Safety and Efficacy of Tissue Plasminogen Activator and DNase for Complicated Pleural Effusions Secondary to Abdominal Pathology

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Abstract

Rationale: Exudative pleural effusions may arise secondary to inflammation of intra-abdominal structures. Pleural space loculations can complicate these effusions, preventing adequate chest tube drainage and leading to consideration of surgical intervention. Previous studies have demonstrated that intrapleural administration of tissue plasminogen activator (tPA) combined with human recombinant DNase can improve fluid drainage and reduce surgery for patients with loculated parapneumonic effusions; however, the efficacy of this treatment has not been evaluated for complicated pleural effusions attributed to intra-abdominal inflammation.

Objectives: We assessed the safety and efficacy of tPA/DNase for 17 pleural effusions associated with nonmalignant intra-abdominal pathology that did not drain adequately after placement of one or more chest tubes.

Methods: Efficacy was measured by comparing post- to pretreatment fluid drainage rates, volumetric assessment of pleural fluid on radiographic images before and after treatment, and clinical improvement, including the need for surgical intervention. Symptomatic relief was assessed using the Borg scale for breathlessness.

Measurements and Main Results: After a median of two doses of tPA/DNase, 23.5% of patients had chest pain and none had pleural bleeding. The volume of pleural fluid drained increased from a median of 325 ml to 890 ml per 24 hours after therapy ($P = 0.018$). The area of pleural space opacity on chest radiographs decreased from a median of 42.8–17.8% of the hemithorax ($P = 0.001$). tPA/DNase reduced the pleural fluid volume on chest computed tomographic imaging from a median of 294.4 ml to 116.1 ml. Borg scores improved from a median of 3 (interquartile range = 1–6) to 0 (interquartile range = 0–2) after therapy ($P = 0.001$). The median duration of chest tube placement and hospital stay were 4 and 11 days, respectively. Two patients required surgical intervention for lung entrapment. Overall, treatment was considered successful for 88.2% of patients.

Conclusions: This retrospective case series suggests that intrapleural tPA/DNase can be safe and effective for patients with complicated pleural effusions attributed to abdominal pathology that do not drain adequately after chest tube placement. Additional studies are needed to determine whether the combination of tPA and DNase is more effective than tPA for this indication.

Keywords: tissue plasminogen activator; DNase; pleural effusion secondary to abdominal pathology; sympathetic pleural effusion; complicated pleural effusion

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Pleural effusions arising from abdominal diseases can lead to significant morbidity and can be difficult to manage. Effective treatment needs to address not only the effusion, but also the underlying abdominal etiology. Previous studies have reported an incidence of 8% after abdominal surgery, with higher rates after upper-abdominal procedures (1, 2). Other common causes include subdiaphragmatic abscesses (hepatic and splenic), pancreatitis, biliary tract infections, and bowel anastomotic leaks.

The pathogenesis of pleural effusions secondary to abdominal pathology is not well understood. Proposed mechanisms include passage of fluid through transdiaphragmatic lymphatics or defects caused by abdominal surgery, inflammation of the vascularized muscular portion of the diaphragm, and lung atelectasis (1, 2). These effusions can be complicated by formation of separations and loculations due to their inflammatory nature. Loculations can reduce the adequacy of chest tube drainage, require multiple chest tubes, or lead to surgical intervention

Accumulating evidence supports intrapleural instillation of tissue plasminogen activator (tPA) combined with DNase to improve fluid drainage, reduce surgical referrals, and shorten hospital stays for patients with complicated parapneumonic effusions (3–5). However, no studies have examined the use of tPA/DNase in complicated pleural effusions secondary to abdominal diseases.

The aim of this study was to assess the safety and efficacy of intrapleural instillation of tPA/DNase for complicated pleural effusions secondary to abdominal pathology refractory after unsatisfactory chest tube drainage. Some of the results of this study have been previously reported in the form of an abstract (6).

Methods

This retrospective study of prospectively collected data was approved by the institutional review board for data collection and analysis (approval no. 2015P-000034) with a waiver of consent at Beth Israel Deaconess Medical Center (Boston, MA). All patients who received intrapleural tPA/DNase therapy for pleural effusions due to abdominal pathology between July 2012 and June 2016 were reviewed.

