

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

# Tissue Plasminogen Activator in Traumatic Hemothorax

## SUMMARY

Recent literature has described the use of fibrinolytic therapy to treat patients with 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 these retained collections and obviate the need for surgical intervention. The use of this agent shows a low incidence of adverse events. The optimal protocol for this intervention has not yet been established.

## RECOMMENDATIONS

### Level I

- No recommendations

### Level II

- Intrapleural TPA is an effective therapy for the resolution of undrained hemothorax with a low incidence of hemorrhagic adverse events.

### Level III

- TPA should be used early in the patient's course to achieve the best results.
- Intrapleural TPA should be used with caution in patients with recent bleeding events.
- Chest CT is recommended to confirm undrained collections before instillation of TPA.
- TPA (50 mg in 100mL 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 dosage may be repeated daily while monitoring drainage volume and chest radiograph.
- 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 tube thoracostomy. Failure of this therapy, as exhibited by retained collections and empyema, leads to either open thoracotomy or video-assisted thoracic surgery (VATS) for drainage/decortication. Fibrinolytic therapy has recently been used in such patients in an effort to reduce the need for surgical intervention (1,3-6).

The use of intrapleural fibrinolysis to treat complicated pleural effusions dates back to 1949 when Streptokinase was first used for this indication (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 had a lower antigenic profile. It became the industry standard for intravascular thrombolysis and proved to be equally efficacious in the

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## 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.

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 the increasing use of tissue plasminogen activator (TPA) in 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 / 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).

Current literature describes a multitude of dosing and treatment protocols for these patients (1,3-8,10,11). Randomized, prospective trials are still needed to establish the optimal treatment protocol and to further validate this therapy.

## **LITERATURE REVIEW**

Jerjes-Sanchez *et al.* reported a series of 48 patients in an open, multi-center trial with loculated effusions in which streptokinase was administered after failed tube thoracostomy. Of this group, 18 were treated for hemothorax using 250,000 IU of streptokinase instilled into the chest tube. This process was repeated daily until radiographic improvement or a set minimal drainage was achieved. Pleural drainage was significantly improved on days one through four of therapy. Fibrinolysis was successful in 92% of patients as measured by radiologic and clinical improvement as well as improved pulmonary function testing. The most common complication encountered was pleuritic pain; no hemorrhagic complications were reported.

Kimbrell and colleagues prospectively observed 203 patients with traumatic hemothorax of which 25 developed undrained collections. Streptokinase and urokinase were used in protocol fashion to treat these patients while they were monitored with serial radiographs for resolution. 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. In terms of safety, none of the 203 patients had hemorrhagic complications. The only noted adverse effect was transient chest pain after instillation. This occurred in one-third of patients.

Inci *et al.* reported similar results in 24 patients treated for clotted hemothorax. Complete or partial response to fibrinolytic therapy was 91.7%.

Bishop, Pon *et al.* described the first use of intrapleural TPA for complicated parapneumonic effusion in the pediatric population. A 16 month-old child with worsening pneumonia and effusion was treated for five consecutive days with 2 mg doses. Radiography illustrated complete resolution of the complex effusion by hospital day ten. The only side effects reported were mild chest discomfort. This was followed by a retrospective review by Wells of 71 children with complicated effusions treated with either urokinase or TPA. Treatment success was defined by resolution of symptoms and prevention of surgery. An overall success rate of 99% was reported. In comparison to the urokinase cohort, the 45 TPA patients exhibited significant differences in regard to reduced pleural thickness, improved chest X-ray, and thoracostomy drainage. Six of the 45 reported minor complications including chest pain and minimal sanguinous drainage.

The efficacy of TPA in the adult population for intrapleural fibrinolysis was described in a case report by Walker *et al.* in 2003. A 62 year-old woman with worsening clinical status secondary to pneumonia and

loculated pleural effusion was treated with TPA 6mg daily for six days. The patient showed improvement in tube drainage, radiographic appearance, and avoided the need for surgery. Levinson expanded on these findings in a review of 30 consecutive patients with pleural infection and complex effusion. Patients were treated with either urokinase or TPA and compared in terms of surgical avoidance. Two mg doses of TPA were given every eight hours for nine doses. Early intervention was found to be more effective. None of the 30 patients required surgery. One episode of limited hemothysis was noted after redirection of a chest tube.

Skeete *et al.* retrospectively reviewed 41 consecutive patients with complicated pleural effusions, retained hemothoraces, and empyema that received intrapleural TPA. 38 total patients completed therapy and were available for analysis. 19% of these patients were treated for retained or complicated hemothorax, and 14% were specifically treated for traumatic hemothorax. Patients received from one to four doses of TPA. Individual doses averaged 30.2 mg with the most common dose being 50mg. 79% of all patients showed radiographic improvement with TPA administration. 78% 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 nonoperative 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 nonoperative group. The authors concluded that TPA therapy was safe with regard to complications and effective in terms of averting the need for surgical intervention.

Thommi and colleagues examined 120 consecutive patients in a prospective, non-randomized fashion with complicated pleural effusion who failed medical management with tube thoracostomy. 8% of these patients had hemothorax from multiple etiologies. Doses of TPA ranged from 10 mg to 100 mg; the most common doses used were 25 mg and 50 mg. TPA was instilled daily for three days, and then every second or third day based on output. 93% of patients showed either a complete or partial response to TPA therapy by the third dose. All patients in the treatment failure group (7%) had empyema. The most notable adverse effects were chest pain (six patients), bleeding at the chest tube site (two patients), and transfusion requirement (one patient). These nine adverse events were identified out of 335 total doses of TPA. In total, the data further demonstrate the efficacy of TPA therapy for complicated effusions. The optimal therapeutic protocol has yet to be determined.

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