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Fibrinolytic treatment of complicated pediatric thoracic empyemas with intrapleural streptokinase

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Abstract

Objective: Proper antibiotic treatment and adequate pleural drainage is essential in successful management of pleural effusions. In complicated effusions the increased production of fibrin results in formation of loculations and septations within the thoracic cavity, leading ineffective chest tube drainage. Intrapleural fibrinolytic agents are employed to avoid thoracotomy in such complicated pleural effusions. Our study reviews the results of streptokinase treatment in children with pleural effusion. **Methods**: Thirty-two patients with parapneumonic pleural effusions were admitted to our hospital. The patients beyond the exudative stage were divided into two groups according to the initial radiological findings and biochemical parameters of pleural fluid. Intrapleural streptokinase treatment was started in an average of 2 days following initial chest tube placement in both Group I (14 patients) in fibrino-purulent phase with pleural effusion and fluid volume estimated to be larger than one-third of the involved lung and Group II (18 patients) with additional findings in radiological examination regarding the presence of air-fluid levels, multiple loculations, necrotic debris and pleural thickening. The effectiveness of therapy was assessed by monitoring the volume of the fluid, the level of LDH, glucose, pH and by radiological imaging, pre- and post-instillation. **Results**: There was statistically significant difference between two groups according to date of admission (6.8 vs 10.4 days), mean of total pleural fluid drainage before (106.9 vs 309.7 ml) and after (258.9 vs 511.2 ml) SK treatment, mean of total number of instillations (2.1 vs 3.6) required and total length of hospital stay (16.6 vs 22.4 days). There was a significant difference regarding pleural chemical analysis. Finally, surgical intervention was necessary in six intractable cases, all of which initially presented a significant small amount of pleural drainage in volume when compared to rest of the patients. The overall success rate of our treatment was calculated as 96% for G-I and 72.2% for G-II cases. **Conclusions**: Intrapleural streptokinase is an effective and safe adjunct in facilitating drainage in early and late stage II empyemas. A tendency of decreased rate of drainage besides persisting fever and respiratory symptoms, despite fibrinolytic treatment may be a clue for early surgical intervention.
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Keywords: Children; Fibrinolysis; Parapneumonic effusion; Streptokinase; Thoracoscopy

1. Introduction

Parapneumonic pleural effusions may occur in 36–57% of patients with pneumonia and about 15–20% of this accumulated fluid becomes infected resulting in empyema [1,2]. Although some classifications have been used for the management and treatment of empyema, we have preferred to use the classification of the American Thoracic Society which has expanded the definition of empyema into three stages [3]. In this classification, initial reaction to the infectious agent is fibrin deposition on both pleural surfaces known as the early exudative phase (stage I). This is followed by an intermediate fibrino-purulent phase characterized by fibrinous septations forming loculations within the pleural space (stage II). Prolonged enhanced fibroblastic activity prevents lung re-expansion by covering the pleural space as a spider web and this is called the late organizing phase (stage III) [1,4,5].

In 2000, a panel was held by the American College of Chest Physicians to develop a guideline on the medical and surgical treatment of parapneumonic effusions using evidence-based methods. Pleural space anatomy, pleural fluid bacteriology, and pleural fluid chemistry, were used in this annotated table to categorize patients into four separate risk levels for poor outcome: categories 1 (very low risk), 2 (low risk), 3 (moderate risk), and 4 (high risk). The panel's consensus opinion supported drainage for patients with

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moderate (category 3) or high (category 4) risk for a poor outcome, but not for patients with very low (category 1) or low (category 2) risk for a poor outcome [6].

Continuous closed chest tube drainage and parenteral antibiotic therapy have been the standard of treatment of empyema in children since the early 1970s [1–5]. A delayed or improper treatment, however, will still result in deposition of fibrinous material, formation of loculations and entrapment of the lung, albeit the mentioned treatment. The contemporary methods for treating complicated parapneumonic pleural effusion and empyema remain debatable. The dispute over the optimal therapeutic approach has accentuated since the introduction of early thoracotomy and decortication, video-assisted thoracic surgery (VATS) and the use of instillation of fibrinolytic agents as an adjunctive or alone [6,7]. Early minimally invasive approach has recently been advocated as the optimal treatment, with fairly good results [7]. The success rate of this approach, however, does include a group of patients for whom we could avoid surgery and enjoy the benefits of fibrinolytic agents alone.

Intrapleural instillation of fibrinolytic agents through the chest tube has been advocated in complicated parapneumonic effusions since 1949 [1,2,8,9]. During the last two decades several reports are published showing effective use of streptokinase (SK) or urokinase with favorable results in adult cases, but reports on pediatric patients are still limited [10,11]. Our study reviews the results of SK treatment in children with complicated pleural effusion disease in the groups of the early and late stage II in our department.

