The Use of Intrapleural Thrombolytic or Fibrinolytic Therapy, or Both, via Indwelling Tunneled Pleural Catheters With or Without Concurrent Anticoagulation Use

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BACKGROUND: Indwelling tunneled pleural catheters (IPCs) are used regularly for recurrent pleural effusion management. Catheter obstruction is not uncommon, often requiring intrapleural medications instillation (ie, alteplase) to restore flow. The safety profile of intrapleural medications has been reported previously; however, most studies exclude anticoagulated patients.

RESEARCH QUESTION: What is the safety profile of intrapleural alteplase, dornase alfa, or both when used in patients with IPCs, including in those who may be undergoing active anticoagulation?

STUDY DESIGN AND METHODS: Retrospective review of patients with previously placed IPCs from January 2009 through February 2020 undergoing intrapleural alteplase therapy. Basic demographics, laboratory studies, anticoagulation medication use, and complications were collected. Descriptive statistics were used to report demographics and outcomes. Univariate Firth’s logistic regression analyses were used to identify factors associated with complications, followed by multivariate regression analyses.

RESULTS: A total of 94 patients underwent IPC placement and intrapleural instillation. The median age of patients was 66.1 years (interquartile range, 57.6-74.9 years). Intrapleural medications were administered 71 times in 30 anticoagulated patients and 172 times in 64 patients who were not anticoagulated. A total of 20 complications were identified in 18 patients, with one patient experiencing more than one complication. Five bleeding complications occurred with no significant increased risk with anticoagulation use (in 2 anticoagulated patients and 3 patients who were not anticoagulated; \( P = .092 \)). Multivariate Firth’s logistic regression demonstrated that alteplase dose \( (P = .04) \) and anticoagulation use \( (P = .05) \) were associated with any complication, but were not associated with bleeding complications.

INTERPRETATION: We report a relatively low incidence of complications and, in particular, bleeding complications in patients receiving intrapleural alteplase for nondraining IPCs. Bleeding episodes occurred in five of 94 patients (5.3%) with no apparent increased risk of bleeding complication, regardless of whether receiving anticoagulation. Additional study is warranted to identify risk factors for complications, in particular bleeding complications, in this patient population.

KEY WORDS: chest tube; coagulation; indwelling tunneled pleural catheter; pleural effusion

ABBREVIATIONS: IPC = indwelling tunneled pleural catheter; IQR = interquartile range

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Use of the indwelling tunneled pleural catheter (IPC) to manage recurring pleural effusions has become more widespread since its introduction.\(^1\)\(^-\)\(^3\) Originally designed for use in malignant pleural effusions, it has begun to see use in other nonmalignant diseases including heart failure, hepatic hydrothorax, and others.\(^4\)\(^,\)\(^5\) Although generally well tolerated, various complications have been documented. Infectious issues often are most feared, but another common management problem is the nondraining IPC. Because this reported finding can result from a variety of causes, it often requires additional evaluation and intervention. In the setting of decreased pleural fluid output, worsening symptoms, and radiographic evidence of persistent or increased pleural fluid, one must be concerned about a blocked or malfunctioning IPC. One management approach of the nondraining IPC in this setting is to use intrapleural medications such as alteplase.\(^6\)\(^-\)\(^8\)

The use of intrapleural medications like alteplase, a thrombolytic agent, have been reported as generally safe. Bleeding complications in patients receiving alteplase (doses of up to 10 mg) and dornase alfa for pleural infection have been reported to range from 0% to 4%.\(^9\)\(^-\)\(^12\) This bleeding risk profile seems to be similar to patients receiving intrapleural thrombolytics (alteplase, urokinase, or streptokinase) for nondraining IPCs, in which it has been reported to range from 0% to 3%.\(^6\)\(^,\)\(^7\)

One limitation in all these studies is they did not report the anticoagulation status of patients enrolled or, if they did report anticoagulation use, no description of any relationship to bleeding complications was included. Therefore, we aimed to identify the safety profile of patients receiving intrapleural thrombolytics for nondraining IPCs, including those receiving active anticoagulation.

