A single institution experience for the management of recurrent pleural effusions with tunneled pleural catheter and its evolution

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Abstract

Background: Indwelling tunneled pleural catheters (TPCs) are increasingly being used to treat recurrent pleural effusions. There is also an increased interest in early pleurodesis in order to prevent infectious complications. We studied the time to removal and other outcomes for all the TPCs placed at our institution.

Methods: After institutional review board approval, records of patients who had had a TPC placed between July 2009 and June 2016 were reviewed; the catheters were placed in an endoscopy suite or during pleuroscopy with or without a sclerosant. The catheters were drained daily or less frequently and were removed after three drainages of less than 50 ml.

Results: During the study period 193 TPCs were placed. Of these 45 (23%) were placed for benign diseases. The commonest malignancy was lung cancer 70 (36%). Drainage 2–3 times a week without a sclerosant (n = 100) lead to pleurodesis at 57 ± 78 days, while daily drainage after TPC + pleuroscopy + talc (n = 41) achieved the same result in 14 ± 8 days (p < 0.001). TPC + talc + daily protocol achieved pleurodesis in 19 ± 7 days, TPC + rapid protocol achieved the same result in 28 ± 19 days (p = 0.013). The TPCs + sclerosant had an odds ratio of 6.01 (95% confidence interval: 2.1–17.2) of having a complication versus TPC without sclerosant.

Conclusions: It is clear that TPCs when placed with a sclerosant had a significantly shorter dwell time; however, they were associated with higher odds of complications. One must be aware of these possibilities when offering what is essentially a palliative therapy.

Keywords: palliation, pleurodesis, pleuroscopy, recurrent pleural effusion, talc, tunneled pleural catheter

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Introduction

Lung cancer is the leading global cause of cancer death. Around 1.8 million people were diagnosed with lung cancer in 2012, accounting for 13% of new cancer cases.1 Malignant pleural effusion (MPE) is a common occurrence in lung cancer, with an estimated annual incidence of 150,000 in the USA alone, and given the year-on-year increase in new cancer diagnoses, the incidence is set to rise.2,3 MPEs are present in 15% of patients with a new diagnosis of lung cancer and will eventually occur in 46%.4 MPE represents advanced malignant disease and current guidelines quote median survivals of between 3 months and 12 months with the average being 3–6 months for nonsmall-cell lung cancer.5,6

There are three main options for the palliation of MPE-related symptoms: obliterating the pleural space by pleurodesis to prevent further fluid re-accumulation, chronically draining the pleural fluid with an indwelling pleural catheter (IPC), also
called a tunneled pleural catheter (TPC), or repeated thoracentesis for patients who either have a slow recollection of fluid or are uninclined to pleurodesis or TPC. Pleurodesis offers a higher chance of rapid resolution of the pleural effusion with an intervention that is time limited but at the expense of a more invasive procedure, the need for a hospital stay, and a higher need for repeat procedures. IPC offers an outpatient solution, which is less invasive, but at the cost of prolonged catheter drainages and care in a significant portion of patients who will not achieve pleurodesis. There is no clear consensus that one is better than the other in terms of impact on quality of life, symptom relief, and costs.7

The purpose of this study is to determine if the rate of spontaneous pleurodesis using the PleurX® catheter (Becton, Dickinson and Company, Franklin Lakes, NJ, (USA), the TPC used at our institution, could be increased with the added intervention of talc pleurodesis via the catheter at the time of insertion. The added benefits of a rapid pleurodesis would be early removal of the catheter thereby preventing catheter-related complications, which are well described. There has been support for this approach in the literature.8,9

There has been interest in using the TPC in non-malignant conditions as well as these usually out-number malignant etiologies.14

**Methods**

After approval by the institutional review board (IRB) of the University of Arkansas for Medical Sciences (IRB no. 205543) we reviewed the charts of all patients that had undergone a TPC placement at our institution from July 2009 to June 2016. Requirement for consent was waived by the IRB.

