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Intrapleural hemorrhage after administration of tPA: a case report and review of the literature

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***Abstract*:**

Objective: Intrapleural fibrinolytic enzymes have been used for over 60 years in the treatment of complicated pleural effusions to lyse loculations and promote resolution. Despite this extensive history of use, however, little is known about complications that may arise with the use of this therapy. Here we discuss a patient with chronic renal failure on hemodialysis who developed an intrapleural hemorrhage after the administration of intrapleural tPA to treat a complicated parapneumonic effusion. A review of the literature examines the efficacy and safety of this therapy, focusing on bleeding complications. Specific attention is paid to patients who have underlying coagulopathies or who are receiving anticoagulation.

Data sources: A review of the literature, as indexed in PubMed, was undertaken using the following search terms in combination: tPA, pleural effusion, complications of thrombolytics, and intrapleural hemorrhage. The search was inclusive of patients under the age of 18, but was limited by English language and human subjects.

Study selection/data extraction: All relevant articles identified during the search were reviewed. Those studies that reported on bleeding complications, or lack thereof, were included in this review. Limitations of each article are noted in the text.

Conclusions: Multiple studies, including a 2000 ACP consensus statement and a 2008 Cochrane review, indicate the need for further investigations to evaluate the safety and efficacy of intrapleural thrombolytics for the treatment of complicated pleural effusions and empyemas. Limited studies specifically address bleeding complications, especially in subpopulations of patients receiving concurrent anticoagulant therapy.

***Keywords*:** tPA, fibrinolytics, intrapleural hemorrhage

Introduction

Fibrinolytic enzymes have been used for over 60 years in the treatment of complicated pleural effusions. Injected intrapleurally, they promote resolution by lysing loculations. Despite an extensive history of use, however, little is known about adverse events that may arise with the use of this therapy. Potential bleeding complications have been well documented with systemic fibrinolytics in the treatment of massive pulmonary embolism, but the literature is sparse regarding complications associated with intrapleural administration.

Case report

A 40-year-old male with a history of HIV on antiretroviral therapy (CD4 354) and end-stage renal disease from insulin-dependent diabetes mellitus presented to the emergency department with complaints of fevers, chills and generalized malaise. Ensuing workup revealed a left lower lobe infiltrate with a small associated effusion. Blood cultures ultimately grew *Enterococcus*. During his hospitalization, the patient underwent two thoracenteses, which yielded 400 ml and 100 ml of exudative fluid. Pleural fluid characteristics are noted in Box 1. Despite treatment with antibiotics, thoracenteses and continued hemodialysis, the left-sided pleural effusion continued to enlarge and became loculated. Computed tomography revealed the effusion to be complex. Pulmonary consult recommended placement of a pigtail catheter by vascular interventional radiology. Pigtail catheter insertion

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Box 1. Pleural fluid characteristics.

Gram stain: 1 + polymorphonuclear cells, no organisms seen
Culture: No growth at 5 days
RBC: 26750/mm^3
WBC: 2475/mm^3
(69% neutrophils)
Glucose 190 mg/dl (serum 185 mg/dl)
Protein 3.4 g/dl (serum 6.3 g/dl)
LDH 754 U/l (serum 392 U/l)
Amylase < 30 U/l
pH 7.42

was attempted but scant fluid was obtained. Cardiothoracic surgery then placed a chest tube but due to loculations within the fluid, poor chest tube output was noted. The patient received alteplase (25 mg/100 ml NS) infused through the chest tube intending to lyse the loculations in the complicated effusion. He developed chest pain and about 1 liter of serosanguinous fluid drained through the chest tube. Despite transfusion of two units of packed red blood cells, his hemoglobin dropped by 1 g. He was stabilized in the MICU overnight.

