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Small Particle-Size Talc Is Associated with Poor Outcome and Increased Inflammation in Thoracoscopic Pleurodesis

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Key Words
Pleural effusion · Malignant effusion · Pleurodesis · Thoracoscopy · Talc · Inflammation

Abstract
Rationale: Talc is very effective for pleurodesis, but there is concern about complications, especially acute respiratory distress syndrome. ***Objectives:*** It was the aim of this study to investigate if talc with a high concentration of small particles induces greater production of cytokines, and if pleural tumor burden has any influence on the local production and spillover of cytokines to the systemic circulation and eventual complications. ***Methods:*** We investigated 227 consecutive patients with malignant effusion submitted to talc pleurodesis. One hundred and three patients received 'small-particle talc' (ST; containing about 50% particles <10 μm) and 124 received 'large-particle talc' (with <20% particles <10 μm). Serial samples of both pleural fluid and blood were taken before and 3, 24, 48 and 72 h after thoracoscopy. Also, mesothelial cells were stimulated with both types of talc in vitro. ***Measurements and Results:*** Interleukin-8, tumor necrosis factor-α, vascular endothelial growth factor, basic fibroblast growth factor and thrombin-antithrombin complex were measured in all samples. Early death (<7 days after talc) occurred in 8 of 103 patients in the ST and in 1 of 124 in the 'large-particle talc' group (p = 0.007). Patients who received ST had significantly higher proinflammatory cytokines in pleural fluid and serum after talc application, and also in supernatants of the in vitro study. Pleural tumor burden correlated positively with proinflammatory cytokines in serum, suggesting that advanced tumor states induce stronger systemic reactions after talc application. ***Conclusions:*** ST provokes a strong inflammatory reaction in both pleural space and serum, which is associated with a higher rate of early deaths observed in patients receiving it.

Introduction

Talc is widely accepted as the agent of choice for pleurodesis in malignant pleural effusions (MPE), but there is concern about possible complications, especially acute respiratory distress, systemic inflammation and extrapleural dissemination of particles [1–5]. It is now established that talc containing small particles is associated with more complications [6–10], but there are still some open questions.

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Table 1. Baseline characteristics of patients in each group (no significant differences)

	Global series (n = 227)	ST (n = 103)	LT (n = 124)
Mean age ± SEM, years	60.36 ± 0.8	60.6 ± 1.2	60.1 ± 1.1
Males/females	112/115	55/48	59/65
Karnofsky			
Normal	162 (71.4)	81 (78.6)	81 (65.3)
Self-care	63 (27.7)	20 (19.4)	43 (34.7)
Disabled	2 (0.9)	2 (2)	0
Origin of tumors			
Breast	57 (25.1)	26 (25)	31 (25)
Lung	56 (24.7)	21 (20.5)	35 (28)
Mesothelioma	38 (16.7)	16 (16)	22 (17)
Lymphoma	15 (6.6)	9 (8.7)	6 (4.8)
Ovary	11 (4.8)	4 (3.9)	7 (5.6)
Colon	12 (5.3)	6 (5.8)	6 (4.8)
Kidney	12 (5.3)	6 (6.8)	6 (4.8)
Other	26 (11.5)	15 (13.3)	11 (10)

Figures in parentheses are percentages.

(1) According to one report, it appears that not all the cases with pulmonary complications associated with talc are due to extrapleural dissemination of the particles: in 1 patient who died 58 h after thoracoscopic talc pleurodesis, no extrapleural particles were found at autopsy, but acute inflammation was present in both lungs in spite of unilateral pleurodesis, and the authors suggested that pleural inflammation may trigger pulmonary inflammation through paracrine and circulating factors without actual extrapleural talc dissemination [11]. If a transfer of proinflammatory mediators occurs between the pleural space and either the lung or the systemic circulation after intrapleural talc application, the question arises as to whether a pleural thickening caused by tumor ('tumor burden') or fibrosis would block that transfer to some degree. Would tumor burden in the pleural space have any influence on the local production of cytokines and the eventual spillover to the lung following talc pleurodesis?

(2) Does talc with a high concentration of small particles induce a greater production of cytokines in the pleural space and in serum?

(3) Is there any transfer of proinflammatory mediators from the pleural space into the systemic circulation?

(4) Are high and persistent levels of proinflammatory cytokines in serum associated with more complications, as suggested by some experimental animal studies [12, 13]?

Aiming to answer these questions, we have studied two sequential series of patients with MPE who were submitted to thoracoscopic talc pleurodesis using two different types of talc in our institution. We hypothesized that the severe adverse effects of talc and the different behavior of mesothelial cells would be related to the size of talc particles and to changes in the release of proinflammatory cytokines, growth factors and coagulation mediators in peripheral venous blood after intrapleural application of talc. We also aimed to study the role of these two types of talc in an in vitro model of human mesothelial cells.

