

Short term safety of thoracoscopic talc pleurodesis for recurrent primary spontaneous pneumothorax. A prospective European multicenter study.

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ABSTRACT

Background

Safety of talc pleurodesis is disputed 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).

Method

Patients (n=418) with recurrent PSP were enrolled between 2002 and 2008 in 9 centres in Europe and South Africa. Main exclusion criteria were infection, heart disease, coagulation disorders. Serious adverse events (ARDS, death, other) were recorded up to 30 days after procedure. Oxygen saturation, supplemental oxygen use and temperature were recorded daily at baseline and after thoracoscopic pleurodesis (Graded talc, 2 g).

Results

During the 30-day observation period after talc poudrage, no ARDS (CI95% 0.0% – 0.9%), intensive care unit admission or death were recorded. Seven patients presented minor complications (1.7% CI95% 0.7 – 3.4). After pleurodesis, mean body temperature rose by 0.41 °C (CI95% 0.33-0.48; p<0.001) at day 1 and return to baseline value at day 5. Pleural drains were removed after day 4 in 80% of patients.

Conclusion:

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

INTRODUCTION

Talc powder is the most inexpensive and efficient agent for pleurodesis as shown in human[1-3] and animal studies[4]. We recently showed in a prospective cohort study that thoroscopic large-particle talc poudrage is safe in the treatment of malignant pleural effusions[5]. Apart from treating malignant pleural effusions such graded talc has been extensively and safely used in Europe for more than 70 years 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 American reports of ARDS after talc application [10-13]. However, the incidence of ARDS after talc poudrage in PSP is low. In a review of the literature from 1958 to 2001, Sahn found reports of 1 case of respiratory failure after talc pleurodesis in 659 patients (0.15%)[14]. Possible explanations for the occurrence of adult respiratory distress syndrome might be the dose of talc used [15, 16], the size of talc particles[17] as preparations vary markedly from 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 primary spontaneous pneumothorax.

METHODS

Patients

Patients were prospectively enrolled between 2002 and 2008. Inclusion criteria were recurrent spontaneous pneumothorax for which the physician considered talc pleurodesis indicated.

Patients with active pulmonary infection, unstable respiratory condition, bleeding 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 hospitals. Informed consent was obtained according to local protocols

Thoracoscopic procedure

Thoracoscopy was performed under general or local anesthesia 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. Two grams of graded talc (Steritalc®, Novatech, La Ciotat, France) were gently insufflated under visual control all over the pleural surface [21]. Graded talc is characterized by the particle size which has to be larger than 10 micrometers and should contain only a small percentage of smaller particles. Thus, particles have little or no capability to cross pleural stomata which have a diameter of 6 micrometers. Median particle size of Steritalc is 31.5 micrometers which is larger than talc manufactured in 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 patients needs.

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

Statistical analyses

Our primary endpoint was ARDS during the first 30 days after the procedure. Based on published literature, we estimated the risk of ARDS below 1%. We used exact confidence

interval according to Clopper and Pearson[23]. After an interim analysis, patients' inclusion was stopped after 418 cases, because no ARDS case was identified. Comparisons of proportion of patients on supplemental oxygen and oxygen flow were done using multilevel logistic and linear regression accounting for repeated measure.

All analyses were performed with Stata 10 (4905 Lakeway Drive, College Station, 77845 Texas).

RESULTS

Table 1 shows the characteristics of included patients (n=418). Most of them were young (age 30.5 [SD 12.7]) males (72.7%). For 61.1% of the thoracoscopies, two entry ports were used. Among the 9 centres in Europe and South Africa participating in the study, 2 centres used exclusively 2 ports (Roma, Brussels).

During the study period, no patients experienced ARDS or ICU admission (CI95% 0.0% – 0.9%). (**Table 2**)

Supplemental oxygen was provided to most patients on day 0. By day 5, only 6 (0.01%) patients were still on oxygen (**Figure 1**). Mean oxygen flow decreased from 1.9 L/min on day 0 to 0.5 L/min on day 5.

