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

A Randomized Clinical Trial

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Question: Is local anesthetic thoracoscopy and talc poudrage more effective than chest drain and slurry at inducing pleurodesis in those with malignant pleural effusion.

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

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

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 talc poudrage during local anesthetic thoracoscopy was more effective than talc slurry via chest tube in leading to successful pleurodesis.

Design, Setting, and Participants Open-label, randomized clinical trial conducted at seventeen hospitals in the United Kingdom. 330 participants were enrolled from August 2012 to April 2018 and followed until October 2018. Patients were eligible if they were aged over 18 years, had a confirmed diagnosis of MPE needing pleurodesis and were sufficiently fit for local anesthetic thoracoscopy. Main exclusions were the need for pleural tissue or evidence of non-expandable lung.

Interventions 166 patients were allocated to the intervention group and had 4g talc poudrage at thoracoscopy under moderate sedation. 164 patients were allocated to the control group and had bedside chest tube insertion followed by 4g 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 in 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, mortality, and percentage radiographic opacification at drain removal, 30, 90 and 180 days.

Results Among 330 patients who were randomized (mean age 68 years; 181 (55%) female), 320 (97%) were included in the primary outcome analysis. At 90 days, pleurodesis failure rate was 36/161 (22%) with poudrage and 38/159 (24%) with slurry (adjusted odds ratio [poudrage vs slurry] 0.91, 95% confidence interval 0.54-1.55, P = .74; difference in percentage points –1.8, 95% confidence interval –

10.7 to 7.2). No statistically significant differences were noted in any of the 24 pre-specified secondary outcomes.

Conclusions and Relevance Among patients with malignant pleural effusion, local anesthetic thoracoscopic talc poudrage, compared with bedside talc slurry through 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.

Trial Registration clinicaltrials.gov Identifier: ISRCTN47845793.

Introduction

Malignant pleural effusion (MPE) is a common condition which may be associated with a variety of cancer subtypes. For many, 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 for the majority with MPE.[5-7] Meta-analysis and large prospective study data 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 under local anesthetic and moderate sedation (also known as pleuroscopy) is now an established alternative to thoracoscopy under general anesthesia,[11] although most previous randomized studies regarding pleurodesis have utilized the latter, meaning existing data are now poorly-representative of current practice.[8]

There is no consensus on whether slurry or poudrage is the more effective technique for delivering talc in MPE and thus clinical practice and recommendations are inconsistent.[4,12] Previous studies have been inconclusive or criticized due to 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, the TAPPS trial, was designed to test the hypothesis that talc poudrage during local anesthetic thoracoscopy was more effective than slurry via chest tube at inducing pleurodesis in patients with MPE.

Methods

Trial Design

The TAPPS trial was a randomized, open-label, parallel-group superiority trial of two established interventions for pleurodesis. Trial design, implementation, analysis, and manuscript preparation were performed by the trial investigators. Study oversight was provided by North Bristol NHS Trust, the trial steering committee, and an independent data monitoring committee. Ethical approval was provided by the National Research Ethics Service Committee (12/NW/0467). See online supplement sections 1a to 1c.

Trial Setting and Participants

Patients were screened and recruited from seventeen hospitals in the United Kingdom. All participants provided written informed consent to enrolment and to the allocated intervention. All sites had established, pulmonologist-led, local anesthetic thoracoscopy services and had experience of providing both trial interventions.

Eligible patients were required to have a MPE which 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. They were required to be able to tolerate thoracoscopy under moderate sedation and have an estimated survival of greater than three months. Patients were ineligible if they were less than eighteen years old; required a thoracoscopy for diagnostic purposes (as, ethically, they could not then be randomized to receive chest tube and slurry); were pregnant or lactating; had known pleural

characteristics which would normally contraindicate pleurodesis (such as lung entrapment or fluid loculation, both 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. See online supplement sections 1day and 1e.

