TISSUE PLASMINOGEN ACTIVATOR IN TRAUMATIC HEMOTHORAX

SUMMARY

The use of fibrinolytic therapy has been reported in the literature to treat patients with pleural effusion, parapneumonic effusion, empyema, and retained hemothorax despite tube thoracostomy. The use of tissue plasminogen activator (tPA), as well as other agents, has been shown to be a successful adjunct to drain retained collections and obviate the need for surgical intervention. tPA has a low incidence of adverse events.

RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **Intrapleural tPA therapy should be considered to resolve an undrained hemothorax.**
  - **Intrapleural tPA plus DNAse should be considered for patients with a retained traumatic hemothorax that has progressed to empyema.**
- **Level 3**
  - **Chest computed tomography (CT) should be performed to confirm an undrained collection before intrapleural fibrinolytic administration.**
  - **Fibrinolytic regimens**
    - **tPA 50 mg in 100 mL normal saline should be instilled directly into the thoracostomy tube. The tube should be clamped for one hour during which the patient is rolled to optimize distribution. This dose may be repeated daily while monitoring drainage volume and chest radiographs**
    - **tPA 10 mg and DNase 5 mg should be instilled directly into the thoracostomy tube twice daily for three days. tPA should be instilled first, then the chest tube clamped for one hour. After unclamping, DNase should be instilled, then chest tube clamped again for one hour.**
  - **Failure to improve or resolve the hemothorax should prompt more invasive intervention.**

INTRODUCTION

Hemothorax occurs in 30-40% of patients sustaining thoracic trauma. 5-10% of these patients may develop retained hemothoraces placing them at increased risk for complications (1). Empyema is the most morbid of these complications, occurring in up to 5% of patients (2). Traditional therapy consists of early drainage with thoracentesis or tube thoracostomy. Failure of this therapy, as exhibited by retained collections and

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

Approved 03/04/2008
Revised 03/31/2018

empyema, requires either open thoracotomy or video-assisted thoracic surgery (VATS) for drainage and decortication. Fibrinolytic therapy has recently been used in such patients to reduce the need for surgical intervention (1,3,6).

The use of intrapleural fibrinolysis to treat complicated pleural effusions dates to 1949 with the use of streptokinase (7). Although successful, this agent had several drawbacks including allergic responses and development of resistance through immune system mediation. This subsequently led to the development of urokinase which has a lower antigenic profile. It became the industry standard for intravascular thrombolysis and proved to be equally efficacious in the treatment of retained intrathoracic collections (3,6-9). Recent concerns over possible disease transmission have greatly reduced the usage of urokinase. This has led to increased use of tPA for intrapleural pathology (9).

tPA is currently used most often for intravascular thrombolysis. In terms of treating complicated pleural effusions and empyema, tPA has been shown to be equally efficacious, if not improved, over urokinase (8). Multiple studies have shown success rates greater than 90% in the resolution of retained collections (3,6-8). More recently, tPA, as well as other fibrinolytics, have been used to treat traumatic hemothorax that has failed traditional tube thoracostomy. These agents have again shown high success rates at resolving retained collections. The avoidance of surgery in these cases often leads to decreased length of stay and reduced morbidity and mortality related to surgical intervention. Early studies show that tPA is both safe and efficacious in the treatment of retained hemothorax in the trauma patient. Benefits include avoidance of surgery and reduced morbidity and mortality. The major concern with the use of tPA is hemorrhagic complications. A review of the current literature shows only a small incidence of these events. The most common side effect is chest pain at the time of instillation (3-5,7,10).

There is now evidence to support the use of tPA combined with DNase in patients with pleural infections; however, there is currently no data for its use in traumatic hemothorax. Current literature describes a multitude of dosing and treatment protocols for these patients (1,3-8,10,11). Randomized controlled trials are still needed to establish the optimal treatment protocol and to further validate this therapy.

LITERATURE REVIEW

Jerjes-Sánchez et al. performed an open, prospective, multicenter trial of 48 patients with unresolved hemothorax or empyema after conventional pleural drainage (5). Patients were administered streptokinase 250,000 units, diluted in 100 mL of normal saline, through a chest tube. The chest tube was then clamped for 4 hours and the patient rotated for better distribution. Streptokinase was administered daily until radiographic improvement or pleural drainage was less than 100 mL in 24 hours. Of these 48 hemothoraces, 11 were infected and 14 were sterile, of which 12 were traumatic. Pleural drainage was significantly increased on days 1-4 of therapy, then decreased slowly until day 10 in those with non-malignant pleural effusions ($p<0.001$). Successful fibrinolysis, determined by quantified pleural drainage and radiographic evidence, was seen in 44 of 48 (92%) patients. The most common adverse event encountered was pleuritic pain upon instillation.

