Randomized Controlled Trial of Talc Instillation In Addition To Daily Drainage Through a Tunneled Pleural Catheter to Improve Rates of Outpatient Pleurodesis in Patients with Malignant Pleural Effusion – The ASAP II Trial

Participating Sites:

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Purpose of the Study

To assess the efficacy of talc instilled via tunneled pleural catheter combined with daily drainage to induce accelerated pleurodesis in patients with malignant pleural effusion. *Our hypothesis is that the combination of talc instillation with daily drainage will increase rates of pleurodesis compared with daily drainage alone.*

Background and Significance

Tunneled Pleural Catheters (TPC's) are an increasingly utilized for the management of malignant pleural effusions (MPEs). TPCs provide rapid relief of dyspnea and improvement in quality-of-life in patients with MPEs.[1,2] Spontaneous pleurodesis may occur through repetitive drainage of the pleural space, however the rates and timing of this event are variable and have been reported to be between 16% and 65%.[1,3,4] Earlier pleurodesis leads to lower supply costs and reduced risk of long term complications such as infection, pain or mechanical failure.[5,6] This is especially important as malignant pleural effusion is associated with a generally poor prognosis and if given limited life expectancy, minimizing medical interference and hospitalized days is paramount.[7,8]

Recent advances in the field of malignant pleural effusion management have prioritized these patient centered goals of maximizing quality of life improvements while minimizing time in the hospital. Recent research by our own group has shown a 20% improvement in the percentage of patients having their TPC removed by 12 weeks with high volume daily drainage of pleural effusions at home.[9] Parallel research has demonstrated that the addition of talc through a TPC achieves a similar 20% improvement in pleurodesis within the first 5 weeks.[10] Somewhat surprisingly, the rates of pleurodesis were nearly identical between the 2 studies at 48% and 43% respectively[9,10]. Notably, patients in the talc study drained their effusions using an every other day or symptom guided strategy rather than daily drainage.

We hypothesize that combining both strategies (daily drainage with the addition of talc sclerosant) will lead to both earlier, and higher incidence of pleurodesis in the majority of treated patients. We believe that this can be achieved on an outpatient basis without additional interactions with the healthcare system.

Design and Procedures

To assess if the addition of talc sclerosant to daily outpatient drainage compared with daily drainage alone leads to more rapid pleurodesis.

Study Type: Non-blinded prospective randomized two-arm cohort

Primary Endpoint: Proportion of cohort able to have TPC removed at 30 days post talc-administration (day of randomization will be defined as study day 1)

Secondary Endpoints: Quality-of-Life Assessment, dyspnea assessment, adverse events

Schedule of Events:

	Screening (up to 14 days prior to baseline visit)	Baseline (Day 0)	30 day follow-up visit	60 day follow-up visit
Tunnel Pleural Catheter insertion (SOC*)	X			
Chest x-ray (SOC)	X		X	X
Physical Exam (SOC)	X	X	X	X
Randomization		X		
Talc instillation (if randomized to Talc Arm) (SOC)		X		
Vital sign monitoring for 2 hours post Talc instillation (if randomized to Talc Arm) (SOC)		X		
SOB VAS questionnaire		X	X	X
SF-36 questionnaire		X	X	X
Daily drainage diary review		X	X	X
AE review		X	X	X

**Standard of Care (SOC) procedures*

Enrollment

Patients will undergo TPC insertion for malignant pleural effusion as per usual clinical indications and protocols in either the inpatient or outpatient setting. Patients will be eligible for study enrollment anytime between catheter insertion and initial clinical follow-up at a maximum of 14 days following TPC insertion. Patients will be instructed to drain that catheter daily until initial follow-up. At this 7-14 day follow-up appointment for suture removal patients will be asked to drain the morning of the clinic visit and a chest x-ray (CXR) will be performed prior to the clinic visit. The catheter may be drained at the time of the clinic visit if not done within 8 hours of the visit. Patients who meet radiographic criteria for inclusion (see inclusion/exclusion criteria below) may proceed with randomization via central computer generated randomization table. Those who do not meet radiographic criteria will be considered screen

failures and withdrawn from the study. At the time of randomization, patients will be given baseline symptom surveys, a drainage diary, and talc instillation or daily drainage alone based on study arm.

Tunneled Pleural Catheter Placement

All patients will have undergone placement of a tunneled pleural catheter prior to consideration for trial enrollment. These are placed utilizing a standard sterile technique under ultrasound guidance. Local Anesthetic will be utilized for placement, which will be performed under sterile conditions on an inpatient or outpatient basis at the discretion of the patient's treatment team. Moderate sedation may be utilized during placement at the treating physicians discretion.

