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A RETROSPECTIVE STUDY TO EVALUATE THE SAFETY AND EFFICACY OF INTRAPLEURAL ALTEPLASE IN PEDIATRIC EMPYEMA

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ABSTRACT

BACKGROUND. Medical treatment of pediatric empyema consists of appropriate antibiotics, chest tube insertion, and intrapleural fibrinolytic drugs to facilitate pleural drainage. There is a lack of consensus about the drug of choice for fibrinolytic therapy, so this study was designed to evaluate the safety and efficacy of intrapleural alteplase in pediatric empyema.

METHODS. The medical records of all children with empyema treated with intrapleural alteplase at a university hospital between January 2016 and December 2020 were retrospectively reviewed. Efficacy outcomes were assessed by chest tube output before and after the first dose of alteplase, pleural fluid volume before and after therapy, a need for surgical intervention, and length of hospital stay. Safety was assessed by the frequency and severity of side effects.

RESULTS. 40 children aged 2 months to 9 years hospitalized with empyema received intrapleural alteplase. Thirty patients (75%) experienced full recovery after three doses of intrapleural alteplase. The median length of hospital stay was 16 days. Chest tube output increased significantly after the first dose of alteplase. Pleural fluid volume decreased significantly after treatment. The most common side effect was pain (30%). Two patients experienced severe complications: 1 had a pulmonary hemorrhage and the other experienced a bronchopleural fistula. These patients recovered fully spontaneously.

CONCLUSION. According to our results, the administration of intrapleural alteplase was safe and effective in facilitating pleural drainage in pediatric patients with empyema. However, further clinical trials will be needed to determine the optimal dose, frequency, and duration of intrapleural alteplase treatment.

Keywords: *pediatric pneumonia, empyema, pleural effusion, alteplase*

INTRODUCTION

Pneumonia is one of the most important causes of morbidity in children in developed countries and also one of the most common causes of mortality and morbidity in children in developing countries (1). This disease is the leading cause of hospitalization of children, and its costs are higher than any other diagnosis (2,3). Despite antibiotic therapy for pneumonia, 2 to 12 percent of children and 28 percent of hospitalized children with pneumonia develop complications such as empyema and parapneumonic effusion (1,4). Parapneumonic effusion is the accumulation of exudative fluid in the pleural space secondary to pneumonia (5). Over time, the bacteria infiltrate in the pleural fluid, resulting in a complicated parapneumonic effusion or empyema, which is defined as the presence of purulent fluid in the pleural cavity (4, 6). Clinical management of empyema is complex, and its duration is often prolonged (7). The most common signs and symptoms are persistent fever, lethargy, loss of appetite, cough, chest pain, and shortness of breath (4). On the other hand, delayed treatment and inadequate drainage of pleural space can lead to progressive sepsis, shock, increased morbidity, and mortality (8). The goal of treatment is to reduce fever, facilitate pleural drainage, and ensure full lung expansion and return to normal function (9). Treatment of empyema in pediatric patients consists of appropriate antibiotics and drainage of the pleural space. In addition, video-assisted thoracoscopic surgery (VATS) or intrapleural fibrinolytic therapy are the other essential treatments for this disease (10, 11). Clinical trials have shown that VATS and fibrinolytic treatment are equally effective in treating pediatric empyema and have similar outcomes, such as length of hospital stay and treatment failure index (defined as persistent fever $\geqslant$ 38.0°C, 4 d after intervention)(7, 9, 11, 12). However, the only difference between these two types of treatment is the higher cost of VATS (7, 9, 11). According to the recommendation of the American Pediatric Association, intrapleural fibrinolysis is preferred for the initial treatment of children with empyema, followed by VATS if the initial treatment fails (13). Fibrinolytic drugs used to treat empyema include urokinase, streptokinase, and alteplase. The use of streptokinase is limited due to its low efficacy and the development of allergic reactions (14). On the other hand, due to the possible problems of viral infection with urokinase, the use of alteplase as a fibrinolytic drug has been of interest to the researchers (15). Alteplase has beneficial properties as a fibrinolytic agent, including hybrid binding and fibrin affinity, short half-life and high fibrin specificity (the

enzyme is active only in the presence of fibrin) (15). Therefore, its good efficacy and low side effects have made it popular as a fibrinolytic drug in the treatment of empyema (15, 16). No study has been performed to evaluate the efficacy of fibrinolytic therapy for pediatric empyema in Iran, so this study was conducted to evaluate the efficacy and safety of intrapleural alteplase administration in children hospitalized with the diagnosis of empyema in Imam Hossein Children's Hospital.

MATERIALS AND METHODS

In this retrospective cross-sectional study conducted at Imam Hossein Children's Hospital of Isfahan University of Medical Sciences, the medical records of all children hospitalized between January 1, 2016, and December 31, 2020 were reviewed. Patients who had a diagnosis documented in the medical record of empyema secondary to pneumonia treated with intrapleural alteplase were included.

The diagnosis of empyema was based on a pus discharge from the pleural space, positive smear or culture of the pleural fluid, or presence of loculation on pleural ultrasound. Patients with incomplete files or non-bacterial pulmonary effusions (due to malignancy or trauma) were excluded from the study. All patients received intrapleural alteplase via chest tube at a dose of 0.1 mg/kg/dose (maximum 4 mg) diluted in 10-20 ml normal saline every 24 hours for three days. Demographic and clinical data including age, sex, length of hospital stay, chest tube output before and after the first dose of alteplase, outcome (death, need for surgery or complete recovery), pleural fluid culture, and complications were used to evaluate differences between patients who responded to fibrinolytic therapy and those who did not respond.

