Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study

Julius P Janssen, Gareth Collier, Phillippe Astoul, Gian Franco Tassi, Marc Noppen, Francisco Rodriguez-Panadero, Robert Loddenkemper, Felix J F Herth, Stefano Gasparini, Charles H Marquette, Birgit Becke, Marios E Froudarakis, Peter Driesen, Chris T Bolliger, Jean-Marie Tschopp

Summary

Background **Talc is the most effective chemical pleurodesis agent for patients with malignant pleural effusion. However, concerns have arisen about the safety of intrapleural application of talc, after reports of development of acute respiratory distress syndrome in 1–9% of treated patients. Our aim was to establish whether use of large-particle-size talc is safe in patients with malignant pleural effusion.**

Methods **We did a multicentre, open-label, prospective cohort study of 558 patients with malignant pleural effusion who underwent thoracoscopy and talc poudrage with 4 g of calibrated French large-particle talc in 13 European hospitals, and one in South Africa. The primary endpoint was the occurrence of acute respiratory distress syndrome after talc pleurodesis.**

Findings **No patients developed acute respiratory distress syndrome (frequency 0%, one-sided 95% CI 0–0·54%). 11 (2%) patients died within 30 days. Additionally, seven patients had non-fatal post-thoracoscopy complications (1·2%), including one case of respiratory failure due to unexplained bilateral pneumothorax.**

Interpretation **Use of large-particle talc for pleurodesis in malignant pleural effusion is safe, and not associated with the development of acute respiratory distress syndrome.**

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Canisius Wilhelmina Hospital, Nijmegen, Netherlands (J P Janssen MD, G Collier MD); **Hôpital Sainte-Marguerite, Marseille, France** (Prof P Astoul MD); **Spedali Civili, Brescia, Italy** (G F Tassi MD); **University Hospital UZ Brussels, Brussels, Belgium** (M Noppen MD); **Hospital Universitario Virgen del Rocio Sevilla, Seville, Spain** (F Rodriguez-Panadero MD); **Lungenklinik Heckeshorn, Berlin, Germany** (Prof R Loddenkemper MD); **Thoraxklinik, University of Heidelberg, Heidelberg, Germany** (Prof F J F Herth MD); **Azienda Ospedali Riuniti, Ancona, Italy** (S Gasparini MD); **Centre Hospitalier Régional Universitaire Lille, Lille, France** (Prof C H Marquette MD); **Johanniter-Krankenhaus, Treuenbrietzen, Germany** (B Becke MD); **University Hospital of Heraklion, Heraklion, Crete, Greece** (M E Froudarakis MD); **St. Elisabeth Ziekenhuis, Turnhout, Belgium** (P Driesen MD); **Tygerberg Academic Hospital, Cape Town, South Africa** (Prof C T Bolliger MD); **and Centre Valaisan de Pneumologie, Montana, Switzerland** (J-M Tschopp MD)

Correspondence to:
Dr Julius P Janssen, Canisius Wilhelmina Hospital, Department of Pulmonary Diseases B01, Postbox 9015, 6500 GS, Nijmegen, Netherlands
j.janssen@cwz.nl

Introduction

Talc is hydrated magnesium silicate, and was first used for pleurodesis in 1935 by the surgeon Norman Bethune.[1] In the second half of the 20th century, talc became increasingly popular for induction of pleurodesis in many pleural diseases—eg, spontaneous pneumothorax, benign pleural effusion, and malignant pleural effusion.[2–6] Compared with other agents for chemical pleurodesis, talc seemed to give the best results in terms of effectiveness, with least recurrence of effusion, after both talc poudrage, and instillation of talc slurry through a chest tube.[7] The effectiveness of talc pleurodesis compared with other forms of pleurodesis has also been supported by animal studies.[8] Additionally, talc is inexpensive and widely available.

However, the safety of intrapleural application of talc has been debated since cases of respiratory failure and acute respiratory distress syndrome after talc pleurodesis were reported.[4,9–11] Other authors noted no complications at all, even in large series of patients.[6,12,13] The occurrence of acute respiratory distress syndrome in some series and its absence in others was independent of the underlying disease (malignant pulmonary effusion or pneumothorax),[6,10,11] the quantity of talc used (2–10 g),[4,6,10–12] or the technique of talc instillation (slurry or poudrage).[4,6,10–12] Several researchers have reported results that suggest that acute respiratory distress syndrome after talc pleurodesis is mainly related to the particle size of the talc used.[14,15]

Our aim was to assess the safety of large-particle talc applied as poudrage for pleurodesis in patients with malignant pleural effusion.

