Once-daily intrapleural urokinase treatment of complicated parapneumonic effusion in pediatric patients

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SUMMARY: Bianchini MA, Ceccarelli PL, Repetto P, Durante V, Biondini D, Bergamini B, Cacciari A. Once-daily intrapleural urokinase treatment of complicated parapneumonic effusion in pediatric patients. Turk J Pediatr 2010; 52: 274-277.

In this paper, we describe our experience in the treatment of childhood empyema using urokinase. Patients' ages ranged from 2 to 12 years. Urokinase (dosage: 3,100 IU/kg/day) was diluted in normal saline to produce 1000 IU/ml (maximum dosage 100,000 IU in 100 ml of normal saline). After 2 hours, the clamped catheters were released and connected to water-seal suction at a negative pressure of 10 cm H_2O. Pleural irrigations were continued once a day until thoracostomy tube output decreased to less than 10 ml/day (urokinase treatment mean duration: 11.5 days). The complete resolution of the chest effusion was assessed on chest ultrasound scan and radiographs. None of the patients experienced any side effects due to urokinase. It would now seem reasonable to advocate small chest tube thoracostomy and intrapleural urokinase as first-line treatment of pleural empyema in children, with surgery indicated as a secondary intervention.

Key words: pleural effusion, empyema, children, urokinase, fibrinolytic treatment.

Pleural effusion is a common complication of pediatric bacterial pneumonia, occurring with an incidence of 3.3 per 100,000 children[1]. When such effusions become loculated or progress to empyema formation, tube thoracostomy may become a necessary adjunct to thoracentesis and antibiotic therapy. Although video-assisted thoracoscopy or thoracotomy and decortication are effective surgical options in the management of complicated pleural effusion, in recent years, some pediatric reports have described the successful use of intrapleural instillation of fibrinolytic agents as treatment for persistent empyemas[7,12].

Tillet and Sherry[11] reported the use of a mixture of streptokinase and streptodornase for intrapleural fibrinolysis in 1949. Urokinase was introduced in 1987 and became the most frequently used agent for fibrinolysis because of concerns about the antigenicity of streptokinase.

This report describes our results with intrapleural instillation of urokinase in the management of multiloculated pleural effusion in children.

Material and Methods

A series of five children (3 girls, 2 boys) is reported. In all patients, anteroposterior and decubitus standard chest radiographs showed pleural effusion. The patients' ages ranged from 2 to 12 years (mean: 7) (Table I).

Indications for chest tube drainage included: 1) evidence of massive pleural effusion detected on chest ultrasonography or computed tomography (CT) chest scan (Figs. 1, 2), and 2) clinical deterioration in the patient's condition, as evidenced either by severe respiratory distress or systemic infection not responding to systemic treatment (Table II).

Drainage was performed under sterile conditions, light general anesthesia and local anesthesia. The chest tube was positioned through the "safe triangle"[4], bordered by the anterior border of the latissimus dorsi, the lateral border of the pectoralis major muscle, a line superior to the horizontal level of the nipple, and an apex below the axilla. Two chest tubes (Portex ® Standard Trocar

Table I. Summary of Patient Data, Pleural Fluid Analysis, Management and Results

Patient No.	Age (yr)	Sex	Etiology of pleural effusion	Pleural fluid analysis Glucose (mg\dl)	Protein (g\L)	Time from admission to UK treatment (d)	No. of instil-lations	Results
1	9	F	Parapneumonic	24	51	9	12	Resolution
2	12	F	Parapneumonic	21	50	6	11	Resolution
3	3	M	Parapneumonic	<20	50	8	11	Resolution
4	10	F	parapneumonic	<20	54	9	12	Resolution
5	2	M	Parapneumonic	<10	40	7	10	Resolution

Catheter Soft) were inserted in each patient. We believe that two chest tu bes enlarge both the drainage and the instillation areas. After drain placement, fluid was aspirated until no more could be obtained. Specimens of the pleural fluid were sent to the laboratory for chemical and bacteriologic analysis.

Indication for intrapleural urokinase instillation was the presence of large loculations of fluid on chest ultrasound scan. For each patient, coagulation studies were recorded, including prothrombin time, partial thromboplastin time, international normalized ratio, and fibrinogen split products. The criterion for initiating fibrinolysis was decreasing thoracostomy tube output during an 8-24-hour period. Urokinase (Urochinasi Crinos, Sirton Pharmaceuticals, Italy) dose was 3,100 IU/kg/day; it was diluted in normal saline to produce 1000 IU/ml[12]. Intrapleural irrigation was performed once daily; the tubes were clamped for 2 hours and then left open with underwater suction of -10 cm H_2O. This treatment was repeated daily until the tube thoracostomy output decreased to less than 10 ml/day.

The effectiveness of treatment was assessed clinically, biochemically (white cell count and C-reactive protein [CRP]), and radiologically, with standard chest X-ray and ultrasound every 3 and 2 days, respectively.

Results

Five consecutive patients, who had persistence of pleural fluid with associated symptoms and inadequate drainage with tube thoracostomy alone, received urokinase as adjunctive treatment. The etiology of pleural effusion was acute pulmonary infection. The pleural fluid chemical analysis determined that all effusions were exudates. In four cases, bacteriological evaluations including Gram's stain and cultures were negative. Case 2 was found positive to *Staphylococcus aureus*. All patients received antibiotics before thoracentesis was performed, mainly because they were admitted primarily in the pediatric department. *Streptococcus pneumoniae* urinary antigen test result was positive in Cases 1 and 4; Cases 2, 3 and 5 were negative.

