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Effectiveness and Safety of Tissue Plasminogen Activator in the Management of Complicated Parapneumonic Effusions

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ABSTRACT. *Objective.* The management of parapneumonic effusions in children is controversial. The objective of this study was to evaluate the effectiveness and safety of intrapleural tissue plasminogen activator (tPA) in children who require tube thoracostomy for drainage of a complicated parapneumonic effusion.

Methods. An observational cohort study was used to compare children who were treated with intrapleural tPA (either early or late administration) with children who were treated with thoracostomy tube drainage alone.

Results. Over a 6-year period, 12 children received early tPA (within 24 hours of diagnosis), 18 children received late tPA (>24 hours after diagnosis), and 23 children received thoracostomy tube drainage alone for the management of a complicated parapneumonic effusion. Total pleural fluid drainage was highest for the late tPA group (691 mL vs 360 mL in the control group); however, the rate of pleural fluid drainage was highest for the early tPA group (7 mL/h vs 3 mL/h in the control group). The duration of chest tube placement was 84 hours for the early tPA group, 209 hours for the late tPA group, and 130 hours for the control group. There was a significant difference in duration of chest tube placement between the early and late tPA groups. No child who was treated with tPA developed local or systemic bleeding.

Conclusions. Early administration of intrapleural tPA seems to be a safe and potentially effective treatment in children with complicated parapneumonic effusions. Randomized controlled trial evidence is needed to confirm this finding. *Pediatrics* 2004;113:e182–e185. URL: <http://www.pediatrics.org/cgi/content/full/113/3/e182>; *alteplase, intrapleural fibrinolytics, parapneumonic effusion, tissue plasminogen activator.*

ABBREVIATIONS. HSC, Hospital for Sick Children; tPA, tissue plasminogen activator.

Parapneumonic effusions in children who are hospitalized with pneumonia are common and associated with significant morbidity.¹ Whereas some effusions resolve with treatment of

the underlying pneumonia, others require drainage. A complicated parapneumonic effusion is characterized by loculated pleural fluid that may not be drained adequately by tube thoracostomy alone.

There is no consensus on the preferred treatment strategy for children with complicated parapneumonic effusions. Options include prolonged antibiotic therapy, repeated needle aspirations, tube thoracostomy, tube thoracostomy plus intrapleural fibrinolytics, video-assisted thorascopic surgery, and open thoracotomy. A recent practice guideline on parapneumonic effusion in adults recommended fibrinolytic therapy, video-assisted thorascopic surgery, or open thoracotomy for patients with complicated effusions.² The studies on which the guideline was based, however, had significant methodologic limitations. In addition, the significant mortality associated with parapneumonic effusion in adults, compared with the low mortality risk in children, makes it difficult to generalize these findings to children.³ Other outcomes, such as length of hospital stay, duration of chest tube drainage, and school absenteeism, are more relevant treatment outcomes in children with parapneumonic effusions.

Intrapleural fibrinolytic agents have been used for >50 years in the treatment of parapneumonic effusions.⁴ Two small sample randomized controlled trials in adults have shown that pleural fluid drainage is increased with fibrinolytics and that significant activation of systemic fibrinolysis does not occur.^{5–7} Both streptokinase and urokinase have been used as intrapleural fibrinolytics in children. A recent placebo-controlled trial of intrapleural urokinase in children with complicated parapneumonic effusions demonstrated a reduced length of hospital stay in children who were treated with urokinase compared with the placebo group.³ Streptokinase, however, is antigenic and associated with fever and chest wall pain, leading to a reluctance to use this therapy.⁸ Furthermore, urokinase is not available in North America because of concerns related to its derivation from human urine.⁹

It is biologically plausible that early administration of intrapleural fibrinolytics improves clinical outcomes in children with complicated parapneumonic effusions. Animal models of experimentally induced exudates have shown that fibrin deposition occurs soon after bacterial infection, suggesting that early intervention with fibrinolytics could potentially limit

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additional adhesion and loculation of the pleural fluid.¹⁰

At the Hospital for Sick Children (HSC), an academic tertiary care pediatric hospital in Toronto, Ontario, Canada, tissue plasminogen activator (tPA) has been used in the treatment of complicated parapneumonic effusions. The objective of this observational cohort study was to determine the effectiveness and safety of intrapleural tPA (alteplase) in the management of complicated parapneumonic effusions.

METHODS

All children with a complicated parapneumonic effusion (and managed with a thoracostomy tube) at the HSC during the 6-year period (1997–2002) were identified using the computerized health records database and the Division of Image Guided Therapy patient database. An effusion was considered complicated when multiple loculations were noted on ultrasound or computed tomography scan. Children with malignant, traumatic, or postsurgical effusions were excluded from the study. Institutional research ethics board approval was obtained.