We observed a significant rise in temperature from baseline through day 4 and a return to baseline value on day 5. The mean temperature rose maximally by 0.41 Celsius (CI95% 0.33-0.49) on day 1 and by 0.37 °C (CI95% 0.29 – 0.44) on day 2 compared to baseline. On day 1, the temperature exceeded 37.9 Celsius in 83 patients (21.2%). Box plots with extreme values shows the temperature changes in **figure 2**.

We recorded 7 (1.7% CI95% 0.3% – 3.4%) non-ARDS complications (**Table 2**). Most frequent complication was pulmonary infections requiring antibiotics (n=3). We observed 4

cases of pleurodesis failure of pleurodesis requiring surgical procedure. Those four patients (<1%) were aged 20 to 84 and had persistent leaks for more than 2 days. In one case bulla had to be surgically resected.

Drains were removed on day 4 or before following thoracoscopy in 80% of patients. In 2 patients, drainage was removed on days 7 and 8 respectively. **(Figure 3).**

Table 1 Patients characteristics

	N	%
Total	418	
Males	304	72.7
Females	114	27.3
Age, mean (SD), Range	30.5 (12.7) [15-84]	
Centres		
Nijmegen (NL)	65	15.5
Montana (CH)	26	6.2
Marseille (F)	8	1.9
Lille (F)	46	11.0
Alexandroupolis (GR)	1	0.2
Brussels (B)	14	3.4
CapeTown (SA)	3	0.7
Turnhout (B)	34	8.1
Roma (I)	221	52.9

Table 2 Post-pleurodesis complications at 30 days

	N	%	CI95%
Acute Respiratory Distress Syndrome	0	-	0.0% – 0.9%*
Intensive Care Admission	0	-	0.0% – 0.9%*
Others †	7	1.7 %	0.7% – 3.4%

*One sided confidence interval † Pulmonary infections requiring antibiotics (n=3), Urinary retention on opiates (n=1), Contralateral pneumothorax on day 2 (n=1), persisting pneumothorax (n=1), Sub-cutaneous emphysema (n=1).

DISCUSSION

The current study confirms the safety of thoracoscopic pleurodesis with graded talc for the treatment of recurrent primary spontaneous pneumothorax. No ARDS, intensive care unit

admission or death were observed in our series of 418 patients. The most frequent adverse event was temperature rise, which was maximal on day 1. This result is in line with 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 less than 1 percent of procedures.

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

Talc pleurodesis has been shown to be efficacious and safe with 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 then cause systemic inflammation, ARDS and even some deaths[12, 19]. Moreover a very recent study from North America using 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 Food and Drug Administration[13]. Recent studies, using graded talc with large particle size, failed to observe ARDS cases [3, 7, 28]. Also, systemic side effects of talc appear to be related in humans to overdoses of talc or uncalibrated talc with small particles [17].

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

Lack of power of our study to demonstrate an increased risk of ARDS might be discussed. However, our series is large enough to estimate this risk below 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.

Figures (see attached files)

