A double blind randomized cross over trial comparing rate of decortication and efficacy of intrapleural instillation of alteplase vs placebo in patients with empyemas and complicated parapneumonic effusions

G. Thommi*, J.C. Shehan, K.L. Robison, M. Christensen, L.A. Backemeyer, M.T. McLeay

Creighton University/Methodist Hospital, Omaha, NE, USA

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Summary

Aim: A double blind randomized cross over trial to compare the rate of decortication, safety and efficacy of intrapleural instillation of Alteplase vs. Placebo in empyema and complicated parapneumonic effusions (CPE).

Methods: Patients diagnosed with empyema or CPE and considered for surgery were given the option to enter into this trial. Intrapleural instillation of the ‘Drug’ was given daily for three days. Patient that failed the first arm of the trial were offered surgery or to cross over to the second arm. Failure was documented if pleural effusions did not improve by 50% on CT scans after three doses of the ‘Drug’ or if these effusions recurred within six weeks.

Results: One hundred and eight patients were evaluated and one hundred enrolled in the trial. 32 patients were excluded, 29 for noninfectious loculated effusions, two for protocol violation and one for bleeding at chest tube site. There were 17 patients with empyema and 51 patients with CPE. 58 of the 61 patients (26 crossed over) with empyema/CPE resolved with Alteplase therapy compared to 4 of the 32 patients (one crossed over) treated with Placebo (p value <0.001). None of the patients went to surgery. Adverse events with Alteplase therapy compared to Placebo were not statistically significant, with chest pain and bleeding complications being the most common.

* Corresponding author. Creighton University/Methodist Hospital, Midwest Pulmonary and Critical Care, 8552 Cass Street, Omaha, Nebraska, USA. Tel.:+1 402 390 0606 (office), +1 402 206 7372 (mobile); fax: +1 402 390 0899.
E-mail addresses: tommi4@cox.net (G. Thommi), shehansix@cox.net (J.C. Shehan), jrmavsmom18@yahoo.com (K.L. Robison), michelle.christensen@nmhs.org (M. Christensen), lbackemeyer@yahoo.com (L.A. Backemeyer), mmcleay59@hotmail.com (M.T. McLeay).

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Introduction

Approximately 1.3 million patients are hospitalized annually with pneumonia and in 36%–66% pleural effusions occur. The majority of these effusions usually resolve with antibiotics and standard medical therapy. However, 10%–20% progress to an exudative stage that requires chest tube drainage or surgical interventions. Mortality is increased as these effusions evolve ranging from 7% to 33% in anaerobic and pneumococcal pneumonia and in the elderly co-morbid patient. Delay in treatment and inadequate drainage of these effusions can result in progressive sepsis, shock, increase in morbidity and mortality. Exudative pleural effusions in these patients have shown to have decreased fibrinolytic activity, high TNF-alpha, high concentrations of plasminogen activator inhibitor and decrease level of tissue plasminogen activator. Simple chest tube drainage with conventional medical treatment is often inadequate to drain these effusions because of increased viscosity, turbidity, and fibrin strand depositions. The rationale for fibrinolytic therapy in empyema and CPE is to lyse loculations, lyse fibrin deposits, decrease the viscosity of the fluid and facilitate drainage.

Method

This was a double blind randomized Placebo controlled cross over trial performed in the United States. Patients with empyema or CPE considered for decortication or VATS were given the option to enter into this trial. These patients failed to resolve their effusions with chest tube drainage and standard medical therapy. This trial was approved by the FDA (IND #11415), IRB (#536, FWA #00003377) at Methodist Hospital and enrolled through the Clinicaltrials.gov (NCT #00468104). The primary end point was a 40% reduction in surgical intervention between Alteplase and Placebo groups. The secondary end point was a 50% difference in resolution of dyspnea, sepsis syndrome and pneumonia between the two groups. Patients were excluded if they refused the trial, were below 18 years of age, had active bleeding (known bleeding diathesis), had recent cerebral vascular accident, had bronchopleural fistula, had severe uncontrolled hypertension, had coagulopathy (INR > 4; PTT > 100, Platelet count < 60,000), had hypersensitivity to Alteplase, diagnosed with acute traumatic hemothorax, had pregnancy/positive pregnancy test, refused standard medical therapy or to follow protocol. Effusions were labeled empyema if pleural fluid glucose level less than 60 mg/dl with normal or high blood glucose values, if the Ph was less than 7.2, if the pleural fluid culture was positive or if frank pus was noted. Effusions were labeled CPE if the pleural fluid was an exudate and if CT scan and ultrasound of the chest showed multiple loculations with a pneumonic process. Chest tubes were inserted if pleural effusions recurred after two thoracentesis within two weeks, if large loculated effusions were present post thoracentesis, if pleural fluid culture was positive or if pus was obtained. All patients were on broad-spectrum antibiotics throughout the trial period. After informed consent was obtained the hospital pharmacist randomized patients by a fixed allocation randomization process using a computer based random sequence generation. All investigators and data coordinators were blinded and the pharmacist(s) had no contact with the patient, in data collection and were not involved in the patient’s care. Primarily 28 French catheters were utilized and connected to a Pleuravac drainage system. However, smaller catheters, 14 to 16 French, were used in a few multi-loculated effusions. Prior to instillation of the ‘Drug’, patients were placed with the chest tube side up, the chest tube was clamped and taken off suction. The chest tube position was checked daily by physical examination and chest x-ray to ensure that the chest tube was not dislodged. Alteplase 25 mg or Placebo in 100 mls of normal saline, divided in two 60 mls syringes, was instilled intrapleurally daily for three days with an 18 gauge needle through the Pleuravac tubing. The chest tube was flushed with 50 mls saline and patients were monitored in the same position for 20 min. The chest tube was clamped for the first hour and suction was applied