Materials and Methods

Study Population

From October 1992 to April 2007, 331 patients with MPE were submitted to thoracoscopic talc poudrage at our institution, always following the same protocol [14]: thoracoscopy was performed in the respiratory endoscopy suite by the same physicians in all cases, using local anesthesia (mepivacaine) plus intravenous analgesia (pethidine). Tumor burden in the pleural space was evaluated in every case following a rating method previously published by our group [15]. After complete removal of the fluid and pleural biopsies taken, 5 g of asbestos-free, sterile talc was used in every case. From the 331 patients submitted to talc pleurodesis, we selected only the ones who had a positive thoracoscopic biopsy with identification of the type of tumor in the pleura (n = 227). Among them, 103 received talc purchased from the Instituto Español™ (Seville, Spain) that will be referred to as 'small-particle talc' (ST) in the present article. When a new talc was available at our institution, another 124 patients were treated with Steritalc® (Novatech, La Ciotat, France) that will be referred to as 'large-particle talc' (LT) (table 1). All talc samples had undetectable levels of endotoxin as determined with the Limulus Amebocyte Lysate assay (Sigma GmbH, Germany).

Talc Particle Studies

Scanning electron microscopy, distribution of particle size and mineralogical and chemical composition (crystal phases) studies were performed at the Instituto de Ciencia de Materiales (University of Seville, Spain) (online supplementary material, www.karger.com/doi/10.1159/000342042).

Clinical Data Collection

Besides demographic data, all complications were systematically recorded in every patient. The outcome of pleurodesis, according to criteria described in the European Respiratory Society/American Thoracic Society consensus statement [16], was also recorded, and all patients were followed until death or for a period ≥4 years after talc poudrage. Pleurodesis was considered as failed if there was a relapse of the effusion at any time during the whole follow-up period.

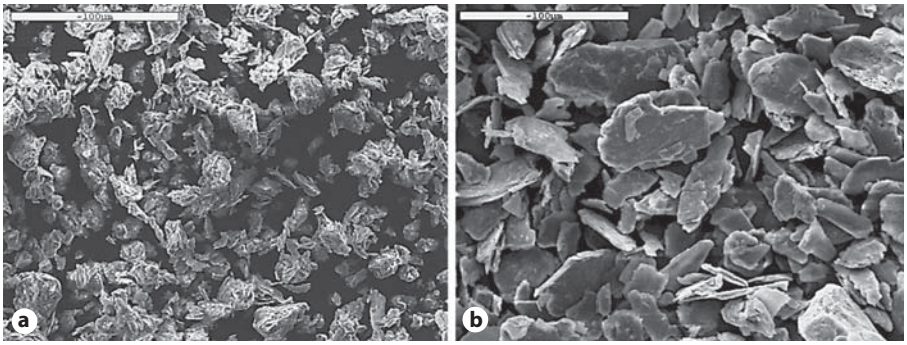

Fig. 1. Scanning electron microscopy photographs of ST (**a**; mean 18.5 ± 14.2 μm) and LT (**b**; 25.3 ± 16.5 μm).

Biological Studies ex vivo

Serial blood and pleural fluid samples were obtained from every patient and then centrifuged and the supernatants frozen just before thoracoscopy (baseline) and at 3, 24, 48 and 72 h following talc pleurodesis. All patients were informed that those samples may be used in the future for research and publication, and all agreed to participate and gave written informed consent. This study was approved by the local ethics committee of our institution. Interleukin (IL)-8, tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) were measured in all samples by ELISA (Quantikine, R&D Systems, Minneapolis, Minn., USA), and the thrombin-antithrombin complex (TAT) was determined with the Enzygnost TAT kit (Dade Behring, Germany).

Cell Culture Study: Coincubation of Talc with Mesothelial Cells in vitro

The mesothelial cell line Met-5A was incubated with 4 $\mu g/cm^2$ (according to previous reports) [17] of the same two types of talc used in patients – as described above – during 24 h, and then IL-8 levels were determined at different time points in supernatants afterwards (online suppl. material).

Statistical Analysis

Statistical analysis was performed using SPSS version 15 software (SPSS Inc., Chicago, Ill., USA). Results were considered significant when $p < 0.05$. Non-parametric tests were used when data did not show a normal distribution. In order to have clear information on the individual response to talc, we calculated the increment (fold) – defined as the ratio between the levels obtained after talc and at baseline – for each marker.