A retrospective cohort study design was used. The “exposed” group consisted of children who were treated with intrapleural tPA; the “unexposed,” or control, group consisted of children with a complicated parapneumonic effusion managed with a thoracostomy tube only. Children who were treated with intrapleural tPA were further divided into 2 groups—early and late—on the basis of the timing of intrapleural tPA administration. The early group were children who received their first dose of intrapleural tPA within 24 hours of diagnosis of complicated parapneumonic effusion; the late group were children who received their first dose of intrapleural tPA >24 hours after diagnosis.

Of note, from 2000 onward, all children at HSC with a complicated parapneumonic effusion were treated with intrapleural tPA. Therefore, the early and late tPA groups were drawn from the years 2000–2002, whereas the untreated or control group was selected from the years 1997–1999.

Children in the 2 treated groups (early and late) received 4 mg of tPA in 30 to 50 mL of saline instilled through the chest tube. The tube was then clamped for 1 hour and left to drain at a suction pressure of -20 cm H_2O . This dose of tPA was empirically chosen and is equivalent to twice the standard dose used to unblock central venous catheters. The majority of chest tubes that are inserted for parapneumonic effusions at HSC are pigtail catheters that are placed by interventional radiologists with the aid of ultrasonography and fluoroscopic guidance.

Demographic and clinical data—age, gender, weight, comorbid conditions, previous chest tube, pleural fluid characteristics, microbiologic studies, and chest tube catheter type—were collected on treated and untreated children. Outcomes of interest included the total volume of pleural fluid drainage (pre- and post-tPA administration), the rate of pleural fluid drainage, duration of chest tube placement, and the occurrence of local or systemic bleeding. The decision to remove the chest tube was made at the discretion of the attending physician. All children who met the eligibility criteria during the 6-year period were included in the study.

The Mann-Whitney *U* test and Fisher exact test were used to test for differences between treatment and control groups on baseline characteristics and clinical outcomes of interest (total volume of pleural fluid drainage, rate of drainage, duration of chest tube placement, and frequency of local or systemic bleeding).

RESULTS

During the period 2000–2002, 30 children at HSC were treated with tPA because of a complicated parapneumonic effusion. Of these, 12 children were treated early (tPA given ≤ 24 hours after diagnosis) and 18 children were treated late (tPA given >24 hours after diagnosis). The median time of tPA administration in the early group was 4 hours after diagnosis (range: 0–21 hours), compared with a me-

dian time of administration in the late group of 64 hours after diagnosis (range: 28–195). For both early and late groups, the median number of tPA doses given was 1 (range: 1–3). During the period 1997–2000, a total of 23 control children, ie, children with a complicated parapneumonic effusion managed with a thoracostomy tube only, were identified.

There were no statistically significant differences between the tPA and control groups on age, gender, weight, comorbid conditions, previous chest tube, pleural fluid glucose levels, microbiologic studies, or type of chest tube used for drainage (see Table 1). Of note, control children were older and weighed more than treated children.

Microbiologic studies included blood/pleural fluid cultures, *Mycoplasma pneumoniae* polymerase chain reaction analysis of throat swabs/nasal swabs/pleural fluid specimens, and viral detection by immunofluorescence of nasopharyngeal swabs. In total, 22% of children in the control group (5 of 23) had an organism identified (3 *Streptococcus pneumoniae*, 1 *M pneumoniae*, 1 *Haemophilus influenzae*), compared with 17% in the early tPA group (2 of 12) and 6% in the late tPA group (1 of 18; all *S pneumoniae*). Most children had received intravenous antibiotic therapy for several days before analysis of the pleural fluid (data not shown).

Table 2 describes the clinical outcomes for the treated and control groups. Total pleural fluid drainage was highest for the late tPA group (691 mL), and this volume was significantly higher compared with the control group (360 mL). Pleural fluid drainage per hour was highest for the early tPA group (7 mL/h), and this rate was significantly higher compared with the control group (3 mL/h). The duration of chest tube placement was 84 hours for the early tPA group, 209 hours for the late tPA group, and 130 hours for the control group. There was a significant difference in duration of chest tube placement between the early and late tPA groups. Of the 30 children who were treated with tPA, there were no episodes of local or systemic bleeding. There were no surgical interventions performed on any of the children in the control or treatment groups, and no deaths occurred.

DISCUSSION

This study found that intrapleural tPA promotes pleural fluid drainage in children with complicated parapneumonic effusions. Although the clinical relevance of pleural fluid drainage (rate and volume) as an outcome measure is unclear, the majority of published studies have used this variable as a primary outcome.^{5,6} In addition, no local or systemic bleeding events were associated with the use of tPA in this patient population. Last, early instillation of tPA (within 24 hours) was associated with a shorter duration of chest tube placement, particularly when compared with late administration of tPA. Although the difference in duration of chest tube placement between the early tPA group and the control group was provocative, this difference was not statistically significant. Definitive evidence for the effectiveness

TABLE 1. Baseline Characteristics of the Treated (Early and Late tPA) and Control Groups

