Original Article

Comparison of Clinical Efficacy between Alteplase 0.1 mg/kg and 4 mg for Complicated Parapneumonic Effusion in Children

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Background: Intrapleural alteplase for the treatment of complicated parapneumonic effusion has been shown to reduce the surgical rate, duration of hospitalization, and time to defervescence, and improve pleural fluid drainage. However, there are various regimens of alteplase administration.

Objective: To compare the efficacy and safety between intrapleural alteplase 0.1 mg/kg and 4 mg in the management of complicated parapneumonic effusion.

Materials and Methods: An observational historical cohort study was conducted in patients aged between three months and 15 years diagnosed with complicated parapneumonic effusion or empyema thoracis. The patients were divided into two groups. The first group was patients enrolled between January 2012 and December 2019 and receiving alteplase 4 mg/dose. The second group was patients were enrolled between April 2020 and March 2021 and receiving alteplase 0.1 mg/kg/dose with a maximum of 4 mg. Intrapleural alteplase was given once a day for three consecutive days. Baseline characteristic, clinical outcome, adverse effect, and treatment costs were recorded. The data were statistically analyzed.

Results: Thirty patients were enrolled with 20 in the 4 mg group and 10 in the 0.1 mg/kg group. There were no significant differences between the two groups with regards to treatment success rate, time to defervescence, and total pleural fluid drainage. One patient in the 0.1 mg/kg group required surgical treatment. Patients in the 0.1 mg/kg group had significantly shorter duration of hospitalization at 10 versus 13 days (p=0.03) and lower costs of treatment compared with the 4 mg group at 15,388.50 versus 22,214.75 Baht (p=0.03). Intrapleural bleeding was found in one patient in the 4 mg/dose group.

Conclusion: Intrapleural alteplase in the dose of 0.1 mg/kg and that of 4 mg have good clinical efficacy for treatment of complicated parapneumonic effusion. The 0.1 mg/kg group is safe and associated with lower cost of treatment, and shorter hospital stays.

Keywords: Intrapleural alteplase; Tissue plasminogen activator; Complicated parapneumonic effusion

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Community-acquired pneumonia (CAP) remains a major cause of morbidity and mortality worldwide among children younger than five years old[1]. Parapneumonic effusion is the most common manifestation of complicated CAP and is characterized by severe illness, prolonged hospitalization, and a protracted disease course[2]. Pleural effusion can be divided into three stages, exudative with simple parapneumonic effusion, fibrinopurulent with complicated parapneumonic effusion, and organization[3].

The British Thoracic Society recommends intrapleural fibrinolytics for any complicated parapneumonic effusion or thick fluid with loculations, or empyema, and shorten hospital stay[3]. Meanwhile, the guideline of Infectious Diseases Society of America suggests intrapleural fibrinolytics as optional treatment. This guideline considers both chest thoracostomy tube drainage with the addition of fibrinolytic agents and video-assisted thoracic surgery (VATS), which have been demonstrated to be effective methods of treatment. Both of these methods are associated with decreased morbidity compared with chest tube drainage alone[4]. Previous studies described the management of complicated

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parapneumonic effusion using streptokinase, urokinase, or alteplase with different protocols and it was evident that the use of fibrinolytics was safe. The success rate was 80% to 90%[5].

In Thailand, alteplase has been widely used for the treatment of complicated parapneumonic effusion in children as contributed by its safety and efficacy. However, the regimens of alteplase administration were so diverse and the literature still lacked the data on the dose of alteplase usage in pediatric population[6]. The two regimens that are commonly used in the present study country, are fixed dosing regimen of alteplase with 4 mg/dose and based on weight dose of alteplase at 0.1 mL/kg/dose. Accordingly, the authors compared the efficacy and safety between intrapleural alteplase 0.1 mg/kg/dose and 4 mg in the management of complicated parapneumonic effusion.

Materials and Methods

The present study was an observational historical cohort study, conducted at Queen Sirikit National Institute of Child Health. Patients aged between three months and 15 years with parapneumonic pleural effusion or empyema thoracis treated with thoracostomy tube placement and intrapleural instillation of alteplase were included in the present study. The procedures were performed with alteplase 4 mg between January 1, 2012 and December 31, 2019, and with alteplase 0.1 mg/kg/dose with a minimum of 1 mg and maximum 4 mg, between April 1, 2020 and March 31, 2021. The present study was approved by the Queen Sirikit National Institute of Child Health Ethics Board (REC 084/2563).