Five days later, due to persistent pleural effusion and low chest tube output, he again received alteplase in the pleural space. Upon unclamping the tube after 4 h, he was noted to have greater than 600 ml of blood from the chest tube. The patient was then noted to have signs and symptoms of hypovolemic shock, with hypotension and tachycardia. Agonal breathing ensued and the patient went into cardiac arrest with pulseless electrical activity. He was successfully resuscitated; however, his hemoglobin dropped from 9.6 g/dl to 3.7 g/dl. The patient underwent emergent thoracotomy. Upon entrance into the thoracic space, significant amount of clot was identified. After evacuation of his hemothorax, no single source of bleeding was identified, yet the patient continued to have diffuse bleeding. The patient's coagulation parameters that were initially normal were elevated. The international normalized ration (INR) increased from 1.5 s to 2.0 s; the activated partial thromboplastin (aPTT) increased from 38.6 s to 84.7 s. The D-dimer was 14,762 ng/ml (normal 0–229 ng/ml); fibrinogen was elevated to 481 mg/dl (normal 208–409 mg/dl). Platelets, fresh frozen plasma, cryoprecipitate, and activated factor VII were given with resolution of the bleeding. The patient's thoracotomy incision was closed and the patient did not have any further blood loss.

Review of the literature

Intrapleural fibrinolytic enzymes have been used since the late 1940s to lyse fibrinous loculations within pleural fluid, decrease viscosity, and promote resolution of complicated pleural effusions [Tillett and Sherry 1949]. Varying success rates have been reported in the literature. First-generation thrombolytics, such as streptokinase and urokinase, have no fibrin binding capabilities and exert their effects via increasing local generation of plasmin [Longstaff *et al.* 2008]. Initial studies evaluated streptokinase, which ultimately lost favor due to concerns over systemic side effects, such as delayed hypersensitivity reactions. Urokinase was introduced and thought to have a lower incidence of adverse events, but marketing was ceased under a Food and Drug Administration mandate over concerns of possible transmission of viral diseases. As a second-generation fibrinolytic with high specificity for fibrin and a short half-life, recombinant human tissue plasminogen activator (tPA) has become the agent of choice since 1998, despite its increased cost.

Potential bleeding complications have been well demonstrated in studies examining the use of systemic tPA for massive pulmonary embolism. Meyer *et al.* [1998] established that major bleeding occurred in 25% of 132 adult patients receiving tPA for pulmonary embolism, including hematoma at the puncture site for pulmonary angiography, ecchymosis, and hemoptysis. The authors also note that the bleeding rates in other studies may vary depending on the criteria used to define bleeding.

In 2000, the American College of Chest Physicians (ACCP) published a consensus statement of evidence-based guidelines for the management of parapneumonic effusions [Colice *et al.* 2000]. An important notation was that only three randomized, controlled clinical trials had been performed, involving less than 100 patients, and significant methodological inconsistencies limited the generalizability of the data. The panel acknowledged that conclusions were unable to be drawn about the defining patient characteristics that would increase the likelihood of success with fibrinolytics. Limited data were available about adverse reactions.

A more recent meta-analysis [Tokuda *et al.* 2006], published after the ACCP consensus statement, indicated that intrapleural fibrinolytics did not

reduce mortality or the need for surgery in adult patients with empyema or complicated parapneumonic effusion. Significant heterogeneity was noted amongst the trials used for the meta-analysis, however. Two studies [Bouros *et al.* 1999; Davies *et al.* 1999] which had been referenced in the 2000 ACCP consensus statement and three additional studies [Maskell *et al.* 2005; Diacon *et al.* 2004; Tuncozgur *et al.* 2001] were included in the meta-analysis. The authors note that while the smaller sample-size studies reported a positive effect with fibrinolytics, the larger trial MISTI [Maskell *et al.* 2005] (208 patients) reported no improvement in death rates, length of hospitalization, radiographic changes or progression to surgery. Tokuda *et al.* [2006] explain that since there was significant heterogeneity among the patient populations and treatment effects, it is possible that intrapleural fibrinolytics may have a role in select patient populations. Despite the limitations of the available data, the use of fibrinolytics remains a common means of increasing drainage from a loculated pleural effusion from a variety of patients [Levinson and Pennington 2007; Hsu *et al.* 2006; Ekingen *et al.* 2004; Feola *et al.* 2003].