Results

Talc Analyses

According to X-ray diffraction (data not shown), our samples were pure talc [$Mg_3Si_4O_{10}(OH)_2$], free of asbestos (absence of fibers) (fig. 1) and of other significant impurities (online suppl. table E1). Average (mean) and median diameters of particles, as well as the 10 and 90% percentile ranks obtained from the volumetric size distribution curves are described in table 2.

Table 2. Morphometric analysis of ST and LT

Type of talc	Diameter of particles		10–90%
	mean ± SD	median	
ST, μm	15.9 ± 13.9	11.5	2.7–35.9
LT, μm	25.3 ± 16.5	22.8	5.6–48.1

Clinical Results

Acute pain or transient dyspnea in the first 15 min after talc application was observed in 16.5% of patients in the ST group and in 18.5% in the LT group (no significant differences).

We observed thrombotic events in 4.9% of the patients who received ST and in 1.6% of those receiving LT. Despite the tendency to a higher rate in the ST group, there were no statistically significant differences.

Pleurodesis was completely successful in 73.7% of the patients in the ST group and in 70.2% in the LT group, with no significant differences (table 3).

Survival and Early Death after Talc Pleurodesis

The median survival was shorter in the ST group (although it did not reach statistical significance) (table 3). Early death (within 7 days after talc application) occurred in 8 of 103 patients in the ST and only in 1 of 124 in the LT group (7.8 vs. 0.8%, respectively; p = 0.007) (table 4; online suppl. fig. E-5A and E-5B). Causes of early death (<7 days) in the ST group (8 patients) were: contralateral pneumonia (n = 1), hypotension and renal failure (n = 2), hyponatremia and coma (n = 1), deep venous thrombosis

Table 3. Outcome of pleurodesis

Global results	Total	ST (n = 76)	LT (n = 104)	p value
Complete success	129 (71.7)	56 (73.7)	73 (70.2)	NS
Partial success	32 (17.8)	14 (18.4)	18 (17.3)	NS
Failure	19 (10.5)	6 (7.9)	13 (12.5)	NS
Mean tumor burden in parietal pleura ± SEM (range 0–3)		2.2 ± 0.07	2.2 ± 0.06	NS
Mean tumor burden in visceral pleura ± SEM (range 0–3)		1.6 ± 0.08	1.6 ± 0.07	NS
Mean survival ± SEM, months	13.6 ± 1.6	16.3 ± 3.1	11.3 ± 1.3	NS
Median survival, months	5.2 [0.03–153.4]	4.4 [0.03–153.4]	7 [0.13–70.6]	NS

Figures in parentheses are percentages; figures in brackets are ranges. The χ^2 test was used for statistical analysis. Those patients who died before 30 days following talc application were considered as 'non-evaluable' regarding the outcome of pleurodesis. Therefore, 180 patients were finally evaluable for results of pleurodesis. NS = Not significant.

Table 4. Patients who died before 7, 15 or 30 days after talc pleurodesis

	Death <7 days	Death <15 days	Death <30 days
ST	8 (7.8)	12 (11.7)	27 (26.2)
LT	1 (0.8)	7 (5.6)	20 (16.1)
p value	0.007	0.1	0.062

Figures in parentheses are percentages. The χ^2 test was used for statistical analysis.

and pulmonary embolism (n = 2), acute respiratory failure (n = 1), and oversedation (n = 1). The cause of early death in the LT group was related to problems caused by the original tumor (carcinoma of the pancreas, with intractable vomiting and rapid deterioration). The only patient who developed acute respiratory distress had a 25.8-fold increase in IL-8 in serum 24 h after talc pleurodesis and a 17.8-fold in TAT levels in serum at that same time point. Most of the deaths registered between days 8 and 15 were not related with the type of talc used, but with other clinical conditions/complications: prolonged air leak (4 cases), cardiogenic pulmonary edema in 4 cases (associated with ischemic heart disease), infection associated with post-chemotherapy neutropenia (1 case), and unexplained coma (with negative CT for brain metastases) in 1 case.

Survival was negatively correlated with tumor burden both in the ST (r = –0.313, p = 0.001) and in the LT group (r = –0.241, p = 0.007).

Relationship between Biological Markers and Clinical Data

Baseline levels of IL-8 and VEGF in serum were significantly higher in patients who died in the first 7 days (fig. 2). Moreover, we found a close relationship between IL-8 baseline values in serum and levels of TAT (r = 0.757, $p < 0.001$).

We found a clear relation between increase in IL-8 in pleural fluid and the success of talc pleurodesis. As shown in figure 3, the group of patients with complete success had the highest increment of IL-8. IL-8 mRNA in pleural fluid was also higher in successful cases at 24 h after pleurodesis. The increments of the other markers studied (TNF-α, VEGF, bFGF and TAT) were not significantly related to the outcome of pleurodesis.

