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Short-term safety of thoracoscopic talc pleurodesis for recurrent primary spontaneous pneumothorax: a prospective European multicentre study

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ABSTRACT: The safety of talc pleurodesis is under dispute following reports of talc-induced acute respiratory distress syndrome (ARDS) and death. We investigated the safety of large-particle talc for thoracoscopic pleurodesis to prevent recurrence of primary spontaneous pneumothorax (PSP).

418 patients with recurrent PSP were enrolled between 2002 and 2008 in nine centres in Europe and South Africa. The main exclusion criteria were infection, heart disease and coagulation disorders. Serious adverse events (ARDS, death or other) were recorded up to 30 days after the procedure. Oxygen saturation, supplemental oxygen use and temperature were recorded daily at baseline and after thoracoscopic pleurodesis (2 g graded talc).

During the 30-day observation period following talc poudrage, no ARDS (95% CI 0.0–0.9%), intensive care unit admission or death were recorded. Seven patients presented with minor complications (1.7%, 95% CI 0.7–3.4%). After pleurodesis, mean body temperature increased by 0.41°C (95% CI 0.33–0.48°C; $p<0.001$) at day 1 and returned to baseline value at day 5. Pleural drains were removed after day 4 in 80% of patients.

Serious adverse events, including ARDS or death, did not occur in this large, multicentre cohort. Thoracoscopic talc poudrage using larger particle talc to prevent recurrence of PSPS can be considered safe.

KEYWORDS: Pleural disease, pneumothorax, talc pleurodesis, thoracoscopy

Talc powder is the most inexpensive and efficient agent for pleurodesis, as shown in human [1–3] and animal studies [4]. In a prospective cohort study, JANSSEN *et al.* [5] recently demonstrated that thoracoscopic large-particle talc poudrage is safe in the treatment of malignant pleural effusions. Apart from treating malignant pleural effusions, graded talc has been extensively and safely used in Europe for >70 yrs for pleurodesis in recurrent spontaneous pneumothorax and has been shown to be well tolerated without long-term sequellae [6–9].

However, there is continued concern about the safety of talc pleurodesis for this indication following US reports of acute respiratory distress syndrome (ARDS) after talc application [10–13]. However, the incidence of ARDS after talc poudrage in primary spontaneous pneumothorax (PSP) is low. In a review of the literature from 1958 to 2001, SAHN [14] found reports of one case (0.15%) of respiratory failure following talc pleurodesis in 659 patients. Possible explanations for the occurrence of ARDS might be the dose of talc used [15, 16], the size of talc particles [17] as preparations vary markedly form one supplier to the other [18], or the form of talc administered (slurry talc *versus* poudrage) [10, 19]. These possible causes were postulated after occurrence of ARDS in patients with malignant pleural effusion and not pneumothorax.

The aim of this study was to assess the safety of large-particle talc applied in a standardised dose as poudrage under thoracoscopy in patients with recurrent PSP.

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TABLE 1 Patient characteristics

Subjects n	418
Males	304 (72.7)
Females	114 (27.3)
Age yrs	30.5±12.7 (15–84)
Centres	
Nijmegen, the Netherlands	65 (15.5)
Crans Montana, Switzerland	26 (6.2)
Marseille, France	8 (1.9)
Lille, France	46 (11.0)
Alexandroupolis, Greece	1 (0.2)
Brussels, Belgium	14 (3.4)
Cape Town, South Africa	3 (0.7)
Turnhout, Belgium	34 (8.1)
Rome, Italy	221 (52.9)

Data are presented as n (%) or mean±SD (range), unless otherwise stated.

METHODS

Patients

Patients were prospectively enrolled between 2002 and 2008. Inclusion criterion was recurrent spontaneous pneumothorax for which the physician considered talc pleurodesis indicated. Patients with active pulmonary infection, unstable respiratory condition, coagulation disorders, bilateral pneumothorax or parenchymal lung disease, prior ipsilateral thoracic surgery or pleurodesis, or pregnancy were excluded. The study was approved by the Ethics committee of each participating hospital. Informed consent was obtained according to local protocols.

Thoracoscopic procedure

Thoracoscopy was performed under general or local anaesthesia by experienced pulmonologists according to current practice in Europe [20]. One or two entry ports were used to insert the videothoracoscope and the pneumatic atomiser. 2 g of graded talc (Steritalc®; Novatech, La Ciotat, France) were gently insufflated under visual control over the entire pleural surface [21]. Graded talc is characterised by the particle size, which has to be >10 μm and should contain only a small percentage of smaller particles. Thus, particles with a diameter of 6 μm have little or no ability to cross pleural stomata. The median particle size of Steritalc® is 31.5 μm, which is larger than talc manufactured in the USA [22].

