc pleurodesis with a mean particle size of less than 15 μm ("mixed" talc) produces more lung and systemic inflammation than tetracycline or "graded" talc (most particles < 10 μm were removed). First, 20 patients with malignant effusions received tetracycline or mixed talc. Changes in lung and systemic inflammation from lung clearance scans, oxygen saturations, and C-reactive protein from baseline to 48 hours after pleurodesis were recorded. Lung inflammation (change in isotope clearance, talc −9.26, SD 14.3 vs. tetracycline 4.10, SD 13.8 minutes; difference = −13.4; 95% confidence interval [CI], −26.6 to −0.2; p = 0.05) and systemic inflammation (change in C-reactive protein, talc 198 SD 79.2 vs. tetracycline 74 SD 79.4 μg/L; difference = 124; 95% CI, 50 to 199; p = 0.004) were greater after talc. Second, 48 patients received mixed or graded talc, and gas exchange was assessed from changes in the alveolar–arterial oxygen gradient. Mixed talc worsened gas exchange (oxygen gradient change, mixed 2.17 SD 1.74 kPa, 16.3 13.1 mm Hg vs. graded 0.72 SD 2.46 kPa 5.4 18.5 mm Hg, difference = 1.45; 95% CI, 0.2 to 2.7; p = 0.03) and induced more systemic inflammation than graded talc. We conclude that the routine use of graded talc for pleurodesis would reduce the morbidity of this procedure.

Keywords: acute respiratory distress syndrome; pleural effusion; pleurodesis; randomized trial; talc

There are approximately 300,000 pleural effusions caused by cancer in the United Kingdom and United States each year (1). Many of these are symptomatic and require pleurodesis for their control. Sterile talc is the most effective agent for pleurodesis (2–4), but there are concerns that it may not be safe. There are over 30 reported cases of acute respiratory distress syndrome after intrapleural talc administration, and 9 of these have been fatal (2, 5–13). In a recent international survey of 859 pulmonologists, over half reported cases of respiratory failure after talc pleurodesis (14). This toxicity is seen after both talc slurry and talc poudrage (8). It is hypothesized that this toxicity may relate to the use of talc preparations that include particles of small (< 15 μm) size because most reports of acute respiratory distress syndrome are from countries where preparations including small particle sizes are prevalent (2, 8, 10, 11). In contrast, large observational series from countries that use talc containing only large particle sizes describe few serious adverse events (3, 15).

There are no randomized trials assessing the potential toxicity of varying talc preparations and no studies describing whether the reported cases of acute respiratory distress syndrome are isolated idiosyncratic adverse reactions or the severe end of a spectrum of diffuse lung damage that could be detected from subtle indices of lung inflammation. This article reports two randomized trials addressing this question.

We hypothesized that inflammation in the lung contralateral to a pleurodesis might be detectable by ^{99m}technetium-labeled DTPA lung scanning because this test is capable of identifying subtle lung inflammation in other settings (16–19). This hypothesis led to the two randomized trials reported here. In the first, we assessed whether talc with a mean particle size of less than 15 μm ("mixed" particle size talc—the standard U.S. and U.K. preparation) produced DTPA scan–detectable lung inflammation and hypoxemia after pleurodesis compared with a non–talc-based control (tetracycline pleurodesis). In the light of the results of this first study, we then performed the second trial to compare the severity of arterial hypoxemia, fever, and systemic inflammation after pleurodesis with mixed (standard United Kingdom and United States) talc and talc that has had the majority of particles less than 10 μm size removed (mean particle size of > 25 μm—"graded" particle size talc—the standard European preparation). Despite its role in original hypothesis testing, DTPA scanning was not used in the second trial, as the results of the first had rendered this complex investigation unnecessary (20).

METHODS

Trial Designs and Setting

Both of these trials are prospective, parallel, randomized trials performed in a single center (the Oxford Pleural Disease Clinic, Oxford Centre for Respiratory Medicine, Oxford, UK). The population served by this unit is 500,000. Patients with proven or suspected malignant pleural effusions are referred to the Oxford unit directly from general practitioners (45%), from the regional oncology center (based on the same site) (35%), and from other local hospital consultants (20%).

