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Effect of Thoracoscopic Talc Poudrage vs Talc Slurry via Chest Tube on Pleurodesis Failure Rate Among Patients With Malignant Pleural Effusions
A Randomized Clinical Trial

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IMPORTANCE Malignant pleural effusion (MPE) is challenging to manage. Talc pleurodesis is a common and effective treatment. There are no reliable data, however, regarding the optimal method for talc delivery, leading to differences in practice and recommendations.

OBJECTIVE To test the hypothesis that administration of talc poudrage during thoracoscopy with local anesthesia is more effective than talc slurry delivered via chest tube in successfully inducing pleurodesis.

DESIGN, SETTING, AND PARTICIPANTS Open-label, randomized clinical trial conducted at 17 UK hospitals. A total of 330 participants were enrolled from August 2012 to April 2018 and followed up until October 2018. Patients were eligible if they were older than 18 years, had a confirmed diagnosis of MPE, and could undergo thoracoscopy with local anesthesia. Patients were excluded if they required a thoracoscopy for diagnostic purposes or had evidence of nonexpandable lung.

INTERVENTIONS Patients randomized to the talc poudrage group (n = 166) received 4 g of talc poudrage during thoracoscopy while under moderate sedation, while patients randomized to the control group (n = 164) underwent bedside chest tube insertion with local anesthesia followed by administration of 4 g of sterile talc slurry.

MAIN OUTCOMES AND MEASURES The primary outcome was pleurodesis failure up to 90 days after randomization. Secondary outcomes included pleurodesis failure at 30 and 180 days; time to pleurodesis failure; number of nights spent in the hospital over 90 days; patient-reported thoracic pain and dyspnea at 7, 30, 90, and 180 days; health-related quality of life at 30, 90, and 180 days; all-cause mortality; and percentage of opacification on chest radiograph at drain removal and at 30, 90, and 180 days.

RESULTS Among 330 patients who were randomized (mean age, 68 years; 181 [55%] women), 320 (97%) were included in the primary outcome analysis. At 90 days, the pleurodesis failure rate was 36 of 161 patients (22%) in the talc poudrage group and 38 of 159 (24%) in the talc slurry group (adjusted odds ratio, 0.91 [95% CI, 0.54-1.55]; $P = .74$; difference, −1.8% [95% CI, −10.7% to 7.2%]). No statistically significant differences were noted in any of the 24 prespecified secondary outcomes.

CONCLUSIONS AND RELEVANCE Among patients with malignant pleural effusion, thoracoscopic talc poudrage, compared with talc slurry delivered via chest tube, resulted in no significant difference in the rate of pleurodesis failure at 90 days. However, the study may have been underpowered to detect small but potentially important differences.

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Visual Abstract

Supplemental content

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Malignant pleural effusion (MPE) is a common condition that may be associated with a variety of cancer subtypes. For many individuals with MPE, associated dyspnea and the resultant functional disability pose a significant management challenge.

Although ambulatory drainage options are becoming common in some regions,[1,2] these are not available to most patients worldwide and do not reliably lead to cessation of fluid production (pleurodesis).[1,3] In addition, many patients or clinicians prefer to pursue pleurodesis as the primary management strategy.[4] As such, pleurodesis remains the default treatment for the majority of individuals with MPE.[5-7] Data from meta-analyses and large prospective studies strongly support sterile talc powder being the optimum agent for inducing pleurodesis,[8] with graded talc being safest.[9,10]

Talc may be delivered at the bedside through an intercostal chest tube in the form of a slurry or sprayed directly onto the pleural surface during a thoracoscopic procedure (poudrage). Pulmonologist-led thoracoscopy with local anesthesia and moderate sedation (also known as *pleuroscopy*) is now an established alternative to thoracoscopy with general anesthesia,[11] although most randomized studies regarding pleurodesis have used the latter, meaning existing data may not be representative of current practice.[8]

There is no consensus on whether slurry or poudrage is the more effective technique for delivering talc to patients with MPE, thus, clinical practice and recommendations are inconsistent.[4,12] Previous studies have been inconclusive or criticized because of small sample sizes, the use of surrogate or non-patient-focused outcomes, and high rates of serious adverse events related to the use of ungraded talc formulations.[13-15]

This study was designed to test the hypothesis that talc poudrage during thoracoscopy with local anesthesia was more effective than talc slurry delivered via chest tube at inducing pleurodesis in patients with MPE.

Key Points

Question Is thoracoscopy with local anesthesia and administration of talc poudrage more effective than chest tube placement with local anesthesia and administration of talc slurry at inducing pleurodesis in individuals with malignant pleural effusion?

Findings In this randomized clinical trial that included 330 patients, thoracoscopic talc poudrage, compared with chest tube insertion and talc slurry, resulted in no significant difference in the rate of pleurodesis failure at 90 days (22% vs 24%).

Meaning Among patients with malignant pleural effusion, there was no significant difference in the rate of pleurodesis failure between the use of talc poudrage and talc slurry; however, the study may have been underpowered to detect small but potentially important differences.