### Methods

A retrospective review of patients undergoing intrapleural alteplase therapy through a previously placed IPC at Swedish Medical Center was performed from January 2009 through February 2020. Institutional review board approval was obtained (identifier, STUDY2020000145) and a waiver of consent was granted. Patients were identified from a database related to IPC insertion and alteplase use (Current Procedural Terminology codes 32550, 32561, and 32562). Some patients have been reported previously.\(^6\)

Basic demographics, laboratory studies, anticoagulation medication use and status, procedural notes, and subsequent progress notes were reviewed for outcomes related to alteplase use, specifically complications of use. Indications for IPC insertion were identified from the underlying pleural disease cause. Malignant pleural effusion was defined by histocytologic proof of malignancy within the pleural space; paramalignant pleural effusion was defined by the presence of a large, recurrent, exudative pleural effusion in the context of histologically proven malignancy outside the pleural space; recurrent transudative pleural effusion was defined by Light’s criteria in the context of underlying cause (ie, cardiac, renal, liver disease); and other or unknown were those not fulfilling these criteria (ie, chylothorax).

### Nondraining IPC and Intrapleural Medication Use

A nondraining IPC generally is defined by patient report of sudden decrease in pleural fluid during drainage (< 10 mL). This coupled with radiographic evidence (chest roentgenography, pleural ultrasound, CT scan, or a combination thereof) of recurrent pleural effusion and reports of symptoms attributable to pleural disease lead to additional evaluation to improve pleural drainage, commonly intrapleural alteplase instillation.\(^6\)

Intrapleural medication instillation was performed in both inpatients and outpatients. For inpatients receiving alteplase and dornase alfa, they were prepared separately, but instilled directly after one another, allowed to dwell for 60 to 120 min, and then allowed to drain, either via PleurX (Becton, Dickinson and Company) drainage bottle or via continuous closed chest drainage system (Atrium, Atrium Medical Corporation). Alteplase was provided as 10 mg within 50 mL of sterile water, whereas dornase alfa was provided as 5 mg within 50 mL of sterile water. For inpatients and outpatients receiving only intrapleural alteplase, dosing was prepared in sterile saline of varying amounts, both regarding dose of alteplase (often 2, 3, or 4 mg) and volume of sterile water (often 2, 4, 10, or 50 mL.). Alteplase was also allowed to dwell for 60 to 120 min and then allowed to drain, either via PleurX bottle or via continuous closed chest drainage system.

Intrapleural medication instillation was performed directly by a staff member (registered nurse, advanced registered nurse practitioner, or medical doctor) of our team per institution protocol. Patients are monitored depending on the location of service (inpatient bed vs infusion center), but are observed directly during the infusion and shortly thereafter. Outpatients are discharged after instillation and asked to follow-up telephonically with pleural fluid output and any concerns or complications. Patient charts were reviewed for any subsequent clinical or telephone encounters that resulted from the procedure, including those possibly indicating a complication.
Anticoagulation Use

As a general practice, anticoagulation medications were not held specifically for intrapleural instillation, although a discussion with patients about the potential risks and benefits also was carried out. Anticoagulation medications reviewed included warfarin, apixaban, dabigatran, rivaroxaban, edoxaban, enoxaparin, and heparin infusions. Some patient medical charts indicated they had been anticoagulated; however, anticoagulation was held for other clinical reasons (ie, need for procedure) and others elected to hold anticoagulation after the informed discussion occurred. As a result, we reviewed medical records and medical administration records to determine if patients were anticoagulated actively at the time of intrapleural medication instillation. We defined active anticoagulation as: yes, likely, unlikely, or no. Patients clearly documented in the medical record (or by laboratory values in the setting of warfarin and heparin) on the day of intrapleural medication instillation as receiving ongoing anticoagulation were defined as yes. Those receiving ongoing anticoagulation and no other documentation that medications were stopped, with subsequent follow-up notes providing documentation of continued anticoagulation use were defined as likely. Those documented as receiving anticoagulation with no documentation supporting ongoing or active use of anticoagulation and subsequent follow-up documentation supporting discontinuation of medications were defined as unlikely. Patients never receiving anticoagulation medication, those receiving anticoagulation but stopping medication in appropriate time frame before intrapleural medication instillation (ie, > 24 h for enoxaparin), or laboratory values in the setting of warfarin and heparin demonstrating nontherapeutic levels were defined as no.

Complications

Complications were identified from the medical record as bleeding, increase in level of care, respiratory failure, or death within 48 h of alteplase administration. Bleeding was defined by decrease in serum hemoglobin by 1 g/dL or more, the receipt of packed RBCs, or the need for interventional radiology procedures or surgical intervention. Ongoing anticoagulation use was present in 30 patients (31.9%), with most of these patients receiving anticoagulation before IPC placement was performed (25/30 [83.3%]). During intrapleural medication administration, the anticoagulation status was defined as yes in 61 instillations, likely in 10 instillations, unlikely in one instillation, and no in 171 instillations.