Few of the early studies have reported hemorrhagic complications associated with intrapleural fibrinolytics. Jerjes-Sanchez *et al.* [1996] claimed an efficacy rate of 92% and reported no hemorrhagic complications in 48 patients with loculated pleural effusions that were treated using streptokinase. Davies *et al.* [1997] examined the systemic fibrinolytic activity of streptokinase and noted no significant systemic effects stemming from intrapleural administration. Moulton *et al.* [1995] treated 98 patients with complicated pleural effusions with intrapleural administration of urokinase and noted no systemic bleeding complications during therapy. They did report 'occasionally an effusion that was initially nonhemorrhagic would become bloody during the final UK aspirations, but this was always a small amount of dark lysed blood and was never active bleeding'. Coagulation parameters were not measured. Further details regarding this bleeding were not available. Sahn [1997] reported on 24 patients with infected parapneumonic effusions who received intrapleural streptokinase and had a significant improvement in the drainage of pleural fluid; no bleeding or systemic fibrinolysis complications were noted. Bouros *et al.* [1997] compared streptokinase with urokinase and found similar efficacies and no increase in adverse reactions other than fevers in 8% of the streptokinase arm. Cochran [2003] reported retrospectively on 19 pediatric patients with complicated pleural effusions persisting despite tube thoracostomy and noted that intrapleural administration of either urokinase (13 patients) or streptokinase (six patients) increased the volume of pleural fluid drainage and allowed for 14 of the patients to be successfully managed without surgical intervention. There were no significant adverse events or side effects in this cohort.

After 1998 when urokinase was withdrawn from the market, studies involving alteplase (recombinant human tPA) were initiated. Bishop *et al.* [2003] reported resolution of a complicated parapneumonic effusion in a 16-month-old girl after the administration of five doses of intrapleural tPA at a dose of 2 mg, the recommended dose for clearance of thrombi from central venous catheters. Skeete *et al.* [2004] completed a 4-year retrospective analysis of 41 patients, all of whom showed radiographic improvement after administration of tPA for pleural effusions. The etiologies of the effusions were varied and included 14% traumatic, 52% loculated pleural effusions, 29% empyemas and 5% line-associated hemothoraces. Six patients required blood transfusion within 48 hours of tPA administration, for reasons ranging from Coombs-positive hemolytic anemia, to hypotension after chest tube clamping, to hematuria while undergoing hemodialysis. No patient developed intrathoracic bleeding. Thommi *et al.* [2007] reported on 120 patients who were treated with recombinant tissue plasminogen activator (tPA) for persistent complicated pleural effusion or empyema after simple chest tube placement. Bolus doses of intrapleural alteplase ranged from 10 to 100 mg, using lower doses (10–25 mg) for complicated malignant pleural effusions and higher doses (50–100 mg) for empyema. Up to eight doses were administered until there was significant reduction in the size of the pleural effusion and improved clinical signs of sepsis or if the return pleural fluid became increasingly bloody. Reported complications included chest pain in seven patients (6%) and bleeding at the site of the chest tube in two patients (2%). One patient who received the 50 mg dose required blood transfusion, although it is not reported if that patient developed hemothorax or another site of bleeding. It is also unclear whether any of these patients were receiving concomitant anticoagulants. Weinstein *et al.* [2004] compared outcomes of complicated

parapneumonic effusions in 12 children who received early tPA (within 24 h of diagnosis), 18 children with late tPA (> 24 h after diagnosis), and 23 children managed with tube thoracostomy only. Rate of fluid removal was highest for the early tPA group (7 ml/h versus 3 ml/h in the tube-only group), whereas total fluid drainage was highest for the late tPA group (691 ml versus 360 ml in the tube-only group). No local or systemic bleeding events were reported. Froudarakis *et al*. [2008] administered 25 units of intrapleural tPA into 20 consecutive patients with empyema or complicated pleural effusions who failed simple chest tube drainage. Clinical resolution was noted in all but one patient; however, there were three cases (15%) of mild local hemorrhage, which did not result in discontinuation of tPA. Coagulation profiles of all patients showed no significant changes.

Most recently, a 2008 Cochrane literature review by Cameron and Davies was conducted to evaluate the benefits and safety of intrapleural fibrinolytics. Searches were conducted through November 2006, updating a previous review in 2004. Endpoints of interest were reduction in mortality and avoidance of intrathoracic surgery. Conclusions were that intrapleural fibrinolytic agents were useful in decreasing the need for surgical intervention in patients with empyema or complicated parapneumonic effusion. Similar to what was noted in the meta-analysis by Tokuda [2006], the MISTI [Maskell *et al.* 2005] trial carried the greatest weight and was the only included study to report adverse event data. The authors note that statistically, intrapleural fibrinolytics have not been shown to increase adverse events, but a wide confidence interval makes it difficult to completely exclude this possibility.