A complicated effusion from abdominal disease was defined as: (*1*) an exudative pleural effusion by Light's criteria (7); (*2*) evidence of loculation on chest computed tomographic (CT) imaging or ultrasound (US); (*3*) an abdominal source of inflammation; and (*4*) no clinical evidence of lower respiratory tract or pleural infection.

Procedure

All patients underwent US guided small bore (≤14 French) chest tube placement, using the Seldinger technique, inserted into the most dependent area of the pleural effusion.

The suitability and timing of intrapleural tPA/DNase therapy after chest tube insertion were determined based on US or chest CT imaging. Complex loculated pleural effusion on US was defined as fibrin strands or septa floating inside the anechoic/hypoechoic pleural effusions along with presence of defined multiple pockets in the pleural cavity (8). On chest CT, pleural effusion was defined as loculated if it had (*1*) lobulated shape with a convex boarder or (*2*) compartmentalized, accumulated in a fissure or a nondependent portion of the pleura (9). All patients had a chest CT within 24 hours before the administration of tPA/DNase to ensure adequate chest tube position and within 24 hours after the last dose of treatment to quantify the change in pleural fluid volume.

The dose of DNase (Pulmozyme; Genentech, San Francisco, CA) was 5 mg and of tPA (Actilyse; Genentech) 10 mg, each mixed in 50 ml of 0.9% sodium chloride solution. The method of tPa/DNase therapy administration has been described before (5). Briefly, tPA and DNase were injected concurrently using different syringes through the chest tube followed by a 60-ml saline flush. The chest tube was then clamped for 120 minutes before being opened to −20 cm H_20 of wall suction. Therapy was given twice daily for a maximum of six doses.

Assessment

The change in the percentage of hemithorax occupied by effusion was measured on chest radiographs using a method described previously in the Multicenter Intrapleural Sepsis Trial 2 (MIST2) (3). The pleural effusion volume was quantified using the OsiriX digital analysis program (OsiriX Imaging Software, v3.6.1; OsiriX Foundation, Geneva, Switzerland) reconstructed from patients' low-dose chest CT scans (Figure 1), as described previously (5).

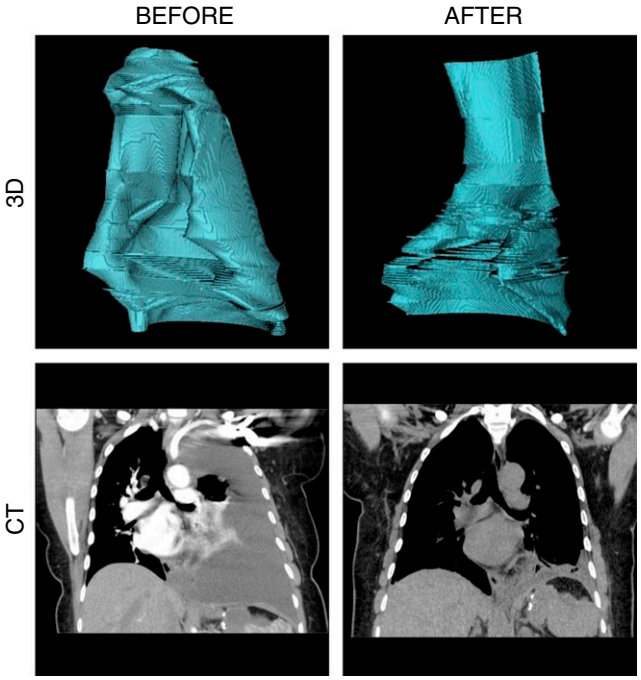

Figure 1. Pleural effusion volume measured by OsiriX digital analysis program and computed tomography (CT) of the chest before and after tissue plasminogen activator/DNase treatment. 3D = three dimensional.

Records were reviewed for patient demographics, abdominal etiologies, pleural fluid analysis, intrapleural therapy, number of chest tubes, length of hospital stay, duration of chest tube in pleural cavity (total and from insertion to first dose of tPA/DNase), cumulative volume of pleural fluid drained 24 hours before and 24 hours after tPA/DNase therapy, change in the volume of pleural effusion on low-dose chest CT imaging, adverse events, including pleural bleeding (defined as drop in serum hemoglobin requiring blood transfusion or causing hemodynamic instability), significant pain requiring escalation of analgesia, and 30-day mortality. Treatment success was defined as radiological and clinical improvement without the need for surgical intervention. Borg perceived scale scores for breathlessness recorded 24 hours before and 24 hours after the last tPA/DNase treatment were compared. Improvement was defined as a decrease of at least 1 point in the Borg score, defined as the minimally clinically important difference for breathlessness (10).