Sclerosant Infusion Procedure

All patients randomized to the Talc arm will receive a slurry composed of 10cc of 1% lidocaine and 4g of graded talc suspended in 50cc of 0.9% saline infused through the pleural catheter. The line will be flushed with a further 10cc of 0.9% normal saline and then de-accessed and dressed in the usual fashion. Control arm patients will not receive any additional therapy. The patients receiving talc will be monitored on-site for 2 hours for the development of dyspnea, followed by drainage of the catheter. Vitals signs will be monitored for stability prior to discharge home. All patients will be instructed to perform drainage daily for the duration of the trial or until catheter removal.

Drainage

All patients will receive drainage bottles after placement and throughout the study to ensure maximum drainage. Patients and their care givers will be instructed on sterile technique for drainage utilizing the tunneled pleural catheters.

Follow up

Study subjects will return for clinic visits at day 30 and 90 after randomization, or a final visit at the time of catheter removal (Figure 1). Review of drainage logs, repeat CXR, SOB VAS and questionnaire, and quality of life measures will be collected at these timepoints. Day 30 and 90 follow up appointments are standard of care for follow up of tunneled pleural catheter management. Additional visits will occur as clinically indicated.

Criteria for Pleurodesis

Pleurodesis is defined as three consecutive drainage attempts with 50cc or less or less than 200cc in 1 week. Patients will be instructed to contact their treatment team who will obtain a CXR to evaluate for resolution of effusion. A CXR showing effusion $\leq$ the size of the effusion at randomization will be considered to be successful pleurodesis. Chest x-ray imaging showing an effusion larger than what was present at randomization (radiographic score 2-5) will be investigated for dysfunction of the pleural catheter. Thoracic ultrasound will be performed at the time of removal of each catheter to assess for presence and size of residual pleural fluid, pleural septations, and for the presence or absence of lung sliding (appendix 1).

Management of Dysfunctional Catheters

Obstructed catheters will be investigated per ASAP I protocol by instillation of 2mg TPA in 8ml sterile water and allowed to dwell for 20 minutes followed by drainage. If the output returns to >200cc

after fibrinolytic infusion then patient will return to study protocol. If fibrinolytic fails to to produce immediate drainage and the patient does not have shortness of breath the catheter will be removed and the patient will be considered to have undergone partial response. Patients with continued shortness of breath will be managed at the discretion of the treating physician and will be considered catheter failures.

Outcome Measures

Primary Outcome: Percentage of cohort undergoing accelerated pleurodesis. Patients able to have their TPC removed at 30 days post-talc instillation will be considered to have achieved the primary endpoint. Pleurodesis is defined as three consecutive drainage attempts with 50cc or less or less than 200cc in 7 days and lack of respiratory symptoms of cough orshortness of breath previously attributed to pleural effusion. Patients will be considered to have experienced complete (CR) or partial response (PR) depending on chest x-ray (CXR) scoring criteria. Patients who experience pleurodesis later than 30 days from randomization will be considered to have a delayed CR or PR using the same CXR scoring criteria.

Chest X-ray scoring (see appendix 1): Chest x-ray scoring will be performed by a blinded pulmonologist viewing images identified with study code on a CD supplied by the treating physician. Patients with CR will have a CXR score of 0-1, and PR $\geq$ 2.

Secondary Outcomes: Dyspnea and Quality-of-Life Measurements. Baseline Dyspnea measurements will be performed by Visual Analog Scale (VAS), a validated measure of dyspnea in pleural disease. Quality-of-Life measurements will be performed using the short form 36 (SF-36) which is a validated survey-based tool that measures 8 aspects of physical and mental well being. Both of these survey tools will be administered at enrollment, 30, and 90 days after randomization, or at the time of catheter removal if prior to the 30 day or 90 day clinical follow-up. Because patients will be randomized after catheter insertion and drainage for 7 to 14 days, we anticipate dyspnea and QOL to be somewhat optimized as related to interactions from pleural fluid at randomization. The assessments will be examining stability of symptom control over the course of study enrollment.

Adverse Events

Anticipated adverse events include pain with drainage, catheter dislodgement, catheter malplacement, insertion site cellulitis, and empyema. Catheter obstruction due to fibrin will be considered catheter failure, but not an adverse event. There is an extremely small chance of a patient developing local anesthetic systemic toxicity from the instillation of lidocaine mixed with the talc slurry. Intralipid, used to treat this serious complication will be stored in the outpatient procedure suite pyxis.

