Concurrent Intrapleural Instillation of Tissue Plasminogen Activator and DNase for Pleural Infection

A Single-Center Experience

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Abstract

Rationale: Treatment of pleural infection with instillation of intrapleural tissue plasminogen activator (tPA) and human recombinant DNase (DNase) has been proven to decrease the length of hospital stay, decrease surgical referral, and improve drainage. The optimal dosage, administration, timing, and frequency of the regimen remain unclear. It is unknown if the two drugs can be administered immediately one after the other (referred to as *concurrent*) instead of instilling them separately with a 1- to –2-hour interval in between.

Objectives: To assess the safety and efficacy of concurrent instillation of intrapleural tPA/DNase guided by radiographic and clinical response in patients with pleural infection.

Methods: We conducted a retrospective cohort study. Consecutive patients with pleural infection who received concurrent tPA/DNase were included. The initiation and number of doses of tPA/DNase therapy were based on pleural fluid drainage, clinical response, and radiographic findings.

Measurements and Main Results: Seventy-three patients received concurrent tPA/DNase therapy. Treatment was successful in 90.4% of them; 80.8% were effectively treated with fewer than six doses of therapy (median, 2; interquartile range [IQR], 1–3.5); and 71.2% received their first dose of tPA/DNase within 24 hours after chest tube insertion. The median hospital stay from the first dose of tPA/DNase to discharge was 7 days (IQR, 5–11 d). The volume of pleural fluid drained increased from a median of 295 ml (IQR, 97.5–520 ml) 24 hours before treatment to a median of 1,102 ml (IQR, 627–2,200 ml) 72 hours following therapy ($P < 0.001$). Nonfatal pleural bleeding occurred in 5.4%, 15.1% had chest pain, and 2.7% died as a result of pleural infection.

Conclusions: This cohort study shows that early administration of concurrent tPA/DNase in patients with pleural infection is relatively safe and effective. Given the high cost of therapy, it is feasible to guide therapy on the basis of clinical and radiographic response.

Keywords: pleural infection; tissue plasminogen activator; humanrecombinant DNase

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Pleural effusion represents one of the most common clinical diagnoses encountered in clinical practice. Approximately 1.5 million people develop pleural effusions each year in the United States (1).

Pleural infections have been associated with increased mortality, morbidity, and increased hospital costs (2–4). Around 90,000 hospital admissions each year in the United States are due to pleural infection, with an overall mortality approaching 10–20%. Pleural infection is found commonly in elderly patients and those with comorbidities that are often not suitable for surgical management (2–4).

Treatment of complicated parapneumonic effusion (CPPE) or empyema requires antibiotics and drainage of the pleural cavity (3). However, in about 30% of patients with pleural infection, fluid is difficult to drain due to loculations, septations, and increased viscosity of the pleural fluid (5, 6). The intrapleural therapy of combined tissue plasminogen activator (tPA) and human recombinant DNase (DNase) in the management of pleural infection has been shown to improve drainage of infected effusion, reduce the need for surgical intervention (6), and decrease the length of hospital stay (6, 7).

The optimal administration (concurrent or sequential) and duration of intrapleural therapy remains unclear. In two previous trials, sequential tPA (10 mg) and DNase (5 mg) were instilled intrapleurally twice daily up to a maximum of six doses over 3 days (6, 7). Following each medication, chest tube was clamped for up to 60 minutes to allow drugs to remain in the pleural space. However, in one study, about 28% (30 of 107) of patients received concurrent administration of drugs intrapleurally, and up to 16% of patients required fewer than six doses of combined therapy to have complete drainage of effusion (7). The aim of this study was to assess, on the basis of pleural fluid drainage, clinical response, and radiographic findings, the safety and efficacy of concurrent intrapleural instillations of tPA and DNase immediately after each other (hereafter referred to as *concurrent*) instead of separately with an interval of 1–2 hours in a large cohort of patients with CPPE or empyema.

Methods

We conducted a retrospective cohort study. The study was approved by the institutional review board for data collection and analysis of Beth Israel Deaconess Medical Center (IRB 2015P-000034) with waiver of consent. Consecutive patients received concurrent intrapleural tPA/DNase therapy for pleural infection between January 2010 and October 2015.