Procedure

After ensuring that the drain was correctly positioned, diluted alteplase in 0.9% saline was instilled into the chest drain. The drain was clamped for 1.5 hours, then unclamped and drainage was allowed. During clamping, patients were lying on the right side, on the left side, and on their back alternately, for 30 minutes for each position. Alteplase was instilled once daily for three days, thus for three doses was provided . All patients were monitored for adverse events and the events were recorded.

The medical records were assessed to ascertain baseline characteristics, medical comorbidities, laboratory results, imaging studies, thoracostomy tube output, treatment details, clinical outcome, adverse effect, and treatment costs. The authors defined primary treatment success as resolution of signs and symptoms at the time of discharge, without surgical intervention.

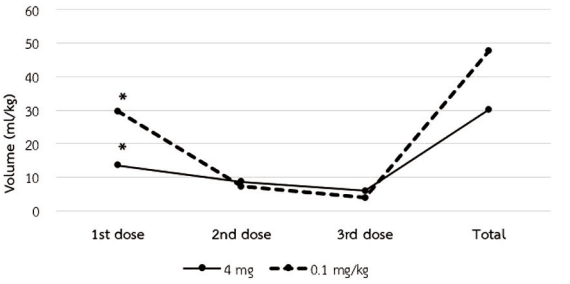

Figure 1. Amount of pleural fluid drainage.

Statistical analysis

Median (interquartile range) was employed for continuous variables and percentage was used for categorical variables. Chi square tests were utilized for comparison between groups of categorical variables. Mann-Whitney U test were used for non-normally distributed continuous data. Group differences associated with a p-value of less than or equal 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Thirty patients with complicated parapneumonic effusion who received intrapleural alteplase were recruited to participate in the present research. Baseline characteristics shown in Table 1, were classified by dosage of alteplase as 4 mg/dose or 0.1 mg/kg/dose. Patients in the alteplase 0.1 mg/kg/dose group had a significantly higher number of PICU admission and those receiving O_2 supplement. Gender, age, underlying diseases, signs, symptoms, and other laboratory measurements at presentation were not different between the two groups (Table 1). None of the patients in the alteplase 0.1 mg/kg/dose group received a maximum dose of 4 mg.

In pleural fluid profiles, patients in the alteplase 0.1 mg/kg/dose group had a lower pH and had a higher number of white blood cells. There were no significant differences in glucose, LDH, protein, and percent of neutrophil (Table 2).

Patients receiving alteplase 0.1 mg/kg/dose had significantly higher amount of pleural fluid drainage after the first dose at 29.7 versus 13.5 mL/kg (p=0.04). In contrast, the figures after the second and third dose and total amount were not significantly different between groups (Figure 1).

Table 1. Baseline characteristics

Demographic Data	Alteplase		p-value
	4 mg/dose (n=20)	0.1 mg/kg/dose (n=10)	
Male; n (%)	13 (56.5)	7 (70)	0.2
Age (month); median (IQR)	53.5 (29.5 to 90)	69 (33 to 127)	0.32
Weight (kg); median (IQR)	15.1 (11.5 to 20.5)	19.5 (12 to 30)	0.28
Underlying disease; n (%)	4 (20)	3 (30)	0.54
Interval between disease onset and 1st dose of alteplase (days); median (IQR)	9 (7 to 15.5)	10.5 (6 to 12)	0.77
Previous IV antibiotics; n (%)	14 (70)	9 (90)	0.06
Initial PICU admission; n (%)	1 (5)	4 (40)	0.01*
Initial O_2 supplement; n (%)	2 (6)	6 (60)	0.04*
Fever; n (%)	20 (100)	10 (100)	1
Dyspnea; n (%)	15 (75)	10 (100)	0.89
Cough; n (%)	17 (85)	8 (80)	0.73
Chest pain/abdominal pain; n (%)	9 (45)	1 (10)	0.06
Temperature (°C); median (IQR)	39.1 (38.6 to 39.7)	39.3 (38.9 to 39.8)	0.62
Systolic BP (mmHg); median (IQR)	106 (98.5 to 115.5)	103.5 (101 to 113)	0.74
Pulse (beats/minute); median (IQR)	135 (130 to 140)	139 (130 to 140)	0.96
Initial SpO_2 (%); median (IQR)	98.5 (97.5 to 100)	98 (97 to 100)	0.67
White blood cell ($\times 10^3/\mu L$); median (IQR)	18.9 (14.7 to 26.5)	18.5 (11.6 to 23.4)	0.42
% Neutrophils; median (IQR)	74.5 (61.5 to 81.5)	74 (61 to 85)	0.74
Moderate amount of effusion by CXR (opacified more than half of thorax); n (%)	20 (100)	10 (100)	0.61