Figure 1 Supplemental post-pleurodesis oxygen use

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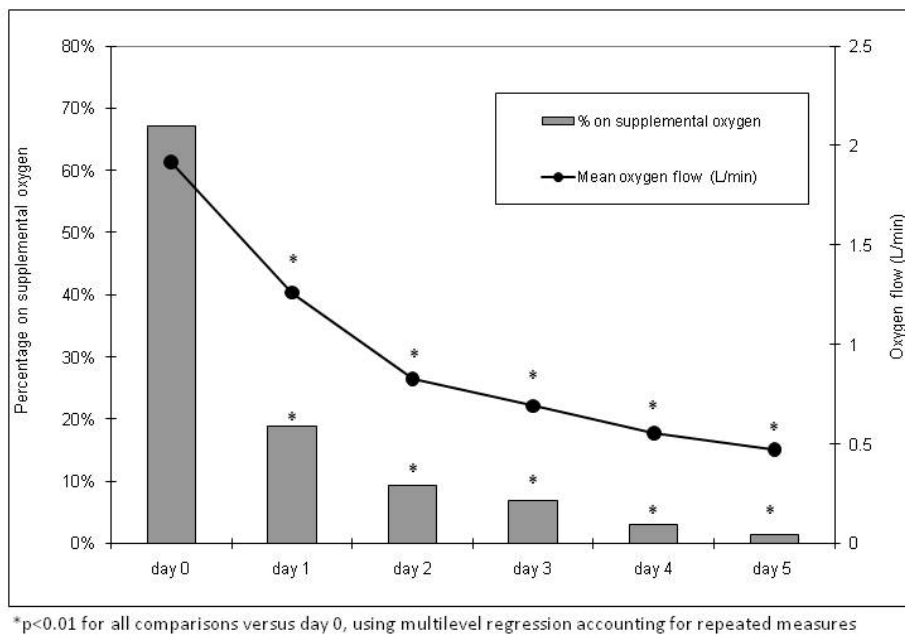
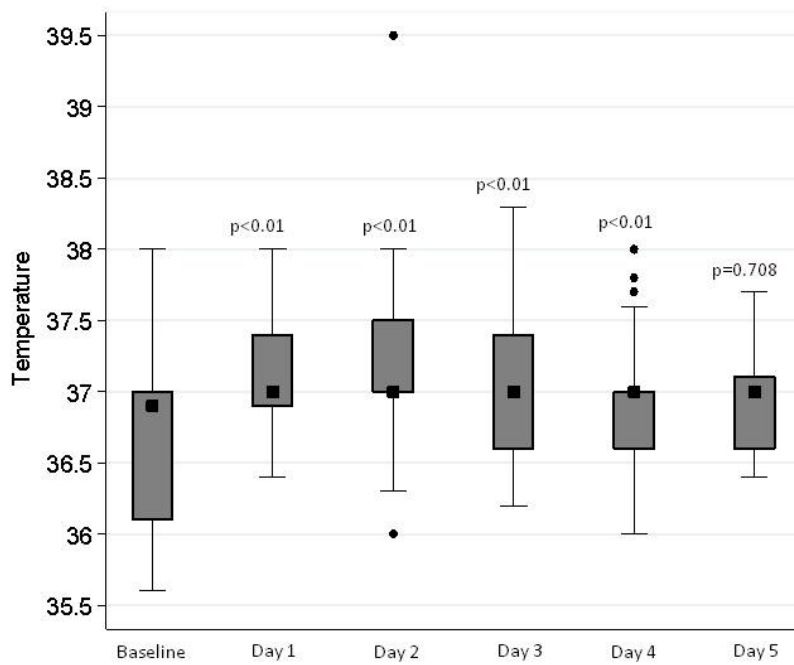