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Statistical Analysis

All data was collected in Research Electronic Data Capture database. Simple descriptive statistics were used to report demographics and outcomes. Analysis included presentation of basic percentages, mean with SD, and median with interquartile range (IQR). Statistical significance was defined as P < .05. All statistical analyses were performed using SPSS version 24.0 statistical software (SPSS, Inc.) and R version 3.6.0 software (R Foundation for Statistical Computing).

Results

A total of 94 patients were identified as having undergone IPC placement and intrapleural medication instillation. The median age of patients was 66.1 years (IQR, 57.6-74.9 years) with most IPC placements related to malignancy (90%). The most common reason for a patient to undergo intrapleural medication instillation was for a nonfunctioning IPC (85% [80/94]). Additional demographics of the population are listed in Table 1.

Intrapleural medications were given a total of 243 times, with patients undergoing a range of one to 16 instillations with multiple dose ranges (Fig 1). A total of 72 patients underwent 164 alteplase instillations and 22 patients underwent 79 alteplase and dornase alpha instillations. Of those undergoing alteplase and dornase alpha instillation, eight patients (27 instances) were being treated for IPC-related infection, 10 patients (48 instances) were being treated for a nonfunctioning IPC, and four patients (four instances) were being treated for known noninfectious loculations.
Five bleeding complications (Table 2) were identified in five patients (5.3% [5/94]). In patients receiving active anticoagulation, the incidence of bleeding was 6.7% (2/30) on a per-patient basis over the lifetime of the catheter, or 2.8% (2/71) on a per-instance basis. In patients not receiving active anticoagulation, the incidence of bleeding was 4.7% (3/64) on a per-patient basis over the lifetime of the catheter, or 1.7% (3/172) on a per-instance basis.

A comparison of patient characteristics related to complications was performed (e-Table 1). Characteristics such as age, BMI, days from IPC insertion to first alteplase dosing, number and strength of alteplase doses, sex, indication for IPC insertion, underlying carcinoma diagnosis, reason for alteplase use, and anticoagulation use all suggested no significant increase in association with complications (total, bleeding, or nonbleeding complications). Multivariate Firth’s logistic regression (e-Table 2) demonstrated that increasing alteplase dose was associated with increased odds of any complication ($P = .037$) and not receiving anticoagulation was associated with a trend toward decreased odds of any complication ($P = .053$). However, when repeating the multivariate Firth’s logistic regression (e-Table 3) for bleeding complications alone, these odds did not remain significant (alteplase, $P = .259$; anticoagulation, $P = .648$).

Kaplan-Meier analysis was used to estimate the time to IPC events, defined as first IPC complication, IPC removal, or death. Figure 2 presents 1 minus the Kaplan-Meier curves displaying the cumulative proportion of patients having a defined event. These events include the first complication, IPC removal, or death. At 9 months after IPC insertion, >80% of the patients had experienced an event. Complications occurred in 18 patients at a median of 70.5 days (IQR, 27.5-164.75 days). Forty-four patients underwent IPC removal at a median of 133 days (IQR, 76.25-219.5 days). Twenty-nine patients died with the IPC still in place at a median of 89 days (IQR, 36-231 days). Three patients were still alive and free of any events as of last known follow-up.

Discussion

We report a relatively low incidence of bleeding complications in patients receiving intrapleural alteplase for nondraining IPCs. A total of 94 patients received 243 intrapleural doses of alteplase with a relatively low-risk bleeding profile, somewhat similar to previously reported studies. Bleeding episodes occurred in five patients (5.3%) over 243 instillations (2.1%), with no patient experiencing more than one bleeding episode. Active anticoagulation use was not associated with increased bleeding risk ($P = .092$), nor does there seem to be a significant association on multivariate regression analysis. This seems to be the first report in the literature demonstrating the risk and safety profile of intrapleural alteplase instillation in patients undergoing active anticoagulation.