IQR=interquartile range; IV=intravenous; PICU=pediatric intensive care unit; BP=blood pressure; CXR=chest X-ray

Table 2. Pleural fluid analysis

Pleural fluid profiles	Alteplase; median (IQR)		p-value
	4 mg/dose (n=20)	0.1 mg/kg/dose (n=10)	
pH	7.26 (7.2 to 7.34)	7 (6.5 to 7.2)	0.04*
Glucose (mg/dL)	10 (1 to 75.5)	10 (1 to 70)	0.94
LDH (IU/L)	3,587 (2,509 to 7,283.5)	5,359 (684 to 1,2739)	0.81
Protein (g/dL)	4.19 (3.8 to 4.6)	4.8 (3.8 to 4.8)	0.68
WBC ($\times 10^3/\mu l$)	1.61 (0.25 to 2.4)	16.3 (12.8 to 39.6)	<0.01*
% Neutrophil	82 (78 to 92)	77 (66 to 90)	0.39

IQR=interquartile range; LDH=lactate dehydrogenase; WBC=white blood cell

Table 3. Outcomes

Variables	Alteplase		p-value
	4 mg/dose (n=20)	0.1 mg/kg/dose (n=10)	
Surgery; n (%)	0 (0)	1 (10)	0.16
Time to defervescence after alteplase (days); median (IQR)	4 (3 to 8)	5 (5 to 8)	0.96
Duration of IV antibiotic (days); median (IQR)	21.5 (17.5 to 23.5)	21 (14 to 33)	0.91
Duration of hospitalization (from admission to defervescence 3 days) (days); median (IQR)	13 (11 to 16.5)	10 (8 to 11)	0.03*

IQR=interquartile range

The alteplase 0.1 mg/kg/dose group had a shorter duration of hospitalization. There was no significant difference in time to defervescence, duration of intravenous (IV) antibiotic and surgical intervention (Table 3). Only one patient receiving alteplase 0.1 mg/kg/dose underwent right upper lobe lobectomy with decortication due to the patient developed lung abscess at right upper lobe.

The alteplase 0.1 mg/kg/dose group had lower alteplase cost at 4,500 versus 9,000 Baht (p=0.01), and lower total cost at 15,388.50 versus 22,214.75 Baht (p=0.03) compared with the 4 mg/dose group.

In the present study, one patient who received alteplase 4 mg/dose developed intrapleural bleeding after alteplase administration. Packed red cell transfusion was given, the patient fully recovered.

Discussion

The present study was an observational historical cohort research aimed to compare the efficacy and safety between intrapleural alteplase 0.1 mg/kg/dose and 4 mg in the management of complicated parapneumonic effusion. It was found that clinical efficacy of intrapleural alteplase in the dose of 0.1 mg/kg/dose and 4 mg/dose are equivalent for the treatment of complicated parapneumonic effusion. Moreover, the treatment with alteplase 0.1 mg/kg is safe and associated with lower cost of treatment.

Recombinant tissue plasminogen activator (rtPA), alteplase, has been used for the management of complicated parapneumonic effusion and empyema thoracis. Fibrinous loculations in complicated parapneumonic effusions impede free drainage and prevent lung re-expansion. The use of alteplase has shown its effectiveness in breaking up loculations. Alteplase binds to fibrin in a thrombus then converts the entrapped plasminogen to plasmin, and finally initiates local fibrinolysis[7].

The retrospective study compared the effectiveness between alteplase 0.1 mg/kg/dose and urokinase. They demonstrated that alteplase had 98% of treatment success with no report major complications and produced greater pleural fluid output than urokinase[8]. Additionally, it has been shown to be an effective and safe therapy, leading to a reduction in the requirement for surgical intervention[9], reducing morbidity and hospital stay[10-12].