The data queried included age, gender, race, etiology of the pleural effusion, protocol of TPC placement, length of TPC placement, need for procedures after the TPC placement or removal on the ipsilateral side, and complications. Complications queried included infections (e.g. cellulitis, positive fluid cultures, and empyema), bleeding complications (e.g. hemothoraces and tract hematomas), pneumothoraces, misplacements, allergic reaction to the adhesive, etc.

Definition of duration was defined as: (a) the days to removal, or (b) the time to death in case of death prior to removal.

**TPC protocol at our center**

**TPC insertion.** At our institute we use several different protocols for TPC placement, they are: (a) TPC placement in the endoscopy suite under moderate sedation without talc or other sclerosant instillation with (i) rapid drainage, which is defined as daily drainage till the drainage stops and the TPC is removed after three drainages of less than 50 ml or (ii) liberal drainage defined as drainage 2–3 times a week and removal after three drainages of less than 50 ml; (b) TPC placement in the endoscopy suite with talc 5 g as a slurry or a chemotherapeutic agent, cisplatin at 20g/m² instillation with (i) rapid drainage or (ii) liberal drainage; (c) TPC placement in concert with pleuroscopy with pleurodesis (a combination of 2.5 g of talc insufflation and 300 mg of doxycycline) with (i) rapid drainage or (ii) liberal drainage.

The decision as to which protocol is used is based on patient performance status as well as patient preference.

For the purpose of this article when we mention pleuroscopy we imply that pleuroscopy is performed with pleurodesis (a combination of talc and doxycycline as described above), and when we mention sclerosant we imply talc unless stated otherwise.

Bilateral TPC insertions were included in the study as two separate events. If an ipsilateral TPC was placed due to a need for a procedure after a TPC, it was counted as a secondary procedure and not a TPC insertion event.

**Chemical pleurodesis using a sclerosant**

The decision to use sclerosant and rapid drainage was based on our clinical and radiologic estimate of trapped lung.

Sclerosant was avoided under the following circumstances:

1. if the lung was trapped at the time of TPC placement or pleuroscopy (if trapped liberal drainage without a sclerosant was performed)
2. if the patient chose to opt out of pleurodesis due to concern for sclerosant-related side effects, possibility of pain, or an inflammatory response
(3) if the patient had a short life expectancy
(4) if the patient had a reliable support system for drainage (e.g. family or home aide services) thereby eliminating the need for rapid pleurodesis
(5) when there was a concern for infection at the time of pleuroscopy

Protocol for removal

The patient is brought to the endoscopy suite and an ultrasound is used to examine the pleural cavity to rule out any remnant fluid or loculations. If neither is present we then drain the catheter one last time and then remove it. If there is fluid an attempt is made to drain it or place alteplase to resolve the loculation, and these patients were re-examined after the drainage decreased to 50 ml or less. Care is taken to ensure that the catheter has been removed in its entirety. We then follow them in clinic with chest imaging (usually chest X-ray) for a year. If there is no re-accumulation, the patients are then released from our care until they require another interventional pulmonology procedure.

The aim of this study was to provide descriptive data on our experience. We performed Student’s $t$ test for the time to removal of an IPC with a liberal approach versus a rapid approach. We also calculated the odds ratio (OR) of patient injury between patients who received sclerosant versus those that did not. We also calculated the number needed to harm (NNH) for the application of sclerosant.

The day to removal of the catheter followed a symmetrical distribution. All statistical tests used a significance level of 0.05 for all statistical analyses. All analyses were conducted using SAS version 9.3 (SAS Institute Inc, Cary, NC, USA). The ORs and NNH were confirmed using a clinical calculator at http://clincalc.com/Stats. The Student’s $t$ tests were confirmed with the website http://www.socscistatistics.com.

Results

During the study period, 658 patients were referred to interventional pulmonology and 193 TPCs were placed for these recurrent pleural effusions. Bilateral TPCs were placed in 14 patients. The rest of the patients opted for pleuroscopy with chest tubes, pigtails with talc and repeated thoracentesis hence were excluded.