Patients

The entry criteria for the two studies were the same. All patients eligible for the trial who presented over the 24-month recruitment period were offered entry into the trials. Patients were enrolled by N.A.M. and R.J.O.D. To be eligible for the trial, patients had to have a symptomatic pleural effusion proven to be due to pleural malignancy by cytology and/or histology. Exclusion criteria were as follows: expected survival of less than 6 weeks, bleeding diathesis sufficient to contraindicate chest tube insertion, extensive "trapped lung" after fluid drainage, previous pleurodesis on the side of the effusion, inability to give informed consent, or age of less than 18. The study was approved by the Central Oxford Research Ethics Committee, and all participants gave informed consent.

Pleurodesis Agents

The talc preparations were both commercially available preparations manufactured for pleurodesis. The mixed talc (Thornton and Ross, Huddersfield, UK) includes a range of particle sizes, with 50% being less than 10 μm in size. This preparation is typical of that usually used in the United States and the United Kingdom. The graded talc (Novatech, Grasse, France) is sorted during manufacture so that it contains less than 50% of particles smaller than 20 μm (*see* Figure E1 in the online supplement). This preparation is typical of that usually used in continental Europe. Both talc preparations are refined by the

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same manufacturer (Luzenac Micro Milling, Porte, Italy) from raw talc mined from European mines and therefore are chemically identical. After manufacture, both talc preparations are prepared in 4-g aliquots and sterilized by irradiation before use. The tetracycline used was manufactured by Grunenthal (Aachen, Germany).

Clinical Follow-up

Patients were followed for 3 months or until death. A chest radiograph was taken at 3 months. A successful pleurodesis was defined as no reaccumulation of pleural fluid sufficient to require drainage at 3 months after randomization.

Individual Trial Designs

Trial 1: mixed (including 50% < 15 μm) talc versus tetracycline. In this trial subjects were randomized to 4 g of mixed (including 50% < 15 μm) talc or tetracycline, 20 mg/kg in 50-ml normal saline (*see* the online supplement for details of the randomization procedure and pleurodesis protocol).

The primary outcome for this study was the change in the DTPA clearance from the lung contralateral to the side undergoing pleurodesis from baseline to 48 hours after pleurodesis. Secondary outcome variables were the changes in the following indices from baseline to 48 hours after pleurodesis: arterial oxygen saturation sitting quietly recumbent and breathing air, the plasma C-reactive protein (μg/L), pleural fluid interleukin (IL)-8 concentrations, and the presence of visible ground glass shadowing on high-resolution thoracic computed tomography (CT) scanning 48 hours after pleurodesis.

The high-resolution computed tomograms were performed on a General Electric light-speed multislice CT scanner (General Electric, Milwaukee, WI) using 1-mm sections every 10 mm from the apex of the lungs to the costophrenic recess. They were reported by F.V.G. blind of the subject's randomization status. Because there have been no previous studies of DTPA lung clearance after pleurodesis, the sample size for this study was based on the size of sample capable of identifying subtle lung inflammation (n = 10) in other studies (16, 17).

Trial 2: mixed (including 50% < 15 μm) talc versus graded (including 50% > 25 μm) talc. In this trial, subjects were randomized to 4 g of mixed (including 50% < 15 μm) or 4 g of graded (including 50% > 25 μm) talc in 50-ml normal saline (*see* online supplement for details of the randomization procedure and pleurodesis protocol). Patients were blinded to which talc preparation they received.

The primary outcome for this study was the change in the alveolar to arterial oxygen gradient (A–a gradient) breathing air, sitting at quiet rest, and semirecumbent from baseline to 48 hours after pleurodesis. Secondary outcome variables were the changes in the following indices from baseline to 48 hours after pleurodesis: arterial partial pressure of oxygen breathing air, sitting at quiet rest and semirecumbent, the presence of a fever of more than 37.5°C at 48 hours after pleurodesis, the plasma C-reactive protein (μg/L), pleural fluid IL-8 concentrations (*see* online supplement for details), and the clinical efficacy of pleurodesis assessed at 3 months after pleurodesis.