Randomization

Participants were randomly assigned 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, 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 and thus participants, clinicians, and data-collectors were aware of treatment allocation. Patient blinding was not practical due to 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 undertaken within 72 hours of randomization. See online supplement section 1h.

Interventions

Participants in the intervention (poudrage) group underwent local anesthetic thoracoscopy under moderate sedation. Following complete drainage and inspection of the chest cavity, four grams of dry sterile graded talc powder (Steritalc, Novatech, La Ciotat, France) were 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 performed 18-24 hours later.

Those in the control (slurry) group initially received a 12-14 French gauge chest tube inserted under ultrasound guidance and local anesthetic. Insertion was

performed or supervised by clinicians who were experienced and fully independent practitioners. A chest radiograph was performed 18-24 hours post-insertion and those without unexpanded lung or significant residual pleural opacification were given four grams of sterile graded talc, instilled intrapleurally 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 talc or if fluid output exceeded 250 mL per day. Following tube removal, discharge from hospital was left to the discretion of local investigators. See eFigures S1 and S2 in Supplement, and section 1i in the online supplement.

Follow-up

Patients were followed up until 180 days after randomization, or death. 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 chest radiography as an initial assessment, with the presence of progressive pleural opacification leading to either ultrasound or CT to identify fluid. If fluid was confirmed on the same side as the previous trial intervention, and the chest radiograph showed greater than one third hemithorax opacification by visual estimation, the clinician could undertake any required interventions to relieve symptoms. However, in cases where the degree of radiographic 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 post-randomization. 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: any thoracentesis of ≥100 mL (threshold chosen to distinguish between a low-volume 'diagnostic' procedure, which would not aim to influence symptoms, and a larger-volume 'therapeutic' procedure); chest tube insertion for fluid management; insertion of an indwelling pleural catheter; or thoracoscopy of any kind. If any of these were deemed necessary by the participant's clinician, but were not done because the patient declined, or had died, this was recorded as treatment failure. In all other cases, if a patient died during follow-up then no failure was recorded. See online supplement section 1l.

Secondary outcomes included pleurodesis failure at 30 and 180 days post-randomization; measured percentage radiographic pleural opacification after tube removal and at 30, 90, and 180 days post-randomization;[17] all-cause mortality up to 180 days post-randomization; time to pleurodesis failure within 180 days; cumulative number of nights spent in hospital post-randomization; self-reported health-related quality of life at 30, 90, and 180 days post-randomization (EuroQoL Group 5-Dimensions 5-Level Questionnaire (EQ-5D-5L),[18] responses to which were converted into a utility score ranging from −0.59 to 1.00,[19] and scores on the visual-analogue scale range from 0 to 100, with higher scores indicating better quality of life) and the RAND Short Form Health Survey (SF-36; with individual domains' scores transformed on to a scale 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);[20-22] and self-reported chest pain and dyspnea measured using a visual-analogue scale at 7, 30, 90, and 180 days (VAS; scales running from 0 to 100mm, with a score of 0 indicating the complete absence of symptoms and 100 the maximum possible level of symptoms). The minimal clinically important difference (MCID) for dyspnea in malignant pleural effusion using 0-100mm VAS scale is 19mm (95% CI, 14 to

24mm), with MCIDs for other measures not established in this population.[23] See online supplement section 1o.

Exploratory outcomes, added during trial recruitment but before data were available to investigators, were percentage radiographic pleural opacification (assessed categorically as no visible fluid, 1%-24% opacification, 25%-49% opacification, and 50% or more opacification) at drain removal, 30, 90 and 180 days post randomization; and degree of visible lung entrapment on chest radiograph at 180 days (categorized as no lung entrapment, minor (1%-24% entrapment), moderate (25%-49%), or severe (50% or more)). See online supplement section 1p.

Adverse events were recorded at each trial visit. Serious adverse events were assessed locally before being verified independently by the 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 online supplement section 3.