Methods

Trial Design

The TAPPS (Evaluating the efficacy of Thoracoscopy And talc Poudrage versus Pleurodesis using talc Slurry) trial was a randomized, open-label, parallel-group superiority trial of 2 established interventions for inducing pleurodesis. Study oversight was provided by North Bristol National Health Service (NHS) Trust, the trial steering committee, and an independent data monitoring committee. The trial protocol can be found in Supplement 1. Ethical approval was provided by the National Research Ethics Service Committee (12/NW/0467) (sections 1a to 1c in Supplement 2).

Trial Setting and Participants

Patients were screened and recruited from 17 hospitals in the United Kingdom. All participants provided written informed consent to be enrolled in the trial and undergo the intervention. All sites had established, pulmonologist-led thoracoscopy services and had experience in providing both trial interventions.

Eligible patients were required to have an MPE that was either proven histocytologically, an unexplained effusion in the context of proven cancer, or suggested by pleural changes consistent with malignancy on cross-sectional imaging. Participants were required to be able to tolerate thoracoscopy with moderate sedation and have an estimated survival of longer than 3 months. Patients were ineligible if they were younger than 18 years, required a thoracoscopy for diagnostic purposes (because they could not ethically be randomized to undergo chest tube placement with talc slurry), were pregnant or lactating, had known pleural characteristics that would normally contraindicate pleurodesis (eg, lung entrapment or fluid loculation, as judged by the local recruiting clinician), did not have sufficient fluid present to safely perform thoracoscopy without inducing a pneumothorax, or had contraindications to any study intervention. For more information on inclusion and exclusion criteria, see sections 1d and 1e in Supplement 2.

Randomization

Participants were randomly assigned to the talc poudrage or talc slurry group in a 1:1 ratio through a centralized, web-based system using a computer-generated minimization algorithm (with a random component of 80%).[16] The minimization algorithm minimized the imbalance between treatment groups with respect to the minimization factors of underlying malignancy (mesothelioma, breast cancer, lung cancer, other) and World Health Organization (WHO) performance status (0-1, 2-3). The study was conducted on an open-label basis; thus, participants, clinicians, and data collectors were aware of treatment allocation. Patient blinding was not practical because of the inherent differences between the interventions, and the use of sham procedures was not felt to be ethical given the limited availability of interventional sessions for thoracoscopy at most participating hospitals. Trial procedures were completed within 72 hours of randomization. See section 1h in Supplement 2 for more details regarding randomization.

Interventions

Patients in the talc poudrage group underwent thoracoscopy with local anesthesia. Following complete drainage and inspection of the chest cavity, 4 g of dry, sterile, graded talc powder (Steritalc, Novatech) was insufflated into the pleural space

with a view to achieving even pleural coverage. A 16-24 French gauge chest tube was inserted at the end of the procedure and a chest radiograph was performed 18 to 24 hours later.

Patients in the talc slurry group underwent insertion of a 12-14 French gauge chest tube using ultrasonography guidance while under local anesthesia. Insertion was performed or supervised by clinicians who were experienced and fully independent practitioners. A chest radiograph was performed 18 to 24 hours after chest tube insertion and patients without unexpanded lung or significant residual pleural opacification received 4 grams of sterile graded talc in the pleural cavity in the form of a slurry.

Patients in both treatment groups received thoracic suction, if tolerated, applied via the chest tube for a minimum of 24 hours. Unless clinically indicated, tubes could not be removed within 24 hours of receiving talc or if fluid output exceeded 250 mL per day. Following tube removal, discharge from the hospital was left to the discretion of local investigators. See eFigures S1 and S2 in section 1i in Supplement 2 for additional details regarding trial procedures.

Follow-up

Patients were followed up until 180 days after randomization or death, whichever occurred first. Trial visits were conducted at the hospital at 30, 90, and 180 days after randomization. Any patient who was noted to have worsening dyspnea was recommended to undergo a chest radiograph as an initial assessment, with the presence of progressive pleural opacification followed by either ultrasonography or a computed tomographic scan to identify fluid. If fluid was confirmed on the same side as the previous trial intervention, and the chest radiographic image showed greater than one-third hemithorax opacification by visual estimation, the clinician could undertake any required interventions to relieve symptoms. However, for patients in whom the degree of opacification was potentially more contentious, defined as less than one-third of the hemithorax by visual estimation, the clinician was required to discuss the need for further intervention with a second clinician who was to remain blind to treatment group.

Outcomes

The primary outcome was pleurodesis failure at 90 days after randomization (section 1l in Supplement 2). Pleurodesis failure was recorded if the patient underwent any of the following interventions on the same side as the trial intervention during the follow-up period: removal of ≥100 mL of fluid during thoracentesis (this threshold was chosen to distinguish between a low-volume diagnostic procedure and a higher-volume therapeutic procedure); chest tube insertion for fluid management; insertion of an indwelling pleural catheter; or thoracoscopy of any kind. If any of these procedures were deemed necessary by the clinician but were not done because the patient declined or died, this was recorded as a treatment failure. In all other cases, if a patient died during follow-up then no failure was recorded.