Men formed a majority at 51% of the complete population. Ethnic distribution was 112 (58%) White, 72 (37%) African-American, 3 Asian, 5 Hispanic, and 1 African. Mean age was 53 years with a range of 19–93 years.

Of these 45 (23%) were placed for recurrent pleural effusions associated with benign disease. These included congestive heart failure, endstage renal disease, and endstage liver disease (ESLD). Of note, out of seven patients with ESLD, four were being discharged to hospice and three patients were still on the transplant list.

Lung cancers at 70 (36%) followed by breast cancer at 47 (24%) were the most common malignant diseases for which placement was required. Ovarian cancers, endometrial cancers, colon cancer, lymphomas, plasmacytoma, etc., constituted the rest. Figure 1 demonstrates the algorithm that was followed in the decision making of the protocol before the placement of the PleurX catheter.

The commonest protocol used was the placement of a TPC in the endoscopy suite without sclerosant instillation with liberal drainage, 87 (45%), followed by TPC with pleuroscopy with rapid drainage, 41 (21%), TPC with sclerosant in the endoscopy suite with rapid drainage, 28 (15%), TPC with pleuroscopy with liberal drainage, 19 (10%), TPC without sclerosant with rapid drainage in the endoscopy suite, 13 (7%), and TPC with cisplatin with rapid drainage, 5 (3%). Figure 2 describes the evolution and additions of the protocols as outlined above to our pleural program.

Time to pleurodesis

The commonest protocol (TPC in the endoscopy suite without sclerosant instillation with liberal drainage) had a mean indwelling time of 57 days with a range of 23–372 days. TPC without sclerosant with rapid drainage in the endoscopy suite had an indwelling time of 28 ± 19 days. When talc was used with a rapid drainage protocol the indwelling time was 19 ± 7 days ($p \leq 0.001$). When the cisplatin was used with rapid drainage the indwelling time was 5 ± 2 days. When TPC with pleuroscopy was used with a rapid drainage protocol, the indwelling time was 14 ± 8 days, however when the liberal strategy was used the indwelling time was noted to be 22 ± 5 days ($p < 0.0001$) (see Table 1 for details).
We removed 78 (40%) of the TPCs. The mean duration of indwelling TPC in patients who survived to removal was 64 days with a range of 2–372 days. Table 2 describes the outcomes for TPCs placed for benign diseases.

There were 11 deaths within 21 days of insertion (lung cancer 5, breast cancer 2, and ESLD 4). Out of the seven patients with cancer all but one changed their goals to comfort measures only. One died after the return of spontaneous circulation (ROSC) could not be achieved after a code blue within 24 h of the TPC + talc; no autopsy was performed. However, the patient was found to be febrile at 39.4 °C with a respiratory rate of 34/min just prior to going into pulseless electrical activity. There had otherwise been no change in his treatment plan. His original malignancy was adenocarcinoma of the lung. The four patients with ESLD had their catheters placed so that they could be discharged home on hospice. All the patients who died had the TPC in place at the time of death.

Figure 1. Algorithm demonstrating the decision tree in the management of recurrent pleural effusion with a tunneled pleural catheter. The decision tree was excessively complicated, thus only the major decision points are highlighted. CHF, congestive heart failure; ESLD, endstage liver disease; ESRD, endstage renal disease; TPC, tunneled pleural catheter.

Figure 2. The increasing variety of protocols offered and used between 2009 and 2016. TPC, tunneled pleural catheter.
Alteplase was required in seven patients to resolve unsatisfactory loculations or catheter obstructions to improve drainage. Two patients developed hemothoraces and had to have a thoracotomy to evacuate the pleural cavity (these patients were not included in the time to TPC removal). Of note both these patients were started on their anticoagulation on day 3 after the procedure. Seven patients required thoracentesis after removal of the TPC. Five of these were performed to rule out infection in areas of loculation and two were required in association with congestive cardiac failure.

