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ORIGINAL PAPER

Intrapleural streptokinase treatment in children with empyema

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Abstract Our aim was to compare intrapleural streptokinase (SK) treatment and simple tube drainage in the treatment of children with complicated parapneumonic pleural effusion. A retrospective review of medical records included patient demographics, clinical presentation, biochemical and microbial studies of pleural effusion, radiographic evaluation of chest tube drainage, use of fibrinolytic agents and type of surgical intervention. During the 2.5-year period (1999–2002), 53 children (29 M, 24 F) with complicated parapneumonic effusions or empyema were identified. Closed tube drainage and antibiotic treatment were administered to patients with a diagnosis of complicated parapneumonic effusion (n=24) until October 2000; after that time point, intrapleural streptokinase was added to this regimen (n=29). The median age at the time of presentation was 2.5 years (range: 5 months-14.6 years). There were no significant differences in terms of clinical outcomes between the two groups. The average length of hospital stay was 19.1±5.5 and 21.9±11.2 days for the drainage and streptokinase groups, respectively; the time to afebrile state after admission was 5.8±4.1 and 7.6±7.5 days. The percentage of patients who eventually required surgical intervention was 8.3% for the drainage group and 20.6% for the streptokinase group. In conclusion, in the treatment of complicated parapneumonic effusions or empyema, the adjunctive treatment with intrapleural SK does not significantly reduce durations of fever, chest tube drainage and hospital stay, and the need for surgery, regardless of the stage of the disease, compared to simple closed tube drainage.

Keywords Children · Empyema · Streptokinase

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Introduction

Parapneumonic effusion usually develops in up to 40% of patients with community-acquired pneumonia [16]. Empyema is a collection of purulent material in the pleural space which occurs as a serious complication. The optimal management remains controversial regarding a variety of treatment options, such as antibiotics alone or in combination with thoracocentesis, tube thoracostomy, fibrinolytic agents, thoracoscopy, minithoracotomy, debridement and decortication [21]. Intrapleural injection of fibrinolytic agents such as streptokinase (SK) and urokinase (UK) are increasingly being used in the management of these conditions [2, 3, 20, 25]; however, most previous studies were uncontrolled [12, 13, 19]. In the few controlled studies on the use of fibrinolytic agents for childhood empyema, a reduction in the length of hospital stay, a reduction in the

duration of fever and an increase in the volume of chest tube drainage have been reported [22, 26].

Our aims were to examine (1) whether the addition of early intrapleural streptokinase therapy to conventional medical management would decrease the durations of chest tube drainage, fever and hospital stay and reduce the need for further surgical procedures and (2) stage-specific results. We report a study with a historical control, comparing intrapleural streptokinase with simple tube drainage in the treatment of 53 patients with complicated parapneumonic pleural effusions or empyema.

Materials and methods

This was a 2.5-year (December 1999 to May 2002) retrospective study of 56 consecutive patients admitted to the university hospital with community-acquired complicated parapneumonic effusions or empyema.

Parapneumonic effusions were classified as a spectrum of disease, with three stages of progression [7]. Stage 1 ('exudative'): collection of free-flowing fluid with pH higher than 7.2, lactate dehydrogenase levels less than 1,000 IU/l, glucose levels higher than 60 mg/dl and negative cultures within the pleural cavity without the presence of loculations. Stage 2 ('fibropurulent'): pH less than 7.2, lactate dehydrogenase levels higher than 1,000 IU/l, glucose levels less than 60 mg/dl and fibrin deposition within the pleural space giving rise to loculations or positive cultures; presence of pus (empyema). Stage 3 ('organizing'): in addition to stage 2, organised multiloculated parapneumonic effusions with lung entrapment and pleural rind formation.

Those patients with stage 1 parapneumonic effusion and patients with underlying lung disease, tuberculosis, post-traumatic and post-operative parapneumonic effusions were excluded from this study.

A diagnosis of parapneumonic effusion was initially made on the basis of clinical examination, chest radiography, ultrasound and/or computed tomography (CT) scan, and the presence of a complicated parapneumonic effusion or empyema was confirmed by pleural fluid culture and analysis.

Diagnostic thoracentesis with a 14-gauge venula was performed for all patients on hospital admission. The pleural fluid samples were sent for biochemical analyses [glucose, protein, lactic dehydrogenase (LDH), pH], differential cell count, Gram's stain, and aerobic and anaerobic cultures.

