Original Article

Understanding the systemic effects of intrapleural tPA and DNase by evaluating effects on coagulation

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Background: Complicated parapneumonic effusions and empyemas are common presentations that carry significant morbidity and mortality. Standard therapy includes antibiotics and chest tube placement. Due to the nature of the fluid, it is often difficult to drain completely using a chest tube. As outlined in multiple studies, intrapleural tissue plasminogen activator (tPA) and dornase alfa (DNase) are effective at helping clear these effusions and the avoidance of surgery. Despite research to better understand the effectiveness of the treatment and possible side effects, there continues to be a lack of data on potential systemic effects.

Methods: This prospective observational pilot study was conducted from May 2021 until June 2022. Basic demographics, complications, prothrombin time, activated partial thromboplastin time, D-Dimer, fibrinogen, and thromboelastography scans were measured both before and after infusion of chest tube tPA and DNase to assess for differences in coagulation using Signed Rank tests.

Results: A total of 17 patients were enrolled in the study. Two patients were excluded due to protocol deviations. The median change score for lysis of clot at 30 minutes (Ly30), our primary outcome of interest, was 0 (P=0.88). There were no significant changes in other coagulation measures when comparing pre and post treatment. One patient (5.9%) had intrapleural bleeding associated with therapy. Three patients (17.6%) underwent surgical intervention to further treat their complicated pleural effusion.

Conclusions: This is the first study to evaluate measurable changes in systemic coagulation after intrapleural tPA and DNase. Our data demonstrates no significant difference in coagulation after intrapleural tPA and DNase infusion, suggesting that there may not be clinically significant absorption.

Keywords: Intrapleural fibrinolytic therapy; thromboelastography (TEG); systemic side effects

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Introduction

Pneumonia is a common problem leading to hospital admission, and up to 20–40% of patients hospitalized with pneumonia may develop parapneumonic effusions (1). Another 5–10% of these patients may progress to an empyema (1,2). Antibiotics and chest tube drainage have improved outcomes, but this disease still carries significant morbidity and mortality (3-5). Parapneumonic effusions develop adjacent to pneumonia and can become complicated as the biochemical makeup of the fluid changes (3,6). These biochemical changes can lead to increased fibrin product build-up and the creation of loculations in the fluid (3). Therapy for parapneumonic effusions includes antibiotics and drainage through a thoracostomy tube (6). Changes to the fluid that occur in complicated parapneumonic effusions and empyema may make this fluid especially difficult to drain. Failure to evacuate all of the effusion can lead to persistent pleural infections and, ultimately, the need for surgical intervention.

Previous research has investigated the use of intrapleural fibrinolytic and enzymatic therapy instilled into chest tubes to aid in the clearance of the effusion and reduce the need for surgical intervention (7-9). The MIST-2 trial demonstrated that infusion of intrapleural tissue plasminogen activator (tPA) and dornase alfa (DNase) effectively cleared infected pleural spaces and reduced surgical referrals at 3 months from 16% in the placebo group to 4% in the tPA and DNase group (7). Additional studies have reaffirmed the original data that tPA and DNase effectively treat complicated parapneumonic effusions, empyemas, and multiloculated malignant effusions (2,5,10-14). Further studies have looked into possible side effects of medications and optimal dosing regimens (2,15-17). These results have shaped the practice patterns and guidelines for complicated pleural effusions and empyema, though questions remain about this therapy and its potential side effects (2).

Some questions that remain are about the risks associated with intrathoracic bleeding. Current literature suggests a 1–7% risk of intrapleural hemorrhage related to the infusion of fibrinolytic therapy into the pleural space (11,12,18-20). While this is not a high percentage of patients, it is clinically significant. Initial data suggested that this side effect is most common in patients on full-dose anticoagulation or those with underlying coagulopathy (2,18,19). Akulian *et al.* recently published a large multicenter retrospective study to identify additional risks and benefits associated with intrapleural tPA and DNase. Their intrapleural bleeding risk was similar to other at 4.1% (15). Their data demonstrated that systemic anticoagulation, increased RAPID (renal, age, purulence, infection source and dietary factors) score, elevated urea, and lower platelets were associated with increased intrapleural bleeding risk (15,21). However, other studies may suggest that full-dose anticoagulation does not cause an increased risk for intrapleural hemorrhage. Gilbert *et al.* demonstrated that systemic anticoagulation did not increase the risk of bleeding complications in patients with indwelling intrapleural catheters (14). Further studies are needed to understand how different patient populations may be at risk for intrapleural hemorrhage and what is the mechanism in which systemic anticoagulation and the pleural space interact to affect intrapleural bleeding.