To the best of the authors knowledge, this is the first report to compare alteplase dosing protocol of 0.1 mg/kg/dose and 4 mg/dose. Most studies used a fixed dosing regimen of alteplase, ranging from 2 to 5 mg/dose given every 8 to 24 hours. Based on the weight regimens reported in these studies, patients were instilled 0.1 to 0.5 mg/kg/dose of alteplase[13-19]. Only three research used a regimen of 0.1 mg/kg/dose with a maximum of 3 mg, or 6 mg/dose, given every 8 to 24 hours[8,20,22]. In the present study, the authors used the protocol for a 90-minute alteplase dwelling time with positional change. This is similar to the alteplase dwell time most commonly reported, which is one hour, but most studies do not describe how the patient is positioned during the instilling time[8,13,14,17,18]. The authors also give three doses of alteplase, which has been validated by a randomized, prospective trial[13].

The efficacy findings of the present study are consistent with previous studies. The Pediatric Infectious Diseases Society and the Infectious Diseases Society of America demonstrated that success rate of intrapleural fibrinolytic agents was 85%[4]. The success rates of alteplase in the literature range from 83% to 100% depending on dose and dwell time[8,13,14,16-18,23]. These published success rates are similar to the 90% for 0.1 mg/kg/dose and 100% for 4 mg/dose alteplase success rate in the present study. The present research found that median length of hospital stay was not significant different between the two groups. The median lengths of hospital stay of the 0.1 mg/kg/dose and 4 mg/dose group were 10 and 13 days, respectively. However, in the 0.1 mg/kg/dose group, the length of hospital stay was longer than that in other studies. This may be due to in the present study 30% of the patients had an underlying disease, while the previous studies were conducted in patients with no underlying diseases[8,12]. As for the amount of pleural fluid drainage, the total output in the 0.1 mg/kg/dose group was not significantly different from that of the 4 mg/kg group at 662.5 versus 501.5 mL. The pleural fluid output in other studies range from 216 to 691 mL/day[17,19,22]. The variation of dwell time, protocol technique, and total alteplase doses might affect the pleural fluid output.

With regards to the treatment costs, the total cost of alteplase 0.1 mg/kg/dose group was lower than the 4 mg/dose group at 15,388.50 versus 22,214.75 Baht (p=0.03). A case of St. Peter et al's work, in which patients who received 4 mg/kg of alteplase had lower hospital charges in comparison with patients who had a VAT procedure at 7,600 versus 11,700 USD (p=0.02)[13]. Nevertheless, studies have not been conducted to compare between the 0.1 mg/kg/dose alteplase group and the surgical group.

The adverse event reported in the present study was one case that developed intrapleural bleeding after receiving 4 mg/kg of alteplase. The patient received a blood transfusion and recovered fully. No life-threatening adverse events or hypersensitivity reactions were found in the present study. This was similar to the case report of a pediatric patient who developed an intrapleural hemorrhage after 0.1 mg/kg/dose of alteplase administration[21]. Feola et al demonstrated that Hb concentration decreased 2.5

g/dL after receiving alteplase 0.1 mg/kg/dose in two cases, but the patients did not require blood transfusion[10].

Despite the foregoing discussion, it is worth mentioning the limitations to the present study. First, the study design was developed from a single institution with a small sample size. Second, the two groups were not prospectively randomized, and they received treatment in different time periods. However, the present study utilized a standardized treatment protocol and reinforced the validity of the treatment method. Finally, the third is the subjective nature of the characterization and documentation of adverse events. Adverse events were documented primarily in physicians' and nursing narrative notes.

Conclusion

Intrapleural alteplase in the dose of 0.1 mg/kg and that of 4 mg have good clinical efficacy for treatment complicated parapneumonic effusion. Particularly, the treatment with alteplase 0.1 mg/kg/dose is safe and reduce the cost of treatment. It also has a same level of effectiveness in treating PPE and empyema.

What is already known on this topic?

Intrapleural alteplase for the treatment of complicated parapneumonic effusion in children is effective and safe.

What this study adds?

The two regimens of alteplase at 0.1 mg/kg/dose and 4 mg/kg provide good clinical efficacy and safety. Alteplase 0.1 mg/kg/dose reduces the cost of treatment.

Conflicts of interest

The authors declare no conflict of interest.

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