Sample Size and Statistical Analysis

Previous literature suggested that patients with performance scores of 2 or better would expect to have a pleurodesis failure rate of 10% using talc poudrage and 30% using talc slurry.[25] Thus, at the 5% significance level, in order to detect an absolute 15% difference in pleurodesis failure rate (assuming failure rates of 10% with poudrage and 25% with slurry, odds ratio 0.33) with 90% power, a total of 325 patients (allocated 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 participants with a recorded outcome were analyzed according to their allocated treatment group; participants with missing outcome data were excluded.[26] All analyses were adjusted for the minimization variables (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 radiographic 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. Number of nights in 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 which included a random-intercept for study site. Subgroup analyses for the primary outcome were performed using interaction tests. Analyses performed were anti-cancer treatment vs no treatment at baseline; WHO performance status 0 vs 1 vs 2 vs 3; steroid treatment vs no treatment at baseline; pleurodesis in last 30 days vs no pleurodesis; and primary malignant diagnosis of breast cancer vs lung cancer vs mesothelioma vs other). All *P* values were 2-sided and considered significant at the 0.05 level. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory.

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

Results

Recruitment

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

Baseline and Post-drainage Characteristics

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

On chest radiograph 18-24 hours after fluid drainage, 85/106 (80%) in the poudrage group had fully-expanded lung compared to 90/109 (83%) in the slurry group. Later, at tube removal, full expansion was seen in 92/105 (88%) in the poudrage group and 90/98 (92%) in the slurry group.

Further details are provided in Table 1; eTables S3-S8 and S19 in Supplement.

Primary Outcome

In the primary outcome analysis, at 90 days post randomization, failure rate was 36/161 (22%) in the poudrage group and 38/159 (24%) in the slurry group (adjusted odds ratio (OR) [poudrage vs slurry] 0.91, 95% confidence interval (CI) 0.54 to 1.55, $P = .74$; difference in percentage points –1.8, 95% confidence interval –10.7 to 7.2) (Figure 2). There were 27 deaths prior to failure (17%) in the poudrage group, and 34 (21%) in the slurry group. A post hoc sensitivity analysis which incorporated mortality as a competing risk showed similar results to the

primary analysis (hazard ratio 0.91, 95% CI, 0.58 to 1.43; eTable S23 in Supplement). Additional sensitivity analyses supported these results (eTables S21 and S22; eFigure S3 in Supplement). For more details regarding primary outcome results, including prespecified subgroup analyses, see eTables S9, S10 and S20 in Supplement.

Additional Outcomes

Additional outcome data are summarized in Table 2; eTables S11-18, S30-32; eFigures S4-6.

Pleurodesis Failure and Time to Pleurodesis Failure

At 30 days post randomization, 16/161 (10%) receiving poudrage had failed pleurodesis compared to 22/159 (14%) in the slurry group (OR 0.69, 95% CI, 0.34 to 1.37, *P* = .29; difference in percentage points –1.7, 95% confidence interval -6.0 to 2.6). At 180 days, failure rates were 46/161 (29%) in the poudrage group compared to 44/159 (28%) in the slurry group (OR 1.05, 95% CI, 0.63 to 1.73, *P* = .86; difference in percentage points 0.0, 95% confidence interval -9.3 to 9.3).

No difference was found between the groups in time to pleurodesis failure (hazard ratio 1.01; 95% CI, 0.67 to 1.52).

All-cause Mortality

No significant difference in mortality was observed up to 180 days. 66/165 (40%) patients died in the poudrage group and 68/163 (42%) patients died in the slurry group (OR 0.91, 95% CI, 0.58 to 1.44, *P* = .35; difference in percentage points –1.1, 95% CI, −11.3 to 9.1).

Hospital Stay

Up to 90 days, patients receiving poudrage spent a mean of 12.1 (95% CI, 10.1 to 14.1) nights in hospital after randomization (inclusive of the initial stay for trial treatment), with those receiving slurry spending 10.8 (9.3 to 12.4) nights (rate

ratio 1.11, 95% CI, 0.89 to 1.37, *P* = .35; difference in means 1.2, 95% CI, −1.3 to 3.7)).