Conclusion: Intrapleural instillation of Alteplase is significantly more effective than Placebo in patients with empyema and PPE (95% vs.12%). This study demonstrates it is safe and efficacious with minimal adverse reactions.
after the second hour. Patients that failed the first arm and agreed to the second arm, the 'Drug' (Placebo or Alteplase) not instilled in the first arm, was then instilled intrapleurally daily for three days. Adverse events were monitored for at least 24 h. The principal investigator was the only one assessing CXR or CT scans and the protocol allowed up to six doses of the drug depending on CXR or CT response. Failure to the first and second arm of the trial was documented if the pleural fluid did not decrease by at least 50% by CT scans on day four. Patients were offered surgery if they failed the first and second arm of the trial. PT/INR, PTT, thrombin time were performed before and 1 h after each instillation. Fibrinogen levels, performed in later half of the study, were obtained prior to and 1 h after instillation. Chest X-rays were performed daily, two weeks post-treatment and six weeks post-treatment. Baseline CT scans of the chest was obtained initially, following the first arm, the second arm and in all but one patient, eight to twelve weeks later. Chest tube was removed when the pleural fluid output was less than 150 mls in 24 h. Success was determined at six weeks if CPE or empyema resolved and did not reoccur.

Statistical analysis

A Univariate analysis was done to identify possible predictors of successful resolution of symptoms. The Chi-Square analysis was used to compare the percent successful and the student’s t-test was used to compare averages between those successful and those not. This study design raised the question whether or not the order of treatment effected the outcome. A logistics regression model was used to evaluate the order of treatment. The dependent variable is success. Independent variables included in the model were order of treatment and treatment (i.e. Alteplase or Placebo).

Results

This trial was conducted over a five-year period. One hundred and eight patients were evaluated for the trial of

Figure 1  Patient A: Initial CT scan of chest (top picture) showing large left empyema with a chest tube in place. CT scan of chest (lower figure) after 3 doses of intrapleural instillation of Placebo showing no change.

Figure 2  Patient A. CT scan of chest after three doses of Alteplase (top picture) showing significant clearing of empyema and CT scan of chest three months after Alteplase use (lower picture) showing complete resolution of empyema.
which one hundred entered the trial. Twenty-nine patients were excluded as they did not meet criteria for CPE or empyema. These loculated effusions were secondary to congestive heart failure/cardiomypathy (CHF/CMP), end stage renal disease (ESRD) or malignant pleural effusion (MPE). Two patients were excluded for protocol violation and one for bleeding at chest tube site after the first dose of Alteplase. Age ranged from 21 to 90 years with a mean of 64 ± 15. Male to female ratio was 37:21. Sixty-eight patients completed the trial, 17 patients with empyema and 51 patients with CPE. These patients had multiple co morbidities and patient’s characteristics are shown in Table 1. Pleural fluid glucose levels were less than 60 mg/dl in eleven patients, three were less than 30 mg/dl and five were less than 10 mg/dl. The pH pleural fluid was less than 7.0 in one of the above patients. Pleural fluid culture was positive in four patients (two MRSA, one Streptococcus and one with Aspergillus) and two patients had frank pus. One patient with presumed chronic empyema was excluded from the study for persistent large pneumothorax despite chest tube suction. Cardiothoracic surgeons declined this patient for decortication. All patients treated with three doses of Alteplase had over 70% resolution of their effusions and three patients that failed Alteplase therapy recurred only after the chest tube was removed. Patients who failed three doses of Placebo therapy showed no change or increase in the amount of pleural effusions on CT scans. (Figs. 1–4) Overall 58 of the 61 patients (95%; 26 cross over) treated with Alteplase therapy resolved compared to four of the 33 patients (12%; one cross over) treated with Placebo (p value < 0.001). All 16 patients with empyema (100%; four crossed over) treated with Alteplase resolved compared to none of the five patients (0%) treated with placebo (p value < 0.001). Alteplase was effective in 42 of the 45 patients with CPE (93%; 22 patients crossed over) compared to four of the 28 patients (13%; one patient crossed over) treated with Placebo (p value < 0.001; Chart 1, Figs. 1–4). Three patients with CPE that failed Alteplase