Six patients required repeat medical pleuroscopy and one required video-assisted thoracoscopic surgery (VATS). Of the six patients who had a repeat pleuroscopy, three were patients who were...
being treated for breast cancer and were diagnosed with adenocarcinoma of the lung on the second procedure. The VATS was performed for one patient in whom the pleural biopsies were unable to confirm a diagnosis of mesothelioma and he eventually required a pleurectomy to establish the diagnosis.

Complications
Patients who had instillation of sclerosant (either in the endoscopy suite or at pleuroscopy) had pain requiring inpatient management more often than patients who did not have instillation of sclerosant. One patient had pain severe enough to have the catheter removed at day 3. Seven required more than 48 h of inpatient pain management after TPC with talc + doxycycline as the pain was not able to be adequately managed as an outpatient. Five of these patients were post-pleuroscopy and could not be discharged the morning after the procedure due to pain, as is our protocol.

Transient fever was found in 24 (27%) patients who had received sclerosant (talc alone or talc with doxycycline). Mild respiratory complaints (including shortness of breath, hypoxia, increase in oxygen requirement) were found in nine (4%) of the patients, two of whom had to be transferred to the intensive care unit. Three patients had a cardiac arrest within 24 h of talc instillation (all of these cases were performed in the endoscopy suite). One of the patients did not achieve ROSC.

The patients without sclerosant instillation had less frequent adverse events. A total of 22 patients complained of chest-wall pain for the first 24 h (this pain was not severe and was managed symptomatically as outpatients). Two patients developed hypoxia after drainage at the time of insertion. Both were inpatient at the time and only required a transient increase in oxygen supplementation. Two patients developed tract infection that then led to pleural infection.

Three patients developed tract infection with empyema. Two of these cases were secondary to *Stenotrophomonas maltophilia* and underwent catheter removal after a final drainage. One patient with ESLD required two thoracentesis after which she did not require any pleural procedures on that side and the second required no further procedures. The third empyema case was due to *Staphylococcus epidermidis*, which was satisfactorily treated through the catheter. The catheter was subsequently removed on day 29.

The OR of having an adverse result from instillation of a sclerosant was 6.01 (95% confidence interval [CI]: 2.1–17.2). There was a total of 24 complications (12%), however only 8 (4%) were considered to be major adverse effects. The latter included infections, hemothoraces, and cardiac arrest. The NNH was 6.3.

Trapped lung
Radiologic or physiologic evidence of lung entrapment was present in about 20 (20%) patients treated with the liberal strategy. Seven (35%) of these patients still achieved pleurodesis at 78 ± 12 days. This rate is not statistically different from the rate of pleurodesis for the whole population (p = 0.87). We did not use the rapid strategy on patients when there was a possibility of incomplete expansion at the time of pleuroscopy.

Discussion
The development of recurrent pleural effusions especially in the context of malignancy is an event that is associated with short life expectancy and significant morbidity. The options include thoracentesis, a TPC or pleurodesis via a chest tube, or pleuroscopy.7–10

The use of TPCs in the management of patients with MPEs (both those with trapped lung and shorter life expectancy as well as those with longer survival and good lung re-expansion) is well known.11–13 The use of TPCs now extends to benign indications as well.14 In our study we had 45 TPCs (23%) placed for recurrent pleural effusions associated with benign disease. These included congestive heart failure, ESRD, and ESLD. The patients with ESLD that had had a TPC placed were part of a pilot study to evaluate the feasibility of TPC for scheduled drainage compared with thoracentesis. The study group had a significantly higher complication rate, hence, this study is no longer being conducted.