Descriptive statistical methods such as mean, standard deviation, frequency, and frequency percentage were used to analyze the data. Also, Mann-Whitney tests (due to the abnormality of age variable data) and paired sample t-test were used to measure the relationship between the variables. Statistical analyses were conducted with SPSS v 23.0 (SPSS Inc, Chicago, IL). P-value < 0.05 was used as the significance threshold.

RESULTS

In this study, the records of 40 patients with empyema were evaluated, of which 60% (24) were boys, and 40% (16) were girls. The mean duration of hospital stay in patients was 16.5 days, ranging from 3 days to 44 day's (Table 1).

The study results showed that 75% of children hospitalized with empyema experienced full recovery without any serious side effects after administering intrapleural alteplase with a dose of 0.1 ml/kg every 24 hours for three days.

Ten patients (25%) required surgery for pleural drainage after fibrinolytic therapy: 8 underwent open thoracotomy, and two underwent VATS. None of them had any problems during the surgery.

Sixteen children (40%) showed an adverse event after alteplase administration. The most common complication was pain (n = 12; 30%). Two patients experienced bleeding: 1 had a pulmonary hemorrhage, and 1 had small bleeding at the chest tube insertion site. These patients recovered fully spontaneously. A 1-year-old female patient experienced a bronchopleural fistula that was resolved spontaneously after one week.

DISCUSSION

Due to the high efficacy and low side effects of alteplase in treating pediatric empyema, most guidelines recommend alteplase as an option for the treatment of complicated pediatric empyema.

In our study, 75% of children hospitalized with empyema experienced full recovery without any serious side effects after administering intrapleural alteplase. This result is similar to other studies. In the study of Alemán et al., the success rate was 85% (17), in the Ben-or et al. study, it was 78% (14), and in the study of Thommi et al. 85% (15).

Pediatric dosing regimens of intrapleural alteplase are varied in the literature. These regimens administer 2 to 5 mg/dose alteplase diluted in 20 to 250 mL of normal saline given every 8 to 24 hours. The current study protocol is similar to Islam et al. and Wells et al.'s study (13, 18).

In literature, the most common outcomes used to evaluate alteplase efficacy were the length of hospital stay, chest tube output, pleural fluid volume in ultrasound study, and need for surgical intervention. In the current study, the median length of patients' hospital stay was 16.5 days which is comparable with the results of other studies (17, 19, 20). The chest tube output increased

significantly after administering the first dose of alteplase ($p<0.01$). Other studies have noted significant chest tube output after alteplase administration.

In this study, pain due to chest tube insertion was the most common adverse event. According to our results, administration of intrapleural alteplase was safe and no allergic reactions were reported. Except for one case of pulmonary hemorrhage and one bronchopulmonary fistula spontaneously recovered, no serious complications were reported. A systematic review showed that the use of an intrapleural fibrinolytic drug in children was safe in seven studies, and none of the pediatric studies reported serious side effects (21).

In two other studies, Thommi et al. (8), and Ben-Or S et al. (14), only 2 (6.25%) patients had a pulmonary hemorrhage. But, in the study of Alemán et al., a significant number of patients treated with alteplase experienced pulmonary hemorrhage, and fibrinolytic therapy was stopped.

In our study, ten patients (25%) required surgery for pleural drainage after fibrinolytic therapy: 8 underwent open thoracotomy, and 2 underwent VATS. In the study of Peter et al., after fibrinolysis three patients required surgery, none of whom had any problems during the surgery (7). In another study by Taylor et al., 25% of patients (18/72) required surgery for pleural drainage: 12 underwent VATS, and 6 underwent open thoracotomy (23).

According to our results, pleural fluid volume decreases significantly after three doses of alteplase. In 75% of patients, residual pleural fluid volume was less than 10 ml. According to the study of Thommi et al., residual pleural fluid is as common as postoperative changes, but they resolve within six to eight weeks and should not be considered as alteplase insufficiency (8).
A study by Alemán et al. showed that the volume of pleural fluid emptied by alteplase was significantly higher than the volume of pleural fluid emptied by urokinase (17). Also, a study by Hanson et al. showed that patients treated with intrapleural alteplase significantly reduced pleural fluid volume more than normal saline (18). Baram et al. in their study showed that intrapleural thrombolytics in complicated pediatric thoracic empyema leads to brilliant outcome and should be encouraged, particularly in countries with inadequate resources (24).

CONCLUSION

In this study, we found that intrapleural fibrinolytic therapy was effective and safe in children with empyema. However, further clinical trials will be needed to determine the optimal dose, frequency, and duration of intrapleural alteplase treatment.

Conflict of Interest

None.

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Table 1. Distribution of patient characteristics

Variable	Component	Value	p-value
Gender (person)	boys	24	-
	girls	16	
Pleural cultures (positive)	boys	7	-
	girls	2	
Microorganisms cultured	*Streptococcus pneumoniae*	4	-
	Staphylococcus aureus	3	
	Acinetobacter	1	
	Pseudomonas	1	
Age, mean (SD)	boys	3.60 (2.66)	0.76
	girls	3.47 (2.81)	
pleural fluid volume (ml) mean (SD)	before	303.4 (160.59)	0.0001
	after	53.72 (30.74)	
the chest tube output (ml/hr) mean (SD)	before	12.7 (4.5)	0.01
	after the first dose	28.5 (8.6)	
Fever (C) before alteplase mean(SD)	38.1 (0.7)		
Hospital stay in days, (range)	16.5 (3-44)		

SD – standard deviation