

Thoracoscopy and talc poudrage compared with intercostal drainage and talc slurry infusion to manage malignant pleural effusion: the TAPPS RCT

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Scientific summary

The TAPPS RCT

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Scientific summary

Background

Data suggest that there are around 40,000 new cases of malignant pleural effusion in the UK each year. Malignant pleural effusion is usually a result of a metastatic process and patient survival is typically poor. In general, average survival is quoted as being 4–6 months from diagnosis, although these data are drawn from highly heterogeneous patient groups. In addition, there are a number of factors that appear to influence survival, meaning that this figure may be less applicable to a number of patients. The underlying cancer type, in particular, appears to exert a strong influence on outcome, with some series reporting that those patients with mesothelioma (12 months) or breast cancer (> 2 years) survived longer.

For many patients, malignant pleural effusion can lead to debilitating symptoms, such as breathlessness or chest pain. Therapeutic aspiration of pleural fluid can lead to rapid relief for patients and is readily performed in the outpatient setting, although the volumes that can be removed in a single sitting are limited by the potential adverse effects of rapid, high-volume lung re-expansion. For this reason, thoracentesis is usually considered to be a temporising measure rather than a definitive treatment, with recurrent aspirations reserved for those patients with a very short life expectancy. Indwelling pleural catheters are an increasingly used option, but this method of repeated drainage does not prevent fluid formation reliably, as recent data suggest that this occurs in approximately 20% of cases when drained at a typical frequency.

The more traditional and established approach to malignant pleural effusion treatment, pleurodesis, entails an attempt at preventing further fluid formation. This begins with emptying the chest of as much fluid as possible, which is usually accomplished following insertion of an intercostal chest drain (at the bedside under local anaesthetic) or during a thoracoscopic procedure (which may be performed under either light sedation or general anaesthesia). Once the pleural cavity is evacuated, an irritant is applied to the pleural linings with the intention of stimulating a local inflammatory response, resulting in fibrosis and adhesion (effectively obliterating the pleural space and, hopefully, preventing any further effusion formation). The primary perceived benefit of the pleurodesis approach is that a single intervention period can lead to long-term fluid prevention; a number of small series have described success rates in excess of 80%.

Talc slurry via chest tube is the current standard treatment approach for pleurodesis in the UK. This method has become ubiquitous as it is easily undertaken in the ward setting, with chest drain insertion possible at the bedside and not typically requiring anything other than local anaesthesia. Talc poudrage requires the capability to perform a thoracoscopy and for the patient to be able to tolerate such a procedure. Thoracoscopy may be undertaken by surgeons under general anaesthetic (video-assisted thoracoscopic surgery) or, as is increasingly the case in the UK, under light sedation (local anaesthetic thoracoscopy), the latter usually being performed by respiratory physicians in a dedicated procedural environment.

There is currently no consensus as to which approach is best. To the best of our knowledge, the largest study addressing the question of talc delivery for pleurodesis was performed by Dresler *et al.* and reported in 2005 (Dresler CM, Olak J, Herndon JE, Richards WG, Scalzetti E, Fleishman SB, *et al.* Phase III intergroup study of talc poudrage vs talc slurry sclerosis for MPE. *Chest* 2005;**127**:909–15). After withdrawals and exclusions, a total of 482 patients (slurry, $n = 240$; poudrage, $n = 242$) were included in the final analysis. Based on intention to treat, no significant difference was found between the two arms at 30 days. Following a per-protocol analysis, whereby patients with trapped lung were excluded, a significant difference ($p = 0.045$) was found, favouring poudrage, although this effect disappeared when only patients who were alive at 30 days (slurry, $n = 130$; poudrage, $n = 152$) were included.

Although undoubtedly important, the Dresler *et al.* 2005 study has not defined practice, as it was felt to have encompassed several potentially important flaws and barriers to wider generalisability, particularly in the UK. With the benefit of hindsight, these included a lack of detail regarding how randomisation, concealment or powering of the trial occurred; the use of ungraded talc; the use of video-assisted thoracoscopic surgery and general anaesthetic; the lack of an economic evaluation to inform broader utility and cost-effectiveness; poor retention to follow-up; major differences in treatment arms, such as assessing trapped lung using radiology in the slurry arm and intraoperatively in the other; no attempt at stratification prior to randomisation; the use of post hoc analyses to draw and report study conclusions; and, perhaps most importantly, a lack of what may be seen to be a clinically relevant or patient-centred definition of pleurodesis success.

How best to deliver talc into the pleural space remains an unanswered but important question, with the relatively poor-quality data described in the sections above failing to provide robust evidence to drive standardised clinical practice. This is particularly the case in the UK, where the pleurodesis approach offered will often be based on the individual preferences or beliefs of the treating clinician and the locally available facilities.

Objectives

The evaluating the efficacy of Thoracoscopy And talc Poudrage versus Pleurodesis using talc Slurry (TAPPS) trial aimed to be the first adequately powered, robustly designed trial comparing the efficacy of talc poudrage (administered using local anaesthetic thoracoscopy) with the current standard treatment of a chest drain followed by talc slurry, for the management of patients with MPE in the UK.