2. Material and methods

Starting from December 2000, thirty-eight consecutive cases (20M, 18F) with mean age of 3.4 years (5 months–10 years) were admitted to our hospital with parapneumonic effusion. The number of admissions increased significantly following the 1999 Marmara earthquake, mostly due to disturbed living and environmental conditions. All the studied children were previously healthy and free of any other underlying chronic disease. The period between onset of symptoms and date of admission ranged from 5 to 20 days. Fever, cough, tachypnea and chest pain were the presenting symptoms, and physical examination revealed dullness on chest percussion, tactile and vocal fremitus, decreased breath sounds, rales and friction rub. All patients had standard postero-anterior and lateral chest radiograms, thoracic USG, and CT pre- and post-treatment. Pleural fluid samples were investigated for Gram stain, cultures and biochemical investigation.

The staging of severity of empyema was divided into three stages based on a combination of radiological studies and pleural fluid chemical analysis according to the American Thoracic Society [10]. Six patients who were determined as exudative phase (glucose $>$ 40 mg, LDH $<$ 500 IU and pH $>$ 7) with serous pleural effusion were not included in this study. Thirty two patients who were determined as fibrino-purulent phase (glucose $<$ 40 mg, LDH $>$ 500 IU and pH $<$ 7) were divided into two study groups; 14 patients (Group I, early stage II) were determined to be in fibrino-purulent phase, with pleural effusion showing septations and fluid volume estimated to be larger than one-third of the involved lung on radiological examination and 18 patients (Group II, late stage II) which showed similar pleural fluid characteristics with additional multiple loculations, necrotic debris and pleural thickening as depicted by CT scan, and USG [13].

These 32 patients with complicated pleural effusion were treated with tube thoracostomy and intrathoracic SK instillation. All patients were initially administered cefotaxim and ampicilline/sulbactam therapy. Then, medical treatment was adjusted subsequently according to antibiogram results.

A 14 or 18 F chest tube was inserted under local anesthesia (1% lidocain). The point of insertion was predetermined by USG in order to avoid unexpected lung injury due to pleural adhesions. If the patient was in Group II with multiple loculations, the chest tube was inserted in the larger loculations with guide ness of USG. All tubes were maintained on 10 cmH_2O suction sealed under water and the amount of fluid drained was recorded every 8 h.

Streptokinase 25,000 IU/kg in 50–100 ml in saline was instilled intrapleurally via the chest tube and clamped for 4 h, a total dose of 250,000 IU per instillation was never exceeded. We repeated the SK dosages at 12–18 h intervals with the findings of persisting multi-loculated septations in repeated USG and if the drainage of fluid was more than 100 ml in a day. The treatment was terminated following resolution of fever and respiratory symptoms, and drainage of fluid less than 50 ml in 24 h with significant improvement in USG screening. Radiographic improvement was defined as full lung expansion in both groups. If we did not recognize any improvement after repeated SK dosages especially regarding the persistence of large loculated cysts, we inserted second chest tube. However, VATS was the treatment modality of the choice in the cases which did not respond to SK and had multiple, small loculations persisting in our series.

2.1. Statistical analysis

The volume of the drained fluid, the level of LDH, glucose, and pH pre- and post-instillation were analyzed according to Wilcoxon-Signed Ranks test. The resulting data according to duration of symptoms, tube drainage and length of hospital stay amongst the two groups were additionally assessed according to Kruskal–Wallis 1-way analysis of variance. The resulting data according to duration of symptoms, tube drainage and length of hospital stay amongst the two groups were additionally assessed according to Kruskal–Wallis 1-way analysis of variance. The difference in the between pleural parameters amongst

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Table 1
Comparison of two groups by clinical characteristic, duration of symptoms, chest tube and hospitalization

	G-I ($n = 14$)	G-II ($n = 18$)	P
Localization R/L	6/8	10/8	
Bronchopleural fistula	1	4	
Intractable case	1	5	
Duration of symptoms (days)	6.8 ± 3.92	10.4 ± 2.90	0.009*
Duration of chest tube (days)	6.1 ± 3.92	12.2 ± 5.88	0.001*
Hospital stay (days)	16.6 ± 1.42	22.4 ± 2.36	0.009*

*The difference between G-I and G-II were significant, $P < 0.05$ (Kruskal–Wallis 1-way).

two groups were initially analyzed using Kolmogorow Smirnow test, which showed an uneven distribution.