Methods

Patients

We did a prospective cohort study to measure the side-effects of thoracoscopy and pleurodesis by poudrage with large-particle talc for treatment of recurrent malignant pleural effusions. 14 centres (all departments of pulmonary diseases) participated in the study, 13 in Europe and one in South Africa, between Oct 1, 2002, and Oct 31, 2005. Our primary endpoint was the occurrence of acute respiratory distress syndrome after talc pleurodesis. Secondary endpoints were other side-effects (eg, fever, hypoxaemia, and respiratory failure without acute respiratory distress syndrome) and death within 30 days.

Patients were included if they had malignant pleural effusion for which the treating physician thought pleurodesis to be appropriate. Patients in whom malignant pleural effusion was strongly suspected during thoracoscopy, and in whom retrospective histological examination of pleural biopsies confirmed malignancy, were also included. We excluded patients who had pulmonary infection, unstable respiratory status, fever of more than 38°C, cardiac failure, myocardial infarction within the past 30 days, bleeding disorders, previous or concomitant ipsilateral mechanical pleurodesis, previous or concomitant ipsilateral chemical pleurodesis, life expectancy of less than 30 days, pregnancy, or performance status of ECOG 4 (Karnofsky score 30 or lower). The study was approved by the ethics committee of each participating hospital. Written informed consent was obtained according to local protocol.

	Baseline value
Number of patients	558
Number of centres	14
Age (years)	64·37 (30–96)
Sex	
Female	284 (51%)
Male	274 (49%)
Primary cancer causing pleural metastasis	
Non-small cell lung cancer	230 (41%)
Breast cancer	120 (22%)
Mesothelioma	85 (15%)
Urogenital tract	35 (6%)
Lymphoma	17 (3%)
Colon	14 (3%)
Melanoma	13 (2%)
Small cell lung cancer	11 (2%)
Unknown primary	19 (3%)
Other	14 (3%)
Patients per institution	
Marseille, France	85 (15%)
Brescia, Italy	66 (12%)
Brussels, Belgium	66 (12%)
Berlin, Germany	52 (9%)
Seville, Spain	52 (9%)
Heidelberg, Germany	47 (8%)
Ancona, Italy	38 (7%)
Lille, France	36 (6%)
Treuenbrietzen, Germany	33 (6%)
Nijmegen, Netherlands	32 (6%)
Heraklion, Greece	27 (5%)
Montana, Switzerland	17 (3%)
Turnhout, Belgium	4 (1%)
Cape Town, South Africa	3 (1%)

Data are n (%) or mean (range).

Table 1: **Patient characteristics**

	Number of patients (%)
Local anaesthesia	436 (78%)
General anaesthesia	122 (22%)
Number of entry points	
1	428 (77%)
2	129 (23%)
3	1 (0.2%)
Day of drain removal*	
1	29 (5%)
2	76 (14%)
3	150 (27%)
4	132 (24%)
5	96 (17%)
6–10	19 (3%)
>10	4 (1%)

All patients received 4 g Steritalc (Novatech, La Ciotat, France). Data missing for 29 patients. *Range 1–14 days, mode=day 3.

Table 2: **Details of thoracoscopy procedure**

Procedures

Our null hypothesis was that use of graded large-particle talc would result in no cases of acute respiratory distress syndrome. Steritalc (Novatech, La Ciotat, France) was chosen as the standard talc to be used in this study. The mean particle size of this talc preparation is 24·5 µm. The concentration of small particles (<5 µm) in Steritalc is 11% by volume, compared with up to 82% in some Brazilian talcs analysed, and 54% in a sample of talc from the USA.[16]

Thoracoscopy was done by pulmonologists in accordance with a standard technique.[17] Physicians had free choice of which medications to use before, during, and after thoracoscopy, which could be done under local or general anaesthesia. Parietal and visceral pleural biopsies were allowed during the procedure. The pleurodesis technique, however, was standardised: only talc poudrage with 4 g of sterile graded talc was allowed. The talc powder was administered by a pneumatic atomiser. After thoracoscopy, a chest tube (size 20–28 French) was inserted.