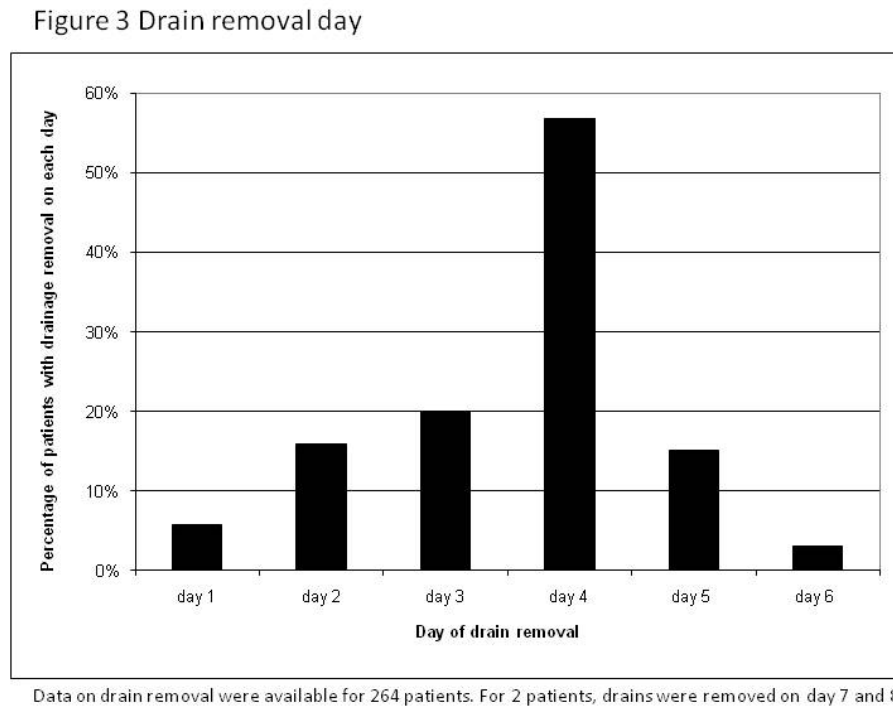
Figure 2 Temperature change

Figure 2 Temperature change (C°)



Squares: median values, circles: extreme values. P values compared to baseline values

Figure 3 Drain removal day



Contributors:

The study protocol was designed by JMT, CHM, MN, PA, PD, MF and JJ. All authors have contributed cases. JJ coordinated the study and collected the data. The spreadsheet for data collection was developed by JMT. POB did the statistical analysis, with external consultation. POB and JMT drafted the manuscript, which was contributed to by all authors. All authors have seen and approved the final version.

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Conflict of interest:

None

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REFERENCES

1. Viallat JR, Rey F, Astoul P, Boutin C. Thoracoscopic talc poudrage pleurodesis for malignant effusions. A review of 360 cases. *Chest* 1996; 110(6): 1387-1393.
2. Berger R. Pleurodesis for spontaneous pneumothorax. Will the procedure of choice please stand up? *Chest* 1994; 106(4): 992-994.
3. Cardillo G, Carleo F, Giunti R, Carbone L, Mariotta S, Salvadori L, Petrella L, Martelli M. Videothoracoscopic talc poudrage in primary spontaneous pneumothorax: a single-institution experience in 861 cases. *The Journal of thoracic and cardiovascular surgery* 2006; 131(2): 322-328.
4. 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(5): 1737-1741.
5. Janssen JP, Collier G, Astoul P, Tassi GF, Noppen M, Rodriguez-Panadero F, Loddenkemper R, Herth FJ, Gasparini S, Marquette CH, Becke B, Froudarakis ME, Driesen P, Bolliger CT, Tschopp JM. Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study. *Lancet* 2007; 369(9572): 1535-1539.
6. Lange P, Mortensen J, Groth S. Lung function 22-35 years after treatment of idiopathic spontaneous pneumothorax with talc poudrage or simple drainage. *Thorax* 1988; 43(7): 559-561.
7. Gyorik S, Erni S, Studler U, Hodek-Wuerz R, Tamm M, Chhajed PN. Long-term follow-up of thoracoscopic talc pleurodesis for primary spontaneous pneumothorax. *Eur Respir J* 2007; 29(4): 757-760.
8. El Khawand C, Marchandise FX, Mayne A, Jamart J, Francis C, Weynants P, Sibille Y, Delaunois L. Spontaneous pneumothorax. Results of pleural talc therapy using thoracoscopy. *Revue des maladies respiratoires* 1995; 12(3): 275-281.
9. Almind M, Lange P, Viskum K. Spontaneous pneumothorax: comparison of simple drainage, talc pleurodesis, and tetracycline pleurodesis. *Thorax* 1989; 44(8): 627-630.
10. Kennedy L, Harley RA, Sahn SA, Strange C. Talc slurry pleurodesis. Pleural fluid and histologic analysis. *Chest* 1995; 107(6): 1707-1712.
11. Campos JR, Werebe EC, Vargas FS, Jatene FB, Light RW. Respiratory failure due to insufflated talc. *Lancet* 1997; 349(9047): 251-252.
12. Rehse DH, Aye RW, Florence MG. Respiratory failure following talc pleurodesis. *American journal of surgery* 1999; 177(5): 437-440.
13. Gonzalez AV, Bezwada V, Beamis JF, Jr., Villanueva AG. Lung injury following thoracoscopic talc insufflation: experience of a single north american center. *Chest* 2010; 137(6): 1375-1381.