3. Results

The side of empyema, the occurrence of bronchopleural fistula, duration of the symptoms, chest tube and hospital stay were listed in Table 1 for 32 patients divided into 2 study groups treated with SK instillation during the study period. Three patients in Group II were referred from another clinic with tube thoracostomy. The estimated mean time from onset of tube thoracostomy to SK instillation was 24 h. Mean number of instillations was 2.1 (1–3) in Group I and 3.6 (2–5) in Group II patients. A second tube was additionally necessary in three patients from Group II due to another large loculated cyst.

The duration of chest tube and the total length of hospital stay in days were significantly longer for Group II when compared to Group I (Table 1). This was mostly because five cases developed a bronchopleural fistula during treatment. All the cases appeared to have air-fluid levels in CT scans prior to tube drainage, while none of them showed air leakage following tube thoracostomy. These initially occult fistulas were observed after an average of two instillations. All the fistulas healed spontaneously.

The mean volume of total fluid drainage was statistically higher for Group II before and after SK treatment. The rate of increasing drainage was similar in both the groups

Table 2
Comparison of two Groups by volume of pleural fluid drained in before and after SK

Total pleural fluid volume (ml)	G-I ($n = 14$)	G-II ($n = 18$)	P
Before SK	106.9 ± 98.7	309.7 ± 428.4	0.03
After SK during first 24 h	172.8 ± 137.3	179.16 ± 117.6	NS
After SK	258.92 ± 131.9	551.2 ± 396.9	0.01
Rate of increase (%)	114	105	NS

*$P < 0.05$ (significant difference pre-streptokinase and post-streptokinase for two groups).

Table 3
Comparison of LDH, glucose, and pH levels before and after SK instillation

	Before SK	After SK	P-value
Group-I			
LDH	1874	995	<0.05
Glucose	19	32	<0.05
pH	6.92	7.0	<0.05
Group-II			
LDH	2092	1018	<0.05
Glucose	17	28	<0.05
pH	6.95	7.12	<0.05

(Table 2). A statistical difference was also noted in the mean pleural LDH, glucose and pH levels in between before and after instillation of SK for both groups (Table 3). Finally, in five cases that eventually required VATS in Group II, the mean volume of fluid drainage post-SK was significantly lower (Table 4).

A microbiological diagnosis was established in only five patients, all from Group II. Pleural fluid Gram stain and culture revealed α-hemolytic streptococcus in three cases and *Streptococcus pneumoniae* in the remaining two.

Another six patients, who had persistent multi-loculations with partial lung expansion, according to radiological examination, ultimately required surgical intervention. All of them were treated with VATS procedure in our series.

Treatment without surgical intervention was accepted as success in the study. The overall success rate for SK treatment was calculated as 96% for Group I and 72.2% for Group II. There were no clinical signs of new or enhanced bleeding changes in coagulation tests. Three patients had transient fever and one complained of sternal pain during instillation of SK. We did not observe any allergic reactions.

4. Discussion

In children severe pneumonia is usually accompanied by accumulation of pleural fluid. The extension of infection in lung parenchyma into pleural cavity and consolidation with accompanying volume loss is the reason for this fluid means of development of an empyema [1–5]. The resulting decreased antibiotics penetration further prevents resolution of the underlying infection. The end point therefore in

Table 4
Comparison of volume of pleural drained amongst cases eventually requiring VATS and rest of G-II

	VATS ($n = 5$)	G-II ($n = 13$)	P-value
Fluid volume before SK	170.1 ± 105.3	393.4 ± 405.1	<0.05
Fluid volume after SK			
During first 24 h	56.6 ± 41.9	283.3 ± 131.1	<0.05
Mean volume	69.1 ± 46.8	189.1 ± 81.4	<0.05
Total volume	264.1 ± 242.1	696.1 ± 385.5	<0.05

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the management is drainage of pleural space [1–12]. Thoracocentes or tube thoracostomy can be effective in patients who have free-following pleural fluid. Closed tube thoracostomy is reported to have 35–80% success rates in primary cases. Incomplete drainage of the pleural fluid following tube thoracostomy is related to several factors of which the most critical are believed to be early formation of thick peel, covering the lung with loculations and highly viscous pleural fluid with fibrinous debris or clots clogging the tube [2,8,10,12].

A loculated empyema is a potentially lethal condition. Failure to control the pleural process may also lead to persistent sepsis, bronchopleural or bronchocutaneous fistula or progress to restrictive lung disease [4,8]. The most serious complication is disseminated abscess and death in 8–33% [3]. Surgical drainage may be necessary, especially in resistant effusions [2,3,13,15].