Pleural infection included either CPPE or empyema. CPPE was defined as nonpurulent effusions in a patient with clinical evidence of infection, such as fever and/or elevated blood leukocyte count, with pleural fluid pH less than or equal to 7.2 (measured using a blood gas analyzer), pleural fluid glucose less than 60 mg/dl, pleural fluid lactate dehydrogenase greater than 1,000 IU/L, and/or radiographic characteristics (loculations) (6–8). Empyema was defined as pus within the pleural space and/or presence of bacteria on the basis of pleural fluid Gram staining or culture (6–8). With ultrasonographic guidance, a chest tube was inserted into the most dependent area of the pleural effusion or into the largest loculation in patients with multiloculated effusions.

Following chest tube insertion, the attending physicians (A.M. and E.F.) determined the suitability and timing of intrapleural tPA/DNase therapy on the basis of pleural fluid drainage (<200 ml within 24 h) and radiographic evidence of septations on chest ultrasound (US) or low-dose chest computed tomography (CT) (9). Complex, loculated pleural effusion visualized by 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 (10). For chest CT, pleural effusion was defined as loculated if it (*1*) had a lobulated shape with a convex border or (*2*) was compartmentalized and accumulated in a fissure or a nondependent portion of the pleura (11). Chest US was performed on all patients at the time of initial insertion of a chest tube for drainage as well as before and after each administration of intrapleural fibrinolytic therapy. In addition, all patients with dry tap or fluid drainage less than 200 ml in 24 hours underwent low-dose chest CT 24–48 hours before and 48–72 hours after concurrent tPA/DNase therapy to ensure adequate chest tube placement, evaluate multiloculated collection, and assess therapy response (Figure 1).

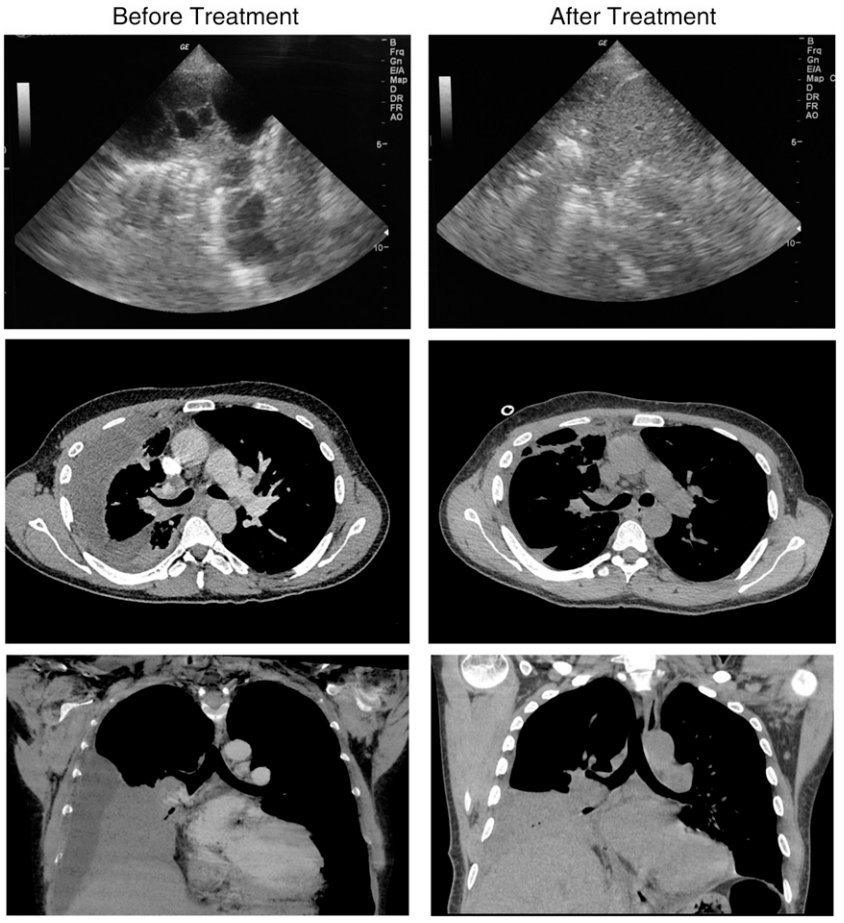

Figure 1. Thoracic ultrasound and computed tomography of the chest with pleural effusion before and after tissue plasminogen activator/DNase treatment.