Chest Pain and Dyspnea

No significant between-group differences were seen in chest pain or dyspnea at 7, 30, 90 or 180 days post-randomization (See Table 2).

Radiographic Pleural Opacification

At tube removal, mean radiographic pleural opacification was 16 (95% CI, 14 to 19) percent in the poudrage group and 17 (95% CI, 14 to 20) percent in the slurry group (difference in means -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 post randomization (See Table 2).

Health-related Quality of Life

No significant between-group differences in health-related quality of life were seen at any trial follow-up point using either the SF-36 or the EQ-5D-5L questionnaires (See Table 2).

Adverse Events

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

Discussion

In this randomized clinical trial that compared the pleurodesis efficacy of talc poudrage, delivered at thoracoscopy with moderate sedation, against that of chest tube and talc slurry in malignant pleural effusion, there was no significant difference between the treatments in the primary outcome of pleurodesis failure rate at 90 days. Sensitivity analyses supported this finding. No significant differences in secondary outcome measures were noted, including pleurodesis failure rate at 180 days or 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] For example, the study by Dresler et al, which analyzed 482 patients, also found no significant difference between poudrage and slurry (failure rates 22% vs 29% respectively at 30 days) but required patients to be well enough to undergo general anesthetic and video-assisted thoracoscopic surgery to perform poudrage; noted high respiratory complication rates as a result of ungraded talc being used; and adopted a primary outcome for pleurodesis which 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 here, at 57% at 35 days post 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 slurry or poudrage 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 regards to fluid production and accessibility. Importantly, however, increasing priority is now given to recognizing patient choice in MPE management.[6,7,31] These data lend further support to the

development of flexible treatment pathways, with intervention for MPE tailored to the wishes, needs and risks 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 a thoracoscopy under moderate sedation, meaning the results may be less generalizable to frailer 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 which might be considered clinically relevant. Fourth, the study follow-up duration of 180 days may not have been long enough to inform long term care decisions in patients with MPE of certain subtypes, especially breast cancer or mesothelioma, who have longer median survival.[33,34]

Conclusions

Among patients with malignant pleural effusion, local anesthetic thoracoscopic talc poudrage, compared with bedside talc slurry through 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.

Article Information

Author Contributions: Mr Maskell and Mr Kahan had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Trial design, implementation, analysis and manuscript preparation were performed solely by the trial investigators. Professor Maskell and Dr Bhatnagar acted as Chief Investigator and trial coordinator respectively. Ms Piostrowska and Ms

Laskawiec-Szkonter were the trial managers. Ms Zahan-Evans was lead trial nurse. Professor Miller chaired the trial steering committee, which also consisted of Dr Kahan, Professor Maskell, Ms Sivier, Dr Hooper, Dr Davies and Dr Harvey. Independent radiological assessments were performed by Dr Edey and Dr Clive. Independent assessment of adverse events was performed by Dr Slade. Data validation and entry was led by Mr Quaddy. Statistical analyses were performed by Mr Kahan. Health economic analyses were performed by Dr Luengo-Fernandez, Dr Little and Ms Mei. The first draft of the manuscript was prepared by Dr Bhatnagar, Professor Maskell, Professor Miller, Mr Kahan, Dr Luengo-Fernandez and Professor Rahman. All authors reviewed and contributed to the manuscript and gave their approval for submission.

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Data Sharing Statement: All requests for data sharing should be submitted to the corresponding author or Chief Investigator for consideration. Access to anonymized data, if available, or statistical code may be granted following review of a proposal.