Power Calculation

The sample size for trial 2 was calculated from the estimated change in Pa_{O_2} in the mixed-talc group in Trial 1, inferred from the change in arterial oxygen saturation. Thus, it was assumed Pa_{O_2} would fall by 15 mm Hg in the mixed-talc group with no change in the graded-talc group (SD of change in Pa_{O_2} = 15 mm Hg). Using these assumptions, a trial of 50 patients was needed to exclude a difference of 15 mm Hg between the groups (90% power, α = 0.05) (Power and Precision Software; Biostat, National Institutes of Health).

Statistical Analysis

In both trials, the data analysis was performed with SPSS version 10 (SPSS Inc., Chicago, IL). Parametric data were analyzed using the independent *t* test, and unless otherwise stated, the data are presented as mean (SD). Chi-squared analysis and Fisher's exact test were used when comparing proportions.

RESULTS

Subjects

Figures 1 and 2 show the two trial profiles. Total recruitment was over 24 months. During the recruitment period, 91 eligible patients were identified, and 87 of these consented to enter the studies.

The characteristics of the subjects agreeing to take part are shown in Tables 1–3. These show the groups were well matched at baseline.

Thirty-one patients were recruited to Trial 1. Eleven were excluded, five because of extensively "trapped lung" on the baseline chest radiograph, three because they were unable to perform the baseline DTPA lung clearance, one because of a myocardial infarction, and two because of chest tube displacement. Twenty patients were randomized to talc or tetracycline and completed this trial (Figure 1).

In Trial 2, 56 patients were identified. Eight were excluded because they had extensively trapped lung, and 48 were randomized. Two patients in the mixed-talc group were excluded after randomization because of chest tube displacement before pleurodesis (Figure 2).

Outcomes

Trial 1: mixed (including 50% < 15 μm) talc versus tetracycline. **Primary end point.** DTPA lung clearance from the lung contralateral to the pleurodesis. One patient (in the tetracycline group) could not perform the DTPA clearance at 48 hours after pleurodesis and was excluded from the analysis.

The fall in the isotope clearance half time was greater in the mixed-talc group than in the tetracycline group (−9.26 [SD 14.3] vs. 4.10 [SD 13.8] minutes; difference = −13.4; 95% CI, −26.6

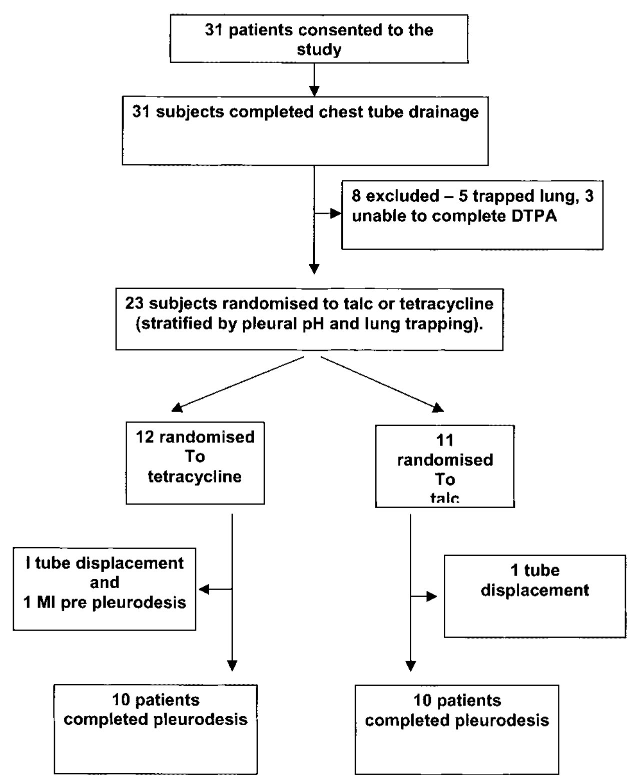

Figure 1. Flow diagram of the first trial (mixed talc vs. tetracycline).