Secondary outcomes included pleurodesis failure at 30 and 180 days after randomization; percentage of pleural opacification on chest radiograph after tube removal and at 30, 90, and 180 days after randomization[17]; all-cause mortality up to 180 days after randomization; time to pleurodesis failure within 180 days of randomization; cumulative number of nights spent in the hospital after randomization; self-reported health-related quality of life at 30, 90, and 180 days after randomization, measured using the EuroQoL 5-dimension 5-level questionnaire (EQ-5D-5L)[18] (responses were converted to a utility score ranging from −0.59 to 1.00[19]; scores on the visual analog scale [VAS] ranged from 0 mm to 100 mm; higher scores indicate better quality of life) and the 36-Item Short Form Survey (SF-36; individual domain scores were transformed to a scale from 0 [worst health] to 100 [best health] before being converted into an SF-6D utility score ranging from 0.257 to 1.00, with higher scores indicating better quality of life)[20-22]; and self-reported chest pain and dyspnea, measured using a VAS at 7, 30, 90, and 180 days (scale range, 0 mm to 100 mm; 0 indicates the complete absence of symptoms and 100 indicates the most severe symptoms). The minimal clinically important difference (MCID) for dyspnea in malignant pleural effusion using the VAS is 19 (95% CI, 14-24), with MCIDs for other measures not established in this population.[23] See section 1o in Supplement 2 for additional information regarding secondary outcomes.

Exploratory outcomes, which were added during trial recruitment but before data were available to investigators, were percentage of pleural opacification on chest radiographic image (assessed categorically as no visible fluid, 1%-24% opacification, 25%-49% opacification, and ≥50% opacification) at drain removal and 30, 90, and 180 days after randomization and degree of visible lung entrapment on chest radiograph at 180 days (categorized as no lung entrapment or minor [1%-24%], moderate [25%-49%], or severe [≥50%] entrapment) (section 1p in Supplement 2).

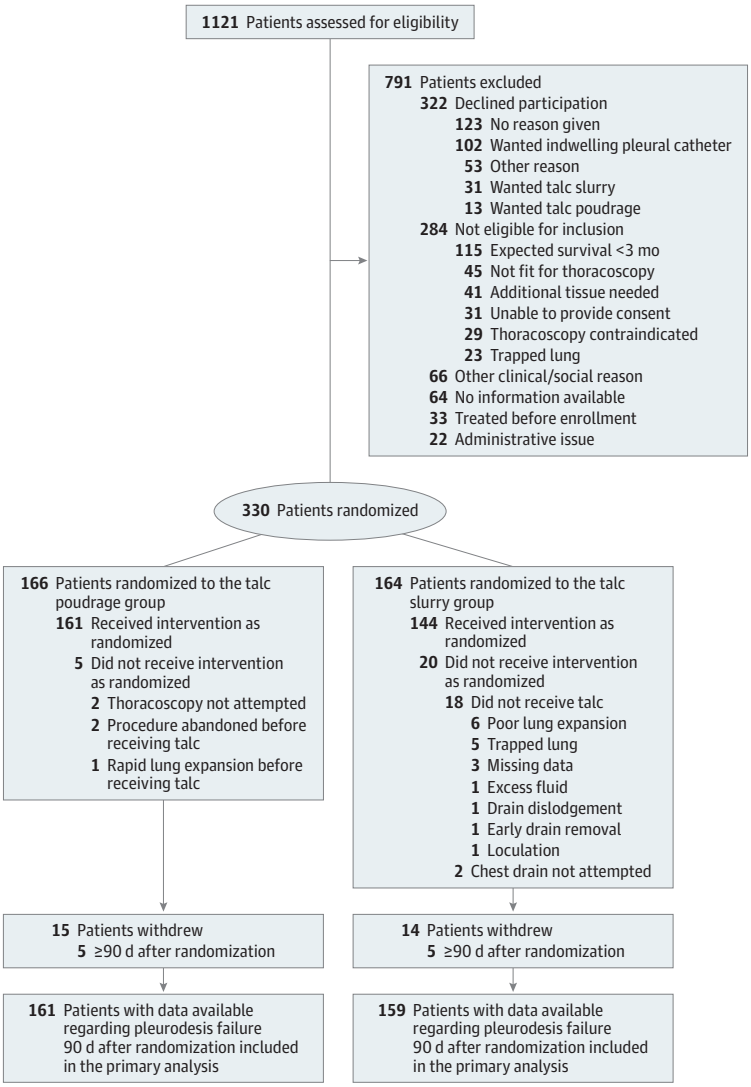
Adverse events were recorded at each trial visit. Serious adverse events were assessed locally before being verified independently by the trial sponsor and subsequently by the chief investigator and the independent data monitoring committee.[24] Final classification of all adverse events was performed by an independent third party who was blind to treatment allocation. See section 3 in Supplement 2 for more information regarding adverse events.