Statistical Analysis

Statistical analysis was performed using SPSS version 21 (IBM, Armonk, NY), with a P value of less than 0.05 defined as significant. Results are expressed as median (interquartile range [IQR]). The Wilcoxon signed-rank test was used to compare Borg score, percent change of hemothorax on chest radiography, pleural fluid drainage, and volume of pleural effusion on chest CT before and after concurrent tPA/DNase treatment.

Results

A total of 17 patients with a qualifying pleural effusion received tPA/DNase treatment. Patients had a median age of 48 years and 53% were male. Chest tubes were placed on the right side for 64.7% (11/17) of patients: 82.4% (14/17) of patients had one chest tube, 11.8% (2/17) had two chest tubes, and 5.9% (1/17) had three chest tubes inserted. Multiple chest tubes were placed if pleural effusion had multiple noncommunicating pockets, as evident by chest CT.

The baseline demographic and clinical characteristics of the patients are shown in Table 1. None of the effusions had a positive Gram stain or culture. Apparent etiologies for the effusion were: intra-abdominal abscesses (four intrahepatic, one subphrenic, one tubo-ovarian, one perinephric, and one pancreatic) (n = 8); colonic anastomotic leak (n = 2); abdominal trauma (n = 1); cholecystitis (n = 1); peritonitis (n = 1); ischemic bowel (n = 1); pancreatic pseudocyst (n = 1); cholangitis (n = 1); and biliary fluid leak (n = 1).

The median time from chest tube insertion to first intrapleural tPA/DNase therapy was 1 day (IQR = 1–1.75). The median number of tPA/DNase doses was 2 (IQR = 1–3). Chest pain requiring escalation of analgesia occurred in four patients (23.5%) and did not require termination of intrapleural therapy.

Borg scale breathlessness scores improved from a median of 3 (IQR = 1–6) before to a median of 0 (IQR = 0–2) after tPA/DNase ($P = 0.0001$). The percentage of hemithorax occupied by effusion on chest radiography decreased from a median of 42.8% (IQR = 19.7–56.7) before treatment to a median of 17.8% (IQR = 9.5–33.1) after treatment ($P = 0.0001$). Therapy with tPA/DNase increased the volume of pleural fluid drained from a median of 325 ml (IQR = 146.25–782.5) over 24 hours before treatment to a median of 890 ml (IQR = 512.5–1,235) over 24 hours after therapy ($P = 0.018$). Treatment with tPA/DNase reduced the pleural fluid volume as assessed by chest CT imaging from a median of 294.4 ml (IQR = 199.3–673.1) to a median of 116.1 ml (IQR = 22.1–312.7).

The decision to stop treatment was based on clinical and radiological improvement. The median duration of chest tube drainage was 4 days (IQR = 3–6). The median total length of hospital stay was 11 days (IQR = 8.5–22). There was no treatment-related pleural bleeding. No patients died secondary to pleural effusion or tPA/DNase therapy during 3-month follow-up after hospital discharge (Table 2).

Overall, administration of tPA/DNase therapy was considered successful for 88.2% (15/17) of patients. Two patients (11.8%) required surgical intervention for lung entrapment. Surgery was performed at Days 3 and 5 after the last tPA/DNase dose, due to lack of clinical improvement and persistence of multiloculated pleural effusion on chest CT.

Table 1. Demographics and clinical characteristics

Characteristics	Values
Age, years, median (IQR)	48 (40.25–69.75)
Men, n (%)	9 (53)
Small-bore tube, ⩽14 French, n (%)	17(100)
Chest tube location, right, n (%)	11 (64.7)
Positive Gram's stain or culture of pleural fluid, n (%)	0 (0)
Pleural fluid pH, median (IQR)	7.39 (7.3–7.47)
Lactate dehydrogenase in pleural fluid, IU/L, median (IQR)	310.5 (255.5–646.25)
Total protein in pleural fluid, g/dl, median (IQR)	4.5 (3.55–4.8)
Glucose in pleural fluid, mg/dl, median (IQR)	100 (85–114)

Definition of abbreviation: IQR = interquartile range.

Discussion

To our knowledge, this is the first report evaluating the use of intrapleural tPA/DNase for patients with complicated pleural effusions secondary to nonmalignant inflammatory abdominal diseases.