Tumor Burden in the Pleural Cavity

There were significant differences in tumor burden in the pleural cavity when comparing complete success cases with failed ones (4.9 ± 0.13 vs. 5.7 ± 0.46; p = 0.02) (online suppl. fig. E1). Tumor burden correlated positively with baseline levels of IL-8 in the pleura (r = 0.415, $p < 0.001$) (online suppl. fig. E2), but it was inversely related to increments of IL-8 at 24 and 48 h (p = 0.019 and 0.203, respectively) and to IL-8 mRNA in pleural fluid, thus suggesting that cases with both high tumor burden and baseline levels of IL-8 did not have much capacity to increase IL-8 production after intrapleural application of talc. This negative correlation between tumor burden and increments of proinflammatory cytokines in the pleural space was observed both in the ST and LT groups.

When levels of proinflammatory cytokines (IL-8 and TNF-α) were considered in serum, we found a positive

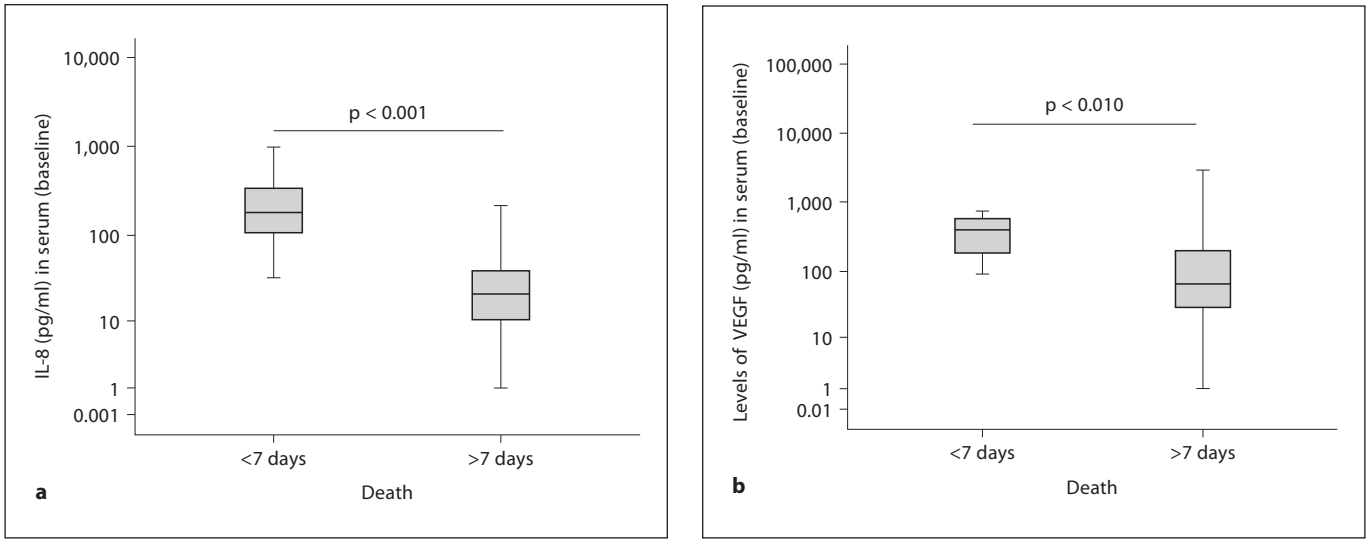

Fig. 2. a Comparison of baseline levels of IL-8 (pg/ml) in serum of patients surviving <7 and >7 days. **b** Comparison of basal levels of VEGF (pg/ml) in serum of patients surviving <7 and >7 days.

correlation with tumor burden in the parietal pleura at several time points. Regarding visceral pleura, correlation was also positive with serum levels of IL-8 and increments of TNF-α at 24 h (lower than in parietal pleura). Those findings suggest that advanced tumor states would favor stronger systemic reactions after intrapleural application of talc. In support of this, we found a strong positive correlation between tumor burden in the parietal pleura and IL-8 mRNA expression in serum 72 h after talc pleurodesis (p = 0.012). Our results suggest that – if there is any transfer between the pleural space and systemic circulation – the parietal pleura would play a predominant role.

Comparison of Biological Markers in Pleural Fluid and Serum in Patients Receiving the Two Types of Talc

When we compared the production of IL-8, TNF-α, VEGF and bFGF in pleural fluid and serum from patients submitted to pleurodesis with ST and LT, we found significant differences between them (table 5). In most cases, ST samples showed higher absolute levels and increments of cytokines when compared with samples from patients receiving LT. Although the TNF-α levels in the serum were higher in the LT group at baseline, the increments at 3 and 24 h following intrapleural talc application were markedly greater in the ST group, and they were also directly related to tumor burden in the parietal pleura (p = 0.005). Increments of TNF-α in serum correlated closely with increments of that marker in pleural fluid at 3 and 24 h after intrapleural talc application (p < 0.001 for both time points) (online suppl. fig. E3). Correlation between increment of IL-8 in serum and pleural fluid was also found at 24 h, although with lower significance (p = 0.04).