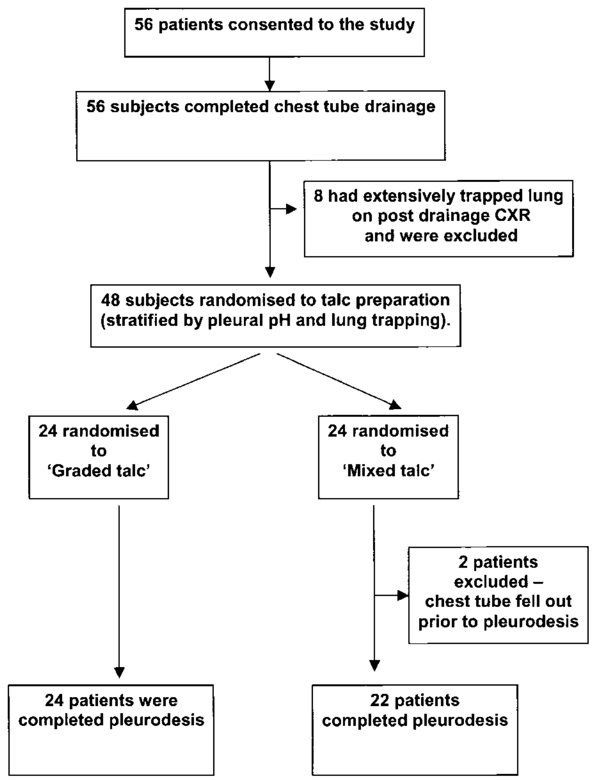

Figure 2. Flow diagram of the second trial (mixed talc vs. graded talc). CXR = chest radiograph.

to −0.2; $p = 0.05$, independent *t* test; Figure 3). A decline in the DTPA clearance half time is associated with increased lung inflammation in most disease states.

Secondary end points.

Arterial oxygen saturation. The arterial oxygen saturation fall was greater after pleurodesis with mixed talc than after pleurodesis with tetracycline (3.23% [1.6%] vs. 0.72% [1.5%]; difference = 2.51; 95% CI, 1.1 to 4.0; $p = 0.003$ independent *t* test; Figure 3). This shows that the increased lung inflammation identified by the DTPA analysis was associated with a fall in arterial oxygenation, indicating functionally significant impairment of gas exchange. This decline in gas exchange efficiency led to the selection of the alveolar to arterial oxygen gradient as the primary endpoint for the second trial.

Blood C-reactive protein. The C-reactive protein rise after mixed-talc pleurodesis was greater than after tetracycline pleurodesis (198 [79.2] vs. 74 [79.4] μg/L; difference = 124; 95% CI, 50 to 199; $p = 0.004$, independent *t* test, Figure 3). This shows that the systemic inflammatory response induced by mixed talc was greater than that induced by tetracycline pleurodesis.

Pleural fluid IL-8 levels. The pleural fluid IL-8 levels at 48 hours after pleurodesis were not different between the trial groups (mixed-talc pleurodesis, 18,584 [20,634] vs. tetracycline 6,314 [15,699] pg/ml; difference = 12,270; 95% CI, −4,955 to 29,495; $p = 0.18$).

High-resolution thoracic CT. No changes were seen on the high-resolution thoracic CT images of the contralateral lung 48 hours after pleurodesis in either trial group.

Trial 2: mixed (including 50% < 15 μm) talc versus graded (50% > 25 μm) talc.

Primary endpoint.

A–a oxygen gradient. Four patients (two in each trial group) declined repeated arterial blood gas measurements 48 hours after pleurodesis.