Despite ongoing studies to help us better understand the risk of intrapleural bleeding, there is little literature on intrapleural fibrinolytic therapy's systemic effects. The MIST-2 trial excluded those with a recent stroke, major hemorrhage, trauma, or major surgery in the previous 5 days (7). These exclusion criteria may have limited evaluation for possible adverse reactions in high-risk populations (7). Multiple previous studies have evaluated patients who had received treatment with intrapleural streptokinase. These studies have evaluated systemic coagulation before and after intrapleural streptokinase by measuring international normalized ratio (INR), activated

Highlight box

Key findings

- There was no measurable difference in systemic coagulation after intrapleural tissue plasminogen activator (tPA) and dornase alfa (DNase) in our patient sample.

What is known and what is new?

- Intrapleural tPA and DNase are effective treatments for complicated pleural effusions but the therapy comes with some increased risk of intrapleural bleeding.
- There is a lack of data on the systemic effects of intrapleural tPA and DNase but this study does not show a measurable change in systemic coagulation after therapy.

What is the implication, and what should change now?

- This pilot study may help better our understanding of systemic risks of intrapleural fibrinolytic therapy and offer a way to further power additional studies.
- With no measurable change in systemic coagulation further investigations should be done to help better understand what risks factors contribute to intrapleural bleeding associated with intrapleural fibrinolytic therapy.

partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen, and D-Dimer before and after therapy. None of the studies showed statistically significant differences in measured values (8,9). While some studies evaluated the possible systemic effects of streptokinase, data is lacking on the potential systemic effects of our current tPA and DNase therapies. Only a few published case reports may suggest a possible correlation between systemic bleeding and intrapleural fibrinolytic therapy (22). However, in the more recent larger trial by Akulian *et al.*, there were no reported episodes of major systemic bleeding associated with intrapleural tPA and DNase (15).

Knowledge gaps remain despite ongoing research and the expanded use of intrapleural fibrinolytic and enzymatic therapy. There are several conditions where intrapleural tPA and DNase are considered relatively contraindicated. Examples would include recent intracranial hemorrhage or gastrointestinal bleeding. Unfortunately, these patients are also often at increased risk for operative intervention and, therefore, would be better suited to be treated by less invasive management. It is unknown if systemic absorption of these medications occurs at clinically relevant amounts and whether intrapleural tPA and DNase can be given safely in these conditions. Evaluating systemic absorption of intrapleural tPA and DNase could help expand this treatment option to more patients and reduce the morbidity and mortality associated with complicated parapneumonic effusions and empyemas. This study aims to explore whether there is a measurable change in coagulopathy after getting intrapleural tPA and DNase to help us better understand these medications' systemic risks. We present this article in accordance with the TREND reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-847/rc).

Methods

Study design

This prospective observational pilot study was conducted at the University of Nebraska Medical Center (UNMC) in Omaha, Nebraska.

Ethics

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board (IRB) of the University of Nebraska Medical Center (Approval 043-21-FB, IRB Number ERB00000671), and informed consent was obtained from all individual participants.

Eligibility

The inclusion criteria were adult patients (≥18 years old) who had been diagnosed with complicated parapneumonic effusions defined as pH <7.2, glucose <60 or lactated dehydrogenase (LDH) >1,000 or multiloculated effusions defined as septations seen on ultrasound imaging or computer tomography (CT) scans. Empyema was defined as frank purulent drainage or culture-positive pleural fluid (2,15). These patients were already identified to need chest tube placement and intrapleural therapy with tPA and DNase. Patients could be on deep vein thrombosis prophylaxis but not on full-dose anticoagulation. Patients could also be on antiplatelet medications. Participants were excluded if they had received fresh frozen plasma, platelets, cryoprecipitate, systemic tranexamic acid, or other blood products 24 hours before the baseline phlebotomy. Patients could not have active or recent gastrointestinal bleeding or intracranial hemorrhage. Due to the ongoing coronavirus disease 2019 (COVID-19) pandemic during this study, the need to minimize personal protective equipment waste, and IRB regulations, patients were only recruited if known to be COVID-19 negative.

