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Intrapleural Streptokinase in Complicated Parapneumonic Effusions and Empyema

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ABSTRACT

Background: Catheter drainage and antibiotics were the standard therapy for parapneumonic effusions and/or empyema. Streptokinase may aid tube drainage if it failed due to fibrinous adhesions.

Objective: This study aimed to identify the benefits of streptokinase in treatment of empyema by evaluating its efficacy and safety.

Patients and Methods: 30 patients with parapneumonic effusions and/or empyema treated at Al-Azhar University Hospitals between April 2020 and June 2022. The diagnosis was made using a frank pus aspiration from a pleura seen on a chest radiograph (X-ray, ultrasonography, or CT), and it was later confirmed by the results of a bacteriological examination of samples collected. Streptokinase was given 24 hours after insertion of intercostal tube by 250,000 IU diluted in 50–100 ml of ordinary saline and given every 12 hours. The success of the technique was evaluated based on the volume of pleural fluid removed, the treatment's impact on chest radiography, and the incidence of post-injection events.

Results: A complete improvement was seen in 21 patients (70%), a moderate effective response in 7 patients (23.3%), and failure was shown in 2 patients (6.7%). Surgical decortication was scheduled in 3 patients who had little to no reaction. Only 6 patients experienced temporary chest discomfort and cough, whereas fever and bleeding were less common.

Conclusion: With a lower rate of surgical referral in our study, the therapy of empyema with intrapleural instillation of streptokinase was a safe and effective procedure.

Keywords: Empyema, parapneumonic effusion, streptokinase.

INTRODUCTION

Parapneumonic effusion (PPE) is generally defined as fluid accumulation in the pleural space secondary to pneumonia or lung abscess. It may progress to become empyema (pus in the pleural space) [(1)] with a mortality rate of 14% to 20%among them [(2)].

The optional management remains controversial varied from antibiotics usage alone or in combination with thoracocentesis, tube thoracostomy, fibrinolytic agents, thoracoscopy, minithoracotomy, debridement and surgical decortication [(3)]. Despite the fact that surgical interventions continue to have a high success rate [(4)], the morbidity and mortality are concerning, especially in a cohort of elderly patients or patients who have a lot of co-morbid conditions. Therefore, less invasive treatments that encourage pleural space drainage and the successful treatment of pleural infection are expected to be very useful in clinical settings [(5)].

In addition to chest tube drainage, several studies found that intrapleural streptokinase decreased the requirement for surgery and increased the clinical treatment success in patients with PPE/empyema [(6-11)].

However, the American Association of Thoracic Surgeons [(12)] and British Thoracic Society [(13)] advise that surgical methods such as video-assisted thoracoscopic surgery (VATS) or thoracotomy should be used if chest tube drainage is inadequate. There hasn't been a set of uniform management guidelines for empyema until today [(14)].

Therefore, current study aimed to investigate the efficacy and safety of streptokinase in order to assess the advantages of adding it to the conservative care of PPE/empyema.

PATIENTS AND METHODS

30 patients who reported PPE/empyema following pneumonia between April 2020 and July 2022 at the Cardiothoracic Surgery Department - Al-Azhar University Hospitals were the subject of our prospective analysis. The diagnosis was made on the basis of the frank pus aspiration from the pleural collection seen on chest radiography (X-ray, ultrasonography, or chest computed tomography (CT), which was later confirmed by bacteriological culture and Gram staining of the aspirated fluid. These patients had intrapleural injection of streptokinase.

Excluded patients were those with long-standing empyema, a tendency to haemorrhage, recent trauma, a recent operation, and those taking anticoagulants. Participants were also excluded if they had streptokinase allergies, comas, severe hypertension, peptic ulcers, aortic aneurysms, aortic dissections, infective endocarditis, or terminal malignancy.

Ethical approval:

The study was approved by the Al-Azhar University Ethics Board, each participant gave their written consent in accordance with the Declaration of Helsinki's Code of Ethics for studies involving humans.

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Enrolled patients were subjected to the following:

- Full history and clinical examination.
- Routine laboratory investigations including bleeding profile.
- Pleural fluid pH, chemistry (lactate dehydrogenase (LDH), protein, glucose) and bacteriological examination.
- Chest X-ray, ultrasonography or CT.