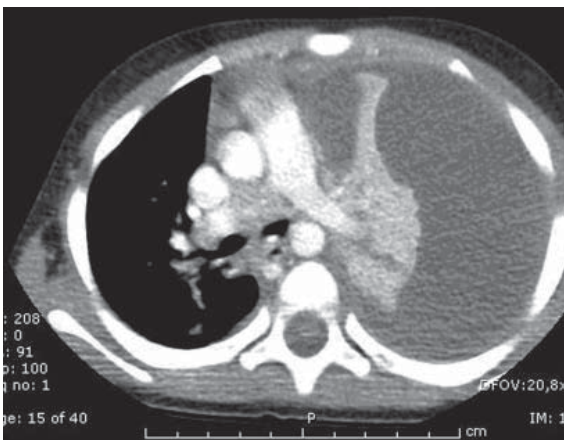

Fig. 1. CT chest scan showing massive left pleural effusion.

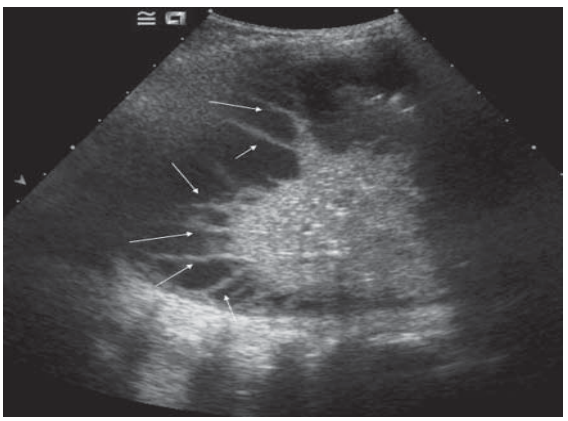

Fig. 2. Transverse ultrasound image of the lower portion of the chest shows multiple thin linear septations within the pleural fluid.

Table II. Clinical Severity Assessment

Infants	Temperature > 38.5°C
	Respiratory rate >70 breaths/min
	SpaO2 < 94%
Older children	Temperature > 38.5°C
	Respiratory rate > 50 breaths/min
	Severe difficult breathing
	SpaO2 < 94%

Urokinase instillation started when chest tube drainage had ceased or almost ceased for at least 24 hours (mean initiating time: 8 days from chest tube placement). Pleural irrigations were continued once a day until thoracostomy tube output decreased to less than 10 ml/day (urokinase treatment mean duration: 11.5 days). In all patients, improvement was gradual. The complete resolution of the chest effusion was assessed on chest ultrasound scan and radiographs. Data results are summarized in Table I.

None of the patients experienced any side effects due to urokinase.

Discussion

Pleural effusions are a common complication of pediatric bacterial pneumonias, occurring with a reported frequency ranging from 21 to 91%[5]. If inadequately treated, empyema may progress through three stages: stage I, the exudative stage; stage II, the fibrinopurulent stage; and stage III, the organizing stage. The latter occurs when fibroblasts grow into the exudate and change the membrane to an inelastic "peel" that completely prevents lung expansion. This stage may require surgical intervention. The traditional approach to managing childhood empyema has been to advocate an aggressive surgical approach with early thoracotomy or preferably "mini" thoracotomy and decortication. Recently, several reports have described the revival of intrapleural fibrinolytic therapy using agents such as streptokinase and urokinase, even in pediatric patients[6,10,12]. Intrapleural fibrinolytic therapy was first introduced in 1949 by Tillet and Sherry[11], who instilled streptokinase to the pleural space to lyse fibrinous pleural material. Urokinase was first introduced in 1989 by Moulton et al.[8], who treated loculated pleural effusion in adults. The first intrapleural use of urokinase in children was reported in 1993 by Handman et al.[2]

Until 2006, our traditional management of pleural empyemas was thoracoscopic "debridement" or thoracotomy and decortication (case not reported in this series). We initiated this treatment regimen after successfully managing a little girl who had failed traditional surgical management after undergoing a thoracotomy and decortication (case not reported in this series). Since then, we decided to introduce the intrapleural fibrinolysis instillation as the first-line intervention in children with complicated parapneumonic effusion.

The mean length of treatment in our study was 11.5 days. This is longer than that reported in some other pediatric series[1,7,12]. The reason could be explained by the fact that we chose arbitrarily to discontinue the treatment when chest tube output was less than 10 ml/day. Nevertheless, none of our patients experienced any side effects due to urokinase.

The optimal dosage of urokinase remains to be defined. We administered 3,100 IU/kg diluted in normal saline to produce a concentration of 1,000 IU/ml[12], once a day. The maximum dosage did not exceed 100,000 IU in 100 ml of normal saline.

As has been observed elsewhere, the identification of causative pathogens in our study was very low, probably because of the broad spectrum antibiotic treatment administered before pleural aspiration[9].

At the time of hospital discharge, residual pleural thickening was observed in our patients, but complete normalization was observed during the follow-up.

In conclusion, it would now seem reasonable to advocate small chest tube thoracostomy and intrapleural urokinase as first-line treatment of empyema thoracis in children, with surgery indicated as a secondary intervention.

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