The dose of DNase (Pulmozyme; Genentech, South San Francisco, CA) was 5 mg, and the dose of tPA (Actilyse; Genentech) was 10 mg, each in 50 ml of 0.9% NaCl. tPA and DNase were not mixed together in one syringe. Concurrent tPA and DNase were administered intrapleurally through the chest tube, followed by a 60-ml saline flush. The tube was then clamped for 120 minutes before the chest tube was opened to −20 cm H_2O of wall suction. Therapy was given twice daily for a maximum of six doses. Hospital records were reviewed for patient demographics, comorbidities, laboratory data (blood leukocyte count, pleural fluid biochemistry, and microbiologic cultures), medications (antibiotics and anticoagulation therapy), intrapleural therapy (frequency and timing), number of chest tubes, size of chest tube, chest tube days, and days of hospital stay.

The area of pleural opacity was quantified by creating three-dimensional reconstructions of pleural effusions using patients' low-dose chest computed tomographic scans with the OsiriX digital analysis program (OsiriX Imaging Software, v3.6.1; OsiriX Foundation, Geneva, Switzerland). The area of pleural effusion was delineated on each 5-mm scan. The software was then used to calculate pleural effusion volume in milliliters (1 ml = 1 cm^3) before and after tPA/DNase treatment (Figure 2).

Clinical outcome data collected included the following:

1. Treatment outcomes:
   a. Treatment success, defined as clinical (normalization of blood white blood cell count and defervescence) and radiological improvement without the need for surgical intervention
   b. Adverse events, including pleural bleeding (defined as drop in serum hematocrit requiring blood transfusion or causing hemodynamic instability) and significant pain requiring escalation of analgesia
   c. Change in the area of pleural opacity pre- and post-treatment determined by low-dose chest CT
   d. Need for surgical interventions
2. Other outcomes
   a. Death related to pleural infection
   b. Cumulative volume of pleural fluid drained 24 hours before and 72 hours after concurrent tPA/DNase therapy
   c. Length of hospital stay (total and from first dose of tPA/DNase to hospital discharge)
   d. Duration of chest tube in pleural cavity (total and from insertion to first dose of tPA/DNase)
   e. Number of fibrinolytic therapies needed
   f. Number and size of chest tubes

Statistical analysis was performed using IBM SPSS Statistics version 21 software (IBM, Armonk, NY). A *P* value less than 0.05 was defined as significant. Results were expressed as mean (SD) if normally distributed and otherwise as median (interquartile range [IQR]). The Wilcoxon signed-rank test was used to compare pleural fluid drainage and volume of pleural effusion visualized by chest CT before and after concurrent tPA/DNase treatment.

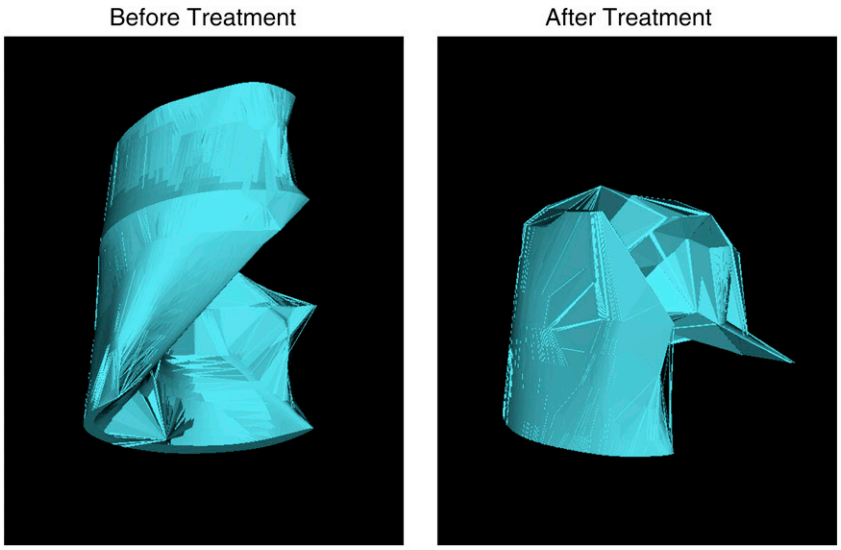

Figure 2. Pleural effusion volume before and after tissue plasminogen activator/DNase treatment measured by OsiriX digital analysis program.

