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CHEST Submission – Case Series

Title:

Thoracic ultrasound as an early predictor of pleurodesis success in malignant pleural effusion

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MPE = malignant pleural effusion; TUS = thoracic ultrasound; NHS = National Health Service; UK = United Kingdom; CT = computed tomography; VAS = visual analogue scale; ICC = intraclass correlation coefficient; ROC = receiver operating characteristic

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MAIN TEXT
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ABSTRACT

Malignant pleural effusion (MPE) is common and imposes a significant burden on patients and healthcare providers. Most patients require definitive treatment, such as drainage and chemical pleurodesis, to prevent fluid and symptom recurrence. Thoracic ultrasound (TUS) can identify pleural adhesions in other clinical scenarios, and might therefore predict long-term pleurodesis success in MPE.

18 patients undergoing chest tube drainage and talc slurry instillation for MPE underwent TUS examination immediately before, and 24 hours after talc instillation to derive pleural adherence scores for the affected hemithorax. Recorded TUS scans were additionally scored by two independent assessors blinded to the patient's clinical status. Participants who suffered pleurodesis failure had a lower adherence score at 24 hours post-talc instillation than those who were successful (difference 6.27, 95% CI 3.94 to 8.59). A TUS-derived pleural adherence score may predict long-term outcomes following chemical pleurodesis. Further research is needed to evaluate this novel finding.

INTRODUCTION

Malignant pleural effusion (MPE) is common [1, 2], and with an aging population and more patients with metastatic cancer surviving long-term [3, 4], the number of cases will continue rising for the foreseeable future. MPE typically carries a limited prognosis [5], with most patients requiring therapeutic drainage to provide symptomatic relief [5, 6].

Many patients with recurrent MPE are managed with chemical pleurodesis, most commonly using sterile talc [1, 5, 7]. This process generates inflammation, adhesion formation, and pleural space obliteration; with the long-term aim of preventing MPE recurrence [5, 6, 8]. Randomised trial data [9] report a success rate of around 70% for talc pleurodesis via intercostal chest tube, with no means of predicting which patients will suffer pleurodesis failure [5]. There is little data to guide chest tube removal [5]; a randomised trial [10] reported no difference in pleurodesis success between chest tube removal at 24 and 72 hours post-talc, but was underpowered and only used radiological measures of pleurodesis success.

An animal model of chemical pleurodesis demonstrated correlation between TUS scoring of lung sliding and the development of a successful pleurodesis [11]. Human studies using TUS to detect pleural adhesions prior to thoracic surgery [12, 13] and following surgical pleurodesis for recurrent pneumothorax [14] have also shown this technique to have potential utility. However, there is no data relating to TUS in the context of talc pleurodesis for MPE.

We hypothesised that TUS could detect the early formation of pleural adhesions following talc pleurodesis for symptomatic MPE, thereby predicting long-term pleurodesis success, and facilitating earlier chest tube removal.

METHODS

Study design and participants

This was a prospective observational cohort pilot study, recruiting between May 2015 and April 2017. Adult patients (≥ 18 years old) undergoing MPE drainage and talc slurry pleurodesis via chest tube (12Fr per usual local practice) were approached to participate. MPE was defined using widely accepted guidelines and per previous publications [1, 5, 9, 15, 16]. Patients were excluded if they were < 18 years old; unable to provide informed consent; had an allergy or other contraindication to intrapleural talc; had evidence of unexpandable lung felt by the responsible clinician to represent insufficient pleural apposition that would preclude pleurodesis; and/or had an expected survival of less than one month.

The study was sponsored by the University of Oxford, managed by the University of Oxford Respiratory Trials Unit, and registered with ClinicalTrials.gov (NCT02625675). The protocol and subsequent amendments were approved by the UK National Research Ethics Service (15/LO/0382). Study participants provided informed written consent before recruitment and study-related procedures.

Study procedures

Study participants underwent standardised bedside brightness (B-)mode TUS assessment immediately prior to (day 0) and 24 hours (day 1) following talc slurry instillation. Lung sliding was scored in nine zones (upper, middle, and lower zones in the anterior, lateral, and posterior chest wall) across the affected hemithorax by the primary TUS operator in real-time as present ($=0$), questionable ($=1$), or absent ($=2$) [11], generating a total pleural adherence score for the hemithorax. Ultrasound video clips were recorded

concurrently to facilitate remote scoring by two independent assessors blinded to the original scoring and participants' clinical status. All scorers held Royal College of Radiologists level 1 or 2 TUS accreditation [17].

Study participants completed a questionnaire relating to their experience of TUS assessment prior to leaving hospital. This included a visual analogue scale (VAS) score of pain caused by TUS examination (0-100 mm, no pain at 0 mm and worst possible pain at 100 mm), and assessment of willingness to undergo TUS examination again.

Study procedures, including TUS, were performed by a researcher independent of the medical inpatient team. The inpatient team were blind to TUS findings, and managed participants according to national guidelines [5] adapted for local practice with respect to timing of talc slurry instillation and subsequent chest tube removal.