Prior studies have reported relatively low complication risk profiles of intrapleural alteplase, be it as monotherapy or in combination with another drug (often dornase alfa), as well as the same phenomenon in different populations (infection vs loculated malignant pleural effusions). \cite{6,7,10,12} Two prior studies described alteplase use via IPCs.\cite{5,7} Only Thomas et al’ reported

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Patient Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td>Data (No. (%))</td>
</tr>
<tr>
<td>Age at IPC placement, y</td>
<td>66.1 (57.6-74.9)</td>
</tr>
<tr>
<td>Days from IPC insertion to first intrapleural medication use</td>
<td>52 (23-120)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>62 (66)</td>
</tr>
<tr>
<td>Male</td>
<td>31 (33)</td>
</tr>
<tr>
<td>Transgender</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Indication for IPC insertion</td>
<td></td>
</tr>
<tr>
<td>Malignant pleural effusion</td>
<td>52 (55)</td>
</tr>
<tr>
<td>Paramalignant effusion</td>
<td>33 (35)</td>
</tr>
<tr>
<td>Recurrent transudative pleural effusion</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Top three underlying carcinoma diagnosis</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>29 (31)</td>
</tr>
<tr>
<td>Breast</td>
<td>28 (30)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Anticoagulation use</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>64 (68)</td>
</tr>
<tr>
<td>Yes</td>
<td>30 (32)</td>
</tr>
<tr>
<td>Reason for intrapleural medication use</td>
<td></td>
</tr>
<tr>
<td>Nonfunctioning catheter</td>
<td>80 (85)</td>
</tr>
<tr>
<td>Pleural space infection</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Known noninfectious loculations</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

Data are presented as No. (%) or median (interquartile range). IPC = indwelling tunneled pleural catheter.
bleeding complications—two of 66 patients (incidence, 3%) experienced bleeding—with neither patient being anticoagulated. Both patients were supported with blood transfusions, and no additional need for radiologic or surgical interventions were required. The authors suggest that no easily identifiable features can predict pleural bleeding, and therefore caution is needed. We also report a fairly low incidence of bleeding complications, including those patients who were receiving active anticoagulation at the time of alteplase instillation. Previous authors have suggested that in patients with underlying malignant pleural disease, the risk of systemic absorption of intrapleural thrombolytics in fact may be decreased in light of abnormal pleural surfaces and reduced local lymphatic drainage. The clinical reality of these theories remains unclear; however, it seems that anticoagulation use was not associated with an increased bleeding risk during intrapleural medication instillation via IPC within this patient population.

Although our main focus was the use of alteplase, the effect that dornase alfa may have within this population remains unknown. As previously noted, the combined use of alteplase and dornase alfa has been popularized by the positive results from the Second Multi-centre Intrapleural Sepsis Trial (MIST 2) trial in pleural infection. We report on using intrapleural medications at other dosages, as well as for other causes. Some reports of alternative regimens and alternative uses (noninfectious loculations) exist; however, these may not be considered the standard as was described previously in the MIST 2 trial. The efficacy or usefulness of its use in some of these situations remain unclear. However, determining this was not the intent of this study and remains a potential limitation. The variable use of doses and regimens also may reflect the learning process that has occurred over time with pleural disease as more publications emerge. Our trial likely is poorly designed for efficacy because it covers a long period during which multiple pleural intervention articles have been published. However, we do believe that this long time frame remains appropriate for describing complications, in particular bleeding complications related to intrapleural instillation and anticoagulation use.

Further chart review of the patients who experienced bleeding complications (n = 5) did reveal some interesting additional information. No patient demonstrated hemodynamic instability, required interventional radiology procedures, or surgical intervention. Four patients experienced bleeding during the first alteplase instillation. Two patients showed bleeding on the first and only instillation (one was...
Two patients demonstrated bleeding during the first instillation (one was anticoagulated and one was not anticoagulated). Nonbleeding complications also were present within this population, but as with the bleeding risk evaluation, it can be difficult to identify whether the complications are related to alteplase instillation or to progression of disease. We elected to identify these as complications in an attempt to remain conservative, knowing that this population unfortunately is at high risk of complications. We also identified one patient who died within 48 h of intrapleural medication instillation. On further review, it seemed that the patient had advanced, progressive breast cancer, and death was thought to be related to progressive cancer, with no evidence of progressive pleural disease on imaging.

Previous studies used similar definitions for bleeding adverse events, but restricted them to only bleeding that requires transfusion or hemodynamic compromise. We elected to use a somewhat more liberal definition. Table 2 shows the bleeding complications seen in our study population. The table includes the age and underlying disease of each patient, as well as details about the bleeding site(s), any anticoagulation or antiplatelet use, the platelet count, the intrapleural medications used, the number of intrapleural instillations, the instance when the complication occurred, and the bleeding management.