Results

Patients

A total of 73 consecutive patients with pleural infection received concurrent tPA/DNase treatment. Their mean age was 59.3 years, and 70% (51 of 73) were men. Forty patients (54.8%) underwent right-sided chest tube insertion. Small-bore chest tubes (≤14 French) were inserted in 91.8% (67 of 73) of patients, of whom 78.1% (57 of 73) had one chest tube, 19.2% (14 of 73) had two chest tubes, and 2.7% (2 of 73) had three chest tubes inserted. Large chest tubes (>15 French) were used in seven patients with thick pus. The baseline demographic, clinical, and microbiological characteristics of the patients are shown in (Table 1). Medical comorbidities were present in most patients (91.8%; 67 of 73) (Table 2).

The median pleural fluid pH and lactate dehydrogenase levels were 6.93 IU/L (IQR, 6.82–7.12) and 1,163 IU/L (IQR, 406–3,737), respectively (Table 1). The effusions were purulent in 30.1% of patients, and 26% had a positive Gram stain or culture result (Table 1). Microbiology culture yielded *Streptococcus milleri* (n = 7), *Staphylococcus aureus* (n = 2), *Streptococcus pneumoniae* (n = 1), *Staphylococcus epidermidis* (n = 1), *Prevotella* (n = 1), viridans streptococci (n = 1), *Morganella morganii* (n = 1), *Klebsiella pneumoniae* (n = 1), *Fusobacterium* (n = 1), *Streptococcus pyogenes* (n = 1), and *Bacteroides fragilis* (n = 1). Chest US showed moderate to large pleural effusions in 75.3% of patients, and pleural loculations were seen in 76.7% of patients (Table 1).

Treatment Outcomes

tPA/DNase therapy was successful in 90.4% (66 of 73) of the patients. Fifty-nine (80.8%) of 73 patients responded effectively to fewer than six doses of therapy. Less than 24 hours after chest tube insertion, 71.2% of patients received their first dose of concurrent tPA/DNase. The

Table 1. Demographics and clinical characteristics

Characteristic	Data
Mean age (SD), yr	59.3 (16.2)
Male sex, n (%)	51 (70)
Small-bore tube, ⩽14 French, n (%)	67 (91.8)
Chest tube location right, n (%)	40 (54.8)
Ultrasonographic evidence of loculation, n (%)	56 (76.7)
Ultrasonographic estimated pleural effusion volume, n (%)	
Small	18 (24.7)
Moderate	40 (54.8)
Large	15 (20.5)
Purulent pleural fluid, n (%)	22 (30.1)
Positive Gram stain or culture of pleural fluid, n (%)	19 (26.0)
Median pleural fluid pH (interquartile range)	6.93 (6.82–7.12)
Median lactate dehydrogenase in pleural fluid (interquartile range), IU/L	1,163 (406–3,737)
Median leukocyte count (interquartile range), $\times 10^9$/L	13.1 (9.9–17.0)
Antibiotics, n (%)	
Vancomycin	32 (43.8)
Metronidazole	21 (28.8)
Quinolones	19 (26.0)
Cefepime	19 (26.0)
Piperacillin-tazobactam	16 (21.9)
Ceftriaxone	11 (15.1)
Macrolides	7 (9.6)
Amoxicillin	5 (6.8)
Clindamycin	5 (6.8)
Carbapenems	4 (5.4)
Aminoglycosides	2 (2.7)

median number of fibrinolytic therapies administered was two (IQR, 1–3.5). Seven patients (9.6%) had no clinical or radiographic response and required surgical intervention (Table 3).

tPA/DNase therapy increased the volume of pleural fluid drained from a median of 295 ml (IQR, 97.5–520) 24 hours before treatment to a median of 1,102 ml (IQR, 627–2,200) 72 hours following therapy ($P < 0.001$) (Figure 3). tPA/DNase reduced pleural fluid volume determined by chest CT from a median of 361 ml (IQR, 239–677) to a median of 80 ml (IQR, 37.2–154.3) ($P < 0.001$) (Figure 4).