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Figure 1. CONSORT diagram showing screening, enrollment and treatment allocation of participants

WHO = World Health Organization

Figure 2. Kaplan-Meier curve for pleurodesis failure to 180 post-randomization

Primary outcome analysis took place at 90 days post randomization. At this point, 36/161 (22%) in the poudrage group had experienced pleurodesis failure compared with 38/159 (24%) in the slurry group (adjusted odds ratio (OR) 0.91, 95% confidence interval (CI) 0.54 to 1.55, *P* = .74). At 180 days, failure rates were 46/161 (29%) in the poudrage group compared to 44/159 (28%) in the slurry group (OR 1.05, 95% CI, 0.63 to 1.73, *P* = .86).

Table 1. Summary of Baseline Characteristics

Characteristic	Summary Measure, No. (%)	
	Thoracoscopy and Poudrage (N = 166)[a]	Chest Tube and Slurry (N = 164)[a]
Age, mean (SD), y	68 (11)	68 (12)
Female	96 (58)	85 (52)
Smoking status		
Current smoker	13/165 (8)	12 (7)
Ex-smoker	104/165 (63)	98 (60)
Never smoker	48/165 (29)	54 (33)
WHO score		
0	17/165 (10)	18 (11)
1	82/165 (50)	81 (49)
2	46/165 (28)	49 (30)
3	20/165 (12)	16 (10)
Pleural interventionb in previous three months	117 (70)	121 (74)
Pleurodesis attempt in previous month	2 (1)	3 (2)
Length of symptoms, wk		
<1	5 (3)	6 (4)
1-3	40 (24)	35 (21)
>3	121 (73)	123 (75)
Percentage radiographic (x-ray) pleural opacification, mean (SD) [No.]	54 (20)[c] [37]	47 (20)[c] [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 GI	6 (4)	9 (5)
Kidney	5 (3)	11 (7)
Ovarian	6 (4)	7 (4)
Upper GI	4 (2)	4 (2)
Unknown	3 (2)	4 (2)
Lymphoma	3 (2)	2 (1)
Medications		
Oral corticosteroid	22 (13)	24/163 (15)
Non-steroidal anti-inflammatory	21 (13)	29/163 (18)
Other analgesic	118 (71)	107/163 (66)
Cancer treatment		
Radiotherapy	48 (29)	40/163 (25)
Chemotherapy	15 (9)	33/162 (20)
Cancer-modulating hormone therapy	27 (16)	17/163 (10)
Anti-cancer monoclonal antibodies	5 (3)	6/163 (4)
Other anti-cancer therapy	2 (1)	6/163 (4)
Anticoagulant therapy	29 (17)	35/163 (21)

[a]Unless otherwise stated.

[b]Pleural interventions were: diagnostic or therapeutic thoracentesis, image guided biopsy, intercostal drain insertion, indwelling pleural catheter insertion, local anesthetic or surgical thoracoscopy, other.
[c]Chest radiography was not required at time of enrolment unless clinically indicated. Suitability for study entry was typically assessed using thoracic ultrasound.
WHO score = World Health Organization performance status score, measured as either 0, 1, 2, 3 or 4, with 0 indicating a fully active individual with no functional limitation; 1 indicating limitation only when undertaking strenuous activity; 2 indicating limitation when undertaking any work activity but ambulatory and able to self-care; 3 indicating restriction such that only limited self-care is possible; and 4 indicating complete disability with no ability to self-care.
See eTable S3 in Supplement for full baseline characteristics data.

