Original Article

Safety and Efficacy of Streptokinase in Multiloculated Pleural Effusion in Pediatric Population

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Abstract

Introduction: Management of complicated parapneumonic effusions (CPEs) and empyema is difficult, as no clear guidelines exist. The use of intrapleural fibrinolytics has shown promising results in several studies. **Objective:** The objective was to study the safety and efficacy of streptokinase (STK) in multiloculated empyema in children. **Patients and Methods:** This is a comparative descriptive study which included initial 50 patients in the STK group and subsequent 50 patients in the placebo group. Intrapleural STK was given twice daily at a dose of 5000 IU/kg for 7 days. In the placebo group, 50-ml normal saline was instilled intrapleurally through the chest tube. The patients were assessed for safety and efficacy of STK. The efficacy of STK was assessed by expansion of lung on chest-X-ray and breakage of loculi on thoracic ultrasound. Success of STK therapy was assessed by decrease in number of surgical referrals for decortication. **Results:** The amount of intercostal tube drainage output as well as mean duration of its insertion was statistically significant in the STK group. The percentage of overall success was 84% of patients in the STK group versus 52% in the placebo group, and the difference was statistically significant. Decortication was required in 24% of patients in the STK group and 60% of patients in the placebo group, which was again statistically significant. **Conclusion:** Instillation of STK in multiloculated empyema is safe and effective and decreases referrals for surgery. Awareness needs to be created among health-care workers for prompt diagnosis and treatment of patients of CPE and empyema with intrapleural fibrinolytics before surgical referral.

Keywords: Multiloculated, parapneumonic effusion, pediatric, streptokinase

Introduction

Parapneumonic pleural effusion is a common health problem in developing countries, seen in 36%–57% of patients with pneumonia, and around 15%–20% of these patients develop empyema.[1] The management of uniloculated pleural effusion is simple, however, once effusion becomes infected and multiloculated, the management becomes difficult. This complicated parapneumonic effusion (CPE)/empyema is a potentially dangerous condition with serious consequences such as persistent sepsis, bronchopleural or bronchocutaneous fistula or progress to restrictive lung disease, and sometimes even death.[2,3]

Various management protocols have been tried for management of multiloculated empyema, but still, there are no standard guidelines that can be followed in all the cases.[4] In dealing with CPE, intrapleural fibrinolytics may be a safe, easy, cost-effective management option.[5] Streptokinase (STK) was the first fibrinolytic agent used for intrapleural adhesiolysis by Tillet *et al*.[6] Other fibrinolytic agents such as urokinase or tissue plasminogen have also shown successful results.[7] The safety and efficacy of fibrinolytic agents in adults are well established by numerous randomized trials,[3] however, only a few trials have been done in pediatric population.[7] Another important context to efficacy of fibrinolytics is that the success of fibrinolytic therapy should be judged as patients not needing surgical interventions rather than volume of pleural fluid output and radiological improvement.[8] The dispute over the optimal therapeutic approach has been accentuated since the introduction of early thoracotomy and decortications via video-assisted thoracic surgery (VATS).[9]

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We hypothesized that fibrinolytic therapy not only leads to early clearance of entrapped pleural fluid but also reduces the need for surgical referrals. To our knowledge, very few studies have been done in pediatric population in Indian subcontinent. The purpose of our study was to assess the safety and efficacy of STK for intrapleural fibrinolysis in pediatric patients with CPE and empyema.

Patients and Methods

This was a single-center, comparative descriptive study. The study was approved by the Institutional ethics committee. All pediatric empyemas admitted to the hospital who fulfilled our inclusion criteria were included. The initial 50 patients were allocated to the STK group and subsequent 50 patients in the placebo group.

Patients whose age was <18 years, whose parents/legal guardians gave consent for study, had multiloculated empyema requiring intercostal tube drainage intercostal tube drainage (ICTD), failure of satisfactory pleural fluid drainage 24 h following ICTD or with sonographically documented CPE were included in the study.

Patients with massive air leak, recent thoracic trauma, or hemothorax, patients with bleeding disorders, those on anticoagulant therapy, those sensitive to STK, or those who had prior exposure to STK in the past 2 years were excluded.