Kimbrell et al. prospectively observed 203 patients with traumatic hemothorax of which 25 developed undrained collections, defined as >300 mL of residual fluid on CT after 3 days of tube thoracostomy (3). Streptokinase 250,000 units or urokinase 100,000 units were diluted in 50 mL of normal saline were instilled daily through the chest tube or pigtail catheter. The chest tube was clamped for 4 hours and the patient mobilized to facilitate distribution. The decision to use streptokinase or urokinase was based on drug availability and physician choice. Evacuation of the undrained hemothorax was rated as complete or partial in 21 of 23 patients (92%). Two required surgical intervention and eventually made complete recoveries. On average, patients had intrapleural thrombolysis for 3.4 ± 1.4 days. In terms of safety, none of the 203 patients had hemorrhagic complications. The only noted adverse effect was transient chest pain after instillation in one-third of patients.

Inci et al. reported comparable results in 24 patients treated for clotted hemothorax with streptokinase 250,000 units or urokinase 100,000 units daily (6). Patients were treated with intrapleural fibrinolytics for an

Approved 03/04/2008
Revised 03/31/2018

average of 5-6 days. Complete response (resolution of symptoms with complete drainage of fluid and no residual space radiographically) or partial response (resolution of symptoms with a small pleural cavity) to fibrinolytic therapy was 91.7%.

Skeete et al. retrospectively reviewed 41 consecutive patients with 42 complicated pleural effusions, retained hemothoraces, and empyema that received intrapleural tPA (1). Six patients (14%) had traumatic hemothoraces. Thirty-eight patients completed therapy and were available for analysis. Patients received one to four doses of tPA. Individual doses averaged 30.2 mg with the most common dose being 50 mg. Of all patients, 79% showed radiographic improvement with tPA administration. Seventy-eight percent of patients avoided surgery with the use of tPA; this includes 67% of the patients with retained hemothoraces. Two patients with hemothorax required operative intervention. Overall, five non-operative patients required blood transfusion within 48 hours of tPA administration, one of the six required intraoperative transfusion. One patient also developed transient hematuria. Overall mortality in the group was 7.3%, with 3% representing the non-operative group. The authors concluded that tPA therapy was safe with regards to complications and effective in terms of averting the need for surgical intervention.

Thommi et al. investigated the efficacy and safety of intrapleural tPA in 120 patients with complicated pleural effusion or empyema who failed chest tube drainage and conventional medical treatment (4). Ten (8%) of these patients had a hemothorax; 5 were malignant, 2 were postoperative, and 3 were spontaneous while on anticoagulation. Doses of tPA ranged from 10-100 mg. Patients with complicated pleural effusions or empyema were given higher doses of alteplase (50-100 mg). The tPA was inserted into the chest tube while in the contralateral position. The chest tube was then clamped for 1 hour then placed on suction. The most common dose utilized was 25 mg. tPA was instilled daily for three days and then every second or third day based on output. Complete response (80% or greater resolution) occurred in 85% of patients, partial response (50-70% resolution) in 8%, and no response (<50% resolution) in 7% of patients. The most notable adverse effects were chest pain (6 patients), bleeding at the chest tube site (2 patients), and transfusion requirement (1 patient). These nine adverse events were identified out of 335 total doses of tPA.

Rahman et al. conducted a double-blind, double-dummy, 2-by-2 factorial trial in patients with pleural infection (12). Patients were randomized to receive double placebo, intrapleural tPA and recombinant human DNase, tPA and placebo, or DNase and placebo. DNase 5 mg (diluted in 30 mL of sterile water), tPA 10 mg, or placebo was given intrapleurally twice daily for 3 days. Medications were given separately and allowed one hour of distribution time with the chest tube clamped. There were a total of 210 patients enrolled in this study; however 193 patients were included in the primary analysis, of which 51 received double placebo, 48 received tPA only, 46 received DNase only, and 48 received both tPA and DNase. The difference in the mean change in pleural opacity, measured as the percentage of the ipsilateral hemithorax occupied by effusion on chest radiograph, from day 1 to day 7 between tPA-DNase group (29.5%) and placebo (17.2%) was statistically significant (p=0.005). There was a decreased frequency in surgical referrals at 3 months using tPA-DNase (4% vs 16%; p=0.03). Combined therapy was also associated with a reduction in hospital length of stay when compared to placebo (difference, 6.7 days; p=0.006). There was no improvement when either drug was used alone compared to placebo. Mortality was similar between groups. Six serious adverse events were recorded during this trial; 2 intrapleural hemorrhages and 1 episode of hemoptysis occurred in the tPA-DNase group, 2 episodes of gastrointestinal bleeding occurred in the DNase group, and 1 clinical deterioration in the placebo group.