At the end of the procedure a standard chest tube (20 to 28 French) was inserted for drainage of air and fluid. Anti-emetics and analgesics were administered according to the patient's needs.

During the following 5 days, vital signs, temperature, use of supplemental oxygen and all medical and surgical complications were recorded. If necessary, additional chest radiographs were ordered. Drain removal day was left at the discretion of performing physicians.

TABLE 2 Post-pleurodesis complications at 30 days

Acute respiratory distress syndrome	0	0.0–0.9¶
Intensive care admission	0	0.0–0.9¶
Other#	7 (1.7)	0.7–3.4

Data are presented as n (%) or 95% CI. #: pulmonary infections requiring antibiotics (n=3), urinary retention on opiates (n=1), contralateral pneumothorax on day 2 (n=1), persisting pneumothorax (n=1) and sub-cutaneous emphysema (n=1); ¶: one-sided confidence interval.

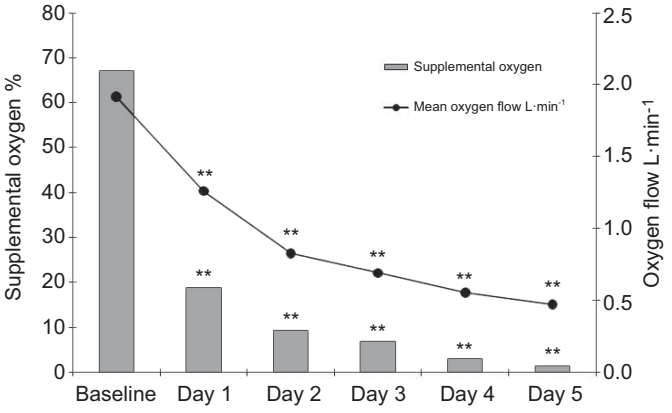

FIGURE 1. Supplemental post-pleurodesis oxygen use from baseline to day 5. **: p<0.01 for all comparisons *versus* day 0, using multilevel regression accounting for repeated measures.

Statistical analyses

Our primary end-point was ARDS during the first 30 days after the procedure. Based on published literature, we estimated the risk of ARDS to be <1%. We used exact confidence interval according to the method of CLOPPER and PEARSON [23]. After an interim analysis, patient inclusion was stopped after 418 cases because no case of ARDS was identified. Comparisons of proportion of patients on supplemental oxygen and oxygen flow were performed using multilevel logistic and linear regression accounting for repeated measure.

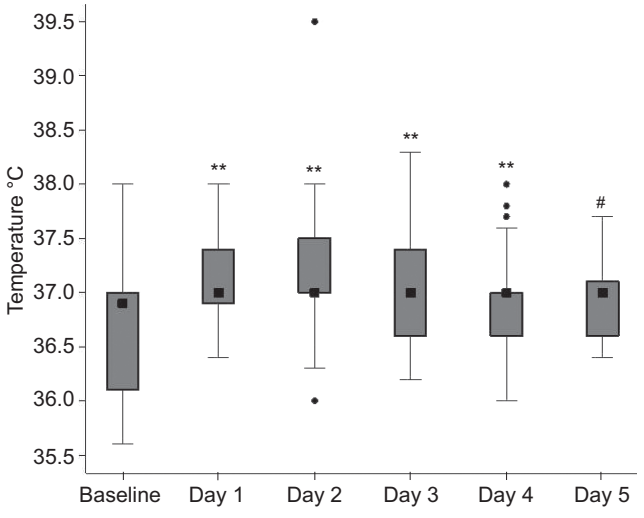

FIGURE 2. Temperature change from baseline to day 5. Box plots represent median values and circles represent extreme values. #: p=0.708. **: p<0.01.

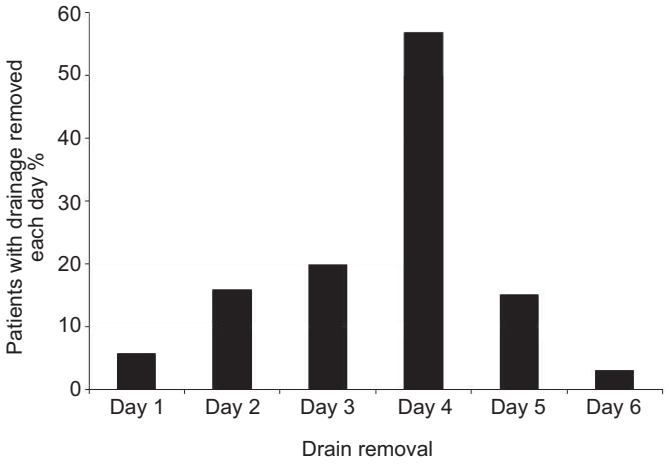

FIGURE 3. Drain removal day. Data on drain removal were available for 264 patients. For two patients drains were removed on day 7 and 8, respectively.