Other Outcomes

Two patients (2.7%) died at 10 and 11 days, respectively, after intrapleural therapy. One patient had acute respiratory failure with pneumonia, and the other developed acute respiratory distress syndrome. Both patients had at least one comorbidity and major life-limiting diseases; one had liver cirrhosis, hepatitis C virus infection, and hypertension, and the other had autoimmune disease with end-stage renal failure, coronary artery disease, and diabetes mellitus.

Four patients (5.4%) had treatment-related pleural bleeding without hemodynamic instability requiring blood transfusion (Table 3). Only two patients had underlying coagulopathy. One had a history of liver cirrhosis, and the other had atrial fibrillation being treated with anticoagulation. However, at the time they received intrapleural therapy, both patients had normal platelets and coagulation profiles. All patients were managed with interruption of intrapleural therapy and transfusion without the need for surgical intervention. Also, all patients received more than two doses of tPA/DNase treatment (two received three doses, one received four doses, and one received six doses). Chest pain requiring escalation of opioid analgesia occurred in 11 patients (15.1%) and did not require termination of intrapleural therapy.

The median duration of chest tube placement in the pleural cavity was 5 days (IQR, 4–8). The median time from catheter insertion to first intrapleural therapy was 1 day (IQR, 0–2). The median total length of hospital stay was 11 days (IQR, 7–15). The median hospital stay from the first dose of intrapleural treatment to discharge was 7 days (IQR, 5–11) (Table 3).

Discussion

In patients with CPPE and empyema, there is an intense inflammatory response causing cytokine release and stimulating plasminogen activator inhibitor 1, leading to a profibrotic state, fibrin deposition, and eventually loculations (12, 13). Also, there is an increased viscosity of pleural fluid caused by high levels of deoxyribonucleoprotein along with DNA from leukocyte degradation (14). An oversimplified theory is that DNase decreases fluid viscosity, while tPA breaks down loculations within the pleural space and induces large volumes of pleural fluid (15, 16).

Although the mechanism of action of tPA/DNase on the cellular and molecular levels has not yet been well established, the synergistic effect, safety, and efficacy of sequential intrapleural therapy with an interval of 1–2 hours between instillation of the two drugs in patients with pleural infection is evident on the basis of an animal model of empyema and two recent

Table 2. Patient comorbidities

Comorbidities	n (%)
Cardiovascular disease	
Hypertension	32 (43.8)
Coronary artery disease	13 (17.8)
Congestive heart failure	8 (11.0)
Atrial fibrillation	7 (9.6)
Valvular heart disease	3 (4.1)
Respiratory disease	
Chronic obstructive pulmonary disease	6 (8.2)
Asthma	6 (8.2)
Chronic pleural effusion	3 (4.1)
Bronchiectasis	1 (1.4)
Gastrointestinal and hepatic disease	
Hepatitis B or C	7 (9.6)
Gastroesophageal reflux disease/ulcer	7 (9.6)
Liver cirrhosis	3 (4.1)
Malignancy	
Lung	5 (6.8)
Breast	4 (5.5)
Other	3 (4.1)
Psychiatric illness	15 (20.5)
Substance-related condition	12 (16.4)
Neurological disease	6 (8.2)
Chronic kidney disease	5 (6.8)
Immunodeficiency	5 (6.8)
Autoimmune disorders	4 (5.5)
Metabolic disease	
Hyperlipidemia	21 (28.8)
Diabetes mellitus	12 (16.4)
Thyroid disease	4 (5.5)

Table 3. Clinical outcomes

Outcome	Data
Patients receiving intrapleural therapy with treatment success, n (%)	66 (90.4)
Patients receiving fewer than six doses of intrapleural therapy with treatment success, n (%)	59 (80.8)
Patients who received first dose of intrapleural treatment after chest tube insertion ⩽24 h, n (%)	52 (71.2)
Surgical intervention, n (%)	7 (9.6)
Median number of intrapleural treatments (interquartile range)	2 (1–3.5)
Median days from chest tube insertion to first dose of intrapleural treatment (interquartile range)	1 (0–2)
Median days of chest tube in pleural cavity (interquartile range)	5 (4–8)
Median hospital stay (interquartile range)	11(7–15)
Median hospital stay from first dose of intrapleural treatment to discharge (interquartile range), d	7 (5–11)
Mortality due to pleural infection, n (%)	2 (2.7)
Adverse events, n (%)	
Pain requiring escalation of analgesia	11 (15.1)
Pleural bleeding	4 (5.4)

clinical trials (6, 7, 15). The optimal dosages, frequency, timing, and combination (concurrent or sequential) of intrapleural therapy are still not established. In the Multicenter Intrapleural Sepsis Trial (MIST2), therapy was given sequentially at the time of diagnosis of pleural infection, whereas researchers in another recent study administered intrapleural therapy sequentially after conventional treatment with antibiotics and drainage had failed (6, 7).