All patients had closed tube thoracentesis. A size 24F chest tube was used at the bedside in patients with large, dependent pleural collections. In patients with multiloculated effusions and/or in non-dependent areas, a 14F or 18F chest tube was placed under ultrasound guidance. The chest tube was placed by paediatric surgeons.

For treatment of community-acquired pneumonia, initially empirical treatment consisting of ampicillin-sulbactam plus cefotaxime was given just after the diagnosis, based on a paediatric respiratory medicine textbook [18] which recommends as initial therapy administration of a β-lactamase-resistant penicillin and an extended spectrum cephalosporin together. Since there is no β-lactamase-resistant penicillin such as oxacillin or nafcillin available in our country, we gave ampicillin-sulbactam; then the patients were switched to a more microorganism-specific treatment according to the results of bacterial culture and the sensitivity test. Ampicillin-sulbactam was changed to vancomycin if initial empirical antibiotic therapy had not been associated with a clinical response within 72 h, i.e. the patient's disease failed to improve and deteriorated clinically, such as respiratory failure. This was done because the possibility of highly penicillin-resistant pneumococcal infection or community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection could not be excluded (although not demonstrated by culture) in patients without a clinical response to the treatment despite the combination of ampicillin-sulbactam and cefotaxime [27]. The duration of antibiotic therapy was based on the response of the patient to the medical and surgical therapy.

After October 2000, all patients additionally received intrapleural streptokinase (IP-SK). In the IP-SK protocol, 250,000 U SK in 100 ml saline was instilled into the pleural cavity on a daily basis starting within the first 24 h following tube placement. SK was left in the pleural cavity for about 4 h, after which fluid was manually aspirated and left to drain passively into a water-sealed chamber. Adverse effects of SK such as bleeding, chest pain, fever or allergy were noted. The outcome measures to determine the number of SK instillations were no clinical and radiological improvement and no increase in pleural fluid drainage.

CT examinations were made in all patients with suspected multiloculation and who failed to respond to treatment promptly. If there had been no response to treatment protocols and complicated parapneumonic effusions or empyema had formed a pleural peel visible on the CT, further surgical evaluation was made. Video-assisted thoracoscopic surgery (VATS) was the treatment modality of choice in these cases. The patients were followed by the same medical and surgical team using the same medical and surgical treatment protocol throughout the study period except intrapleural streptokinase administration after October 2000.

Medical records were reviewed at the end of the study for demographic data, clinical presentation, chest tube drainage, use of fibrinolytic agents, type of surgical

intervention, biochemical and microbial examinations of pleural effusion and radiographic evaluation. Patients who received conservative management with antibiotics and chest tube drainage (drainage group, December 1999-September 2000) were compared with the patients who received conservative treatment plus fibrinolytic agent (SK group, October 2000-May 2002). Reductions in the duration of chest tube drainage, fever, and hospital stay and a decrease in the need for further surgical procedures were accepted as treatment success.

Collected data were entered into a statistical program (SPSS version 11.0 for Windows 98, SPSS Inc., Chicago, IL, USA) for analysis. Results are expressed as mean ± SD. The Mann-Whitney U test was used for between-group comparisons; the chi-square test was used for comparisons of group proportions with qualitative data. A p value less than 0.05 was considered significant.

Results

Of 56 patients included, 53 were evaluable. Two patients died and one immunocompromised patient was excluded. One of them died before the placement of the thorax tube, and the other patient died within the 24 h of tube insertion. During the 2.5-year period (1999–2002), a total of 53 children (29 M, 24 F) with complicated parapneumonic effusions or empyema were identified. Thirty-one patients (58.5%) had empyema and the rest of them had complicated parapneumonic effusions. The mean age at the time of presentation was 4.16±3.63 years (range: 5 months-14.6 years), and 71.7% of the patients were 0.4–5 years old (Fig. 1). Most patients (75.4%) were admitted between the months of January and May. The left side was involved in 26 (49%) cases and there were 2 cases with bilateral effusion. The mean duration of symptoms prior to admission was 11.4 days (range: 2–50 days). Seventy-seven percent of the children had been pretreated with antibiotics at the time of sample collection for culture. Cough (87%), fever (85%) and decreased breath sounds (74%) were the most common symptoms. There were no significant differences in terms of age, sex ratio, peripheral blood leukocytosis, bacterial isolates and pleural biochemistry between the two groups (Table 1). Twelve patients (22.6%) had positive pleural fluid cultures: four (33.3%) *Streptococcus pneumoniae*, three (25%) *Streptococcus* spp. and two (16.6%) *Staphylococcus aureus.*