The primary research question was, for patients with a confirmed malignant pleural effusion and good performance status, does thoracoscopy and talc poudrage increase the proportion of patients with successful pleurodesis at 3 months post procedure, when compared with standard therapy with chest drain insertion and talc slurry instillation?

Methods

Design

This was a pragmatic, multicentre, UK-based, open-label, randomised controlled trial. A within-trial economic evaluation was conducted to assess the cost-effectiveness of both approaches. The TAPPS trial was given initial ethics approval by the National Research Ethics Service Committee (reference number 12/NW/0467), sponsored by North Bristol NHS Trust and jointly managed by research teams based at the University of Bristol and University of Oxford.

Inclusion criteria were as follows:

- a clinically confident diagnosis of MPE requiring pleurodesis, defined as –
 - pleural effusion with histocytologically proven pleural malignancy, or
 - pleural effusion in the context of histocytologically proven malignancy elsewhere, without a clear alternative cause for fluid, or
 - pleural effusion with typical features of malignancy with pleural involvement on cross-sectional imaging without a clear alternative cause for fluid
- fit enough to undergo local anaesthetic thoracoscopy
- expected survival > 3 months
- written, informed consent to trial participation.

Exclusion criteria were as follows:

- patients in whom thoracoscopy is the only reasonable approach to making a diagnosis and in whom such a diagnosis would significantly influence further management
- aged < 18 years
- females who are pregnant or lactating
- evidence of extensive lung entrapment on chest radiography or computed tomography, or significant fluid loculation on thoracic ultrasound, to a level that would normally be a contraindication to attempted talc pleurodesis
- insufficient volume or position of pleural fluid on lateral decubitus thoracic ultrasound to safely perform local anaesthetic thoracoscopy without further intervention being necessary
- previously documented adverse reaction to talc
- clear contraindication to thoracoscopy or chest tube insertion.

Sample size

Previous literature and local audit data suggested that patients with a World Health Organization performance status score of 2 or better have approximate pleurodesis failure rates of 10% with a thoracoscopy and 30% with standard chest tube and talc slurry pleurodesis.

Thus, to detect a 15% difference in pleurodesis failure at 3 months (10% thoracoscopy and poudrage vs. 25% chest drain and talc slurry), with 90% power, a 5% significance level and 10% loss to follow-up, a total of 325 patients was required.

The final recruitment target was rounded up to 330 patients, with 165 patients to be allocated equally to each treatment arm.

No interim analyses were planned.

Consent and treatment allocation

All patients provided informed consent to trial entry. Patients were randomly assigned, in a 1 : 1 ratio, to one of the trial treatments. Randomisation was performed centrally by the trial management team in Oxford, using a computer-based system. Minimisation with a random element was utilised. The minimisation factors were type of underlying malignant disease (mesothelioma, lung cancer, breast cancer, other) and World Health Organization performance status (0–1, 2–3).

Because of the inherent and substantial differences between the two methods being tested, this trial could not be performed ethically or safely in a blinded manner using dummy or sham procedures.

Trial treatments

Participants allocated to the control group underwent 12–14 French gauge chest drain insertion and were then administered 4 g of sterile talc slurry. Drain removal and consideration for discharge occurred once < 250 ml of fluid output was recorded in a 24-hour period.

Participants allocated to the intervention group underwent local anaesthetic thoracoscopy and talc poudrage with 4 g of sterile talc slurry and insertion of a 16–24 French gauge chest drain at the end of the procedure. After a minimum of 24 hours, drain removal and consideration for discharge occurred once < 250 ml of fluid output was recorded in a 24-hour period.

Follow-up period

Trial follow-up appointments took place at 1 month (day 28 ± 7 days), 3 months (day 84 ± 10 days) and 6 months ($168 \text{ days} \pm 14 \text{ days}$) post randomisation.

Outcome measures

The primary end point was the number of patients who experienced pleurodesis failure up to 3 months (90 days) post randomisation.

A patient was defined as experiencing pleurodesis failure if they underwent a therapeutic procedure on the side ipsilateral to their trial intervention, or if this procedure was needed but not performed.

A range of secondary outcomes was also assessed, including patient-reported symptoms and quality of life, pleurodesis failure rates at 30 and 180 days, and mortality.

Cost-effectiveness was assessed taking into account quality-adjusted life-years and resource use during the initial procedure and over the trial period.

Results

Recruitment took place between August 2012 and October 2017, with 17 centres contributing participants.

The target of 330 patients was achieved, with 164 allocated to the control (slurry) arm and 166 to the intervention (poudrage) arm. A total of 159 (97%) and 161 (97%) patients from the control and intervention arms, respectively, were included in the primary outcome analysis. Fourteen (8.5%) and 15 (9.0%) patients from the control and intervention arms, respectively, withdrew during the 6-month follow-up period. The treatment groups were well matched at baseline.