Sample Size and Statistical Analysis

Previous literature suggested that patients with WHO performance scores of 2 or better would be expected to have a pleurodesis failure rate of 10% with talc poudrage and 30% with talc slurry.[25] Thus, to detect an absolute difference of 15% in the pleurodesis failure rate (assuming failure rates of 10% with poudrage and 25% with slurry; odds ratio, 0.33) with 90% power at the 5% significance level, a total of 325 patients (randomized in a 1:1 ratio) was required, accounting for 10% loss to follow-up. The final recruitment target was rounded up to 330 patients.

All patients with a recorded outcome were analyzed according to their randomized treatment group; participants with missing outcome data were excluded from analysis.[26] All analyses were adjusted for the minimization variables

Figure 1. Flow of Patients in a Study of the Effect of Thoracoscopic Talc Poudrage vs Talc Slurry via Chest Tube on Pleurodesis Failure Rate Among Patients With Malignant Pleural Effusions



(underlying malignancy, WHO performance status 0-1 vs 2-3),[27] with analysis of VAS scores also adjusted for baseline values. Pleurodesis failure outcomes (including the primary outcome) and mortality were analyzed using a logistic regression model. A mixed-effects linear regression model was used to analyze pleural opacification, thoracic pain, and dyspnea. A competing risk time-to-event regression model (with mortality as the competing risk) was used for time to pleurodesis failure within 180 days. The number of nights in the hospital was analyzed with a negative binomial regression model. Quality of life measures were analyzed using linear regression.

Sensitivity analyses were performed to assess robustness of results under different missing data assumptions.[26,28] Additional post hoc sensitivity analyses were performed for the primary outcome, including a competing risk time-to-event model for pleurodesis failure at 90 days, an unadjusted analysis, and a mixed-effects logistic regression model that included a random intercept for study site. Subgroup analyses for the primary outcome were performed using interaction tests. Analyses performed compared patients who were receiving cancer treatment vs no treatment at baseline; with WHO performance status 0 vs 1 vs 2 vs 3; steroid treatment vs no treatment at baseline; with attempt at pleurodesis in last 30 days vs no attempt at pleurodesis; and with primary malignant diagnosis of breast cancer vs lung cancer vs mesothelioma vs other. All *P* values were 2-sided and considered significant at $P < .05$. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

No interim analyses were planned or conducted. Analyses were performed using Stata version 15 (StataCorp). See sections 1f, 1g, 1j, to 1q and eTables S1 and S2 in Supplement 2 for further details of the analyses, including statistical code used

Table 1. Summary of Patient Baseline Characteristics in a Study of the Effect of Thoracoscopic Talc Poudrage vs Talc Slurry via Chest Tube on Pleurodesis Failure Rate Among Patients With Malignant Pleural Effusions

Characteristic	No. of Patients (%)	
	Talc Poudrage Group (n = 166)[a]	Talc Slurry Group (n = 164)[a]
Age, mean (SD), y	68 (11)	68 (12)
Women	96 (58)	85 (52)
Men	70 (42)	79 (48)
Smoking status	(n = 165)	
Current smoker	13 (8)	12 (7)
Former smoker	104 (63)	98 (60)
Never smoker	48 (29)	54 (33)
WHO status[b]	(n = 165)	
0	17 (10)	18 (11)
1	82 (50)	81 (49)
2	46 (28)	49 (30)
3	20 (12)	16 (10)
Pleural intervention[c] in the past 3 months	117 (70)	121 (74)
Pleurodesis attempt in the past month	2 (1)	3 (2)
Duration of symptoms, wk		
<1	5 (3)	6 (4)
1-3	40 (24)	35 (21)
>3	121 (73)	123 (75)
Pleural opacification, mean (SD), %	54 (20)[d] [n = 37]	47 (20)[d] [n = 37]
Underlying cancer type		
Lung	59 (36)	54 (33)
Breast	50 (30)	49 (30)
Mesothelioma	15 (9)	19 (12)
Other	15 (9)	5 (3)
Lower gastrointestinal tract	6 (4)	9 (5)
Kidney	5 (3)	11 (7)
Ovarian	6 (4)	7 (4)
Upper gastrointestinal tract	4 (2)	4 (2)
Unknown	3 (2)	4 (2)
Lymphoma	3 (2)	2 (1)
Medications		(n = 163)
Anticoagulant therapy	29 (17)	35 (21)
Oral corticosteroid	22 (13)	24 (15)
Nonsteroidal anti-inflammatory	21 (13)	29 (18)
Other analgesic	118 (71)	107 (66)
Cancer treatment		(n = 163)
Radiotherapy	48 (29)	40 (25)
Chemotherapy	15 (9)	33 (20)
Cancer-modulating hormone therapy	27 (16)	17 (10)
Anticancer monoclonal antibodies	5 (3)	6 (4)
Other anti-cancer therapy	2 (1)	6 (4)

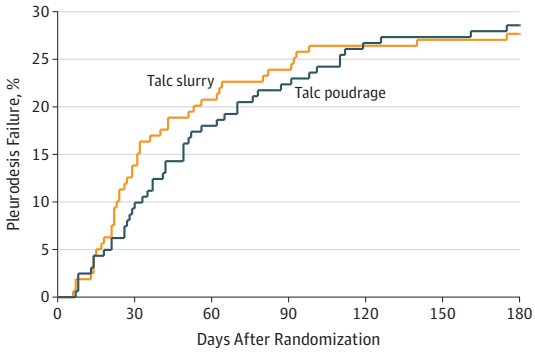
[a] Unless otherwise stated.