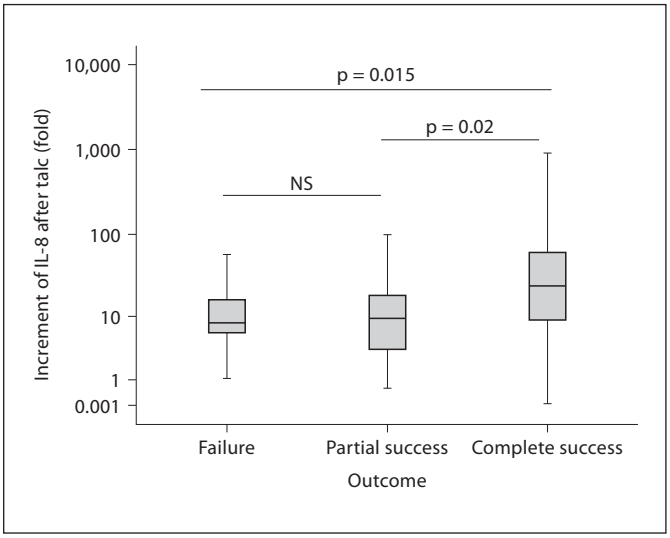

Fig. 3. Increment of IL-8 in pleural fluid at 3 h following talc application and outcome of pleurodesis. Cases with complete success had significantly increased IL-8 in pleural fluid, as compared to those with complete or partial failure. NS = Not significant.

Table 5. Differences in proinflammatory cytokines in both pleural fluid and serum samples from patients receiving two types of talc (delta values were calculated by dividing actual values of cytokines at different time points by those values obtained at baseline)

a Differences regarding IL-8 in pleural fluid and serum

Cytokines, pg/ml	ST		LT		p
	mean	SEM	mean	SEM	
Pleural IL-8					
Baseline	1,291	219	1,083	195	0.478
3 h	*13,835*	*3,405*	*5,052*	*705*	*0.009*
24 h	*27,323*	*6,541*	*6,251*	*804*	*0.000*
48 h	*23,467*	*6,498*	*6,846*	*879*	*0.005*
72 h	26,151	17,377	5,498	729	0.066
Fold IL-8 in pleural fluid					
3 h vs. baseline	106	41.6	36	7.4	0.088
24 h vs. baseline	*163*	*53*	*48*	*9.9*	*0.016*
48 h vs. baseline	162	66.6	62	18	0.107
72 h vs. baseline	*41*	*14.5*	*13*	*3.1*	*0.010*
IL-8 in serum					
Baseline	*184*	*61.8*	*56.9*	*22.2*	*0.040*
3 h	*92*	*24*	*25*	*3.6*	*0.014*
24 h	*152*	*49*	*46*	*10*	*0.037*
48 h	241	186	53	18	0.277
72 h	39	9.9	108	70	0.474
Fold IL-8 in serum					
3 h vs. baseline	1.99	0.6	1.5	0.4	0.483
24 h vs. baseline	2.5	0.7	2.7	0.5	0.774
48 h vs. baseline	9.5	7.5	2.2	0.6	0.278
72 h vs. baseline	1.4	0.4	6.3	2.5	0.182

b Differences regarding TNF-α in pleural fluid and serum

Cytokines, pg/ml	ST		LT		p
	mean	SEM	mean	SEM	
Pleural TNF-α in pleural fluid					
Baseline	9.9	2.7	8.4	1.3	0.607
3 h	*105*	*20.7*	*42*	*8.5*	*0.003*
24 h	*98*	*25.1*	*47*	*6.7*	*0.027*
48 h	75	23.3	157	118	0.544
72 h	42	11	258	211	0.499
Fold TNF-α in pleural fluid					
3 h vs. baseline	*59*	*16.0*	*13*	*2.5*	*0.002*
24 h vs. baseline	*41*	*12.2*	*15*	*3.9*	*0.024*
48 h vs. baseline	42	20.8	129	118	0.524
72 h vs. baseline	4.6	1.1	232	212	0.478
TNF-α in serum					
Baseline	*2.6*	*0.5*	*5.4*	*1.1*	*0.033*
3 h	2.6	0.4	4.2	0.8	0.084
24 h	*3*	*0.5*	*6.3*	*1.1*	*0.007*
48 h	3.8	0.5	10	3.6	0.079
72 h	5	1.4	6.7	2.4	0.617
Fold TNF-α in serum					
3 h vs. baseline	*99*	*20.7*	*34*	*8.5*	*0.002*
24 h vs. baseline	*91*	*23.9*	*38*	*6.3*	*0.015*
48 h vs. baseline	2.2	0.4	4.6	2.5	0.349
72 h vs. baseline	3.4	1.4	5.1	2.5	0.641

Significant differences are given in italics.