Intrapleural fibrinolytic therapy agents offer a promising alternative and have been reported as an effective adjunct to accelerate drainage of loculated effusions in complicated empyema [5,11,12,14]. Fibrinolytic agents are believed to work through decreasing fibrinous strands and reopening pleural pores blocked by fibrinous material, permitting pleural resorption. Streptokinase was first used by Tillett in 1949 to lyse fibrinous pleural material and break down loculi [1,5,8].

Intrapleural fibrinolytic treatment should be started early to benefit from the potential advantages before severe pleural adhesions develop. Development of complex pleural exudates leading loculations and viscous intrapleural fluid may lead to failure of streptokinase treatment [2]. The optimal dosage and required number of daily instillations for streptokinase is unknown. Multiple (as many as 10) instillations were required to improve drainage in the largest reported series [1,5]. Repeat treatments are guided by the appearance of the effusion on imaging studies. Moultan et al. advocates the use of more than one dose of SK per day considering an increase in effectiveness [12,16]. Early intrapleural administration of streptokinase has been shown to lessen the need for repeat numbers of intrapleural instillation [4]. In our study, Group I patients showed better improvement in imaging studies with less number of instillations.

Urokinase has been advocated for better results [3,5,8,17]. A recent randomized trial advocates use of intrapleural urokinase as an effective agent, significantly shortening hospital stay [17]. On the other hand, urokinase is also reported to enhance adhesive intrapleural loculations and increase the difficulty of the VATS procedure [18]. The effectiveness of SK therapy is mostly monitored by amount of pleural fluid drainage following instillation [3,9]. This, however, should be interpreted with caution since other than break down of loculized pleural fluid SK itself may chemically induce fluid production [3,5,6]. The mean volume of total fluid drainage post-streptokinase showed a statistically significant increase in both groups in our study. But there was no statistical difference in total gradient increase between two groups. This result may support the fact that SK related pleural fluid production is responsible for the increased amount of fluid drainage. In some of our cases from Group II, we had to continue our treatment for a longer period than predicted, even though the initial increase obtained in volume was dramatic. The possible explanation may be that streptokinase is mainly effective on fibrinolysis and pus viscosity of pleural accumulation rather than re-establishing pleural circulation. The mean volume of fluid drainage was statistically higher for Group II before SK treatment when compared to Group I. On the contrary, the amount of pleural drainage was significantly less in five Group II cases, all referred to VATS, from the rest of the group despite the fibrinolytic therapy. Failure to respond to chest tube drainage or fibrinolytic therapy, are indications to proceed with operative intervention [1,7,17,19]. Jaffé et al. report that 39% of patients treated with tube drainage only are referred to surgery in contrast to 15–20% treated with adjuvant fibrinolytic activity [18]. Clinical and radiological improvement was observed in 26 patients in our series following SK instillation whereas only six cases (18.7%), mostly from Group II intractable to treatment underwent thoracoscopic decortication (Table 3).

VATS is regarded as a better and effective surgical procedure enabling the surgeon to evacuate free fluid, drain loculations and to remove pleural pleural debris with shorter hospital stay and much lower morbidity when compared to open surgery. VATS [7,20].

In some series SK treatment is reported to have no beneficial effect on hospital stay, given a mean of three weeks [11,16]. In our study, however, mean hospital stay was significantly shorter for Group I patients. The prolonged hospital stay for Group II was mostly related to four cases that developed a clinical bronchopleural fistula. All thee cases appeared to have air-fluid levels in the CT scans prior to tube drainage, but none of them showed air leakage following an average of two instillations and healed spontaneously. These patients are believed to benefit from SK treatment since proper lung expansion prevented further surgical intervention. Previous reports on SK treatment as an adjunctive modality, suggested that it might be highly effective with success rates ranging from 50 to 90% [9,10,13,17]. The overall success rate was 72–92% in our study. The relatively low success rate in Group II in our study may be due to late hospital admission and therefore delay starting the treatment. Adverse allergic reaction and antibody neutralization during prolonged SK therapy has been described in the literature [1,2,9,10]. In previous reported series, two anaphylactic reactions and major hemorrhage have been reported after instillation of SK [5,9,15]. We have no any serious complications where only six patients developed fever and two patients complained of back pain.

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5. Conclusion

Even though, the intrapleural administration of fibrinolytics and VATS procedure are ineffective treatment during the organizing stage of empyema, this study have showed that daily instillation of intrapleural streptokinase at a dose of 250,000 IU, is efficacious and safe in treating complicated parapneumonic effusions in early and late stage II empyemas. However, this study also provided us to conclude that fibrinolytic treatment may not be effective in cases of late stage II in which the initial chest tube drainage is lower. It is obvious that empyema is an evolving disease and selected patients may benefit from fibrinolytic treatment alone and avoid an early minimally invasive or open surgical approach.

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