14. Sahn SA. Talc should be used for pleurodesis. *Am J Respir Crit Care Med* 2000; 162(6): 2023-2024; discussion 2026.
15. Aelony Y. Talc pleurodesis. Talc slurry vs talc poudrage. *Chest* 1995; 108(1): 289.
16. Montes JF, Ferrer J, Villarino MA, Baeza B, Crespo M, Garcia-Valero J. Influence of talc dose on extrapleural talc dissemination after talc pleurodesis. *Am J Respir Crit Care Med* 2003; 168(3): 348-355.
17. Maskell NA, Lee YC, Gleeson FV, Hedley EL, Pengelly G, Davies RJ. Randomized trials describing lung inflammation after pleurodesis with talc of varying particle size. *Am J Respir Crit Care Med* 2004; 170(4): 377-382.
18. Ferrer J, Montes JF, Villarino MA, Light RW, Garcia-Valero J. Influence of particle size on extrapleural talc dissemination after talc slurry pleurodesis. *Chest* 2002; 122(3): 1018-1027.
19. Rinaldo JE, Owens GR, Rogers RM. Adult respiratory distress syndrome following intrapleural instillation of talc. *The Journal of thoracic and cardiovascular surgery* 1983; 85(4): 523-526.
20. Boutin C, Viallat J, Aelony Y. Practical Thoracoscopy. Springer-Verlag, Berlin, 1991.
21. Tschopp JM, Boutin C, Astoul P, Janssen JP, Grandin S, Bolliger CT, Delaunois L, Driesen P, Tassi G, Perruchoud AP. Talcage by medical thoracoscopy for primary spontaneous pneumothorax is more cost-effective than drainage: a randomised study. *Eur Respir J* 2002; 20(4): 1003-1009.
22. Navarro Jiménez C, Gómez Izquierdo L, Sánchez Gutiérrez C, Montes Worboys A, de Torres Solís I, Romero Falcón A, Martín Juan J, Rodríguez Panadero F. Morphometric and mineralogical analysis of 14 samples of talc used for pleurodesis in several European and American countries (in Spanish). *Neumosur* 2005; 17: 197-202.
23. Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial *Biometrika* 1934; 26: 404-413.
24. Froudarakis ME, Klimathianaki M, Pougounias M. Systemic inflammatory reaction after thoracoscopic talc poudrage. *Chest* 2006; 129(2): 356-361.
25. Weissberg D, Ben-Zeev I. Talc pleurodesis. Experience with 360 patients. *The Journal of thoracic and cardiovascular surgery* 1993; 106(4): 689-695.
26. Kennedy L, Sahn SA. Talc pleurodesis for the treatment of pneumothorax and pleural effusion. *Chest* 1994; 106(4): 1215-1222.
27. Rodriguez-Panadero F, Antony VB. Pleurodesis: state of the art. *Eur Respir J* 1997; 10(7): 1648-1654.
28. Tschopp JM, Rami-Porta R, Noppen M, Astoul P. Management of spontaneous pneumothorax: state of the art. *Eur Respir J* 2006; 28(3): 637-650.
29. Schmidt-Horlohe N, Rudig L, Azvedo CT, Habekost M. Fulminant unilateral pulmonary edema after insertion of a chest tube: a complication after a primary spontaneous pneumothorax. *Dtsch Arztebl Int* 2008; 105(50): 878-881.