Follow-up took place at 1 and 3 months, or until death if sooner. Study participants were assessed for pleurodesis failure; objectively defined as fluid recurrence in the ipsilateral hemithorax requiring further therapeutic pleural intervention, with radiological evidence (chest X-ray, CT, and/or TUS) of the same fluid recurrence at any point during follow-up. Consistency in the diagnosis of pleurodesis failure was ensured by assessment of participants' data by a researcher and independent chest physician not involved in the participant's clinical care.

Outcomes and analyses

The primary endpoint was pleurodesis failure at 1 and 3 months. Secondary endpoints were patient satisfaction with TUS assessment, measured using VAS pain score and a Likert-type scale; and the difference between a hypothetical discharge date based on TUS findings and the actual discharge date from hospital based on standard care.

SPSS version 24 was used for statistical analyses. *t*-tests were used for parametric data, and Fisher's exact test for categorical variables. A *p*-value of <0.05 was considered significant. Interrater reliability was calculated using the intraclass correlation coefficient (ICC) for continuous variables. Descriptive statistics were used to summarise patient characteristics.

RESULTS

18 participants were recruited; baseline characteristics are in **table 1**. Three participants (16.7%) died before one-month follow-up; a further six (nine in total, 50.0%) died before three-month follow-up.

Primary endpoint

15 (83.3%) participants reached one-month follow-up and were included in the primary analysis. 4/15 (26.7%) suffered pleurodesis failure, as defined in the study methodology, by this timepoint.

There was a significant difference between mean total pleural adherence score at day 1 for patients with successful vs. failed pleurodesis (**table 2**). The area under receiver operating characteristic (ROC) curves for total pleural adherence scores on day 0 and 1 (**figure 1**) were 0.798 (95% CI 0.671 to 0.925) and 0.900 (95% CI 0.812 to 0.988) respectively. Interrater reliability was good to excellent, with ICC(2,1) = 0.762 (95% CI 0.605 to 0.872; *p*<0.001).

None of the 11 participants with a successful pleurodesis at one month follow-up suffered delayed failure, either prior to death (4/11, 36.4%) or at three-month follow-up (7/11, 63.6%).

Secondary endpoints

15 (83.3%) participants completed the questionnaire relating to their satisfaction with TUS. The mean VAS pain score associated with TUS examination was 8.9 mm (SD 12.9, 95% CI 1.8 to 16.1). On a three-point Likert-type scale (not, slightly, and very time consuming), 10/15 (66.7%) participants did not find TUS examination time consuming, whilst 5 (33.3%) found it slightly time consuming. All 15 participants would have the same TUS examination(s) again if necessary in the future.

The mean time from chest tube insertion to talc instillation was 4.3 days (SD 1.53; $n = 18$ participants). 5/18 (27.8%) participants suffered a delayed discharge from hospital due to issues unrelated to their pleural disease. As such, time from talc instillation to chest tube removal (actual vs. hypothetical based on TUS findings), rather than discharge from hospital, was analysed. A total pleural adherence score of ≥ 10 at day 1 (sensitivity 82%, specificity 91% for pleurodesis success; **figure 1**) was used as the cut-off for hypothetical chest tube removal.

The mean time from talc instillation to chest tube removal was 2.9 days (SD 1.1; $n = 18$ participants). 3/18 (16.7%) participants had their chest tube removed after 24 hours as part of usual clinical care, compared to 13/18 (72.2%) participants in the hypothetical TUS-based model ($p = 0.002$, Fisher's exact test).

DISCUSSION

This study shows TUS can detect early pleural adhesion formation following talc pleurodesis for MPE, as manifest in the loss of normal lung sliding artefact. This is consistent with prior data [12, 13] demonstrating the same sonographic features in a different setting. The extent of loss of lung sliding on TUS following talc administration appears to predict longer-term pleurodesis success. Study participants with a successful pleurodesis at one month had a higher mean total pleural adherence score at 24 hours post-talc administration compared to those whose pleurodesis failed (difference of 6.27, 95% CI 3.94 to 8.59).

TUS examination for this purpose appears acceptable to patients and deliverable at the bedside by physicians, with the potential to enhance decision making around timing of chest tube removal. TUS interpretation appears consistent with excellent interrater reliability across the original bedside operator and two remote blinded observers, meaning the study technique and outcomes can be regarded as robust.

This study establishes proof of concept for TUS as an outcome prediction tool following talc pleurodesis for symptomatic MPE. It is novel in demonstrating the ability of TUS to detect early loss of lung sliding and predict longer-term pleurodesis success, whereas prior data in animals [11] and humans [14] were obtained at a delayed interval (two and four weeks post-intervention respectively). TUS assessment delayed by up to a month post-intervention would have limited utility in the context of intended definitive treatment for MPE. However, early identification of patients at risk of pleurodesis failure would allow clinicians to consider alternative strategies; for example, planning for indwelling pleural catheter insertion.