Selection of Subjects and Data Collection

Diagnosis and Inclusion Criteria:
Subjects must meet all of the following:
1. Male or female, at least 18 years of age, inclusive.
2. Subject has a symptomatic MPE requiring intervention. For an effusion to be defined as malignant, at least one of the following must be true:
a. There is histocytological confirmation of pleural malignancy
b. The effusion is an exudate (per Light's criteria) in the context of histocytologically proven malignancy elsewhere, with no other clear cause

for fluid identified.
3. Subject has a history of at least 1 ipsilateral pleural effusion causing dyspnea that responded to thoracentesis where the lung expanded and the dyspnea was improved.
4. Subject is willing and able to provide written informed consent.
5. Subject is willing and able to meet all study requirements, including follow-up visits and receiving study-related telephone calls.
6. Subject has sufficient pleural fluid to allow safe insertion of an IPC.
7. Subject has negative pregnancy test if appropriate.
8. Subject or caregiver is able to perform home drainage of the pleural effusion (a caregiver can be a friend, family member, or paid healthcare professional).

Exclusion Criteria:
Potential study subjects will be excluded if 1 or more of the following exclusion criteria is present:
1. Subject has significant trapped lung, or a proximal bronchial obstruction which is likely to lead to trapped lung. For a subject to be eligible for this study, two separate study center clinicians must agree that there is no significant trapped lung on the same CXR using visual estimation (reference guide). The CXR used to make this decision must have been performed ≤30 days preceding the consent form being signed, and must have been performed preferably on the same day, but no more than 7 calendar days after tunneled pleural catheter insertion.
Significant trapped lung is deemed present if any 1 of the following criteria is met:
a) A CXR shows hydropneumothorax other than small (< 1 cm between chest wall and pleural line) apical pneumothoraces.
b) A CXR shows ≥20% of the affected hemithorax to be free of the expected lung parenchymal markings and there is no suggestion of pleural fluid.
c) A CXR shows ≥20% of the affected hemithorax to be occupied with pleural fluid AFTER a pleural aspiration which resulted in symptoms suggestive of trapped lung (e.g., chest pain or cough).
2. Subject has a Karnofsky score <50, or a World Health Organization (WHO)/ Eastern Cooperative Oncology Group (ECOG) performance status ≥3. Subjects who have a performance status of 3 may be considered for the study if the removal of their fluid would likely improve their performance score by 1 or more.
3. Subject is pregnant, planning to become pregnant, or is lactating.
4. Subject has a history of empyema.
5. Subject has a history of chylothorax.
6. Subject has an uncorrected coagulopathy.

Randomization and Allocation

Randomization will be performed utilizing a computer system at Duke (the coordinating center) with permuted block randomization of random block length. Allocation will occur at the time of initial clinic visit following catheter insertion.

Data Collection

Data will be collected using paper clinical research forms at the clinical sites followed by direct entry into a web based, password protected REDCAP database. Duplicate databases will be stored on Duke and VA servers to safeguard data security.

Initial Data Collection

Data to be collected at the time of enrollment include age, sex, race, ethnicity, effusion side, type of maliganancy, date of diagnosis, date of initial thoracentesis, Karnofsky performance score, ECOG performance score, comorbidities (anemia, asthma, cerebrovascular accident, chronic kidney disease, chronic obstructive pulmonary disease, coagulopathy, congestive heart failure, coronary artery disease, diabetes, deep vein thromobosis, pulmonary embolism, hypertension, hypothyroidism, hyperthyroidism, interstitial lung disease, nephrotic syndrome, peripheral vascular disease, cirrhosis of the liver), pleural fluid characteristics (pH, LDH, Protein, % lymphocytes, glucose, cytology results), prior chemotherapy, prior radiotherapy, prior immunomodulatory therapy, VAS dyspnea score, and SF-36 questionnaire. Data collected at randomization will be CXR score by treating and blinded physician.

Follow-up Data Collection

Karnofsky score, ECOG score, VAS dyspnea score, SF-36 questionnaire, and CXR scoring will be collected at the 30 day and 90 day clinic visits, or at the time of catheter removal. Thoracic ultrasound examination will be performed at time of catheter removal.