Procedure:

For PPE/empyema patients, big size 34-36 F intercostal tubes were placed. Aspirated pus samples were used for bacterial and chemical sensitivity testing. The amount of drainage was calculated after the intercostal tube was placed, and daily chest X-rays were taken. When results started to show, we gave a combination of antibiotics empirically at first and then based on culture and sensitivity. If the tube was put improperly, it was reinserted guided by sonographic assistance. Streptokinase (Streptase® 1500000 1/amp; CLS, Behring, Germany) was injected 24 hours after insertion of intercostal tube by 250,000 IU diluted in 50–100 ml of ordinary saline and given every 12 hours. The tube was clamped for 8 hours after the instillation and then flushed with 20 mL of normal saline. Streptokinase was administered with the patient in a lateral position so that the entire volume would enter the chest, and the tube was then clamped as closely as possible. The patient was instructed to alternate between lying flat, prone, right-lateral, left-lateral, and sitting positions during the period of clamping. Streptokinase was progressively administered over a period of five minutes. We discontinued the procedure if any significant problems from this maneuver showed up.

The amount of daily drainage, temperature, pain, the number of streptokinase dosages, and the length of the hospital stay were recorded.

A satisfactory radiological image, sufficient pleural drainage, and a noticeable improvement in the clinical condition were considered good results.

Criteria for failure and surgical intervention included the appearance of residual space or collection on chest X-rays or CT scans together with a progressive decline in clinical state after two weeks following streptokinase insertion.

Chest tubes were withdrawn from individuals who responded well to streptokinase treatment and the underlying cause of their condition was still managed. Surgery interference was determined using either traditional methods or video assisted thoracoscopy (VATS) in individuals who had failed to respond to streptokinase or had only a partial response.

Primary outcomes

Mortality, referral for thoracic surgery (open or thoracoscopic) and serious adverse events.

Statistical analysis

Data were collected and entered on a 'Microsoft Excel' spread sheet. Analysis was performed with SPSS version 20.0 software. Continuous variables were summarized by mean and standard deviation (SD), where categorical variables were described by number and percent.

RESULTS

Patients and clinical profile:

Patients' ages ranged from 20 to 65, with a mean of 45.53. They were mostly men (86.7%). Preoperative clinical presentation, concomitant comorbidities, and radiological findings are displayed in Table (1).

Table (1): Baseline clinical and radiological findings of studied cases (no=30)

Variable	Value
Age (years) Mean±SD	45.53±11.35
Range	(20-65)
Gender….n (%)	
Male	26 (86.7%)
Female	4 (13.3%)
Clinical presentations….n (%)	
Dyspnea	28 (93.3%)
Chest pain	16 (53.3%)
Cough	12 (40.0%)
Fever	8 (26.7%)
Associated comorbidities….n (%)	
Diabetes	14 (46.7%)
Hypertension	2 (6.7%)
Heavy smoking	7 (23.3%)
Recent cardiac surgeries	2 (6.7%)
Chronic kidney diseases	4 (13.3%)
Intravenous addiction	5 (16.7%)
No comorbidities	5 (16.7%)
Preoperative radiology….n (%)	
Right multiple encysted effusion	7 (23.3%)
Right lower encysted effusion	8 (26.7%)
Left multiple encysted effusion	9 (30.0%)
Left lower encysted effusion	6 (20.0%)

SD: standard deviation

Microbiological and laboratory characteristics:

The exudative aspirated fluid has the following characteristics: specific gravity 1.032 kg/L, pH 7.01. Mean blood levels of pleural LDH, protein and glucose were 866.6 U/L, 4.27 g/dL and 45.6 mg/dL, respectively (Table 2). Gram negative bacilli were the most prevalent among the causal organisms, followed by Streptococcus pneumoniae, Staphylococcus aureus, Escherichia coli (E. coli), Klebsiella, Pseudomonas and mixed (n=2) (Table 3).

Table (2): Laboratory findings of studied cases (no=30)

Variable	Mean±SD
Blood tests	
WBCs (mm^3)	14.8±3.6
Hb (g/dL)	10.4±2.2
Platelets (mm^3)	255.4±50.6
ESR (mm/h)	68.6±17.05
CRP (mg/L)	56.7±14.15
Pleural effusion	
pH	7.01±1.10
Specific gravity (Kg/L)	1.032±0.014
Pleural LDH (U/L)	866.6±140.5
Pleural protein (g/dL)	4.27±1.05
Pleural glucose (mg/dL)	45.6±11.2

WBCs: white blood cells, Hb: hemoglobin, ESR: erythrocyte sedimentation rate, CRP: C reactive protein, LDH: lactate dehydrogenase

Table (3): Causative organisms

Gram negative bacilli	8	26.7%
Streptococcus pneumoniae	5	16.7%
Staphylococcus aureus	5	16.7%
E. Coli	5	16.7%
Klebsiella	4	13.3%
Pseudomonas	1	3.3%
Mixed growth	2	6.7%

E.Coli: Escherichia Coli

Outcome of streptokinase injection:

In 60% of the patients that were included, the total dose of streptokinase was less than 1,500,000 units. After one week, there had been a considerable rise in the amount of fluid aspirated from before to after the streptokinase injection in 21 patients (70%), partial improvement in 7 patients (23.3%) and failure in 2 patients (6.7%) with mean tube insertion duration of 8.25 days. As seen in the table, the mean length of hospital stays was 9.22 days (Table 4).