Data collection

Baseline thromboelastography (TEG), prothrombin time/INR (PT/INR), aPTT, fibrinogen, and D-Dimer were obtained from the patient after informed consent had been signed and the patient had agreed to participate. The baseline serologic analysis was done before any tPA and DNase infusions or at least 1 hour after the chest tube had been allowed to drain from any previous chest tube tPA and DNase infusions. If patients had received any intrapleural tPA and DNase, a 1-hour washout period after draining intrapleural tPA and DNase was used to minimize any previous dose effects on the baseline coagulation profile. One hour was chosen as an adequate washout period as the half-life of systemic alteplase is five minutes, and systemic effects last up to 1 hour (23). After infusion of the tPA and DNase, a TEG, PT/INR, aPPT, fibrin, and D-Dimer were also obtained. Post-infusion coagulation profile was collected between 50–120 minutes post tPA and DNase infusion. Post-infusion phlebotomy was completed at this

interval to give adequate dwell time to allow for possible absorption but not longer than one hour after the chest tube had been unclamped, as fibrinolytic effects can be for up to one hour. Data for only one tPA and DNase therapy was used for each patient. Each patient had assessment of their coagulation profile before and after intrapleural therapy.

The dosing regimen was 10 mg alteplase and 5 mg DNase, given twice daily. The number of doses was individualized by providers based on patient need and response to therapy. The median length of treatment for patients in the study was 6 doses [interquartile range (IQR: 5, 6)]. Intrapleural tPA and DNase were allowed to dwell for one hour before chest tubes were unclamped.

Data was then collected from the electronic medical record, including serologic analysis, demographics, pleural fluid analysis, and diagnosis. Adverse events were also collected from the electronic medical record.

Primary and secondary outcomes

This study's primary outcome was comparing clot lysis as seen on the TEG scan when comparing pre and post tPA and DNase therapy phlebotomy. TEG scans are functional tests looking at whole blood clot formation and have been used to assess fibrinolysis associated with tPA in other studies (24,25). Studies in trauma literature have shown that the lysis of clot at 30 minutes (Ly30) in TEG scans can identify the hyperfibrinolysis caused by tPA (25,26). Pre and post phlebotomy was done to evaluate changes in other TEG measurements, PT/INR, aPTT, fibrinogen, and D-Dimer. Assays at our institution are reported as quantified values with normal ranges, and values above or below the ranges are reported as greater than or less than the minimum or maximum range. For the purposes of this study, either the maximum or minimum value was used as the reported value. Pleural fluid pH less than 6.6 was recorded as the value of 6.6. Pleural fluid glucose less than 10 mg/dL was reported at 10 mg/dL. Pleural fluid LDH less than 25 (U/L) was reported with the value of 25 (U/L), and greater than 25,000 (U/L) was recorded as 25,000 (U/L). Systemic fibrinogen assays greater than 1,000 (mg/dL) were reported as 1,000 (mg/dL). Other outcomes included the number of patients with intrapleural hemorrhage after receiving therapy. Any systemic bleeding was also investigated while on treatment. The number of patients with successful drainage not undergoing further surgical intervention and resolution of symptoms was also collected.

Statistical analysis

Data was summarized using medians and IQRs. Differences in measures between the two time points were calculated (i.e., change scores) and compared to a value of zero using Signed Rank tests to assess significant change over time. All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). P values less than 0.05 are considered statistically significant.

Results

Nineteen patients were enrolled in our study. However, two patients were excluded from the analysis: one patient transitioned to comfort care prior to biochemical analysis, and the other patient had phlebotomy performed less than 30 minutes after the infusion of intrapleural medications. Seventeen patients were included in the final data analysis, of which 14 (82.4%) were non-Hispanic Whites (see *Table 1* for descriptive statistics). The median age of patients in the study was 67 years (IQR: 62, 71), and 76.5% (n=13) were male. Thirty percent of patients (n=5) had chronic kidney and/or liver disease, and none of the patients in our study had any prior history of major bleeding or coagulopathy. The median baseline platelet count of all study patients was $302\times10^3/\mu L$ (IQR: 255, 390). The most common etiology of pleural effusion in our cohort was complicated parapneumonic effusion or empyema (94.1%). One patient enrolled had a multiloculated malignant effusion.