Treatment protocol

One hundred patients aged 0–18 years were enrolled in this study from October 2017 to February 2020. Detailed history and clinical examination were carried out, along with routine blood investigations, biochemical parameters, and coagulation profile. The period between onset of symptoms and date of admission ranged from 10 to 30 days. All patients had posteroanterior chest X-ray (CXR) and thoracic ultrasonogram (USG). Pleural fluid samples were investigated for Gram stain, aerobic and anaerobic cultures, and biochemical parameters.

All patients had the ICTD with a size 20–28 Fr. CXR was repeated at 24 h, if it showed incomplete expansion, a repeat thoracic USG was done to assess the amount of collection and loculi in thorax. If collection was multilocular, patients were enrolled in two groups of 50 each, with initial 50 in the STK group and subsequent 50 in the placebo group.

Streptokinase group

Hypersensitivity to injection STK was tested by injecting 25,000 IU intradermally; treatment was started only if there was no reaction. All patients were given injection STK twice daily at a dose of 5000 IU/Kg, and a maximum dose of 250,000 IU per instillation was never exceeded. The patient was placed in the lateral decubitus position, with the unaffected lung being dependent during instillation. The ICTD was then clamped for 2 h, and the patient and his attendants were explained to change posture over the next 2 h. The patient remained in bed until the tube was unclamped. Instillation was repeated twice daily for a maximum of 7 days. None of the patients had any serious side effects requiring termination of treatment. Radiographic improvement was defined as full lung expansion with disappearance of septa.

Placebo group: 50 ml of normal saline was instilled in the pleural cavity through the chest tube. The protocol of instillation of normal saline was exactly similar to the STK group. Instillation was repeated twice daily for a maximum of 7 days.

All demographic data were recorded and details about pleural fluid output were collected daily. CXR and chest USG were performed on the 1st day and the 7th day of treatment. Any side effects if any were recorded.

The primary outcome of our study was to assess the safety and efficacy of STK for intrapleural fibrinolysis in pediatric patients with CPE and empyema.

The safety of STK was assessed by:

a. Hypersensitivity reaction (in the form of wheal and flare reaction around site of injection, itching over body, facial flushing)
b. Unexplained fever in patients who were earlier afebrile
c. Burning sensation in the chest after instilling STK.

The efficacy of STK was assessed by:

a. Monitoring the volume of fluid drained from the chest tube daily
b. Chest USG to check dissolution of septa at 1 week
c. CXR to see lung expansion at the end of 1 week.

Evaluation of lung expansion on the 7th day was assessed by CXR as follows:

- Score 0 – No change in expansion of lung
- Score 1 – Incomplete expansion of lung
- Score 2 – Complete expansion of lung.

Evaluation of lung expansion on the 7th day was assessed by USG chest as follows:

- Score 0 – No dissolution of septa
- Score 1 – Partial dissolution of septa
- Score 2 – Complete dissolution of septa in pleural cavity.

The outcome of our study was based on the combined score of CXR findings and USG chest after 7 days of management. Treatment failure was considered when combined score of CXR findings and USG of thorax was 0, partially successful when combined score was 1 or 2, and completely successful when combined score was more than 2.

The secondary outcome was the number of patients needing surgical decortications due to partial or no expansion of lung.

Statistical analysis

Categorical variables were described by number and percentage, whereas continuous variables were described by mean and standard deviation. $P < 0.05$ was considered statistically significant. All analyses were performed with the

SPSS 20.0 software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).

Results

Sixty-four percent of our patients were below the age of 10 years. The mean age of the study population was 9.16 ± 4.90 years. In both the groups, the age distribution and mean were comparable. Sixty-two percent of our patients were males and 38% females. Right side of lung was more frequently involved (52%). The presenting complaints were fever (81%), cough (72%), breathlessness (66%), chest pain (59%), and loss of appetite (34%) [Table 1].