Table (4): Drainage amount, total dose of streptokinase and results

Variable	Value
Total dose of streptokinase	
750000-1500000	18 (60%)
> 1500000	12 (40%)
Results after one week	
Complete improvement	21 (70%)
Partial improvement	7 (23.3%)
No response	2 (6.7%)
Duration of chest tube insertion (days)	8.25±2.05
Total pleural fluid drainage (mL)	
Before streptokinase injection	314±70.8
After streptokinase injection	878±168.6
Hospital stays	
Mean±SD	9.22±1.72
Range	(6-14)

SD: standard deviation

The patient was either discharged or continued receiving treatment for the initial pathology after the chest tube was withdrawn in the successful group. We began planning for surgical intervention (decortication and evacuation) for three individuals who had limited or no response. Other problems were extensively examined in the patients. Six patients experienced brief chest pain and coughing, whereas fever and bleeding were less common (Table 5).

Table (5): Complications of streptokinase injection

Complication	No	%
Chest pain	6	20%
Cough	6	20%
Bleeding	4	13.3%
Fever	3	10%
Decortications	3	10%
Anaphylaxis	0	0%
Death	0	0%

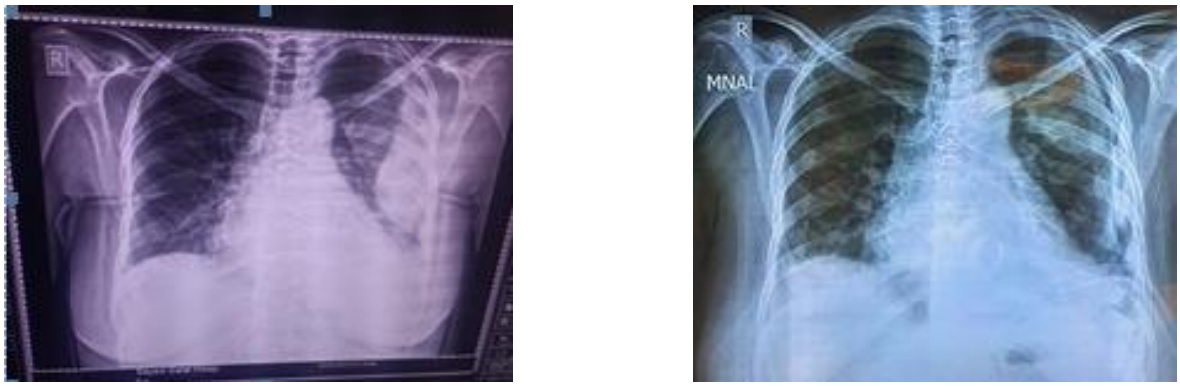

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Figure (1): Chest X-ray of 54 years old female patient with left sided pleural effusion before thoracocentesis (a) and 7 days after streptokinase injection (b).

DISCUSSION

This study involved 30 patients with persistent loculated or collected empyema. We made an effort to gather more information about the effectiveness and safety of injecting fibrinolytics intrapleurally to treat such situations. Patients ranged in age from 20 to 65 (mean 45.53 years), and the vast majority were men (n=26, 86.7%), which is in line with recent research that showed a preponderance of males [8-11]. This might be because men engage in more outdoor activities, making them more vulnerable to trauma and infections.

Regarding clinical manifestations, dyspnea (93.3%) was the most frequent symptom, followed by chest discomfort (53.3%), a cough (40%) and a fever (26.7%). In **Singh *et al.*** study's [9], 90% of the participants in the streptokinase group had cough and fever, 80% had dyspnea, and 10% had chest discomfort and gastrointestinal (GI) symptoms. In the study by **Reza *et al.*** [10], the most common complaints were fever (81%), cough (72%), shortness of breath (66%), chest discomfort (59%), and appetite loss (34%). According to a recent study by **Saxena and Maturu** [11], the most prevalent symptoms included fever (68.2%), cough (77.3%), dyspnea (89.4%), loss of appetite (57.6%), weight loss (54.5%), and chest pain (36.4%).

The improvement in clinical, laboratory, and radiological outcomes was used to assess streptokinase's impact. Our investigation found a significant rise in the mean drainage volume between the time before and after streptokinase injection (from 314±70.8 mL to 878±168.6 mL respectively). **Saxena and Maturu** [11] discovered that the average amount of fluid drained by using the streptokinase was 1,379.23± 771.9 mL. Also, **Bouros *et al.*** [15], reported that the total amount of fluid evacuated following therapy for streptokinase was 1,596±68 mL, which is higher than our statement.