Figure 3  Patient B. Initial CT scan of the chest (top picture) showing large left CPE with adequate chest tube placement. CT scan of chest (lower picture) showing worsening of left CPE after three doses of Placebo.

Figure 4  Patient B. CT scan of chest (top picture) after 3 doses of Alteplase showing significant clearing of the left CPE but note residual effusion/infiltrate. CT scan of chest (lower picture) 3 months after Alteplase use showing complete clearing of the left CPE.
therapy reoccurred within six weeks, were mild to moderate, did not require thoracentesis, chest tube placements or surgical intervention for up to six months. These patients refused surgery and two of them were in New York Heart Association class III to IV CHF. Twenty-five patients that failed Placebo therapy refused surgical intervention and three of them refused to be crossed over. Small bore catheters in two patients with empyema kept getting blocked and kinked, required frequent flushing and one patient needed four doses of Alteplase. The secondary end points could not be measured as all but one patient that failed the first arm were crossed over to the second arm on day four.

Pleural fluid drainage measured daily was 100 mls—300 mls more with Alteplase than Placebo therapy in a majority of patients and in both groups the pleural fluid drainage decreased with subsequent instillations. The time from initial presentation to initiation of therapy was from two days to two weeks in empyema and CPE patients. The order of treatment was not significant ($p = 0.602$). Overall chest pain for Alteplase and for placebo was statistically not significant ($p$ value $= 0.952$). Other adverse events showed no statistical difference between Alteplase and Placebo. No abnormalities in coagulation obtained pre and one-hour post-treatment, were noted either with Alteplase or Placebo use. CRP (C reactive protein) values measured daily did not correlate with efficacy either with Alteplase or Placebo therapy. No significant change in WBC and platelet counts was noted with Alteplase or Placebo use.

Two of the eight patients that did not enter the trial were sent directly for decortication and both needed mechanical ventilation for a few days. One patient with empyema was not enrolled for bleeding complications secondary to sepsis and necrotizing pneumonia. This patient underwent decortication requiring multiple chest tubes for bronchopleural fistulas resulting in a prolonged hospital course. Two patients refused to enter the trial (one post decortication) and three patients that agreed to the trial had their chest tubes discontinued inadvertently. One of these patients that had his chest tube removed inadvertently post VATS continued to have persistent loculated effusions/infiltrate six months later.

Complications

Two patients had blood loss with Alteplase therapy (not statistically significant $p < 0.952$). One patient bled at the chest tube site immediately after Alteplase instillation, required transfusion and was taken off the trial. Hypotension and anemia occurred several hours after the second dose of Alteplase therapy in the second patient. This
This is the first study to our knowledge, comparing Alteplase to Placebo in a randomized double blind trial in patients with empyema or CPE. The primary finding in this study showed Alteplase to be significantly more effective than Placebo in reducing surgical interventions in patients with empyema and CPE (95% vs. 12%). Secondary end points and length of stay were not measured as all but one patient was crossed over on day four. The ideal fibrinolytic agent for loculated pleural effusions should have high fibrin affinity and binding, a short half-life, high fibrin selectivity and specificity and can be administered by a non-invasive method. Alteplase has such properties with high fibrin affinity and fibrin selectivity with a half-life of four to 8 min.14,15 However, SK has low fibrin affinity and fibrin selectivity, has little effect on pus viscosity and may simply work by breaking down loculations mechanically.16,17 Rahman et al concluded that Alteplase is effective only when combined with DNase.18 However these investigators used chest radiographs and not chest CT to determine the response to therapy. Chest Radiographs, including decubitus views, are inaccurate in detecting and quantifying pleural effusions and cannot differentiate associated pneumonic processes, elevated diaphragm, lung abscess and even a mass.19–22 The dose of Alteplase used in Rahman’ study (10 mg vs. 25 mg) may be insufficient and could have contributed to its failure.12,13,23,24 However, if surgical intervention was the primary end point there was very little difference between Alteplase and Alteplase/DNase group (3/48 vs. 2/48). Moreover, surgical referrals were actually increased in the DNase group compared to the Placebo group (18/46 vs. 8/51) implying that DNase may have minimal or no fibrinolytic activity. Several studies have shown Alteplase to be effective as a single agent in patients with empyema or CPE in adults and children.12,13,24–27