A chest radiograph was taken at baseline and within 24 h of thoracoscopy. Additional chest radiographs were done according to local treatment protocol. Daily chest radiographs were taken to monitor for severe complications. A normal postoperative chest radiograph was classified as no clinically significant additional pulmonary infiltrate. Acute respiratory distress syndrome was defined according to the American-European consensus:[18] acute onset of symptoms, partial arterial pressure of oxygen/concentration of oxygen in inspired air of less than 200 mm Hg, bilateral infiltrates on frontal view of chest radiograph, pulmonary artery pressure less than 18 mm Hg when measured, or no clinical evidence of left atrial hypertension. Patients had their temperature recorded twice daily before thoracoscopy and on days 1–5 after the procedure. The amount of supplementary oxygen (L/min) and oxygen saturation were recorded. To guard against hypoxaemia (oxygen saturation <90%) an arterial blood gas measurement was taken.

Statistical analysis

We estimated a maximum frequency of acute respiratory distress syndrome of 1%. To show the risk of acute respiratory distress syndrome to be less than 1% with a one-sided 95% CI, we needed to include at least 300 patients. Statistical analyses were done with SPSS version 12.0.1. We used the paired *t* test to compare patient's temperature, oxygen saturation, and oxygen supplementation at baseline with days 1–5 post-procedure.

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Julius Janssen and Gareth Collier had access to all the

data and Julius Janssen had final responsibility for the decision to submit for publication.

Results

558 patients aged 30–96 years, (mean 64·4 years) were recruited. Table 1 shows the patients' baseline characteristics and the contribution of each institution. Table 2 shows details of the thorascopic procedures. Non-steroidal anti-inflammatory drugs were used in 178 (32%) patients. Parietal pleural biopsies were obtained in 475 (85%) patients (range 1–30, mean 6·3, mode 5 per patient). Visceral biopsies (range 1–10, average 3·7, mode 3) were obtained in 23 (4%) patients. If no biopsy sample was taken, the diagnosis had been established before thoracoscopy. Table 3 shows details of the side-effects reported after thoracoscopy. No patients developed acute respiratory distress syndrome.

Chest radiography showed that seven patients had a new infiltration after thorascopy; one developed because of transient cardiogenic pulmonary oedema. In two patients the infiltrates resolved. Chest radiographs also showed that two patients had re-expansion oedema that resolved after treatment with oxygen and diuretic drugs. No intensive care was necessary. One patient developed respiratory failure not caused by acute respiratory distress syndrome, for which treatment in the intensive care unit was necessary. This patient had an unexplained contralateral pneumothorax on the day of the thoracoscopy, which was discovered after the procedure. After bilateral pleural drainage, the patient recovered without mechanical ventilation. One patient had a pulmonary embolism on day 8, which resolved after treatment. One patient, who was on chemotherapy, developed non-pulmonary sepsis 48 h after thoracoscopy. She was monitored in the intensive care unit for 2 days, but recovered. One patient with new infiltrates developed high fever, and was given antibiotic drugs, resulting in resolution of infiltration. One patient developed pericardial effusion and congestive heart failure on day 2 after thoracoscopy, and was given diuretic drugs. 11 (2%) patients died within 30 days (2–29 days after thoracoscopy, mean 11·8 days). Table 4 shows details of causes of death.

A significant increase in mean temperature was seen on days 1–4 after thoracoscopy compared with baseline (figure 1). No significant difference in oxygen saturation was seen after procedure (data not shown). A significant rise in the volume of supplemental oxygen used was recorded on days 1 and 2 post-thoracoscopy compared with baseline (0·25 L/min increase on day 1 in the 339 patients using supplemental oxygen [p=0·001]; 0·21 L/min increase on day 2 in the 317 using supplemental oxygen [p=0·025]; figure 2).