TPCs are favored because of the ease of outpatient placement and management without sedation or general anesthesia with rapid and persistent symptomatic improvement and low complication rates. A recent study based on the Second
Therapeutic Intervention in Malignant Effusion Trial (TIME-2)\textsuperscript{15} demonstrated the overall mean costs over a 1-year follow up of US$ 4993 for TPC versus US$ 4581 for pleuroscopy with pleurodesis. The incremental mean cost difference of US$ 401 (95% CI: −1387 to 2261) was nonsignificantly different, but if patients survived for fewer than 14 weeks IPC became significantly less costly (US$ −1719, 95% CI: −3376 to −85). TPCs can be placed in the endoscopy suite or at the time of pleuroscopy. Pleuroscopy may require the use of an operating theater, or properly equipped procedure room, anesthesiology staff to administer sedation or general anesthesia, as well as hospital admission leading to significant procedure-related costs. Most importantly, a substantial number of patients with advanced malignancy and short life expectancy are too debilitated to undergo either chest-tube pleurodesis or pleuroscopy, and neither of these techniques is applicable to patients with trapped lung, which accounts for at least 30% of patients with MPE.\textsuperscript{10} In our study, radiologic or physiologic evidence of lung entrapment was present in about 20 (20%) patients.

Pleurodesis can be performed with the instillation of a chemical agent through a standard chest drain including a TPC or via pleuroscopy\textsuperscript{16,17} and when talc in particular is used, pleurodesis has been reported to have high success rates.\textsuperscript{18} In our study the liberal protocol defined as TPC with drainage 2–3 times a week without a sclerosant (n = 100), led to pleurodesis at 57 ± 78 days while daily drainage after TPC placed via pleuroscopy with talc placement (n = 41) achieved the same in 14 ± 8 days (p < 0.001). There certainly was a quicker time to pleurodesis, however this was obtained at significant cost. The TPCs placed with a sclerosant (most commonly talc) had an OR of 6.01 (95% CI: 2.1–17.2) of having a complication when compared with patients who did not receive a sclerosant. These complications included a requirement for a higher level of care for respiratory distress including hypoxia, severe pain, or cardiac arrest within 24 h of TPC with talc placement.

Talc pleurodesis induces an inflammatory response, which has been reported to cause fever and pain in 26% and 31% of patients, respectively, according to a Cochrane meta-analysis.\textsuperscript{18} Pain may be severe enough to necessitate the use of a patient-controlled anesthesia in as many as 5% of patients.\textsuperscript{19} Pain was only reported in 5.6% of patients during IPC insertion and pain persisting beyond the immediate postprocedural period was reported in 3.2% of patients.\textsuperscript{20} Pain post-IPC insertion is usually mild enough to be managed without opiates. Pleurodesis techniques are associated with a risk of empyema of 0.4–4.0%,\textsuperscript{10,17} which is in the same range as that reported with IPC insertion. Talc pleurodesis has also been associated with rates of acute respiratory distress syndrome as high as 9%,\textsuperscript{21} particularly with the use of higher doses and small-particle-size talc. Use of other talc preparations should be considered with caution and preferably with knowledge of talc particle-size distribution and clinical data with the specific preparation. Other complications encountered following talc pleurodesis included pneumothorax, re-expansion pulmonary edema, infection of the procedure site, pneumonia, pulmonary embolism, and atrial fibrillation.

In recent years there have been studies that compared a combination of the procedures listed above to create an optimal approach to MPE. The hope is to create an approach that combines the advantages of a TPC (ease of outpatient placement and management without sedation or general anesthesia with rapid and persistent symptomatic improvement and low complication rates) with chemical pleurodesis to shorten the time to pleurodesis and therefore to catheter removal. Studies have looked at the combination of talc pleurodesis by pleuroscopy with simultaneous insertion of a TPC.\textsuperscript{22,23} A 30-patient pilot study\textsuperscript{23} demonstrated a 1.79-day median hospital stay with a 92% pleurodesis rate at 6 months and universal improvement in dyspnea and quality of life. Similar results were noted in another small study that looked at talc slurry through a TPC.\textsuperscript{24} The randomized controlled IPC-plus trial is comparing the efficacy of IPC alone versus IPC plus talc through IPC as an outpatient (EUdraCT number: 2012-000599-40).