Piccolo et al. retrospectively reviewed tPA/DNase treatment for pleural infection (complicated parapneumonic effusion and empyema) in a large cohort of unselected patients (13). DNase 5 mg (diluted in 50 mL of normal saline) and tPA 10 mg were instilled intrapleurally twice daily up to a maximum of six doses. tPA was instilled first and chest tube clamped for 40-60 minutes. The chest tube was then unclamped and allowed to freely drain for an additional 40-60 minutes before repeating the process with DNase. However, in one center (30 patients) both medications were instilled at the same time before the chest tube clamping. There were 107 total patients reviewed for this study. The median time from chest tube insertion to first dose was 2 days (IQR 1-4). Treatment with tPA/DNase was successful (composite endpoint of survival and discharge from the hospital without need for surgical intervention at 30 days) in 89.7% of

Approved 03/04/2008
Revised 03/31/2018

patients. Survival rates were 97.8% and 91.2% at 30 and 90 days. Treatment reduced pleural opacity on chest radiograph from a median of 35% to 14% ($p<0.001$). Eight patients required surgery despite treatment with tPA/DNase. Twenty-three adverse events were recorded; 21 (19.6%) required escalation of analgesia secondary to pain and 2 (1.8%) had non-fatal pleural bleeding.

In conclusion, the data demonstrates the efficacy of tPA therapy for complicated pleural effusions in patients that fail tube thoracostomy. The optimal dose and therapeutic protocol has yet to be determined, including the addition of alternative medications to aid in effusion resolution.

REFERENCES

1. Skeete DA, Rutherford EJ, Schlidt SA, et al. Intrapleural tissue plasminogen activator for complicated pleural effusions. *J Trauma* 2004; 57:1178-1183.
2. Livingston DH, Hauser CJ. Tauma to the chest wall and lung. In: Trauma, 5th edition. Mattox KL, Moore EE, Feliciano DV, eds. New York, NY:McGraw-Hill, 2004; pp 507-538.
3. Kimbrell BJ, Yamzon J, Petrone P, et al. Intrapleural thrombolysis for the management of undrained traumatic hemothorax: a prospective observational study. *J Trauma* 2007; 62:1175-1179.
4. Thommi G, Nair CK, Aronow WS, et al. Efficacy and safety of intrapleural instillation of Alteplase in the management of complicated pleural effusion or empyema. *Am J Ther* 2007; 14:341-345.
5. Jerjes-Sanchez C, Ramirez-Rivera A, Delgado R, et al. Intraplerural fibrinolysis with streptokinase as an adjunctive treatment in hemothorax and empyema: A multicenter trial. *Chest* 1996; 109:1514-1519.
6. Inci I, Ozcelik C, Ulku R, et al. Intrapleural fibrinolytic treatment of traumatic clotted hemothorax. *Chest* 1998; 114:160-165.
7. Wells RG, Havens PL. Intrapleural fibrinolysis for parapneumonic effusion and empyema in children. *Radiology* 2003; 228:370-337.
8. Levinson GM, Pennington DW. Intrapleural fibrinolytics combined with image-guided chest tube drainage for pleural infection. *Mayo Clin Proc* 2007; 82:407-413.
9. Harnell GG, Gates J. The case of Abbokinase and the FDA: the events leading to the suspension of Abbokinase supplies in the United States. *J Vasc Interv Radiol* 2000; 11:841-847.
10. Bishop NB, Pon S, Ushay M, et al. Alteplase in the treatment of complicated parapneumonic effusion: a case report. *Pediatrics* 2003; 111:E188-E190.
11. Walker CA, Shirk MB, Tschampel MM, et al. Intrapleural Alteplase in a patient with complicated pleural effusion. *Ann Pharmacother* 2003; 37:376-379.
12. Rahman NM, Maskell NA, West A, et al. Intrapleural Use of Tissue Plasminogen Activator and DNase in Pleural Infection. *N Engl J Med* 2011; 365:518-26.
13. Piccolo F, Pitman N, Bhatnagar R, et al. Intrapleural Tissue Plasminogen Activator and Deoxyribonuclease for Pleural Infection. *Ann Am Thorac Soc* 2014; 11(9):1419-25.

Surgical Critical Care Evidence-Based Medicine Guidelines Committee

Primary Author: Bailey Constantine, PharmD
Co-Author: Brandon Hobbs, PharmD
Editor: Michael L. Cheatham, MD
Last revision date: March 31, 2018

Please direct any questions or concerns to: mailto:webmaster@surgicalcriticalcare.net