Mixed talc resulted in a greater increase in the A–a oxygen gradient than did graded talc (which did not produce any significant increase) (2.17 [SD 1.74] kPa; 16.3 [13.1] mm Hg; vs. 0.72 [SD 2.46] kPa; 5.4 [18.5] mm Hg; difference = 1.45; 95% CI, 0.2 to 2.7; $p = 0.03$, independent *t* test; Figure 4). This shows that the pleurodesis with mixed talc produced a deterioration in blood oxygenation that was not seen with chemically identical graded talc.

Secondary endpoints.

Arterial partial pressure of oxygen. The arterial partial pressure of oxygen fall was greater after pleurodesis with mixed talc than it was after graded talc (1.9 [1.84] kPa; 14.6 [13.8] mm Hg; vs. 0.4 [1.7] kPa, 3.75 [12.5] mmHg; difference = 1.5; 95% CI, 0.45 to 2.55; $p = 0.01$, independent *t* test, Figure 4).

Fever after pleurodesis. Nine of 22 (41%) patients receiving mixed talc had a fever of more than 37.5°C at 48 hours after their pleurodesis, whereas this only occurred in 1 of 24 (4%) patients receiving graded talc (difference = 37%; 95% CI, 15% to 59%; $p < 0.001$, chi-squared test; Figure 5).

C-reactive protein. The rise in plasma C-reactive protein was greater after mixed-talc pleurodesis than it was after graded-talc pleurodesis (161 [72.2] vs. 111 [69.3] μg/L tetracycline group; difference = 50; 95% CI, 8–92; $p = 0.04$, independent *t* test; Figure 4).

Pleural fluid IL-8. The change in pleural fluid IL-8 levels at 24 hours after pleurodesis showed no difference after the two talc preparations (mixed talc, 36,313 [27,424]; graded talc, 21,075 [22,237] pg/ml; difference = 15,238; 95% CI, 457 to 30,019; $p = 0.18$, independent *t* test).

Clinical outcome and the success of the pleurodesis. Three patients were lost to follow-up (two in the mixed-talc group and one in the graded-talc group). In the mixed talc group, 7 of 21 (33%) patients died by 3 months. The pleurodesis was successful in 11 of the 14 (79%) survivors. In the graded-talc group, 8 of 22 (36%) patients died by 3 months. The pleurodesis was successful in 12 of 14 (85%) of the survivors.

DISCUSSION

These trials have shown that pleurodesis using mixed talc (containing small talc particles) produces more lung and systemic inflammation and more hypoxemia than graded talc (sorted during manufacture to exclude the vast majority of particles of less than 10 μm), or tetracycline. The magnitude of this effect is substantial. The A–a oxygen gradient increased after mixed talc by 2.17 (SD 1.74) kPa and 16.3 (SD 13.1) mm Hg with 43% of subjects experiencing an increase of more than 2 kPa (15 mm Hg)—sufficient to render a subject with moderate hypoxemia (8 kPa,

TABLE 1. PATIENT CHARACTERISTICS—TRIAL 1: MIXED TALC VERSUS TETRACYCLINE

	Mixed Talc Pleurodesis (*n* = *10*)	Tetracycline Pleurodesis (*n* = *10*)
Age, yr, mean (SD)	57.6 (11.7)	61.4 (8.9)
Sex, n, male:female	3:7	2:8
Pleural fluid pH, mean (SD)	7.35 (0.1)	7.34 (0.15)
Type of malignancy, n		
Breast cancer	5	6
Lung cancer	1	1
Unknown primary cancer	1	1
Pleural mesothelioma	1	0
Bowel carcinoma	0	1
Other	2	1

TABLE 2. PATIENT CHARACTERISTICS—TRIAL 2: MIXED VERSUS GRADED TALC

	Mixed Talc (*n* = *24*)	Graded Talc (*n* = *24*)
Age, yr, mean (SD)	64.2 (11.8)	69.8 (14.1)
Sex, male:female, n	7:17	10:14
Pleural fluid pH, mean (SD)	7.35 (0.14)	7.34 (0.12)
Pleural fluid protein, g/L, mean (range)	38 (26–74)	40 (18–67)
Pleural fluid LDH, IU/L, mean (range)	282 (150–1,874)	226 (119–743)
Partially trapped, n	8	8
Total pleural drainage before pleurodesis, ml	3,161 (1,800)	2,407 (1,803)

Definition of abbreviation: LDH = lactate dehydrogenase.