In regards to using chemotherapeutic agents for malignant pleural involvement, there has been consistent interest from multiple centers. Iannitto and colleagues successfully used intravenous and intrapleural bortezomib in a patient with multiple myeloma with pleural involvement.\textsuperscript{25} Ichinose and colleagues\textsuperscript{26} showed that intrapleural cisplatin decreased the incidence of carcinomatous pleuritis but made no significant impact on survival. Rusch and colleagues showed that intrapleural cisplatin-based chemotherapies achieved...
49% response rate in the control of MPE associated with solid cancers. Agarwal and colleagues described a novel method of using TPC with cisplatin to treat myelomatous pleuritis with a marked decrease in both plasma cells and pleural effusion. We continue to use cisplatin in concert with our myeloma physicians with the ability to achieve pleurodesis at a rapid rate without complications.

Our study had the advantage of comparing five different approaches to recurrent pleural effusions. A large percentage of these were malignant in origin (77%). Our study showed a significant increase in complications with the use of talc whether it be via TPC or via pleuroscopy. We want practitioners to be aware of these possibilities especially in the context of MPEs where pleural disease management is essentially a palliative intervention. Our study did suggest a shorter dwell time when sclerosant was used either via TPC or via pleuroscopy potentially providing short-term definitive treatment for MPE, however this comes at some cost of complications. The complications were not severe for the most part with pain and hypoxia being the main events. It is sobering that three patients had a cardiac arrest within 24 h of the sclerosant instillation. It is not clear that it was the cause of the event, but it underscores the fact that not all patients need or tolerate the same type of procedure. This in turn supports the development and practice of a variety of options for patients that offer them the most benefit and choice.

It should be noted that there is a perceived burden of ongoing care associated with the IPC (e.g. dressing changes, drainages, etc.). Nevertheless, this burden does not appear to have an adverse effect on overall quality of life in the TIME-2 trial, which noted similar improvement in both arms with a nonsignificant trend favoring IPC. The TIME-2 randomized trial of IPC versus talc pleurodesis also did not find a difference in the primary outcome measure of dyspnea improvement at 42 days on a visual analog scale, although improved symptoms became significant at the 6 months’ time point in favor of the IPC group.

The commonest protocol (TPC in the endoscopy suite without sclerosant instillation with liberal drainage) had a mean indwelling time of 57 days with a range of 23–372 days. TPC without sclerosant with rapid drainage in the endoscopy suite had an indwelling time of 28 ± 19 days. Although the number of patients subjected to rapid drainage was smaller, the data suggest that a rapid drainage protocol even without sclerosant leads to a quicker pleurodesis, thus allowing the physicians potentially to remove the catheter sooner.

While we await the results of the randomized controlled IPC-plus trial, we advise cautious and careful selection of patients for talc pleurodesis and instead strongly support a strategy of outpatient TPC placement foregoing talc pleurodesis. We also encourage patients to perform and physicians to recommend daily drainage to reduce catheter dwell times and hasten pleurodesis.

**Limitations**

Although the study had a large sample size, it was retrospective. The chart review over 8 years could have led to data loss and incorrect classification of complications. Even the veracity of the patients actually following the rapid versus liberal strategy could be questioned.

The study endeavors to evaluate a myriad of protocols from which the patient can choose, however the buffet offered makes it difficult to compare the outcome of the different options. We compared the strategies that resembled each other to some degree to calculate the time to pleurodesis, however the different doses of the sclerosants likely had an impact on the time to pleurodesis. We were only able to remove 40% of the TPCs and a majority of the patients died with the TPC in place. The study could have been more robust if we had had data on the amount of fluid drained close to death as an indirect estimation of imminence of pleurodesis.

**Conclusion**

Though TPCs when placed with a sclerosant had a significantly shorter dwell time (a surrogate for time to pleurodesis), they were associated with higher odds for complications. One must be aware of these possibilities when offering what is essentially a palliative therapy. Of note, when sclerosant was avoided, the TPC with a rapid drainage protocol still lead to a quicker pleurodesis when compared with TPC with a liberal...
drainage protocol with the added advantage of fewer complications.

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Conflict of interest statement
The authors declare that there is no conflict of interest.

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