Sixty percent of our patients were of pyogenic origin and 40% were posttubercular. Adverse reaction occurred in 10 (20%) patients in the STK group, of which 4 had hypersensitivity reaction, 4 had burning sensation in chest, and 2 had unexplained fever. In the placebo group, 3 (6%) patients had adverse reaction, of which none had hypersensitivity reaction, 2 had burning sensation in chest, and 1 had unexplained fever. The mean duration of ICTD insertion in the STK group was 9 ± 1.64 days, whereas in the placebo group, it was 15 ± 1.63 days. Total ICTD output in the STK group was 1006.60 ± 270.59 ml and 747 ± 153.18 ml in the placebo group [Table 2].

In the STK group, there were complete failure in 16% and partial failure in 28% of patients, while it achieved complete lung expansion in 56% of patients. In the placebo group, there were complete failure in 48% of patients and partial failure in 44% of patients, while it achieved complete lung expansion in only 8% of patients, respectively [Table 3].

In our study, decortication was required in 24% of patients in the STK group and 60% of patients in the placebo group. The mean duration of hospital stay in the STK group was 10 ± 1.48 days, while in the placebo group, it was 17 ± 2.03 days [Table 4].

Discussion

Loculations develop due to delayed initiation and inappropriate use of antibiotics and delayed initiation of pleural space drainage. Open thoracotomy or video-assisted thoracoscopic surgery (VATS) achieves the best drainage in gross empyema or loculated effusions but is limited by operative risk, cost, and local availability.[9] However, current treatment guidelines also suggest the use of fibrinolytics to lyse the fibrinous septations in patients of empyema.[4] The confusion to use of STK got accentuated when a randomized control trial by Maskell *et al*. showed no benefit of STK in empyema patients.[10] The present study was undertaken to investigate the safety and efficacy of STK in multiloculated pleural effusion in children.

Table 1: Comparison of demographic and clinical characteristics of both groups

	Streptokinase group (*n*=50)	Placebo group (*n*=50)	*P*
Age (years)			
<10	36	28	0.097
≥10	14	22	0.160
Gender (male/female)	32/18	30/20	0.837
Localization (right/left)	29/21	23/27	0.232
Fever (yes/no)	42/8	39/11	0.184
Cough (yes/no)	39/11	33/17	0.447
Breathlessness (yes/no)	35/15	31/19	0.097
Chest pain (yes/no)	33/17	26/24	0.837
Loss of appetite (yes/no)	16/34	18/32	0.832

ICTD: Intercostal tube drainage

The Mean age of the study population was 9.16 ± 4.90 years. Majority of our study population (64%) was below the age of 10 years. In both the groups, the age distribution and mean were comparable (8.36 ± 4.17 vs. 9.96 ± 5.42 years). In a randomized control trial from India, the mean age of the subjects in the conventional and STK groups was also <10 years.[11] The male-to-female ratio of 1.63:1, other studies have also reported male preponderance.[11] This could be due to the fact that males are more involved in outdoor activities and hence more prone to infection as well as trauma. Right-sided involvement was more common, but the difference was not statistically significant.

The presenting complaints were fever (81%), cough (72%), breathlessness (66%), chest pain (59%), and loss of appetite (34%). The symptoms reported by other studies are more or less similar to our study with slight variation in actual percentage of symptoms as empyema patients follow their natural course of illness.[11] Sixty percent of our patients had pyogenic empyema and 40% were posttubercular empyema. In other studies also, nontubercular empyema is more common.[12] A subgroup analysis of pyogenic and tubercular patients was not done, but like others, STK was found to be useful in tubercular multiloculated effusions also.[13]

Some form of adverse reaction occurred in 20% of patients of the STK group and only 6% in the placebo group. Other studies have also reported minimal adverse effects to STK.[14] The most fearful complication of STK is bleeding, however, it is rare and doses of up to 1.5 million units of STK have been shown to be safe in humans.[15] There have been isolated case reports of ventricular fibrillation following urokinase but not with STK.[16]

The mean duration of ICTD in the STK group and the placebo group was 9 ± 1.64 days and 16 ± 1.63 days, respectively; the *P* value was statistically significant. In another randomized trial from India, the mean duration of chest tube drainage in the conventional group was 5.8 ± 4.5 days and in the STK group was 9.2 ± 8.8 days.[11] Unlike other studies, the duration of ICTD was longer in our study because as per protocol we gave STK for 7 days in all patients.