Table 2. Summary of Secondary Outcome Results

	Thoracoscopy and Poudrage (N = 166)[+]	**Chest Tube and Slurry (N = 164)[+]**	**Adjusted^ Treatment Effect Estimate [Poudrage vs Slurry] (95% CI)**	***P* Value^**
Pleurodesis failure, No. (%) of patients at 30 d	16/161 (10)	22/159 (14)		
Odds ratio			0.69 (0.34 to 1.37)	.29
Difference in percentage points[a]			−1.7 (−6.0 to 2.6)	-
Pleurodesis failure, No. of patients (%) at 180 d	46/161 (29)	44/159 (28)		
Odds ratio			1.05 (0.63 to 1.73)	.86
Difference in percentage points[a]			0.0 (−9.3 to 9.3)	1.00
Time to pleurodesis failure within 180 d*, median (IQR)	-	-	1.01 (0.67 to 1.52)	.98
All participants	NR (91 to NR) [N = 161]	NR (80 to NR) [N = 159]		
Participants who experienced pleurodesis failure	46 (26 to 78) [N = 46]	30 (21 to 59) [N = 44]		
All-cause mortality at 180 d, No. of patients (%)	66/165 (40)	68/163 (42)		
Odds ratio			0.91 (0.58 to 1.44)	.70
Difference in percentage points[a]			−1.1 (−11.3 to 9.1)	.84
Nights as hospital inpatient within 90 d, mean (SD); median (IQR)	12.1 (13.0); 7 (4 to 16) [N = 165]	10.8 (10.0); 7 (4 to 14) [N = 162]		
Rate ratio			1.11 (0.89 to 1.37)	.35
Difference in means[a]			1.2 (−1.3 to 3.7)	
Thoracic pain, mean (SD) change in VAS from baseline in mm, d	N = 142 with ≥1 measurement	N = 146 with ≥1 measurement		
Baseline	17.0 (23) [N = 165]	17.7 (25) [N = 163]	-	-
7	1.0 (25) [N = 108]	2.3 (28) [N = 98]	−1.2 (−6.9 to 4.6)	.69
30	−1.5 (25) [N = 123]	−5.6 (26) [N = 124]	1.2 (−3.5 to 6.0)	.61

90	−2.5 (23) [N = 91]	−6.9 (24) [N = 93]	0.5 (−4.8 to 5.8)	.85
180	−2.0 (23) [N = 68]	−6.2 (23) [N = 69]	0.8 (−4.6 to 6.2)	.78
Breathlessness, mean (SD) change in VAS from baseline in mm, d	N = 142 with ≥1 measurement	N = 146 with ≥1 measurement		
Baseline	53 (29) [N = 165]	53 (33) [N = 163]	-	-
7	−31 (32) [N = 106]	−29 (35) [N = 99]	−2.0 (−8.0 to 4.0)	.51
30	−28 (32) [N = 123]	−23 (39) [N = 124]	−4.4 (−11.1 to 2.3)	.20
90	−25 (35) [N = 91]	−29 (36) [N = 93]	2.1 (−5.4 to 9.6)	.58
180	−30 (33) [N = 68]	−29 (43) [N = 68]	−3.8 (−12.7 to 5.2)	.41
Percentage radiographic pleural opacification, mean (SD); median (IQR), d	N = 125 with ≥1 measurement	N = 115 with ≥1 measurement		
Baseline	54 (20) [N = 37]	47 (20) [N = 37]	-	-
Tube removal	16 (12); 15 (7 to 23) [N = 105]	17 (15); 14 (5 to 28) [N = 98]	−0.8 (−4.5 to 2.9)	.66
30	25 (19); 21 (10 to 37) [N = 89]	26 (18); 21 (13 to 37) [N = 76]	−1.5 (−6.7 to 3.7)	.58
90	20 (19); 15 (5 to 28) [N = 65]	21 (19); 18 (6 to 31) [N = 47]	−2.5 (−8.9 to 3.9)	.45
180	17 (14); 14 (4 to 23) [N = 35]	16 (13); 15 (6 to 23) [N = 37]	−0.8 (−6.7 to 5.1)	.79
EQ-5D-5L** utility, mean (SD), d				
Baseline	0.57 (0.26) [N = 163]	0.55 (0.26) [N = 164]	-	-
30	0.60 (0.26) [N = 132]	0.60 (0.27) [N = 132]	0.00 (−0.06 to 0.07)	.89
90	0.60 (0.29) [N = 95]	0.65 (0.27) [N = 100]	−0.05 (−0.13 to 0.04)	.23
180	0.71 (0.22) [N = 69]	0.68 (0.26) [N = 72]	0.04 (−0.04 to 0.12)	.31
EQ-5D-5L VAS in mm, mean (SD), d				
Baseline	50 (22) [N = 160]	50 (22) [N = 164]	-	-
30	59 (23) [N = 132]	55 (25) [N = 132]	4 (−2 to 9)	.24
90	63 (23) [N = 95]	60 (23) [N = 98]	3 (−4 to 9)	.41