The use of concurrent rather than sequential therapy is quite appealing. Concurrent tPA/DNase treatment is less cumbersome for the medical team, nurses, and patients because it (*1*) decreases the need to access a chest tube to two times per day (maximum of 6 times in 3 d) as compared with four times per day (maximum of 12 times in 3 d) in sequential treatment, (*2*) shortens the treatment time from 3 hours to 2 hours per instillation, and (*3*) and makes protocol easier to implement in a twice-per-day delivery regimen. In our study, we used a concurrent tPA/DNase therapy for patients with pleural infections that had an overall treatment success rate of 90.4%, which is comparable to that in the study by Piccolo and colleagues (92.3%) (7). It should be emphasized that around 71% of our patients received concurrent tPA/DNase therapy within 24 hours (early in the disease course), as compared with the patients in the study by Piccolo and colleagues, who received treatment after 24 hours (7). This might explain why patients in our present study required a median of only two doses of tPA/DNase, as compared with the other study (7), where the majority of patients required six doses of treatment. The results of another recent study, by Mehta and colleagues, confirm our study findings. In that study, 92% of patients who received once-daily intrapleural sequential tPA/DNase for 3 days were successfully treated without the need for surgical intervention (17).

Furthermore, our decision to start and guide fibrinolytic therapy was based upon clinical as well as radiographic (pleural US or low-dose chest CT) evidence rather than being initiated upon admission or as a rescue therapy (6, 7). This translated to a shorter median hospital stay from the first dose of intrapleural treatment (7 d) than that (10 d) reported by Piccolo and colleagues, as well as a better treatment success rate (80.8% vs. 16%) in patients receiving fewer than six doses of intrapleural therapy (7). Also, the average cost of six doses of combined therapy (10 mg of tPA and 5 mg of DNase) is around $6,840 (18, 19). Given the high cost of tPA/DNase, it might be feasible to guide the timing and number of doses on the basis of clinical and radiographic response, leading to a decreased number of doses and less cost. In our study, the median number of fibrinolytic therapies was two, translating to an approximate cost of $2,280.

The role and timing of surgical intervention in patients with pleural infection remains to be established. In a recent study, researchers advocated the role of early video-assisted thoracic surgery (VATS) for drainage and decortications defined as less than 4 weeks from symptom duration (19). However, most patients who underwent VATS were relatively young and had a low comorbidity index; therefore, the elderly population with multiple comorbidities was excluded (20, 21). The mean age of patients undergoing surgical intervention in our study was 56.4 years (overall mean age, 59.3 yr), confirming the above-mentioned studies (20, 21). In our study, around 9.6% of patients were referred for surgical intervention, as compared with 4% and 7.5% in two of the previous studies (6, 7). A probable explanation is that we guided our therapy on the basis of radiographic evidence (pleural US and/or chest CT rather than

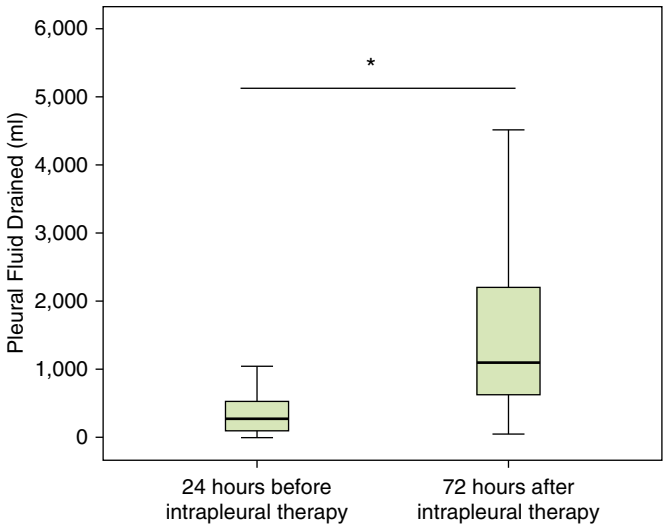

Figure 3. Volume of pleural fluid drained (median with interquartile range and numerical range) drained in the preceding 24 hours before and then at 72 hours of tissue plasminogen activator/DNase instillation. *$P < 0.05$.