<table>
<thead>
<tr>
<th>Age</th>
<th>Bleeding Site(s)</th>
<th>Underlying Disease</th>
<th>Anticoagulation Use</th>
<th>Antiplatelet Use</th>
<th>Platelet Count</th>
<th>Intrapleural Medications</th>
<th>No. of Intrapleural Instillations</th>
<th>Instance When Complication Occurred</th>
<th>Bleeding Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>71</td>
<td>Pleural: bloody effusion</td>
<td>Multiple myeloma</td>
<td>No</td>
<td>No</td>
<td>55</td>
<td>Alteplase 2 mg</td>
<td>3</td>
<td>1</td>
<td>Outpatient PRBC</td>
</tr>
<tr>
<td>72</td>
<td>Pleural: bloody effusion</td>
<td>Breast cancer</td>
<td>Yes</td>
<td>No</td>
<td>514</td>
<td>Alteplase 4 mg</td>
<td>1</td>
<td>1</td>
<td>PRBC and discharged from hospital within 24 h, warfarin continued</td>
</tr>
<tr>
<td>49</td>
<td>Pleural: bloody effusion</td>
<td>Breast cancer</td>
<td>No</td>
<td>Aspirin</td>
<td>96</td>
<td>Alteplase 10 mg/dornase alfa 5 mg</td>
<td>1</td>
<td>1</td>
<td>No transfusion or additional intervention, remained stable</td>
</tr>
<tr>
<td>83</td>
<td>Nosebleed and melena</td>
<td>Lung cancer</td>
<td>No</td>
<td>No</td>
<td>129</td>
<td>Alteplase 4 mg</td>
<td>3</td>
<td>2</td>
<td>Discharged home after PRBC in ED</td>
</tr>
<tr>
<td>57</td>
<td>Subcutaneous tumor bed</td>
<td>Breast cancer</td>
<td>Yes</td>
<td>No</td>
<td>234</td>
<td>Alteplase 10 mg/dornase alfa 5 mg</td>
<td>2</td>
<td>1</td>
<td>Topical silver nitrate and dressing, no transfusion, anticoagulation held</td>
</tr>
</tbody>
</table>

PRBC = packed RBC transfusion.
*Age in years.

Platelets per microliter.
bleeding in an attempt not to miss any bleeding complications. The true impact that a bleeding complication had in the identified population remains unclear. Of the small number of bleeding complications identified, no patient showed hemodynamic compromise, some remained outpatients, and some did not even receive transfusion support. No patients underwent additional interventions (besides blood transfusion) to manage bleeding complications. In one patient, the anticoagulation was discontinued. All patients previously had received blood transfusions during the course of the disease, and so although the decrease in hemoglobin was related temporally to alteplase instillation, it can remain difficult at times to link bleeding and alteplase use with certainty.

An additional limitation is that we did not collect information on other potential coagulopathies, including antiplatelet therapy use (aspirin, clopidogrel, and so forth), thrombocytopenia, or other potential causes. Previous literature related to thoracentesis suggests that thrombocytopenia may not be a significant risk factor for predicting complications; however, a fairly large analysis of risk factors among anticoagulated patients with cancer (n = 3,283,140) suggested that thrombocytopenia is a factor associated with increased bleeding. In light of our reported low bleeding complication incidence, in particular in those receiving anticoagulation, we suspect this is a minimal limitation, but cannot discount the potential this may play in a larger population-based study. The low incidence of complications and small overall population size also are potential limitations. Nevertheless, we attempted to collect data over a 10-year period and also used Firth’s logistic regression analyses to reduce small sample bias in maximum likelihood estimation. To evaluate our decision to use the Firth model further, we additionally evaluated the standard logistical model and Firth’s logistic model, in which the results were similar (data not shown).

**Interpretation**

We report an overall low risk of complications related to intrapleural alteplase instillation, in particular bleeding complications. We also report no significant increased risk of bleeding in anticoagulated patients during intrapleural alteplase instillation. Risk factors for bleeding related to intrapleural medication instillation remain unknown, and additional research is needed. The reported rate of complications, in particular bleeding complications, is low and may make conclusions difficult to draw. However, we report that the use of anticoagulation is not associated clearly with an increased risk of bleeding during intrapleural alteplase use, but nevertheless suggest ongoing, informed discussion with patients during proposed use.
Acknowledgments

Author contributions: C. R. G. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. C. R. G., C. L. W., S.-C. C., and J. A. G. contributed substantially to the study design, data analysis and interpretation, and writing of the manuscript.

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

References