Although we found significantly higher levels of VEGF in pleural fluid samples from patients receiving ST, there were no significant differences in the increments versus baseline values, nor significant differences in serum values. Levels of bFGF did not show any significant differences between groups in pleural fluid, but they were significantly higher in the serum for the ST compared with the LT group at 3 and 24 h following intrapleural application of talc (17 and 24 pg/ml in ST vs. 4.3 and 7.2 pg/ml in LT; $p = 0.01$ and 0.038, respectively). As with other cytokines, these high levels in serum might contribute to the higher rate of complications observed in the ST group in our study.

TAT levels were significantly higher in serum for the ST versus the LT group at 24, 48 and 72 h (606, 661 and 317 μg/ml in the ST group vs. 224, 194 and 55 μg/ml in the LT group; $p < 0.001$, $p < 0.001$ and $p = 0.019$, respectively) (online suppl. fig. E4), which might be related to the higher rate of thrombotic events observed in the ST group.

Response of Mesothelial Cell Lines to Different Types of Talc

Once we analyzed the in vivo response of two different types of talc, we further studied the inflammatory response in an in vitro model of human mesothelial cell culture treated with the same types of talc.

We found that both talc types (ST and LT) stimulated the mesothelial cell line by releasing higher levels of IL-8 as compared to the controls. When we compared the response to both types of talc, we observed that the ST provoked higher inflammatory response for each time point compared to LT (fig. 4), and these results were in agreement with those found in the in vivo study.

Discussion

Talc is certainly inexpensive and highly effective as a sclerosing agent. However, its intrapleural administration can induce acute respiratory distress syndrome [18].

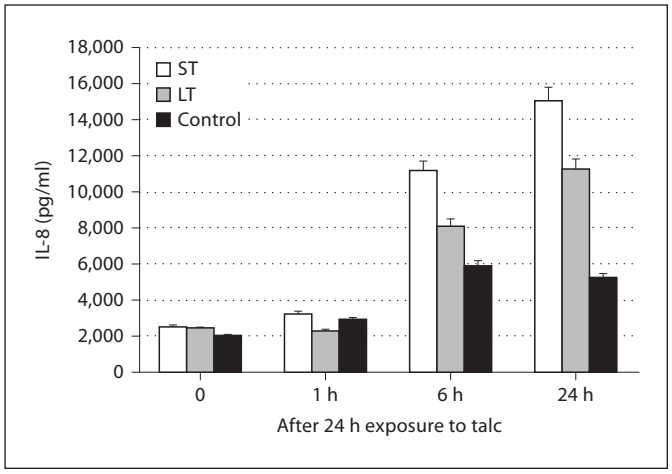

Fig. 4. Levels of IL-8 produced by mesothelial cells at different time points after 24 h exposure to 4 μg/cm^2 of ST and LT. Cells were incubated with talc for 24 h, and then IL-8 levels were determined at different time points in supernatants afterwards.

The systemic spillover of proinflammatory cytokines from the pleural space has been reported as a possible cause of the acute respiratory distress syndrome [11], in addition to the possible extrapleural dissemination of talc particles. Werebe and coworkers [8] found talc crystals in distant organs from rats submitted to talc pleurodesis, but Fraticelli et al. [9] did not find extrapleural dissemination when using talc of larger particle size. Experimentally, Ferrer et al. [6] demonstrated in rabbits that the intrapleural injection of talc with small particles (<10 μm) elicits greater pulmonary and systemic talc particle deposition compared to LT. Maskell and coworkers [7] found acute inflammation of the lung parenchyma (including the contralateral side to the side of pleurodesis) after randomized administration of talc of varying size in humans and concluded that the routine use of 'graded' talc (in which most particles <10 μm were removed) would reduce the morbidity of this procedure. Moreover, Genofre and coworkers [12] intrapleurally injected talc containing small or mixed particles (4.2 vs. 25.4 μm average size) in rabbits and found talc dissemination in both groups, although there was greater systemic inflammation in the small-particle group of animals. However, unspecific systemic inflammation after thoracoscopy can occur even without application of talc [19], and it could be argued that thoracoscopy by itself might have some influence on the proinflammation markers in our study. However, the same procedure was applied to every patient in both ST and LT, and therefore, we believe that the differences observed in our study are mostly related to talc characteristics themselves.