[b] World Health Organization (WHO) performance status score ranges from 0-4; 0 indicates a fully active individual with no functional limitation; 1, limitation only when undertaking strenuous activity; 2, limitation when undertaking any work activity but ambulatory and able to self-care; 3, restriction such that only limited self-care is possible; and 4, complete disability with no ability to self-care.

[c] Pleural interventions were diagnostic or therapeutic thoracentesis, image-guided biopsy, intercostal drain insertion, indwelling pleural catheter insertion, local anesthetic or surgical thoracoscopy, and other.

[d] Chest radiograph was not required at time of enrollment unless clinically indicated. Suitability for study entry was typically assessed using thoracic ultrasonography.

Figure 2. Pleurodesis Failure Within 180 Days After Randomization in a Study of the Effect of Thoracoscopic Talc Poudrage vs Talc Slurry via Chest Tube on Pleurodesis Failure Rate Among Patients With Malignant Pleural Effusions



No. at risk							
Talc slurry	159	137	126	121	117	116	115
Talc poudrage	161	146	132	125	118	117	115

The primary outcome analysis took place 90 days after randomization. At this point, 36 of 161 patients (22%) in the talc poudrage group had pleurodesis failure compared with 38 of 159 (24%) in the talc slurry group (adjusted odds ratio [OR], 0.91 [95% CI, 0.54-1.55]; $P = .74$). At 180 days, failure rates were 46 of 161 patients (29%) in the talc poudrage group and 44 of 159 (28%) in the talc slurry group (OR, 1.05 [95% CI, 0.63-1.73]; $P = .86$).

for analysis. The trial statistical analysis plan can be found in Supplement 3.

Results

Recruitment and follow-up took place between August 2012 and April 2018. The target of the inclusion of 330 patients was achieved after 1121 patients were assessed for eligibility, of whom 284 did not meet the inclusion criteria and 322 declined to participate. A total of 166 patients were randomized to the talc poudrage group and 164 to the talc slurry group. Of these randomized patients, 161 (97%) in the talc poudrage group and 159 (97%) in the talc slurry group were included in the analysis of the primary outcome; 161 of 166 patients (97%) in the poudrage group and 144 of 164 (89%) in the slurry group received talc as intended (**Figure 1**).

Baseline and Postdrainage Characteristics

The treatment groups were well matched at baseline, although fewer patients in the poudrage group were receiving chemotherapy at enrollment (15 of 166 [9%]) than in the slurry group (33 of 164 [20%]). The majority of randomized patients had a WHO performance score of 1 or 2 (258 of 330 [78%]) at baseline and had either lung or breast cancer (212 of 330 [64%]).

On chest radiograph 18 to 24 hours after fluid drainage, 85 of 106 patients (80%) in the poudrage group had fully expanded lung compared with 90 of 109 (83%) in the slurry group. At the time of tube removal, full expansion was seen in 92 of 105 patients (88%) in the poudrage group and 90 of 98 (92%) in the slurry group. Further details are provided in **Table 1** and eTables S3-S8 and S19 in Supplement 2.

Table 2. Secondary Outcome Results in a Study of the Effect of Thoracoscopic Talc Poudrage vs Talc Slurry via Chest Tube on Pleurodesis Failure Rate Among Patients With Malignant Pleural Effusions