Discussion

The absence of acute respiratory distress syndrome in patients with malignant pulmonary effusion supports our hypothesis that pleurodesis with large-particle talc is safe. Side-effects from thoracoscopic pleurodesis were mild in our study. The small increases in temperature and oxygen use after talc pleurodesis were not clinically significant, and might be due to mild systemic and lung inflammation caused by talc.[14,19] Our results also accord with the hypothesis that acute respiratory distress syndrome and severe hypoxaemia are caused by talc toxicity, which can be avoided by the use of large-particle talc.[14]

About 2% of our patients died within 30 days of thoracopy. However, in such patients, who had a limited life expectancy and serious comorbidity, postoperative complications and mortality within 30 days can be expected in a small proportion. None of our patients had serious pulmonary complications within 48 h of procedure, which provides further evidence of the safety of this procedure.

At present there is no consensus about the safety of talc for pleurodesis.[20,21] Sahn[22] reviewed publications about the development of acute respiratory distress syndrome in talc pleurodesis. Of the 4030 patients with malignant pleural effusion who were treated with talc pleurodesis that he identified, 41 (1%) patients had acute respiratory failure after administration of talc. However, almost all

	Number of patients
Acute respiratory distress syndrome	0 (0%; 0–0·54*)
Death within 30 days	11 (1·97%; 0·8–3·1)
Respiratory failure not due to acute respiratory distress syndrome	1 (0·17%; 0–0·53)
Other serious adverse event	6 (1·07%; 0·24–1·9)

Data are n (%; 95% CI). *One-sided 95% CI.

Table 3: **Side-effects of thoracoscopy**

	Age (years)	Sex	Time from procedure to death (days)
Acute gastrointestinal bleeding on day 6, family requested no further intervention, palliative care only	82	Female	8
Massive pericardial effusion and cardiac failure on day 2	67	Male	2
Pleural empyema on day 8, operation for intrathoracic bleeding on day 14, ICU treatment afterwards, death due to respiratory and cardiovascular failure	63	Male	29
Tumour progression, malignant pericardial effusion, tachyarrythmia, circulatory failure	64	Male	13
Disease progression, brain metastasis	61	Male	18
Sudden death, suspected massive pulmonary embolism	46	Female	8
Progressive disease, carcinomatous lymphangitis	79	Female	20
Progressive disease, carcinomatous lymphangitis	64	Male	14
Progressive disease	51	Male	10
Sepsis	78	Male	5
Infected peritoneal carcinomatosis, died from sepsis, no ICU care, but palliative treatment given	54	Female	3

ICU=Intensive care unit.

Table 4: **Causes of death within 30 days of thoracoscopy**

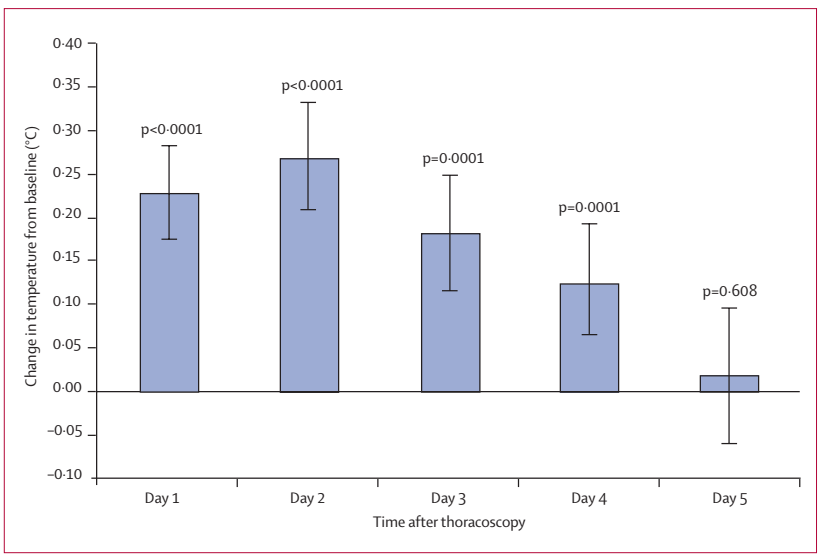

Figure 1: **Mean temperature increase from baseline**
Bars show 95% CI.