In our study, we analyzed clinical and biological differences after thoracoscopic application of both types of talc with a high concentration of large or small particles in humans and, in agreement with previous studies, we found important differences in clinical and biological parameters. The two talcs were adequate and similar in chemical composition, but they were significantly different in physical characteristics and in biological response, possibly associated with the size of the particles. Although the size of our ST was larger than the one used by Genofre and coworkers [12] in their animal experiments, it is important to emphasize that our ST had 50% of particles <11.5 μm, as compared to the 22.8 μm in the LT group (median values in table 2). Thus, ST about doubles the amount of particles <10 μm when compared with the LT group in our study, and this would account for significant differences in outcome and inflammation markers. Thus, those particles with smaller size could be responsible for the side effects/complications described in some of our patients.

One desirable feature for a pleurodesis agent is the induction of an inflammatory response in the pleural space. This acute response is mediated by proinflammatory cytokines like IL-8 [20, 21], and the relation between success of pleurodesis and inflammatory response has been analyzed in our study (fig. 3). We found a clear positive correlation between the increase in pleural IL-8 (which means more inflammatory response to talc) and the outcome of pleurodesis. On the other hand, tumor burden was directly correlated with baseline IL-8 levels in the pleural space, thus suggesting that inflammatory baseline states in the pleural space are associated with a heavier tumor burden and a poorer outcome of pleurodesis.

To our knowledge, this is the first study investigating the relationship of tumor burden in the pleural space with production of cytokines in pleural fluid and serum, and our results support the concept that patients with more advanced tumor disease do have a poorer outcome of pleurodesis and short survival and have less capacity to induce a strong proinflammatory response in the pleural space after talc application. On the other hand, there was a positive correlation between tumor burden (especially in the parietal pleura) and levels of proinflammatory cytokines (IL-8 and TNF-α) in serum, suggesting that some leakage of cytokines might occur from the parietal pleura (rather than from the visceral one) into the systemic circulation. Those findings also suggest that advanced tumor states would favor stronger systemic reactions after intrapleural application of talc.

Is there any transfer of proinflammatory mediators from the pleural space into the systemic circulation? There was a striking correlation in the increments of TNF-α in serum and pleural fluid at 3 and 24 h following intrapleural talc application, and this finding suggests that there was a transfer of that cytokine from the pleural space into the systemic circulation, and this phenomenon appears to be independent of the type of talc used in our study. IL-8 correlation was also significant, although to a lesser extent.

As expected, ST provoked a stronger biological response than LT, which was supported by our findings in vitro. Moreover, we found that ST produces a higher increment of VEGF and TAT in serum samples than LT. VEGF is involved in angiogenesis and increases vascular permeability, and TAT indicates activation of the coagulation cascade. Our finding of a close correlation between IL-8 baseline values in serum and subsequent levels of TAT suggests that patients with high levels of this marker at baseline were more prone to develop thrombotic events, especially in the ST group.

The ST group had a higher early death rate than the LT group (7.8 vs. 0.8% in the first 7 days, respectively; p = 0.007). If we assume that talc-associated complications occur within the first few days, the clear differences observed between groups is striking in our study (table 4). Rather than the characteristics of the population included (table 1), our study emphasizes that short survival was related to higher levels of cytokines (especially IL-8) in serum of patients receiving ST. Our group has previously demonstrated that IL-8 is involved in the activation of coagulation after talc pleurodesis, and it might also be implicated in the early death of patients with MPE [22]. On the other hand, the levels of VEGF and TAT found in the serum samples from patients of the ST group would suggest a spillover of the mediators from the pleural cavity to the systemic circulation after intrapleural talc application.

Are high and persistent levels of proinflammatory cytokines in serum associated with more complications? We believe that the answer is positive, but the question remains open as to whether the systemic use of non-steroid anti-inflammatory drugs would palliate this problem (probably with some cost on the side of the effectiveness of pleurodesis).

Lack of randomization in recruiting patients might introduce a potential bias in our study, especially concerning the rate of complications in each group (the LT group was posterior to the ST group), and it could be argued that both clinical characteristics of the patients and the operator's experience could have some influence on the results. However, clinical characteristics of the patients were very similar in both groups, as shown in table 1. As for operator experience, this study was started only after 280 thoracoscopies (including more than 200 talc poudrage procedures) had been performed by the same team. We thus believe that the learning curve has little influence on the results reported in our study.

A few comments on prolonged air leak in some of our patients: in most of the cases, this complication arises during lung re-expansion in patients who have undergone chemotherapy prior to the pleurodesis procedure, and we believe that rupture of some necrotic tumoral nodules on the visceral pleura are the main cause of this troublesome complication in patients with MPE.