Thirty-two of the patients had stage 2, and 21 had stage 3 disease. The length of hospital stay was 18.3±8.2 days for stage 2 and 24.2±9.4 for stage 3 patients (p=0.02). The time to afebrile state after admission was 5.3±3.9 days for stage 2 patients and 9.3±8.4 days for stage 3 patients (p=0.04). The duration of chest tube placement was 7.5±6.9 days for stage 2 patients and 13.2±12.1 days for stage 3 patients (p=0.05). The percentage of patients who eventually required VATS was 9.4% for stage 2 patients and 23.8% for stage 3 patients (p>0.05).

Twenty-four patients received conservative management (antibiotics with chest tube drainage), and 29 patients received conservative treatment plus fibrinolytic agents. On average, SK was administered 3.2±1.8 times (range: 1–7). No adverse effect of SK was noted. The two groups were compared with respect to mean age, sex ratio, length of hospital stay, total number of days with fever after admission, time to afebrile state after chest tube insertion or fibrinolytic therapy and duration of chest tube placement (Table 2). The length of hospital stay was 19.1±5.5 days for the drainage group and 21.9±11.2 for the SK group. The time to afebrile state after admission was 5.8±4.1 days for the drainage group and 7.6±7.5 days for the SK group. The duration of antibiotic therapy was 17.70±5.18 days (10–32) in the drainage group and 19.62±5.90 days (7–33) in the SK group (p=0.16). Ampicillin-sulbactam was changed to vancomycin in five cases (three cases in the SK group and two cases in the drainage group). The percentage of patients who eventually required VATS was

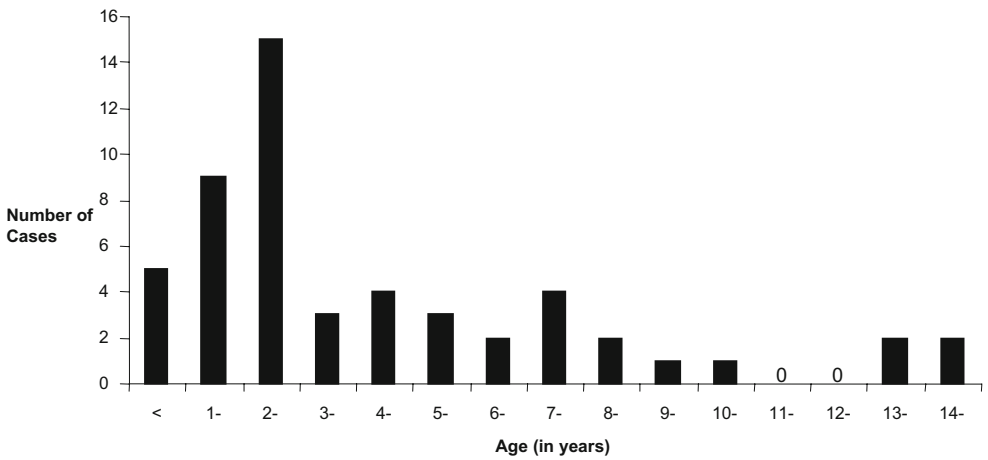

Fig. 1 Age distribution of patients with complicated parapneumonic effusions or empyema

Table 1 Demographics, signs and symptoms, imaging studies, blood and pleural analysis in patients with thoracic complicated parapneumonic effusions or empyema. *GI* gastrointestinal, *ESR* erythrocyte sedimentation rate, *sO2* oxygen saturation, *NS* not significant