60 mm Hg) at baseline severely hypoxemic with an arterial partial pressure of less than 6 kPa (45 mm Hg). In this study, 8 of 23 (35%) of patients receiving mixed talc developed a postpleurodesis Pa_{O_2} of less than 8 kPa (60 mm Hg) in contrast to only 4 of 23 (17%) of those receiving graded talc (*see* Figure E2 on the online supplement).

This observation is likely to be helpful in understanding the cases of life-threatening hypoxemia after pleurodesis reported from the United Kingdom and the United States (2, 5–13) but rarely reported from Europe (3, 15). In the United Kingdom and the United States, the talc used for pleurodesis is of the mixed type studied here, whereas in Europe, graded talc is usually used. In the United States and the United Kingdom, there are approximately 300,000 malignant effusions each year, and many of these patients receive pleurodesis with mixed talc. Thus, these results suggest that many patients may be experiencing clinically significant hypoxemia, which could be reduced by the use of graded talc with its smallest particles removed. Therefore, we would recommend that all patients undergoing pleurodesis have oximetry measurements taken during and for 48 hours after pleurodesis.

The hypoxemia after mixed-talc pleurodesis is a reasonably consistent feature in the patients studied. This shows that the prevalence of hypoxemia is much higher than is suggested by the few reports of severe and life-threatening acute respiratory distress syndrome and implies that these severe cases are simply the extreme end of a predictable adverse reaction, rather than isolated idiosyncratic events.

It is hypothesized that the mechanism for talc pleurodesis-induced hypoxemia may be the escape of very small talc particles from the pleural space through the parietal pleural pores (21). There is evidence to substantiate this hypothesis from animal models and an isolated human case where systemic talc dissemination after pleurodesis with small caliber talc has been demonstrated (22–24). These studies provide some indirect evidence to support this "escaped talc" mechanism. Our results suggest that postpleurodesis hypoxemia is due to generalized lung inflammation as well as increased systemic inflammation because we have seen both clinical and laboratory evidence of a greater systemic inflammatory responses with mixed talc but no difference in the intensity of the pleural inflammation. Nine of 22 (41%) patients receiving mixed talc developed fever after their pleurodesis, whereas fever was almost absent (1 of 24, 4%) in those receiving graded talc. The concentrations of C-reactive protein were higher after mixed talc when measured from the systemic compartment (blood), whereas the pleural IL-8 concentrations were similar after each of the three pleurodesis agents.

In trial 1, the hypothesis being tested was that subtle talc-induced lung inflammation would be detectable from the lung