In conclusion, ST provokes a stronger inflammatory reaction in the pleural space, which leads to better results in pleurodesis. However, this is associated with shorter survival in our patients and with higher levels of proinflammatory cytokines in serum and a higher rate of complications. Further studies are needed in order to find the talc with ideal – and homogeneous – particle size to support its use as a safe agent for pleurodesis.

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References

1 Rinaldo JE, Owens GR, Rogers RM: Adult respiratory distress syndrome following intrapleural instillation of talc. J Thorac Cardiovasc Surg 1983;85:523–526.
2 Bouchama A, Chastre J, Gaudichet A, Soler P, Gilbert C: Acute pneumonitis with bilateral pleural effusion after talc pleurodesis. Chest 1984;86:795–797.
3 Kennedy L, Rusch VW, Strange C, Ginsberg RJ, Sahn SA: Pleurodesis using talc slurry. Chest 1994;106:342–346.
4 Rehse HD, Aye WR, Florence GM: Respiratory failure following talc pleurodesis. Am J Surg 1999;177:437–440.
5 Campos JR, Werebe EC, Vargas FS, Jatene FB, Light RW: Respiratory failure due to insufflated talc. Lancet 1997;349:251–252.
6 Ferrer J, Montes JF, Villarino MA, Light RW, García-Valero J: Influence of particle size on extrapleural talc dissemination after talc slurry pleurodesis. Chest 2002;122:1018–1027.
7 Maskell NA, Lee YC, Gleeson FV, Hedley EL, Pengelly G, Davies RJO: Randomized trials describing lung inflammation after pleurodesis with talc of varying particle size. Am J Respir Crit Care Med 2004;170:377–382.

8 Werebe EC, Pazetti R, Milanez de Campos JR, Fernandez PP, Capelozzi VL, Jatene FB, Vargas FS: Systemic distribution of talc after intrapleural administration in rats. Chest 1999;115:190–193.
9 Fraticelli A, Robaglia-Schlupp A, Riera H, Monjanel-Mouterde S, Cau P, Astoul P: Distribution of calibrated talc after intrapleural administration: an experimental study in rats. Chest 2002;122:1737–1741.
10 Janssen JP, Collier G, Astoul P, Tassi GF, Noppen M, Rodriguez-Panadero F, et al: Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study. Lancet 2007;369:1535–1539.
11 Gill AJ, Mathur MN, Tattersall SF: Systematic response to talc pleurodesis. Am J Respir Crit Care Med 2004;169:1074–1075.
12 Genofre EH, Vargas FS, Acencio M, Antonangelo L, Texeira LR, Marchi E: Talc pleurodesis: evidence of systemic inflammatory response to small size talc particles. Respir Med 2009;103:91–97.
13 Rossi VF, Vargas FS, Marchi E, Acencio MM, Genofre EH, Capelozzi VL, Antonangelo L: Acute inflammatory response secondary to intrapleural administration of two types of talc. Eur Respir J 2010;35:396–401.
14 Rodriguez Panadero F: Medical thoracoscopy. Respiration 2008;76:363–372.
15 Sanchez-Armengol A, Rodriguez-Panadero F: Survival and talc pleurodesis in metastatic pleural carcinoma, revisited. Report of 125 cases. Chest 1993;104:1482–1485.
16 Antony VB, Loddenkemper R, Astoul P, Boutin C, Goldstraw P, Hott J, Rodriguez Panadero F, Sahn SA: Management of malignant pleural effusions. Eur Respir J 2001;18:402–419.
17 Nasreen N, Mohammed KA, Dowling PA, Ward MJ, Galffy G, Antony VB: Talc induces apoptosis in human malignant mesothelioma cells in vitro. Am J Respir Crit Care Med 2000;161:595–600.
18 Miller Q, Meschter C, Neumaster T, Pratt J, Moulton M, Downey D, Harre J: Comparison of pleurodesis by erythromycin, talc, doxycycline, and diazepam in a rabbit model. J Surg Educ 2007;64:41–45.
19 Froudarakis ME, Klimathianaki M, Pougounias M: Systemic inflammatory reaction after thoracoscopic talc poudrage. Chest 2006;129:356–361.
20 Psathakis K, Calderon-Osuna E, Romero-Romero B, et al: The neutrophilic and fibrinolytic response to talc can predict the outcome of pleurodesis. Eur Respir J 2006;27:817–821.
21 Rodriguez-Panadero F, Montes-Worboys A: Mechanisms of pleurodesis. Respiration 2012;83:91–98.
22 Montes-Worboys A, Rodriguez-Portal JA, Arellano-Orden E, Digón-Pereiras J, Rodriguez-Panadero F: Interleukin-8 activates coagulation and correlates with survival after talc pleurodesis. Eur Respir J 2010;35:160–166.