The mean total ICTD output was 1006 ± 270.5 ml in the STK group and 747 ± 153.1 ml in the placebo group; the *P* value was statistically significant. In a study performed by Chung *et al*., the mean pleural drainage in the STK group and the placebo group was statistically significant.[17] In our study, the

Table 2: Intercostal tube drainage output and duration of intercostal tube drainage insertion in both groups

	Streptokinase group ($n=50$)	Placebo group ($n=50$)	*P*
Duration of ICTD insertion (number of days)	9±1.64	15±1.63	<0.001
Total ICTD output (ml), mean±SD	1006.60±270.59	747.60±153.18	<0.001

ICTD: Intercostal tube drainage, SD=Standard deviation

Table 3: Comparison of outcome of the groups

Group	Outcome		
	Failure of treatment	Successful treatment (partial + complete successful)	
		Partially successful	Completely successful
Streptokinase group (%)	8 (16)	14 (28)	28 (56)
Placebo group (%)	24 (48)	22 (44)	4 (8)
P	<0.001	>0.05	<0.001

Table 4: Final outcome and duration of stay

	Streptokinase group ($n=50$)	Placebo group ($n=50$)	*P*
Surgery required (%)	12 (24)	30 (60)	<0.001
Duration of hospital stay (number of days), mean±SD	10±1.48	17±2.03	<0.001

SD=Standard deviation

total ICTD output was less than other studies because we had recruited only pediatric patients.

In our study, the percentage of overall success was 84% of patients in the STK group and 52% of patients in the placebo group, and again, the *P* value was statistically significant. Other studies have also reported success rates ranging from 60% to 100%.[18,19] Our study had a higher success rate due to more relaxed definition of success as we also included patients with partial response as successful treatment and secondarily dissolution of septa in easier in pediatric age group. Another important thing to be noted is that benefit conferred by fibrinolytics is dependent on stage of empyema. It is more effective in stage 2 and not stage 3 empyema where thick pleural peel has already thickened to >2 mm.[18,20]

Decortication was required in 24% in the STK group and 60% in the placebo group, which was statistically significant. Nie *et al*. also showed that treatment with fibrinolytics decreased referrals for decortications.[21] Failure to respond to chest tube drainage or fibrinolytic therapy, are indications to proceed with operative intervention.[1] In our study, a higher percentage of patients in the placebo group underwent decortications (60%) compared to other studies because we were very liberal in selecting patients for surgery, as we selected kids even with partial response to placebo therapy. The authors believe that we should keep a lower threshold for decortications in children because if any amount of lung remains entrapped in fibrinous peel, it would ultimately affect the pulmonary function in the long run.

The mean duration of hospital stay in the STK group and the placebo group was 9 ± 1.48 and 16 ± 2.03 days, respectively, and the *P* value was statistically significant. Other studies also show that fibrinolytic therapy shortens hospital stay significantly.[7,21] However, there is a lot of variation in total hospital stay in different studies, probably due to the fact that some studies have included postsurgery stay as a part of hospital stay, while others have quoted postsurgical stay separately.[11,13]

The optimal dosage and required number of daily instillations for STK are unknown. Some studies have reported single instillation per day for 7 days or even longer, however, other studies have done much lesser instillations for 5 days or less with good results.[8] One study had advocated more than one instillation per day to increase effectiveness.[22] Similarly, there is a wide variation in dose of STK from 5000 to 25,000 IU/kg.

Weakness of our study was less number of participants. Furthermore, chest tube placement was not done under USG guidance.

Conclusion

Management of empyema and CPE is multidisciplinary. If a patient has thoracic USG-confirmed multiloculated empyema, then instillation of STK should definitely be done, as it is safe and effective, and decreases referrals for surgery. Another important aspect of STK therapy in Indian context is that it is cost-effective as compared to other fibrinolytics. Awareness needs to be created among health-care workers for prompt diagnosis and treatment of patients of CPE and empyema with intrapleural fibrinolytics before surgical referral.

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Conflicts of interest

There are no conflicts of interest.

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