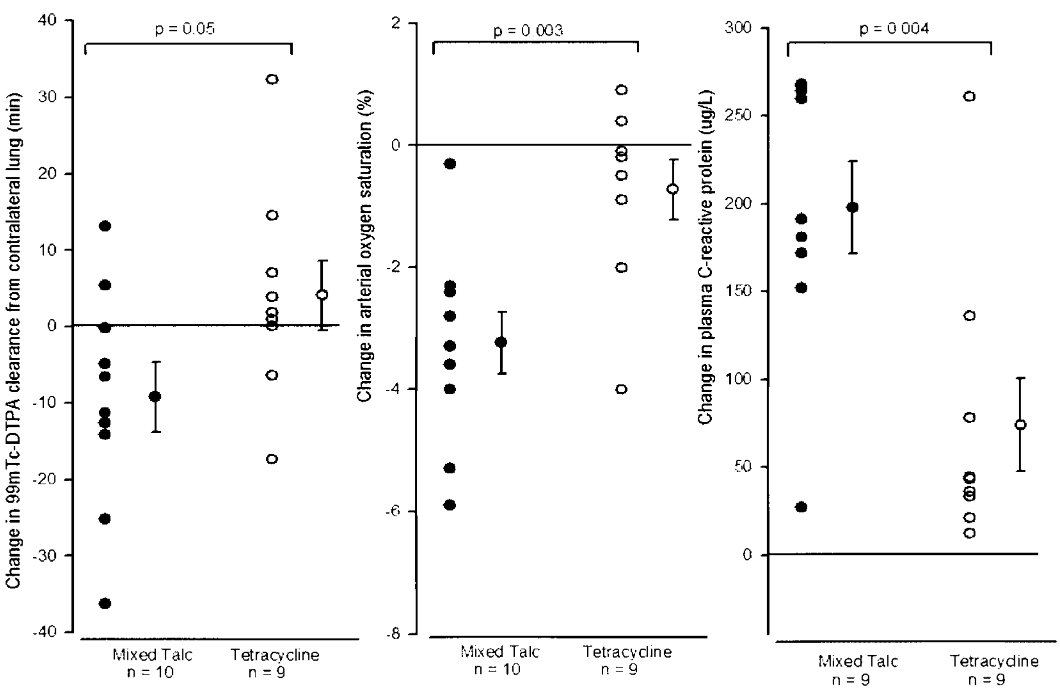

Figure 3. The primary and secondary outcomes of the first trial (mixed talc vs. tetracycline). The primary endpoint was the clearance of DTPA from the lung contralateral to the pleurodesis. Sa_{O_2} and C-reactive protein were secondary endpoints. Results after mixed talc are shown as *filled circles* and tetracycline as *empty circles*.

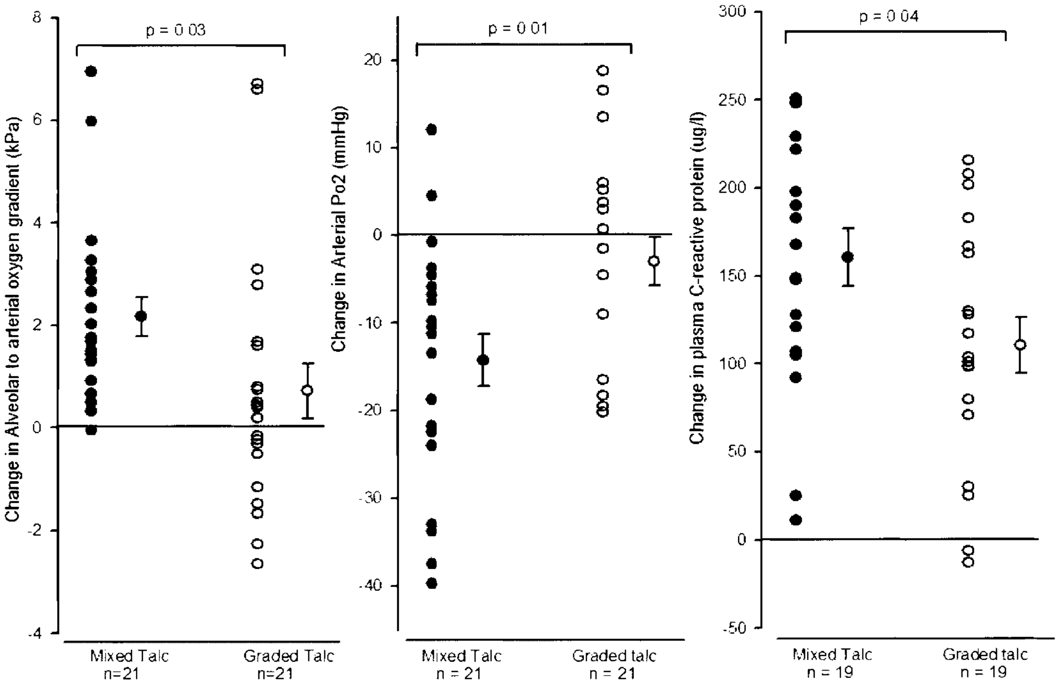

Figure 4. The primary and secondary outcomes of the second trial (mixed talc vs. graded talc). The primary endpoint was the change in alveolar to arterial oxygen gradient. Pa_{O_2} and C-reactive protein were secondary endpoints. Results after mixed talc are shown as *filled circles* and graded talc as *empty circles*.