The primary outcome was examining any difference in pre- and post-infusion biochemical analysis for the Ly30 in the TEG scan. *Table 2* depicts the pre and post tPA and DNase therapy laboratory values of the TEG scan and markers of coagulopathy. No statistically significant difference was identified in LY30, which had a median change score of 0 (IQR 0, 0; P=0.88). No other parameters, including R-time, K-time, maximum amplitude (MA), or alpha angle, on the TEG scan showed significant changes when comparing pre and post tPA and DNase therapy values. Changes in PT/INR, aPTT, fibrinogen, and D-Dimer pre and post tPA and DNase therapy were also analyzed, and no statistically significant difference was found (see *Table 2*). While some patients were enrolled after their first intrapleural tPA and DNase treatment, the combination of a one-hour washout period and the direct comparison of pre and post coagulation profiles should not affect the detection of absorption as we would expect that

Table 1 Demographic and clinical characteristic of study sample

Variables	Values
Sex	
Male	13 (76.5)
Female	4 (23.5)
Race	
Non-Hispanic/White	14 (82.4)
Hispanic	1 (5.9)
American Indian	1 (5.9)
Black	1 (5.9)
Comorbidities	
None	11 (64.7)
Chronic kidney disease	2 (11.8)
End stage renal disease	2 (11.8)
Cirrhosis	0 (0.0)
End stage renal disease and cirrhosis	1 (5.9)
Unknown	1 (5.9)
Etiology of pleural effusion	
Complicated parapneumonic effusion/ empyema	16 (94.1)
Multiloculated complex malignant effusion	1 (5.9)
Past systemic bleeding history	
Yes	0
No	17 (100.0)
Timing of lab draw during tPA and DNase treatment	
1st treatment	9 (52.9)
2nd treatment	4 (23.5)
3rd treatment	3 (17.7)
4th treatment	1 (5.9)
Positive pleural blood cultures	
Yes	10 (58.8)
No	7 (41.2)
Age (years)	67 [62, 71]
BMI (kg/m^2)	26.1 [23.8, 34.7]
Pleural fluid pH	7.1 [6.9, 7.3]
Time from tPA/DNase dose to post-blood draw (minutes)	75 [64, 98]

Data are presented as n (%) or median [IQR]. tPA, tissue plasminogen activator; DNase, dornase alfa; BMI, body mass index; IQR, interquartile range.

there would still be a measured change if tPA or DNase were absorbed.

One patient in our cohort (5.9%) had intrapleural bleeding with the intrapleural infusion of tPA and DNase, which was managed conservatively by withholding further treatments (*Table 3*). This patient had hemorrhagic discoloration of fluid without the need for blood transfusions. This patient had no significant changes in comparing their pre and post coagulation profiles. There was no incidence of systemic bleeding in our study. Three (17.6%) patients underwent surgical intervention after starting intrapleural therapy to eradicate their complicated pleural effusions.

Discussion

To our knowledge, this is the first study to evaluate measurable differences in systemic coagulation after chest tube infusion with tPA and DNase. Previous data evaluating intrapleural streptokinase did not show that this therapy changed systemic coagulation (8). Since the MIST-2 trial, tPA and DNase have become the standard of care for intrapleural fibrinolytic and enzymatic therapy. With this evolution in treatment, evaluating whether intrapleural tPA and DNase have systemic coagulation effects is essential. Our data suggests no significant difference in systemic coagulopathy after intrapleural tPA and DNase.

We evaluated multiple measurements of systemic coagulopathy, including TEG scans, to look at the Ly30. The Ly30 is a good measure of tPA effects (25,26). With no significant difference in Ly30 seen after intrapleural tPA and DNase therapy, our data suggests there may not be clinically significant absorption of tPA from the pleural space. Further, without any measurable change in coagulopathy, this data would suggest that there may not be a significant risk of developing systemic coagulopathy with intrapleural tPA and DNase treatment. Our study population had a 5.9% risk of intrapleural hemorrhage, consistent with other studies' findings. No patients had systemic bleeding in our study.

There are several possible explanations for our findings. One reason there may not be a measurable change in systemic coagulation is that small doses used in intrapleural treatment, even if systemically absorbed, may not be enough to cause measurable changes. Another possibility is that there is no systemic absorption of tPA and DNase from the pleural space. Though less likely, it is also possible that the measurable changes of fibrinolytic absorption are brief, and