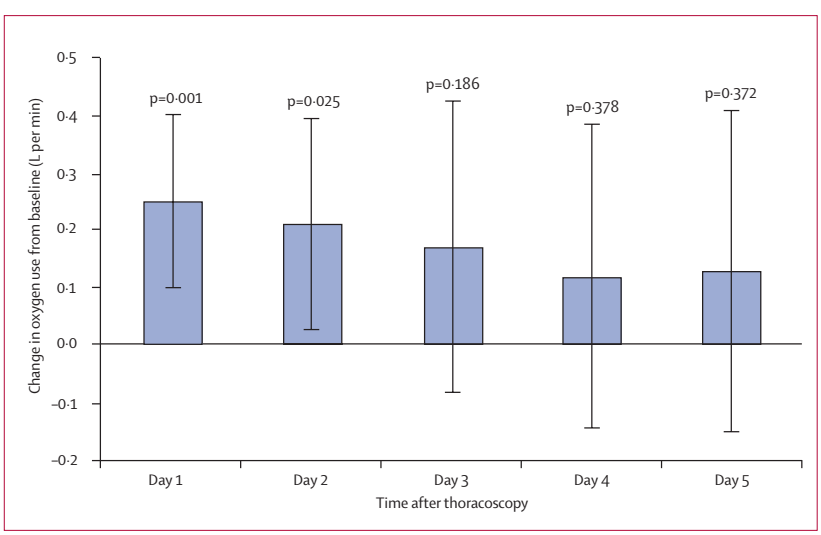

Figure 2: **Mean increase in supplemental oxygen use from baseline**
Bars show 95%CI.

the data was retrospective, without detailed documentation of the clinical course of disease and outcome. He questioned whether there was a causal association between respiratory failure and talc pleurodesis, since no important side-effects were reported in more than 5000 patients who underwent talc pleurodesis between 1958 and 2001.

Researchers in the USA and Brazil have described cases of acute respiratory distress syndrome after talc pleurodesis; by contrast, no such cases have been recorded in large review series in Europe and Israel. Animal studies in the USA and Brazil showed deposition of talc in the lung parenchyma and other organs,[24,25] whereas such deposition in other organs was absent in a European study.[26] In animal studies in Wistar rats, talc was seen in 100% of organs of all animals in a Brazilian study, versus 2% in a European study.[25,26] In the European study, the researchers proposed that the talc seen in four of 198 assessed organs was probably caused by contamination during storage of the organs.[27]

This geographic discrepancy is probably due to the size of the particles of talc. Ferrer and colleagues[28] showed that talc preparations for pleurodesis varied greatly. They also showed that damage to the lung parenchyma took place after pleurodesis with small-particle talc in rabbits, but not when large-particle talc was used.[15] In human beings, Maskell and colleagues[14] showed that pleurodesis with mixed talc, including small particles, worsened gas exchange, and induced more systemic inflammation than did graded talc, from which most particles less than 10 μm were removed.

Indeed, of the publications that described acute respiratory distress syndrome after talc pleurodesis, details of the particle size of the talc were given only in one.[11] Thus the causal role of particle size in the side-effects associated with talc pleurodesis was overlooked, and talc, in general, was thought to be dangerous as a pleurodesis agent by some investigators.[20]

In view of growing evidence to suggest that talc particle size is the main cause of side-effects, we did not think comparing small and large-particle talc in a prospective randomised way in human beings was ethical. We therefore chose to do a prospective cohort study to test our hypothesis that pleurodesis with large-particle talc would not cause acute respiratory distress syndrome. Our results suggest that acute respiratory distress syndrome after pleurodesis with large-particle talc would happen in six patients in every thousand, which is well below the 1% estimated from a review of the retrospective studies.[22]

Our results are limited to the side-effects of talc poudrage, we therefore cannot draw any conclusions about the safety of talc applied as slurry. Additionally, our study did not assess the efficacy of talc pleurodesis.

The most important clinical implication of our study is that large-particle talc can safely be used for pleurodesis. Other talc preparations should not be used for this indication.

Contributors

JJ, PA ,GT, MN, FR-P, RL, SG, CHM, MF, CB, and JMT designed the study protocol. All authors enrolled patients. JJ and GC collected the data. The spread sheet for data collection was developed by JMT. GC did the statistical analysis, with external consultation. JJ drafted the manuscript, which was contributed to by all authors, and all authors have seen and approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest.

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