contralateral to a talc pleurodesis. Therefore, we chose to use the half time of the epithelial lung clearance of aerosolized DTPA as the primary outcome for this trial. DTPA clearance predominantly assesses the permeability of the epithelium of the terminal respiratory units to solutes and is a sensitive index of lung inflammation in diffuse inflammatory lung disease (16–18), including acute minor pneumonitis after radiotherapy to the other lung (17). Measurements of DTPA clearance are influenced by smoking and position. Both of these variables were controlled in this study, with similar numbers of smokers and ex-smokers in each group and all of the scans being undertaken in the supine position.

By studying DTPA clearance from the lung contralateral to the pleurodesis, we aimed to avoid the confounding effects of changes in chest tube placement, local pleurodesis inflammation, lung atelectasis, and changes in the volume of the pleural effusion on the side where the pleurodesis was performed. This contralateral lung clearance fell by 20% in the standard mixed-talc group, and no fall was seen in the tetracycline group. The magnitude of this fall is similar to that seen with postradiotherapy pneumonitis (17) and between patients with clinically progressive lung fibrosis and those with stable disease (18). It is therefore evidence of clinically significant lung inflammation.

Both talc preparations were traced back to the same mining region in Europe, and thus, the constituents of the talc preparations should have been identical apart from their size difference. This makes it unlikely that the differences seen were due to impurities in one preparation that were not present in the other.

The frequency of the control of recurrent pleural fluid was similar with the two talc preparations (79% vs. 85%) used in the second trial. This study was not adequately powered to define efficacy accurately, but these results suggest that there is not a large difference in treatment efficacy between the two preparations.

In conclusion, we have shown that pleurodesis with mixed talc causes a greater systemic inflammatory response than graded talc and tetracycline. This is associated with greater hypoxemia and a fall in the clearance half time of inhaled DTPA from the contralateral lung, demonstrating significant lung inflammation. These results suggest that the severe hypoxemia and adult respiratory distress syndrome described after talc pleurodesis are probably the severe ends of a widely detectable spectrum of toxicity and are likely to be minimized by using graded talc (with its smallest particles removed). We conclude that talc from which most particles of less than 15 μm have been removed is probably a safer agent for pleurodesis than standard mixed talc.

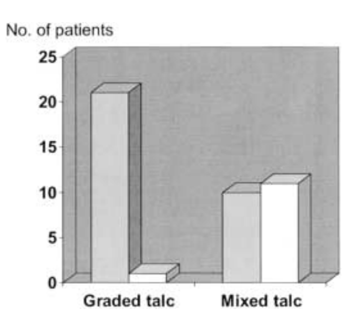

Figure 5. The proportion of individuals who remained pyrexial (> 37.5, *open bars*) and apyrexial (*gray bars*) 48 hours after pleurodesis in the second trial (mixed talc vs. graded talc; $p < 0.001$, χ^2).

TABLE 3. TUMOR TYPES IN TRIAL 2: MIXED VERSUS GRADED TALC

	Mixed Talc (*n* = 24)	Graded Talc (*n* = 24)
Primary tumor type, n		–
Breast	8	6
Lung	7	6
Pleura (mesothelioma)	3	2
Ovary	2	3
Sarcoma		1
Bladder	1	–
Renal	–	1
Non-Hodgkins lymphoma	–	1
Bowel (metastatic carcinoid)	–	1
Unknown (adenocarcinoma)	2	3
Unknown (squamous cell)	1	–

***Conflict of Interest Statement*:** N.A.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; Y.C.G.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; F.V.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; E.L.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; G.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; R.J.O.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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