180	66 (23) [N = 70]	66 (21) [N = 71]	0 (7 to 8)	.98
SF-6D** utility, mean (SD), d				
Baseline	0.58 (0.11) [N = 157]	0.56 (0.12) [N = 153]	-	-
30	0.59 (0.11) [N = 125]	0.60 (0.12) [N = 123]	0.00 (−0.03 to 0.03)	.78
90	0.63 (0.11) [N = 89]	0.64 (0.14) [N = 96]	0.00 (−0.04 to 0.03)	.90
180	0.65 (0.12) [N = 67]	0.64 (0.12) [N = 71]	0.01 (−0.03 to 0.05)	.77

Abbreviations: NR, Not reached; VAS, Visual Analogue Scale.

All treatment effects are difference in means (standard deviation in parentheses), except for pleurodesis failure and all-cause mortality (odds ratios); time to pleurodesis (hazard ratio from a competing risk analysis with mortality was a competing risk); and nights in hospital (rate ratio). All treatment effects are adjusted for the minimisation factors.

[+] Unless otherwise stated

^ All analyses 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.

[a] Post-hoc analysis. Differences in percentage points were estimated from a generalized linear model, with a binomial family and identity link. Difference in means was estimated from a linear regression model. All models were adjusted for the stratification factors.

* 49/159 (31%) of patients in the control group and 42/161 (26%) patients in the intervention group died before experiencing pleurodesis failure, and 44 (28%) and 46 (29%) in the control and intervention groups respectively experienced pleurodesis failure within 180 days of randomization. Analysis includes all patients (n = 159 slurry group, n = 161 poudrage group). The adjusted hazard ratio from a post-hoc Cox model which does not incorporate mortality as a competing risk was 1.01 (0.67 to 1.52).

**EQ-5D-5L responses were converted into a utility score ranging from −0.59 to 1.00,25 and scores on the visual-analogue scale range from 0 to 100, with higher scores indicating better quality of life.

**For the SF-36, individual domains' scores were transformed on to a scale 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

Self-reported chest pain and dyspnea were measured using a visual-analogue scale running from 0 to 100mm, with a score of 0 indicating the complete absence of symptoms and 100 the maximum possible level of symptoms. The minimal clinically important difference (MCID) for dyspnea in MPE (using 0-100mm VAS scale) is 19mm (95% CI, 14 to 24mm), with MCIDs for other measures not established in this population.

Table 3. Summary of Reported Adverse Events

	Thoracoscopy and Poudrage (179 Events)	Chest Tube and Slurry (152 Events)
Pneumonia/chest infection	25	19
Disease progression, dyspnea due to fluid	23	20
Other pleural intervention related, pneumothorax/bronchopleural fistula	15	18
Anemia	10	4
Trial intervention related[a], Other/unspecified	10	7
Medication/chemotherapy side effect	9	13
Trial intervention related[a], pain	9	6
Trial intervention related[a], surgical emphysema	9	2
Disease progression, death	7	5
Non-chest infection	7	5
Pulmonary embolism	7	9
Trial intervention related[a], pleural infection	6	0
Disease progression, dyspnea not due to fluid	4	4
Lung entrapment	4	1
Trial intervention related[a], hypoxia	4	0
Trial intervention related[a], pneumothorax/bronchopleural fistula	3	4
Trial intervention related[a], subcutaneous infection	3	3
Cardiac arrhythmia	2	2
Trial intervention related[a], bleeding	2	1
Tube dislodgement/accidental removal	2	9
Trial intervention related[a], cough	1	0
Other[b]	17	20

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

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

See eTables S24-S29 in Supplement for full details of adverse and serious adverse events.