Light and George (1) described pleural effusions secondary to abdominal pathology in 200 patients who developed culture-negative pleural exudates after abdominal surgery. Pleural fluid analysis showed key differences between complicated parapneumonic effusions and effusions secondary to inflammatory abdominal pathology, such as high glucose content and comparatively elevated pH in the latter group. However, similar to parapneumonic fluid collections, such effusions have the potential to develop loculations, which can persist even after resolution of the inciting process. Whether the inflammatory milieu leads to imbalances in the fibrinolytic pathway, leading to formation of loculations in a

Table 2. Clinical outcomes

Characteristics	Values
Patients receiving intrapleural therapy with treatment success, n (%)	15 (88.2)
Surgical intervention, n (%)	2 (11.8)
Number of intrapleural treatment, median (IQR)	2 (1–3)
Days from chest tube insertion to first dose of intrapleural treatment, median (IQR)	1 (1–1.75)
Days of chest tube in pleural cavity, median (IQR)	4 (3–6)
Hospital stay, days, median (IQR)	11 (8.5–22)
Mortality due to pleural effusion, n (%)	0 (0)
Volume of pleural fluid drained before therapy, ml, median (IQR)	325 (146.25–782.5)
Volume of pleural fluid drained after therapy, ml, median (IQR)	890 (512.5–1235)
Volume of pleural fluid on chest CT 24 hours before therapy, ml, median (IQR)	294.4 (199.3–673.1)
Volume of pleural fluid on chest CT 24 hours after completion of therapy, ml, median (IQR)	116.1 (22.1–312.7)
Adverse events, n (%)	
Pain requiring escalation of analgesia	4 (23.5)
Pleural bleeding	0 (0)

Definition of abbreviation: CT = computed tomography; IQR = interquartile range.

similar fashion to pleural infection, remains unknown (11).

The use of tPA/DNase therapy has been studied predominantly in patients with pleural infections (3–5). The multicenter MIST2 trial in the United Kingdom showed that this combination improved drainage of complicated parapneumonic effusions, reduced the need for surgical intervention, and decreased the length of hospital stay (3–5). The combination of tPA/DNase was superior to placebo, or to either component administered alone, with the authors suggesting that the reason may lie in improved neutrophil-derived DNA cleavage, leading to reduced fluid viscosity, thereby allowing pleural clearance by the fibrinolytic agent (12, 13). Pleural fluid drainage with the combination of tPA/DNase led to a doubling of clearance compared with placebo, and approximately translated to a 60% reduction in hemithorax fluid opacity compared with baseline (3).

Those findings led us to assess tPA/DNase therapy for patients with neutrophilic predominant pleural effusion secondary to nonmalignant inflammatory abdominal diseases in the absence of pulmonary infection. Our results are clearly exploratory, and do not establish a standard of care for management of patients with pleural effusion secondary to abdominal diseases. Future randomized, comparative studies between tPA and tPA/DNase are needed to determine whether DNase is necessary in this specific type of pleural effusion in the absence of pleural infection. Nevertheless, our study adds to the growing literature confirming the safety and efficacy of tPA/DNase therapy in loculated pleural effusions with etiology other than pleural infection.

Moreover, similar to our previous study about concurrent tPA/DNase in pleural infection (5), our data suggest that assessing the efficacy of this therapy with volumetric analysis on low-dose CT chest or comprehensive chest US with clinical response is effective, and may reduce the number of doses needed to achieve pleural clearance and reduce the overall cost of treatment.

Limitations

This small, retrospective case series analysis conducted at a single institution was susceptible to selection bias. Prospective, randomized, placebo-controlled studies are needed to evaluate the effect and optimal dose of combination tPA/DNase or tPA-alone treatment in noninfectious complicated pleural effusions and, due to small numbers seen in individual institutions, a multicenter study would be ideal. Due to the abdominal etiologies in this population, many patients would be considered "high-risk" thoracic surgical candidates. Safe, effective, less-invasive options are particularly appealing in this group.

Conclusions

Administration of intrapleural tPA/DNase therapy to patients with complicated pleural effusion secondary to abdominal pathology refractory to chest tube drainage appears to be safe, feasible, and effective. Future studies are needed to verify these results and to compare the combination of tPA and DNase versus tPA alone for this type of pleural effusion. ■

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