Outcome	Mean (SD)		Adjusted[b] Treatment Effect Estimate of Poudrage vs Slurry (95% CI)	*P* Value[b]
	Talc Poudrage Group (n = 166)[a]	Talc Slurry Group (n = 164)[a]		
Pleurodesis failure at 30 d, No./Total No. (%)	16/161 (10)	22/159 (14)	Odds ratio, 0.69 (0.34 to 1.37)	.29
Pleurodesis failure at 180 d, No./Total No. (%)	46/161 (29)	44/159 (28)	Odds ratio, 1.05 (0.63 to 1.73)	.86
Time to pleurodesis failure within 180 d, median (IQR), d[c]	NR (91 to NR) [n = 161]	NR (80 to NR) [n = 159]	Hazard ratio, 1.01 (0.67 to 1.52)	.98
Participants who experienced pleurodesis failure	46 (26-78) [n = 46]	30 (21 to 59) [n = 44]		
All-cause mortality at 180 d, No./Total No. (%)	66/165 (40)	68/163 (42)	Odds ratio, 0.91 (0.58 to 1.44)	.70
No. of nights spent in the hospital within 90 d, mean (SD)	12.1 (13.0) [n = 165]	10.8 (10.0) [n = 162]	Rate ratio, 1.11 (0.89 to 1.37)	.35
Median (IQR)	7 (4-16)	7 (4-14)		
Change in VAS thoracic pain score from baseline, mean (SD), mm[d]	(n = 142 with ≥1 measurement)	(n = 146 with ≥1 measurement)	Absolute difference	
Baseline	17.0 (23) [n = 165]	17.7 (25) [n = 163]		
7 d	1.0 (25) [n = 108]	2.3 (28) [n = 98]	−1.2 (−6.9 to 4.6)	.69
30 d	−1.5 (25) [n = 123]	−5.6 (26) [n = 124]	1.2 (−3.5 to 6.0)	.61
90 d	−2.5 (23) [n = 91]	−6.9 (24) [n = 93]	0.5 (−4.8 to 5.8)	.85
180 d	−2.0 (23) [n = 68]	−6.2 (23) [n = 69]	0.8 (−4.6 to 6.2)	.78
Change in VAS dyspnea score from baseline, mean (SD), mm[d]	(n = 142 with ≥1 measurement)	(n = 146 with ≥1 measurement)	Absolute difference	
Baseline	53 (29) [n = 165]	53 (33) [n = 163]		
7 d	−31 (32) [n = 106]	−29 (35) [n = 99]	−2.0 (−8.0 to 4.0)	.51
30 d	−28 (32) [n = 123]	−23 (39) [n = 124]	−4.4 (−11.1 to 2.3)	.20
90 d	−25 (35) [n = 91]	−29 (36) [n = 93]	2.1 (−5.4 to 9.6)	.58
180 d	−30 (33) [n = 68]	−29 (43) [n = 68]	−3.8 (−12.7 to 5.2)	.41
Pleural opacification, mean (SD), %	(n = 125 with ≥1 measurement)	(n = 115 with ≥1 measurement)	Absolute difference	
Baseline	54 (20) [n = 37]	47 (20) [n = 37]		
Tube removal	16 (12) [n = 105]	17 (15) [n = 98]	−0.8 (−4.5 to 2.9)	.66
Median (IQR)	15 (7-23)	14 (5-28)		
30 d	25 (19) [n = 89]	26 (18); [n = 76]	−1.5 (−6.7 to 3.7)	.58
Median (IQR)	21 (10-37)	21 (13-37)		
90 d	20 (19); [n = 65]	21 (19); [n = 47]	−2.5 (−8.9 to 3.9)	.45
Median (IQR)	15 (5-28)	18 (6-31)		
180 d	17 (14) [n = 35]	16 (13) [n = 37]	−0.8 (−6.7 to 5.1)	.79
Median (IQR)	14 (4-23)	15 (6-23)		
EQ-5D-5L utility score, mean (SD)[e]			Absolute difference	
Baseline	0.57 (0.26) [n = 163]	0.55 (0.26) [n = 164]		
30 d	0.60 (0.26) [n = 132]	0.60 (0.27) [n = 132]	0.00 (−0.06 to 0.07)	.89
90 d	0.60 (0.29) [n = 95]	0.65 (0.27) [n = 100]	−0.05 (−0.13 to 0.04)	.23
180 d	0.71 (0.22) [n = 69]	0.68 (0.26) [n = 72]	0.04 (−0.04 to 0.12)	.31

(continued)

Table 2. Secondary Outcome Results in a Study of the Effect of Thoracoscopic Talc Poudrage vs Talc Slurry via Chest Tube on Pleurodesis Failure Rate Among Patients With Malignant Pleural Effusions (continued)

Outcome	Mean (SD)		Adjusted[b] Treatment Effect Estimate of Poudrage vs Slurry (95% CI)	*P* Value[b]
	Talc Poudrage Group (n = 166)[a]	Talc Slurry Group (n = 164)[a]		
EQ-5D-5L VAS score, mean (SD), mm[e]			Absolute difference	
Baseline	50 (22) [n = 160]	50 (22) [n = 164]		
30 d	59 (23) [n = 132]	55 (25) [n = 132]	4 (−2 to 9)	.24
90 d	63 (23) [n = 95]	60 (23) [n = 98]	3 (−4 to 9)	.41
180 d	66 (23) [n = 70]	66 (21) [n = 71]	0 (7 to 8)	.98
SF-6D utility score, mean (SD)[f]			Absolute difference	
Baseline	0.58 (0.11) [n = 157]	0.56 (0.12) [n = 153]		
30 d	0.59 (0.11) [n = 125]	0.60 (0.12) [n = 123]	0 (−0.03 to 0.03)	.78
90 d	0.63 (0.11) [n = 89]	0.64 (0.14) [n = 96]	0 (−0.04 to 0.03)	.90
180 d	0.65 (0.12) [n = 67]	0.64 (0.12) [n = 71]	0.01 (−0.03 to 0.05)	.77

Abbreviations: IQR, interquartile range; NR, not reached; VAS, visual analog scale.

[a] Unless otherwise stated.