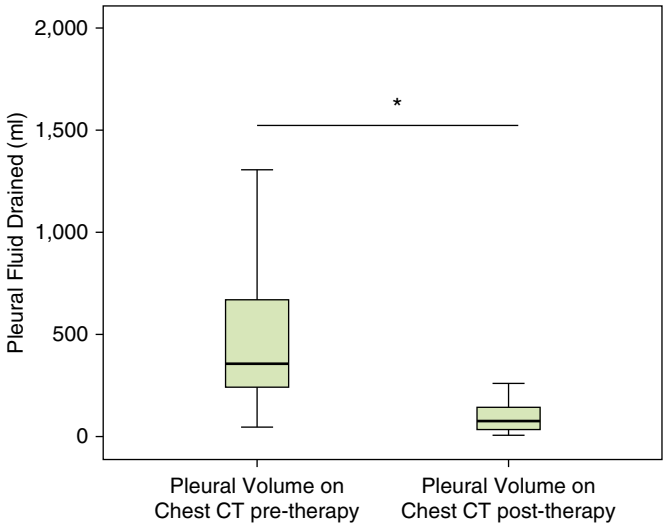

Figure 4. Volume of fluid on chest computed tomography (CT) (median with interquartile range and numerical range) before and after tissue plasminogen activator/DNase instillation. *$P < 0.05$.

chest radiography before and after instillation of therapy) along with clinical response. Furthermore, a thoracic surgical team with great VATS expertise was readily available, and, per institutional protocol, residual pockets of more than 200 ml visualized by chest CT or US without clinical response are often drained using VATS. This could potentially lead to bias in surgical referral, since chest CT and pleural US are more effective than chest radiography for detection of loculations (22).

The instillation of concurrent rather than sequential tPA/DNase therapy was relatively safe and did not adversely increase the complication rate in such a sick population. The rate of bleeding requiring transfusion was 5.4%, which compares very favorably with that in the MIST2 trial (6%) but is higher than the rate reported in the study by Piccolo and colleagues (1.8%) (6, 7). A possible explanation is that 91.8% of our patient population had associated medical comorbidities, as compared with 76.6% in the Piccolo and colleagues study (7). Also, 15.1% of our patients had pain requiring analgesia during intrapleural therapy, as compared with 19.1% of patients in the other study (7). Contraindications to intrapleural tPA/DNase therapy have not been well established. Coagulopathy (such as in patients with chronic kidney disease, liver cirrhosis with coagulopathy, concurrent anticoagulation therapy, recent major hemorrhage), allergy or hypersensitivity to tPA, and/or presence of bronchopleural fistulas are the commonest contraindications (23, 24).

Our study adds to the growing literature about the safety and efficacy of fibrinolytic therapy in patients with pleural infections. Moreover, to our knowledge, our cohort represents the largest group of patients treated with concurrent tPA/DNase therapy. The data derived from the present study might suggest that such a therapy, guided by radiological imaging along with clinical response, is effective and might help clinicians decide about initiation of fibrinolytic therapy. In addition, it might decrease the number of dosages needed and shorten hospital stay in such a sick population, leading to an overall lower cost.

This study has limitations. It was a retrospective cohort study done at a single institution without a study arm, leading to potential selection bias. Also, there were no predefined criteria about when to proceed with surgical intervention, which was decided upon at the physician's discretion. Future prospective comparative studies are needed to evaluate optimal administration of tPA/DNase treatment, dosages needed, and timing of therapy initiation.

In conclusion, early administration of concurrent intrapleural tPA/DNase therapy in patients with CPPE and empyema guided by clinical and radiographic response is relatively safe and effective. This could lead to fewer dosages, reduced hospital stay, and decreased overall cost. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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