Since the publication of the Cochrane review, another study has added to the knowledge regarding adverse events with intrapleural tPA administration. A recent retrospective review [Gervais *et al*. 2008] examined the risk for hemorrhage with tPA administered twice a day via chest tube in a dose of 4–6 mg diluted in 50 ml normal saline, left to dwell for 30 min. Over 6 years, 2241 catheters were placed under imaging guidance in 2089 patients. Out of 66 patients who had tPA instilled through the chest tube, 12 were receiving systemic anticoagulation for other reasons. Out of these, five intrapleural hemorrhages occurred in four patients. This included one patient receiving warfarin, one patient receiving low-molecular-weight heparin, and two receiving unfractionated heparin. Out of the remaining 54 patients who were not receiving full systemic anticoagulation, 38 were the recipients of prophylactic subcutaneous heparin. None of these patients bled. Two of the 66 patients were receiving clopidogrel, and neither bled, even though one was also receiving intravenous heparin. Twelve of the 66 patients were receiving aspirin; seven of the 12 were receiving both systemic anticoagulation and aspirin, and two of these seven bled. The authors concluded that the hemorrhages occurred only in patients who were receiving therapeutic anticoagulation and in no patients who were receiving prophylactic anticoagulation ($p < 0.01$). They provided no data on PT/PTT measurements or platelet counts, nor any mention of patients who were uremic or on hemodialysis. The authors quote an effectiveness rate of 86% and note intrapleural tPA to be safe in patients receiving simultaneous prophylactic anticoagulation; however, patients receiving therapeutic anticoagulation and intrapleural tPA had a significantly higher risk of pleural hemorrhage.

One question that remains unanswered is the issue regarding fibrin-specific fibrinolytics. In the ASSENT-2 trial [1999], which compared tPA to tenecteplase (TNK-tPA), a variant of tPA with higher fibrin specificity, in the treatment of myocardial infarction, significantly fewer patients who received TNK-tPA experienced adverse bleeding complications. The rates of cerebral bleeding were not significant different, however. Van de Werf *et al*. [2001] noted that the difference in bleeding complications was most profound in female patients greater than 75 years of age and with low body weights (< 67 kg). The authors speculated that lower doses of concomitant heparin contribute to lower rates of bleeding complications. A longer half-life of tenecteplase (22 minutes, as compared with 4–8 minutes for alteplase) may allow for decreased frequency of administration. Szabo *et al*. [2002] also elegantly showed paradoxical thrombin activation in patients with acute myocardial infarction who received tPA, but lower levels of thrombin-antithrombin III complexes and a lower extent of activation of the kallikrein-factor XII system in those patients who received TNK-tPA. They concluded that tenecteplase has higher fibrin specificity than alteplase. To our knowledge, similar trials have not been

conducted comparing the use of tenecteplase *versus* alteplase for intrapleural fibrinolysis.

The use of tPA for drainage of complex fluid collections is not limited to the pleural space. Beland *et al*. [2008] injected 4–6 mg twice a day via percutaneous abdominal drains for complex abdominal and pelvic abscesses, and reported no tPA-associated bleeding complications despite four patients receiving full systemic anticoagulation and 24 patients receiving prophylactic anticoagulation.

Our patient was not receiving systemic anticoagulation. However, multiple factors affected his clotting during this hospitalization. First, as a dialysis-dependent patient, he was treated with heparin three times weekly during his dialysis sessions. He also had a history of coronary artery disease, which resulted in him taking a daily aspirin. Additionally, earlier in his hospital course, he did suffer from vitamin K deficiency due to nutritional deprivation. He was repleted with vitamin K but on the day of the first hemothorax, his PT and PTT were still prolonged at 15.4 and 39.5 s, respectively. We also speculate that uremic platelet dysfunction may have contributed to his hemothorax, since the tPA was administered and the hemothoraces occurred on nondialysis days. Despite the fact that he was receiving hemodialysis, dialysis has not been shown to have a consistent effect on improving platelet function [Hedges *et al.* 2007]. Therefore, the instillation of tPA may have disrupted his tenuous balance of coagulant factors and resulted in a life-threatening hemothorax. We suggest that in patients with chronic renal failure, physicians should refrain from the use of currently available intrapleural fibrinolytics for complicated effusion until further studies define the safety and efficacy in this patient population.

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Conflict of interest statement

None declared.

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