[b] All analyses were adjusted for the minimization variables (underlying malignancy [mesothelioma, breast cancer, lung cancer, other] and WHO performance status [0-1, 2-3]) by including them as fixed covariates in a regression model. *P* values were calculated directly from the adjusted regression model.

[c] A total of 49 of 159 patients (31%) in the slurry group and 42 of 161 (26%) in the poudrage group died before experiencing pleurodesis failure, and 44 (28%) in the slurry group and 46 (29%) in the poudrage group experienced pleurodesis failure within 180 days of randomization. Analysis included all patients (159 in the slurry group and 161 in the poudrage group). The adjusted hazard ratio from a post hoc Cox model that did not incorporate mortality as a competing risk was 1.01 (95% CI, 0.67-1.52).

[d] Self-reported thoracic pain and dyspnea were measured using a VAS ranging from 0 to 100 mm, with a score of 0 indicating the complete absence of symptoms and 100 the maximum possible level of symptoms. The minimal clinically important difference for dyspnea in patients with malignant pleural effusion (using a 0-100 mm VAS scale) is 19 mm (95% CI, 14-24), with minimal clinically important differences for other measures not established in this population.

[e] EuroQoL 5-dimension 5-level questionnaire (EQ-5D-5L) responses were converted into a utility score ranging from −0.59 to 1.00 and scores on the VAS ranging from 0 to 100 mm, with higher scores indicating better quality of life.

[f] For the 36-Item Short Form Survey (SF-36), individual domain scores were transformed to a scale ranging from 0 (worst health) to 100 (best health) before being converted into a SF-6D utility score ranging from 0.257 to 1.00, with higher scores indicating better quality of life.

Primary Outcome

At 90 days after randomization, the pleurodesis failure rate was 36 of 161 patients (22%) in the poudrage group and 38 of 159 (24%) in the slurry group (adjusted odds ratio [OR], 0.91 [95% CI, 0.54-1.55]; *P* = .74; difference, -1.8% [95% CI, -10.7 to 7.2]) (**Figure 2**). There were 27 (17%) deaths before pleurodesis failure in the poudrage group and 34 (21%) in the slurry group. A post hoc sensitivity analysis that incorporated mortality as a competing risk showed similar results to the primary analysis (hazard ratio, 0.91 [95% CI, 0.58-1.43]; eTable S23 in Supplement 2). Additional sensitivity analyses supported these results (eTables S21 and S22 and eFigure S3 in Supplement 2). For more details regarding primary outcome results, including prespecified subgroup analyses, see eTables S9, S10, and S20 in Supplement 2.

Additional Outcomes

Additional outcome data are summarized in **Table 2**, eTables S11 to S18 and S30 to S32, and eFigures S4 to S6 in Supplement 2. At 30 days after randomization, 16 of 161 patients (10%) in the talc poudrage group had failed pleurodesis compared with 22 of 159 (14%) in the talc slurry group (OR, 0.69, [95% CI, 0.34-1.37]; *P* = .29; difference, -1.7% [95% CI, -6.0% to 2.6%]). At 180 days, failure rates were 46 of 161 patients (29%) in the poudrage group and 44 of 159 (28%) in the slurry group (OR, 1.05 [95% CI, 0.63-1.73], *P* = .86; difference, 0% [95% CI, -9.3% to 9.3%]). No significant difference was found between the groups in time to pleurodesis failure (hazard ratio, 1.01 [95% CI, 0.67-1.52]). There was also no significant difference in all-cause mortality up to 180 days after randomization (eFigure S4 in Supplement 2); 66 of 165 patients (40%) patients in the poudrage group died and 68 of 163 (42%) in the slurry group died (OR, 0.91 [95% CI, 0.58-1.44]; *P* = .35; difference, -1.1% [95% CI, −11.3% to 9.1%).

The mean number of nights patients spent in the hospital in the 90 days after randomization, including the initial stay for trial treatment, was 12.1 (95% CI, 10.1-14.1) in the talc poudrage group and 10.8 (95% CI, 9.3-12.4) in the talc slurry group (rate ratio, 1.11 [95% CI, 0.89-1.37]; *P* = .35; difference, 1.2 [95% CI, −1.3 to 3.7]). No significant between-group differences were seen in chest pain or dyspnea at 7, 30, 90, or 180 days after randomization (Table 2 and eFigures S5 and S6 in Supplement 2).

At the time of tube removal, the mean percentage of pleural opacification was 16% (95% CI, 14%-19%) in the talc

poudrage group and 17% (95% CI, 14%-20%) in the talc slurry group (difference, −0.8% [95% CI, −4.5% to 2.9%]; P = .66). No significant differences in opacification were subsequently seen between treatment groups at 30, 90, or 180 days after randomization (Table 2). There were also no significant between-group differences in health-related quality of life at any follow-up point based on either the SF-36 or the EQ-5D-5L questionnaire scores (Table 2).