Characteristic	Early tPA Group (tPA ≤ 24 Hours; N = 12)	Late tPA Group (tPA > 24 Hours; N = 18)	Control Group (no tPA; N = 23)
Age (mo; median [range])	44 (26–139)	41 (3–182)	60 (3–204)
Gender (<i>n</i> [%] male)	9 (75)	8 (44)	14 (61)
Weight (kg; median [range])	16 (11–64)	15 (5–40)	20 (5–53)
Comorbid conditions, <i>n</i> (%)	1 (8)	3 (17)	3 (13)
Previous chest tube, <i>n</i> (%)	0 (0)	3 (17)	2 (9)
Pleural fluid glucose (mmol/L; median [range])	2.4 (1.0–4.0)	1.5 (1.0–5.0)	1.6 (1.0–5.0)
Organism identified in pleural fluid, <i>n</i> (%)	2 (17)	1 (6)	5 (22)
Flexible pigtail catheter, <i>n</i> (%)	12 (100)	18 (100)	19 (86)
Chest tube size > 10, <i>n</i> (%)	12 (100)	17 (94)	22 (96)

TABLE 2. Clinical Outcomes for Treated (Early and Late tPA) and Control Groups

Outcome	Early tPA Group (tPA ≤ 24 Hours; N = 12)	Late tPA Group (tPA > 24 Hours; N = 18)	Control Group (no tPA; N = 23)
Total pleural fluid drainage (mL; median [range])	638 (164–2700)	691* (285–7944)	360 (0–2041)
Pleural fluid drainage per hour (mL; median [range])	7† (2–29)	4 (1–19)	3 (0–27)
Duration of chest tube (h; median [range])	84‡ (45–187)	209 (87–528)	130 (29–613)

* $P < .05$; late tPA group vs controls.

† $P < .01$; early tPA group vs controls.

‡ $P < .01$; early tPA group vs late tPA group.

of tPA in this condition in children will require controlled trial evidence.

These findings are clinically important as earlier chest tube removal allows for increased mobilization, diminishes the pain associated with a thoracostomy tube, decreases the amount of nursing care required, and may allow for earlier discharge from the hospital. Conversely, late administration of tPA may prolong the hospital stay despite being associated with increased pleural fluid drainage.

The published literature on this topic includes 1 recent case report of tPA in a child with a complicated parapneumonic effusion.¹¹ Therefore, to our knowledge, this study represents the largest series of children treated with intrapleural fibrinolytics for complicated parapneumonic effusions. Another strength of our study was the selection of a relatively homogeneous group of patients. For example, other investigators have included patients with simple free-flowing effusions and patients with complex loculated pleural effusions or empyemas in a single study, despite that these conditions have different natural histories.² We chose to define a complicated parapneumonic effusion as an effusion with multiple loculations and/or pleural glucose <2.2 mmol/L as there is published evidence that these criteria predict the risk of a poor outcome in children and adults with parapneumonic effusions.^{2,12}

Our study has several limitations. First, although the groups seemed to be comparable on the basis of similar imaging findings, pleural fluid analysis, and microbiologic findings, variation in the degree of disease severity between the groups remains a potential confounding factor. In other words, allocation of the children to “early,” “late,” and “thoracostomy tube only” groups was not under the control of the investigators. Before the availability of tPA, however, children with a complex fluid collection might not have had a chest tube inserted because of the difficulty in draining such effusions with thoracos-

tomy drainage alone. Initial use of tPA at HSC focused on children who were believed to be at risk of a poorer outcome (eg, large multiple loculations not responding to initial thoracostomy drainage). Therefore, if anything, this selection bias would lead to an underestimation of the benefits associated with treatment. Historically at HSC, fibrinolytic treatment was initiated in the setting of reduced pleural fluid drainage and significant residual pleural fluid as demonstrated by imaging studies. Subsequently, fibrinolytic therapy was administered to children with a complex pleural effusion soon after thoracostomy tube insertion. The major limitation of our study, however, was the relatively small sample size. In other words, lack of statistical power may have led to the failure to find a difference in duration of chest tube placement between the early tPA group and the control group. All eligible children at our tertiary academic center were included in the study. Therefore, it is likely that several centers are required to generate an adequate sample size for such a study.

Although the sample size was small, the lack of adverse events associated with intrapleural tPA is important, particularly in view of the concerns related to the safety of streptokinase and urokinase. Furthermore, there are biologically plausible reasons that tPA may be preferred as a fibrinolytic agent. It has been shown that in parapneumonic pleural fluid, there is an imbalance of fibrinolytic and procoagulant activity because of a reduction of endogenous tPA and the presence of plasminogen activator inhibitors.¹³ Last, the cost of a 4-mg dose of tPA is \$90 US, which is not high in view of the potential benefits related to a shorter length of stay.

The ideal management of parapneumonic effusions in children remains an area of controversy, with strategies ranging from conservative treatment with antibiotic therapy alone to early surgical intervention. This observational cohort study suggests that intrapleural tPA may be a safe and effective

therapeutic alternative. A multicenter randomized trial (to examine effectiveness, safety, and dosing) is needed to help guide the management of this common clinical problem.

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