Subject Recruitment and Compensation

Consent Process- Consent form and material subject to IRB approval

Risk/benefit assessment- There are two primary risks to patients associated with this study. The first is the risk of respiratory failure associated with talc pleurodesis. Respiratory failure is a rare but well documented risk associated with the use of talc for pleurodesis. This event is rarely fatal and occurs roughly 1 in every 10,000 patients when utilizing graded talc. The second concern is obstruction of the tunneled pleural catheter by talc. This happens spontaneously in about 10% of patients and can be managed in >90% of these patients with the instillation of tissue plasminogen activator through the catheter. Previous trials of talc instillation through tunneled pleural catheters have not noted a higher than baseline rate of TPC blockage with this treatment regimen. Expected side effects of talc instillation include pain and fever which are temporary and can be treated with over the counter analgesics and anti-pyretics.

Potential benefits of participation in this study include less long-term fluid collection and potential earlier removal of the catheter.

Cost to the Subject- There will be no increased cost of care to the patients as the instillation will occur during routine follow up visit after TPC placement. Talc will be supplied as part of clinical care. Clinic visits are occurring as part of our routine clinical care for malignant pleural effusion treated with tunneled pleural catheters. Drainage bottles will be obtained through usual care pathways.

Data Analysis and Statistics

Power Calculation

Assuming a 45% rate of TPC removal in the control arm, and a 65% rate of TPC removal in the experimental arm (a 20% improvement) and a margin of error of 5% we calculate we would need to enroll 92 patients per group to have 90% power to detect a significant difference with $p<0.05$ using a one sided superiority test. Given a 10% dropout rate seen in the other two major studies within this field, we assume we would need 101 patient's per treatment arm. We anticipate including 2 centers in this study and we estimate that accrual will be reached within 36 months. Study will be completed at 40 months to allow for complete follow up of all patients enrolled.

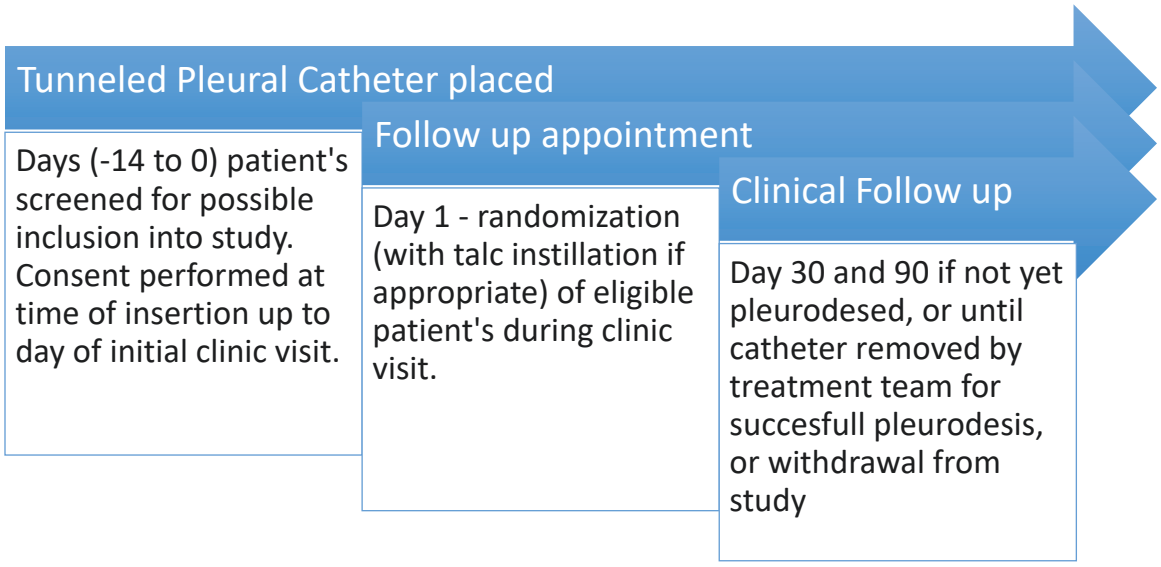
Statistics will be performed by a statistician blinded to which treatment group allocation

Planned Interim Analysis

An interim analysis will be conducted once 100 subjects have been recruited and 90 day data collected. Analysis will be for the primary outcome only. Statistically significant difference in pleurodesis rates as measured by Fisher's Exact Test with $p < 0.05$ will trigger early termination of the study.

Data and Safety Monitoring

All study records will be kept securely by in the study coordinators or local site investigators office. Digital records will utilize secured Redcap database software on the Duke or VA networks. Only the study personnel will have access to the records. Subject data will be coded with a study number after recruitment. The code crosswalk key will be kept in a separate location from the study data.



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