Category	Drainage group[a], n=24 (%)	SK group[a], n=29 (%)	p
Mean age (years)	5.0±4.5	3.5±2.9	NS
Sex ratio (M:F)	15/14	14/10	NS
Cough	20 (83.3)	26 (89.7)	NS
Fever (>38°C rectal)	21 (87.5)	24 (82.8)	NS
Decreased breath sounds	19 (79.2)	20 (69)	NS
Chest pain	6 (25)	3 (10.3)	NS
GI symptoms[b]	5 (20.8)	4 (13.8)	NS
Dyspnoea	17 (70.8)	21 (72.4)	NS
sO2	92.2±4.3	90.6±7.8	NS
Lung location (R/L side)	15/8	17/11	NS
Blood culture (+)	4 (16.7)	6 (20.7)	NS
Pleural effusion culture (+)	8 (33)	5 (17)	NS
Blood or serum			
White blood cell (/μl)	15,516±6,018	18,665±6,551	NS
Hb (g/l)	10.0±2.3	9.6±1.3	NS
PLT (/mm^3)	395,368±236,914	454,134±236,566	NS
ESR (mm/h)	71.9±31.3	94.8±36.6	0.038
Pleural effusion			
LDH (U/l)	3,282±4178	3,228±3278	NS
Protein (g/dl)	4.1±2.3	2.9±1.8	NS
Glucose (mg/dl)	30.9±32.3	27.3±30.2	NS
Ph	6.96±1.10	6.93±1.15	NS
Chest computed tomography scan	16 (66.6)	26 (89.6)	0.05

[a] Drainage group=patients who received conservative management (antibiotics with chest tube drainage); SK group=patients who received conservative treatment plus fibrinolytic agents
[b] Vomiting and/or abdominal pain

Table 2 Comparison of clinical outcomes in patients with stage 2 or 3 complicated parapneumonic effusions or empyema who did or did not receive SK treatment. *NS* not significant

	Stage 2 (fibropurulent)			Stage 3 (organizational)		
	n=32			n=21		
Category	Drainage group[a], n=18	SK group[a], n=14	p	Drainage group[a], n=6	SK group[a], n=15	p
Mean age (years)	4.3±4.1	2.9±2.1	NS	7.1±5.5	4.0±2.9	NS
Sex ratio (M:F)	10/8	7/7	NS	4/2	8/7	NS
Chest computed tomography scan	12 (66.6%)	12 (92.9%)	NS	4 (66.6%)	14 (93.3%)	NS
Length of hospital stay(days)	18.4±4.8	18.1±11.5	NS	21.2±7.5	25.4±10.0	NS
Length of hospital stay after procedure (days)	9.7±4.7	7.2±4.1	NS	9.0±7.6	7.4±5.1	NS
Time to afebrile state after admission (days)	6.1±4.4	4.5±3.3	NS	5.2±3.5	10.7±9.2	NS
Duration of chest tube placement (days)	5.7±4.1	9.7±9.0	NS	6.7±4.9	15.8±13.3	NS
Surgical intervention (VATS)	1 (5.5%)	2 (14.2%)	NS	1 (16.6%)	4 (26.6%)	NS
Complication	2[b]	1[b]	NS	1[c]	4[b, c, d]	NS

[a] Drainage group=patients who received conservative management (antibiotics with chest tube drainage); SK group=patients who received conservative treatment plus fibrinolytic agents
[b] Pneumothorax
[c] Lung cyst formation
[d] Bronchopulmonary fistula

8.3% (n=3) for the drainage group and 20.6% (n=6) for the SK group. In addition, when the group of patients receiving conservative treatment plus fibrinolytic agents was considered, subgroups of patients with stage 2 or stage 3 complicated parapneumonic effusion/empyema were similar in terms of clinical outcomes.

Discussion

The present study was conducted in paediatric patients with complicated parapneumonic effusion or empyema and demonstrated that intrapleural streptokinase was not able to reduce the duration of fever, duration of chest tube drainage, length of hospital stay and the need for surgery. Treatment failure was observed in 9% of the patients with stage 2 and 24% of the patients with stage 3 disease, and fibrinolytics did not provide any additional therapeutic benefit in either of the groups.

Parapneumonic pleural effusions are mostly very simple, small, uncomplicated, pleural effusions that do not require specific treatment. But they may sometimes progress to life-threatening conditions such as multiloculated effusions, pleural fibrosis, trapped lung, systemic sepsis, respiratory failure and metastatic infection [7]. In the face of newer treatment modalities, several management algorithms and guidelines have been published [8], but there are still many unanswered questions about treatment. Although intrapleural administration of thrombolytic agents has been used to treat empyema for more than 50 years [23], one of the most controversial issues concerns the use of fibrinolytics. It is not yet clear whether intrapleural fibrinolytic therapy is beneficial in empyema, and if so, at which stage and at what time it should be administered.