Adverse Events

Details of adverse events are shown in **Table 3** and eTables S24-29 in Supplement 2. A total of 179 adverse events were recorded in the talc poudrage group and 152 were recorded in the talc slurry group. There were no deaths attributable to either of the trial interventions. Excluding dyspnea due to fluid reaccumulation, the most common adverse events were pneumonia/lower respiratory tract infection (25 in the poudrage group and 19 in slurry group) and pneumothorax unrelated to the trial interventions (15 in the poudrage group and 18 in the slurry group). More cases of pleural infection were noted in the poudrage group than in the slurry group (6 vs 0), while tube dislodgement was more common in the slurry group than the poudrage group (9 vs 2).

Table 3. Reported Adverse Events in a Study of the Effect of Thoracoscopic Talc Poudrage vs Talc Slurry via Chest Tube on Pleurodesis Failure Rate Among Patients With Malignant Pleural Effusions

Adverse Event	No. of Events	
	Talc Poudrage Group (n = 166)	Talc Slurry Group (n = 164)
Pneumonia/chest infection	25	19
Other pleural intervention related, pneumothorax/ bronchopleural fistula	15	18
Anemia	10	4
Medication/chemotherapy adverse effect	9	13
Infection other than chest	7	5
Pulmonary embolism	7	9
Lung entrapment	4	1
Cardiac arrhythmia	2	2
Tube dislodgement/ unintentional removal	2	9
Other[a]	17	20
Disease progression		
Dyspnea due to fluid	23	20
Dyspnea not due to fluid	4	4
Death	7	5
Trial intervention-related event[b]		
Other/unspecified	10	7
Pain	9	6
Surgical emphysema	9	2
Pleural infection	6	0
Hypoxia	4	0
Pneumothorax/ bronchopleural fistula	3	4
Subcutaneous infection	3	3
Bleeding	2	1
Cough	1	0
Total events	179	152

[a] Other includes accidental injury, cerebrovascular event, disease progression (metastasis, nausea/vomiting, pain, and other), indwelling pleural catheter blockage, abnormal blood test, other unspecified event, pleural infection (not trial related), and venous thromboembolic event (not pulmonary embolism).

[b] Categorization and likelihood of an event being related to the trial was assessed by a blinded, independent pulmonologist.

Discussion

In this randomized clinical trial that compared the efficacy of talc poudrage delivered during thoracoscopy with moderate sedation vs chest tube and talc slurry in inducing pleurodesis in individuals with MPE, there was no significant difference between the treatments in the primary outcome of pleurodesis failure rate at 90 days. Results of sensitivity analyses supported this finding. No significant differences in secondary outcomes were noted, including pleurodesis failure rate at 180 days and all-cause mortality.

Previous studies addressing the optimal method for talc delivery have been considered inconclusive, resulting in inconsistency in both practice and recommendations.[4,12] The study by Dresler et al,[14] which analyzed 482 patients, also found no significant difference between talc poudrage and slurry (failure rates of 22% vs 29% at 30 days), but required patients to be well enough to undergo general anesthesia and video-assisted thoracoscopic surgery, noted high respiratory complication rates as a result of ungraded talc being used, and adopted a primary outcome for pleurodesis that was assessed radiologically rather than in a clinically oriented fashion.[14]

It has previously been shown that talc slurry can be administered safely and effectively on an outpatient basis through an indwelling pleural catheter.[29] With that approach, pleurodesis failure was substantially more common than noted in this study (57% at 35 days after randomization), although no direct comparison has ever been made with the inpatient methods described in the current study.[30]

Aside from perceived benefits in pleurodesis success, a clinician's choice of talc poudrage or talc slurry has traditionally been based on several factors, including whether a chest tube has already been inserted; local infrastructure, experience, and training; and patient phenotype with regard to fluid production and accessibility. However, increasing priority is now given to recognizing patient choice in MPE management.[6,7,31] The current data lend further support to the development of flexible treatment pathways, with treatment for individuals with MPE tailored to the wishes, needs, and risk factors of the individual patient, with the knowledge that treatment effectiveness is unlikely to be affected by how talc is delivered.[7,30,32]

Limitations

This study has several limitations. First, participants were required to be able to tolerate thoracoscopy under moderate sedation, meaning the results may be less generalizable to more frail patients. Second, the study was conducted on an

open-label basis and thus it was possible that decisions regarding the need for further interventions during follow-up (the primary outcome) could have been influenced by clinicians' knowledge of the randomized procedure, although a requirement for blinded assessment of small effusions attempted to mitigate this risk. Third, the trial was powered to detect a 15% difference between the treatment groups and was therefore underpowered to detect smaller differences that might be considered clinically relevant by some. Fourth, the study follow-up duration of 180 days may not have been long enough to inform long-term care decisions in patients with certain subtypes of MPE, especially breast cancer or mesothelioma, for whom there is a longer median survival time.[33,34]

Conclusions

Among patients with malignant pleural effusion, thoracoscopic talc poudrage, compared with talc slurry via chest tube, resulted in no significant difference in pleurodesis failure rate at 90 days. However, the study may have been underpowered to detect small but potentially important differences.

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