All analyses were performed with Stata 10 (StatCorp LP, College Station, TX, USA).

RESULTS

Table 1 shows the characteristics of the 418 included patients. Most of them were young (mean±SD 30.5±12.7 yrs) males (72.7%). For 61.1% of the thoracoscopies, two entry ports were used. Among the nine centres in Europe and South Africa participating in the study, two centres used exclusively two ports (Rome, Italy and Brussels, Belgium).

During the study period, no patients experienced ARDS or intensive care unit admission (95% CI 0.0–0.9%) (table 2).

Supplemental oxygen was provided to most patients at baseline. By day 5, only six (0.01%) patients were still on oxygen (fig. 1). Mean oxygen flow decreased from 1.9 $L \cdot min^{-1}$ at baseline to 0.5 $L \cdot min^{-1}$ on day 5.

We observed a significant rise in temperature from baseline to day 4 and a return to baseline value on day 5. The mean temperature rose maximally by 0.41°C (95% CI 0.33–0.49°C) on day 1 and by 0.37°C (95% CI 0.29–0.44°C) on day 2 compared to baseline. On day 1, the temperature exceeded 37.9°C in 83 (21.2%) patients. Temperature changes are shown in figure 2, with box plots representing extreme changes in temperature.

We recorded seven (1.7%, 95% CI 0.7–3.4%) non-ARDS comfplications (table 2). The most frequent complication was pulmonary infections requiring antibiotics (n=3). We also observed four cases of pleurodesis failure requiring surgical procedure. These four (<1%) patients were aged 20–84 yrs and had persistent leaks for >2 days. In one case bulla had to be surgically resected.

Drains were removed on day 4 or before day 4 following thoracoscopy in 80% of patients. In two patients, drains were removed on days 7 and 8, respectively (fig. 3).

DISCUSSION

Our study confirms the safety of thoracoscopic pleurodesis with graded talc for the treatment of recurrent PSP. No ARDS, intensive care unit admission or death were observed in our cohort of 418 patients. The most frequent adverse event was an increase in temperature, which was maximal on day 1. This result is in line with a previous study which documented the systemic inflammatory response induced by talc [24]. Supplemental oxygen was provided for a short period of time after talc pleurodesis. This suggests that talc-induced systemic inflammation is limited in severity and duration. Complications were pulmonary infections in <1% of procedures.

The absence of ARDS found in our prospective study supports the safety of graded talc use for pleurodesis in recurrent PSP, as has been previously reported in large retrospective studies [3, 20, 25].

Talc pleurodesis has been shown to be efficacious and safe with a success rate of 95% in PSP in large series [6–9, 25–27]. However, concerns about the safety of talc for pleurodesis were based on a small number of retrospective anecdotal reports of acute respiratory failure in patients with malignant pleural effusion [11–13]. In these reports, non-graded talc was used, which has been described to cross the visceral pleura and cause systemic inflammation, ARDS and even some deaths [12, 19]. Moreover, a recent study from North America using a higher dosage of talc (6 g) of unknown calibration raised concern about respiratory deterioration after thoracoscopic talc poudrage, even if the used talc was the only one approved by the US Food and Drug Administration [13]. Recent studies using graded talc with large particle size failed to observe ARDS cases [3, 7, 28]. In addition, in humans, systemic side-effects of talc appear to be related to overdoses of talc or uncalibrated talc with small particles [17].

In addition, acute respiratory failure can occur after re-expansion of the lung in the treatment of pneumothorax due to re-expansion oedema without pleurodesis, as has been reported recently [29].

Lack of power of our study to demonstrate an increased risk of ARDS might be discussed. However, our study is large enough to estimate this risk at <1%, which is clinically meaningful in regard of the risk of associated pneumothorax recurrence if left without pleurodesis.

In summary, our prospective study confirms, on a large scale, the short-term safety of talc pleurodesis in the treatment of patients with recurrent spontaneous pneumothorax.

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STATEMENT OF INTEREST

None declared.

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