Five small randomized controlled trials have been reported in adult patients. In 1997, a double-blind trial comparing streptokinase and urokinase in 50 patients found that both were equally effective although urokinase was safer [4]. In the same year, another randomized controlled study compared streptokinase and saline (as placebo) administered through a chest tube in 24 patients [9]. Clinical endpoints did not show any significant difference between the intervention and the control groups, though the volume of pleural fluid drained and the improvement in the chest radiograph were significantly greater in the SK group. Two and four years thereafter, two subsequent randomized trials compared urokinase and normal saline. In the first trial, a successful pleural drainage was obtained with urokinase and the second trial showed a reduced need for decortication with urokinase treatment [5, 24]. In 2004, Diacon et al. [10] reported a higher clinical success rate and fewer referrals for surgery with streptokinase compared to placebo in their double-blind trial with 53 patients. However, no significant radiological or functional differences were observed between the groups during the follow-up of more than 6 months. A meta-analysis evaluating four of these trials [4, 5, 9, 24] concluded that although fibrinolytics reduce hospital stay and the duration of fever, and provide radiological improvements, the trials were not sufficiently powered to determine the true efficacy of fibrinolytics such as in terms of mortality and the need for surgery [6]. In the following year, a double-blind trial comparing intrapleural streptokinase with placebo in 454 adult patients with pleural infection did not show any benefit of streptokinase in terms of mortality, rate of surgery, radiological outcomes or length of hospital stay [17].

In paediatric patients, the experience with fibrinolytics and their actual efficacy are still limited. There have been several small case series with streptokinase, urokinase or tissue plasminogen activator with a successful outcome without surgery [2, 12–15, 17, 20] and one randomized controlled trial of 60 children comparing urokinase and normal saline with a shortened hospital stay [22]. As reported in a recent meta-analysis, in most of the paediatric studies fibrinolytic therapy was used for children who failed to exhibit improvement with non-operative therapy (antibiotics and thoracentesis and/or tube thoracostomy) alone [1]. Three studies of primary fibrinolytic therapy were evaluated in this review: the abovementioned randomized controlled trial, one study with a historical control group comparing streptokinase and saline in 42 patients [26] and one retrospective case note review of intrapleural urokinase in 48 patients [11]. Overall, a reduction in failure rate but a higher reported complication rate was obtained compared to primary non-operative therapy. Our results do not support the use of intrapleural fibrinolytic therapy in paediatric empyema cases as shown for adults in a large multicenter randomized trial [17].

In an uncontrolled retrospective study of 78 children, the efficacy of adjunctive intrapleural fibrinolytic agents (streptokinase, urokinase) in complicated parapneumonic effusions or empyema (stage 2 and stage 3) was evaluated [25]. The authors concluded that fibrinolytic treatment might have significant benefit in most children with stage 2 empyema but do not seem to be effective in stage 3. In another retrospective case note review of intrapleural urokinase in 100 patients consisting of children mostly with stage 2 or 3 empyema, surgical intervention was required in 2% of cases. However the results were not interpreted in terms of stages [3]. In our study, treatment failure was observed in 9% of the patients with stage 2 and in 24% of the patients with stage 3 disease, and fibrinolytics did not provide any additional therapeutic benefit compared to controls, regardless of the stage. Length of hospital stay, time to afebrile state and duration of tube drainage were

greater in stage 3 compared to stage 2 cases as would be expected and this was unrelated to fibrinolytic therapy.

The retrospective design allowing only historical controls is the limitation of our study. Although reports of successful outcome without surgery exist among previous paediatric studies, the majority of them are retrospective case note reviews and were done at different centres without a uniform protocol and mortality was not evaluated as a major outcome. Most adult and paediatric studies, including the large randomized trial of 454 adult cases [17], did not report results in terms of disease stage. The design consisting of stage-specific control groups, although historical, strengthens our study.

We conclude that, in the treatment of complicated parapneumonic effusions or empyema, the adjunctive treatment with intrapleural SK does not significantly reduce durations of fever, chest tube drainage and hospital stay, and the need for surgery, regardless of the stage of the disease (2 or 3), compared to simple closed tube drainage. Further large multicentre randomized controlled trials following a specific protocol and consisting of stage-specific results and mortality rates as well as the need for surgery as major outcomes are required for the careful evaluation of any potential benefit of fibrinolytic treatment.

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