Table 2 Changes in coagulation measures

Outcome	Normal reference ranges	Median pre-value	Median post-value	Median change score (IQR)	Signed rank P value
LY30 (%)	0–8	0	0	0 (0, 0)	0.88
R time (minutes)	5–10	5.3	5.5	0.5 (–0.4, 1.0)	0.12
K time (minutes)	1–3	1.2	1.0	0.0 (–0.2, 0.1)	0.96
Alpha angle (degrees)	53–72	74.4	75.1	–0.3 (–1.7, 1.6)	0.90
MA (mm)	50–70	77.9	76.9	0.2 (–1.5, 1.6)	0.68
D-Dimer (ng/mL)	<500	5,629	5,590	62 (–206, 513)	0.22
Fibrinogen (mg/dL)	160–450	822	779	0 (–72, 24)	0.15
INR (seconds)	0.9–1.1	1.1	1.2	0.0 (0.0, 0.0)	0.25
aPTT (seconds)	24–38	30.8	31.5	0.6 (–0.3, 1.5)	0.13

IQR, interquartile range; MA, maximum amplitude; INR, international normalized ratio; aPTT, activated partial thromboplastin.

Table 3 Adverse events

Complication	Yes, n (%)	No, n (%)
Intrapleural hemorrhage	1 (5.9)	16 (94.1)
Systemic bleeding	0	17 (100.0)
Undergoing surgical intervention	3 (17.6)	14 (82.4)

the timing of phlebotomy has missed a short-lived change.

While a few case studies suggest a possible correlation between intrapleural tPA and DNase and systemic bleeding, multiple more extensive trials exploring intrapleural fibrinolytic effects have not reported significant systemic bleeding (15,22). Without evidence of measurable systemic absorption, the question remains whether this is a safe therapy even in those who with higher systemic bleeding risks, such as those with recent gastrointestinal bleeding or intracranial hemorrhages. Our data suggests that there is no measurable change in systemic coagulation with intrapleural tPA and DNase; however, larger studies are needed to better examine how this affects the potential systemic bleeding risks.

There is a small risk (0–7%) of intrapleural hemorrhage associated with intrapleural tPA and DNase (2). Inconsistent definitions and protocols about intrapleural hemorrhages associated with treatment have limited understanding of risk factors for intrapleural bleeding. Multiple studies have shown that there may be an increased risk of intrapleural hemorrhage related to patients with systemic coagulopathy or those on systemic anticoagulation (2,15). However, some data has not consistently found a correlation between systemic anticoagulation and intrapleural hemorrhage (14). Further studies are needed to better understand the mechanism by which systemic anticoagulation increases the risk for intrapleural hemorrhage. While we acknowledge further studies are needed to continue to evaluate if there is a measurable change in systemic coagulation associated with intrapleural tPA and DNase, we hope this study can also drive further hypotheses on the mechanism in which pleural space and systemic circulation may communicate. Further studies are still needed to better characterize risk factors for intrapleural hemorrhage associated with intrapleural tPA and DNase.

This study has several strengths. It is the first study to measure intrapleural tPA and DNase effects on systemic coagulopathy. While this therapy is becoming more common and is often first-line therapy in patients, we are still learning more about potential side effects and risks. While current literature suggest bleeding risks are low, our data adds to the current understanding of bleeding risks. We were also able to use multiple ways to measure systemic coagulopathy, including TEG scans, which may be very helpful in identifying the potential absorption of tPA and its fibrinolytic effects. This study does have several limitations, including the small sample size. We acknowledge that our study's definition of intrapleural hemorrhage is limited and would have benefited from further testing, including pleural fluid hematocrit. Further investigation on the fluid was not performed as it was left to the treating team's discretion. While this is a pilot study, we hope this study will

encourage additional studies and more extensive databases where further investigations can be done to look for signs of systemic absorption, evaluate any potential links between therapy and systemic bleeding, and understand the causes of intrapleural hemorrhage better. There is limited literature on effect sizes for TEG scans and other coagulation measures, so we hope that our data may help power future studies. The short half-life of tPA also limits us, and more frequent phlebotomy may have been beneficial to ensure any systemic effects were not missed.

Conclusions

This is the first study to evaluate measurable changes in systemic coagulation after intrapleural tPA and DNase. Our data demonstrates no significant difference in coagulation after intrapleural tPA and DNase infusion, suggesting that there may not be clinically significant absorption. Our study adds to the current literature and helps add to our understanding of the risks for systemic bleeding as well as intrapleural bleeding associated with this therapy. Further studies continue to be necessary to help understand the potential systemic bleeding risks as well as help identify those at risk for intrapleural hemorrhage.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-847/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-847/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the University of Nebraska Medical Center (Approval 043-21-FB, IRB Number ERB00000671), and informed consent was obtained from all individual participants.

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