Prior to intrapleural fibrinolytic therapy, patients with empyema and CPE that failed chest tube placement and antibiotics therapy usually required surgical intervention. In elderly patients with multiple co morbidities mortality can be up to 5% in Video Assisted Thoracic Surgery (VATS) and 10% with decortication. Recurrence of empyema of up to 2.6% occurs in decortication or VATS. Complications of VATS or decortications include bleeding, infection, intolerance to single lung ventilation, re-expansion pulmonary edema, prolonged ventilatory support, intercostal neuralgia, multiple chest tube placements for persistent air leaks and bronchopleural fistulas.28,29 Post operative pain control can be a major problem resulting in over sedation, atelectasis, pneumonia, urinary retention, hypoxemia and worsening respiratory depression. Nonsurgical candidates or those who refused surgery often have multiple image-guided catheters placed by interventional radiologists (IR) at different locations. While there are case reports of success with this method, adjusting chest tubes every two to three days under CT guidance have not been proven by controlled trials.30 Multiple chest tubes placements and adjustments under CT scan guidance result in pain control problems, increase cost, increase lung injury and prolong hospital stay. In contrast, patients in the current study treated with Alteplase did not require mechanical

**Photograph 1** Large debrni noted in chest tubes in different patients post Alteplase instillation (open arrows). These easily obstruct smaller chest tube catheters.
ventilation, had no bronchopleural fistulas or problems with persistent air leaks, did not have respiratory distress or depression and had no problems with pain control.

Rahman et al reported no change in clinical outcomes using different size chest tubes. However, placements of these chest tubes were not randomized and larger chest tubes were placed for more purulent effusions. Moreover, chest radiographs and not chest CT scans were performed to document outcome.31 The size of chest tube catheters, in our experience, is critical to prevent failure as catheters less than 20 cm French require flushing several times daily, tend to loop and kink frequently and have a failure rate of up to 20%.30,32–34 Large debris occurs with Alteplase use, especially in empyema and CPE, causing smaller chest tube catheters to get obstructed. (Photograph 1) Significant pain and catheter blockage can also be a problem if these catheters are inserted through large muscle groups.

Bleeding complications has been a primary concern for intrapleural instillation of Alteplase and has prevented its use. In the current study the risk of bleeding was small, there was no evidence of systemic absorption of Alteplase and bleeding was not seen in any other site other than the chest.35 Bleeding complications can be avoided if Alteplase is not used when the INR > 4, PTT above 50, Platelet <50,000 and if bleeding time or platelet function assay is abnormal. Following a significant bleed in the first patient, subsequent instillations of the ‘Drug’ were performed with the chest tube side up for 20 min to prevent the ‘Drug’ from coming in contact with the chest wall incision. Bleeding complications did not occur when Lovenox 40 mg or heparin 10,000 units was administered subcutaneously with intrapleural instillation of Alteplase.

Residual pleural effusions similar to postsurgical changes were common after the third dose of Alteplase but these resolve in six to eight weeks and should not be considered Alteplase failure. Furthermore, associated consolidation with these effusions may take up to 12 weeks to resolve, emphasizing the importance of differentiating an effusion from consolidated lung by CT scans (Fig. 5). The pleural space appears to get ‘sealed’ after the first or second dose of Alteplase therapy in some empyema patients and subsequent administration becomes difficult and painful. Further instillation of Alteplase was discontinued and follow up of these patients in six weeks showed complete resolution of their empyema.

## Conclusion

Alteplase therapy was significantly more effective than Placebo therapy (95% vs. 12%; \( p < 0.001 \)) in empyema and CPE. Three doses of Alteplase instillation prevent surgical interventions with its associated morbidity, mortality and higher costs. Intrapleural instillation of Alteplase is easy to administer, safe, efficacious, and has minimal adverse effects.

## Conflict of interest

A restricted grant was sponsored by Genetech, Inc. for this trial. The primary investigator was involved in all patients.
Monies was distributed to the IRB at Methodist hospital and to the Pharmacy department per patient. Monies were also distributed per patient to the MD (co-investigators), nursing staff and PA that were involved in following the patient’s care and collecting the data. Genetech did not have any input in any part of the protocol, in patient care or collection of data. Genetech was informed wherever a patient entered the trial and the drug Alteplase was supplied free of charge to the patient. Genetech was not involved in writing this manuscript.

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References