Primary outcome

For the primary outcome, no significant difference in pleurodesis failure was observed between the treatment groups at 90 days, with rates of 36 out of 161 (22%) and 38 out of 159 (24%) noted in the poudrage and slurry groups, respectively (odds ratio 0.91, 95% confidence interval 0.54 to 1.55; $p = 0.74$).

Secondary outcomes

No differences (or trends towards difference) were noted in any of the secondary outcomes at any time point, including pleurodesis failure at 30 days [poudrage 16/161 (10%), slurry 22/159 (14%), odds ratio 0.69, 95% confidence interval 0.34 to 1.37; $p = 0.29$]; pleurodesis failure at 180 days [poudrage 46/161 (29%), slurry 44/159 (28%), odds ratio 1.05, 95% confidence interval 0.63 to 1.73; $p = 0.86$]; mean number of nights in hospital over 90 days [poudrage 12 nights (standard deviation 13 nights), slurry 11 nights (standard deviation 10 nights); $p = 0.35$]; all-cause mortality at 180 days [poudrage 66/166 (40%), slurry 68/164 (42%); $p = 0.70$]; thoracic pain ($p = 0.69$, $p = 0.61$, $p = 0.85$ and $p = 0.78$ at days 7, 30, 90 and 180, respectively); dyspnoea ($p = 0.51$, $p = 0.20$, $p = 0.58$ and $p = 0.41$ at 7, 30, 90 and 180 days, respectively); or percentage radiographic opacification ($p = 0.66$, $p = 0.58$, $p = 0.45$ and $p = 0.79$ at drain removal, at 30, 90 and 180 days, respectively).

Adverse events

There was no significant difference between the groups in the number of adverse events or serious adverse events recorded at 7, 30 or 180 days. A total of 179 and 152 adverse events were recorded in the intervention and control arms, respectively. The most commonly seen adverse events were worsening dyspnoea due to disease-related fluid (poudrage, $n = 23$; slurry, $n = 20$), pneumothorax or bronchopleural fistula (poudrage, $n = 15$; slurry, $n = 18$) and pneumonia or chest infection (poudrage, $n = 25$; slurry, $n = 19$).

Cost-effectiveness

The mean total NHS and hospice care costs were £10,146 (95% confidence interval £9119 to £11,212) for patients randomised to standard chest tube talc slurry pleurodesis and £10,687 (95% confidence interval £9621 to £11,627) for patients randomised to thoracoscopy-delivered talc poudrage, a mean difference of £541 (95% confidence interval difference –£953 to £1933). The mean quality-adjusted life-year gain was 0.239 in the standard chest tube talc slurry pleurodesis group and 0.246 in the thoracoscopy-delivered talc poudrage group, a mean difference of 0.007 quality-adjusted life-years (95% CI –0.019 to 0.034). Therefore, the incremental cost per quality-adjusted life-year gained when poudrage was compared with slurry was £77,286. At the conventional £20,000 per quality-adjusted life-year gained threshold, thoracoscopy-delivered talc poudrage would have a 0.36 probability of being cost-effective.

Conclusions

The results of the TAPPS trial appear to be conclusive, in that there was no evidence of any difference between the two treatment arms in the primary outcome measure: pleurodesis failure at 90 days post randomisation. Indeed, no significant difference or trend towards difference was noted in any of the secondary outcome measures, including pleurodesis failure up to the final follow-up visit at 180 days post randomisation, mortality, time spent in hospital, radiological appearances or patient-reported outcomes. Absolute values for pleurodesis failure were low (approximately 23% in both arms) at 90 days and this was maintained for the duration of the trial (approximately 30% in both arms at 180 days). The health economic analysis suggested that talc poudrage has a low probability (36%) of being cost-effective when compared with talc slurry.

To the best of our knowledge, the TAPPS trial is the first randomised controlled trial to examine the efficacy of talc poudrage delivered at LAT compared with traditional talc slurry. It addresses a clear and important area of uncertainty in clinical practice and has been able to inform this definitively. The trial processes, including randomisation and treatment allocations, were robustly designed, with the likelihood of bias minimised as far as possible. The trial interventions were performed in a standardised fashion that was reflective of current practice, meaning the results are likely to be generalisable to the wider population.

However, the trial entry criteria specified that patients be sufficiently fit to undergo local anaesthetic thoracoscopy under light sedation, which may make the results less applicable to those patients presenting with a greater degree of frailty. Furthermore, the trial was conducted on an open-label basis, which may have influenced the results of patient-reported measures, such as pain or breathlessness. It is also probable that those clinicians responsible for the recruitment and trial interventions were also required to assess patients for pleurodesis failure, introducing the potential for bias (although this was considered and addressed through blinded re-assessment).

Overall, the TAPPS trial has robustly demonstrated that there is no additional benefit in performing talc poudrage at local anaesthetic thoracoscopy over bedside chest drain and talc slurry for the management of malignant pleural effusion.

Trial registration

This trial is registered as ISRCTN47845793.

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