An interesting observation was a trend for the total pleural adherence score at day 0 (i.e. prior to talc administration) to predict pleurodesis success (**table 2**). Although combined TUS scores reached significance for detecting a difference between the patient groups (pleurodesis success vs. failure), this was not the case for individual scorers' data and cannot be considered a reliable finding. Nonetheless, this

observation may be linked to the concept of spontaneous (auto-)pleurodesis in MPE; frequently described with indwelling pleural catheters [15, 16] where up to 50% of patients pleurodesed after 12 months without a chemical sclerosant. There is limited data describing auto-pleurodesis following chest tube drainage of MPE without use of a sclerosant [8, 18-20], although the mechanism is probably similar with the chest tube acting as an inflammatory stimulus, or an unrecognised biochemical or immunological characteristic of the MPE promoting auto-pleurodesis. Regardless, it may be that TUS can identify patients who will develop auto-pleurodesis following MPE drainage without the need for talc, saving time and resources.

This study has potential limitations. Participant numbers were small and recruited from a centre with expertise in TUS and pleural disease; as such, the findings need validation in a multicentre randomised trial (ISRCTN16441661). Half of the participants failed to survive to 3 month follow-up; this was not unexpected given the patient population and MPE being a marker of advanced disease [5]. The study methodology was however strong, including blinded assessors to demonstrate consistency in TUS scoring, which has not been a feature of previous studies [12, 13].

In conclusion, a pleural adherence score obtained using TUS at 24 hours post-talc administration in the context of symptomatic MPE predicted longer-term pleurodesis success in this pilot study. This has implications for individualised TUS-guided management of patients with MPE, but remains an experimental technique. Further research is needed to evaluate TUS as an outcome prediction tool for patients with MPE undergoing definitive treatment with chemical pleurodesis.

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TABLE 1:

Baseline characteristics of the study population (total $n = 18$ participants); data are presented as either n (%age) or mean (SD).

Sex	- Male - Female	4 (22.2%) 14 (77.8%)
Age, years		67.6 (9.7)
Primary cancer	- Lung - Gynaecological - Breast - Renal - Colorectal - Pleural mesothelioma	5 (27.8%) 5 (27.8%) 4 (22.2%) 2 (11.1%) 1 (5.6%) 1 (5.6%)
Active oncological treatment	- Yes - No	7 (38.9%) 11 (61.1%)
Side of effusion	- Right - Left	8 (44.4%) 10 (55.6%)
LENT score [23]	- Low, 0-1 - Moderate, 2-4 - High, 5-7	2 (11.1%) 14 (77.8%) 2 (11.1%)
Volume of pleural fluid drained, mL		2703 (1062)

TABLE 2:

Total pleural adherence scores (minimum 0, maximum 18) on days 0 (pre-pleurodesis) and 1 (24 hours post-pleurodesis) for study participants ($n = 15$) with either successful or failed pleurodesis at subsequent 1-month follow-up; data are presented as mean (SD).

	Pleurodesis success n = 11 participants	Pleurodesis failure n = 4 participants	p-value (unpaired t-test)
DAY 0			
- Original scorer	10.73 (3.80)	6.50 (1.29)	0.0522
- Blind scorer 1	8.91 (4.87)	5.00 (2.16)	0.1515
- Blind scorer 2	10.18 (4.26)	5.00 (3.46)	0.0492
- COMBINED SCORES	9.94 (4.26)	5.50 (2.35)	0.0014
DAY 1			
- Original scorer	13.36 (3.11)	6.75 (2.63)	0.0023
- Blind scorer 1	11.91 (3.88)	7.00 (3.74)	0.0480
- Blind scorer 2	13.27 (3.95)	6.00 (2.58)	0.0049
- COMBINED SCORES	12.85 (3.62)	6.58 (2.78)	0.0001

FIGURE 1:

Receiver operating characteristic (ROC) curves and coordinates for total pleural adherence score on days 0 and 1 using a combined dataset (original and blind scorers) - the proposed score (highlighted) for detecting pleurodesis success using thoracic ultrasound was chosen using a threshold of $\geq 90\%$ specificity.

Day 0: ROC area 0.798 (95% CI 0.671 to 0.925)

Day 0 ROC curve coordinates		
Successful pleurodesis if pleural adherence score $\geq$	Sensitivity	1 - Specificity
0	1.000	1.000
1	1.000	1.000
2	1.000	1.000
3	0.970	0.833
4	0.909	0.750
5	0.879	0.667
6	0.818	0.500
7	0.788	0.417
8	0.667	0.333
9	0.606	0.000
10	0.545	0.000
11	0.515	0.000
12	0.394	0.000

Day 1: ROC area 0.900 (95% CI 0.812 to 0.988)

Day 1 ROC curve coordinates		
Successful pleurodesis if pleural adherence score $\geq$	Sensitivity	1 - Specificity
0	1.000	1.000
1	1.000	1.000
2	1.000	1.000
3	1.000	0.917
4	1.000	0.750
5	1.000	0.750
6	1.000	0.667
7	0.909	0.667
8	0.879	0.417
9	0.848	0.250
10	0.818	0.083
11	0.758	0.083
12	0.697	0.000