Regarding the success rate of the streptokinase injection in the current study, complete improvement with good lung expansion happened in 21 patients (70%), partial improvement in 7 patients (23.3%) and failure in 2 patients (6.7%). Our findings concur with those of **Diacon *et al.*** [16], who reported an 82% success rate. 67% success was reported by **Taylor *et al.*** [17]. 92% success was achieved by **Jerjes-Sanchez *et al.*** in 1996 [18].

Reza and colleagues [10] found that 56% of patients completely improved, 16% completely failed, and 28% partially failed. According to **Saxena and Maturu**, 43.75% of patients after streptokinase experienced complete radiological clearance, while 18% of patients saw partial response. 6 of the 13 patients who did not react to treatment needed additional treatments, including thoracoscopic adhesive lysis (n=3), surgical decortication (n=2), and relocation of the pigtail catheter (n=1). It is difficult to pinpoint the exact cause of success variability, but it may be related to a variety of things, including case selection, experience, and techniques of results evaluation [11].

Regarding the adverse events that happened in the current study, 20% of the recruited patients reported temporary chest pain and cough, 13.3% experienced bleeding, and 10% experienced fever after receiving streptokinase instillation. Neither a serious allergic reaction nor any harmful side effects was found. Only one instance of moderate, temporary chest discomfort with streptokinase instillation was documented by **Taylor *et al.*** [17]**.** Between the fourth and seventh day following the start of treatment, the positive effects of streptokinase become apparent.

Reza *et al.* study found that 2% of participants had an inexplicable fever and 4% experienced a burning feeling in their chest. Decortication was necessary for 24% of patients receiving streptokinase and 60% of patients receiving a placebo [(10)].

Pain was the most frequent side effect seen following fibrinolysis (91.1%) according to **Saxena and Maturu's** study [(11)]. In the streptokinase group, 14.3% of patients experienced fever following fibrinolysis. Two patients experienced hemorrhagic conversion of pleural effusion, and one patient experienced an allergic reaction to streptokinase. Five patients experienced adverse events that were treatment-limiting. Acute pain (n=1), hemorrhagic conversion (n=2), an allergic reaction (n=1), and hypoxia (n=1) were among them.

Only 3 patients (10%) with partial or no response were scheduled for surgical intervention in the current study due to a considerable reduction in surgical referrals (decortication and evacuation). In keeping with our findings, research by **Diacon *et al.*** [(16)] discovered lower referral rates for surgery and higher success rates in the streptokinase group. According to a meta-analysis research by **Cameron and Davies** [(19)], streptokinase aids in shortening hospital stays and observable radiographic improvements, however these trials offer no insight into fibrinolytics' role in lowering mortality and the necessity for surgery. There was no discernible difference between the streptokinase group and the placebo group in terms of referral for surgery, according to **Thomson *et al.*** findings in another research they did in 2002 with 24 patients [(20)].

These worries appeared to be confirmed by a sizable study published in 2005 by **Maskell and colleagues** that tested the use of intrapleural fibrinolytics in complex pleural effusions. 427 individuals got an intrapleural injection of either streptokinase or a placebo. The key outcomes of the study—the number of deaths or the requirement for surgical treatment—were not significantly different between the groups (streptokinase 31%, placebo 27%; p=0.43). Furthermore, there was still no conclusive evidence of a benefit of streptokinase use when secondary outcomes including rates of death, surgery, length of hospitalization, and radiographic improvement were taken into account. In fact, the study found that the streptokinase group experienced more severe adverse events (7% vs. 3%; p=0.08) [(21)].

An attempt was made to gather everything together in a 2008 Cochrane collaborative review. Although there seems to be an overall potential benefit, the authors came to the conclusion that results needed to be interpreted carefully. They noted problems such heterogeneous data, poor trial quality, and an excessively large confidence range that made it challenging to rule out the possibility of negative impacts [(19)].

Streptokinase has a range of recommended dosages and daily injection requirements. However, other studies have done considerably smaller instillations for 5 days or less with good results. Some researchers have reported a single instillation each day for 7 days or even longer [(15, 17,22)]. In order to increase effectiveness, one study recommended more than one injection every day [(23)].

The primary goal of this trial should ideally have been at least 1-year death, and the secondary endpoint should have been severe morbidity. Due to the relatively limited sequential number of patients with parapneumonic effusions and empyema, this would have necessitated the inclusion of a large number of patients over a very long period of time. This issue may have been resolved by bringing in patients from other hospitals to make the study multicenter, but that would have required more funding than what was available for this project.

CONCLUSION

Intrapleural fibrinolytics can facilitate pleural fluid drainage and may be a safer, simpler, and more affordable management choice. In our study, we took into account the high rate of clinical improvement (70%) as well as the acceptable safety and efficiency of the intrapleural streptokinase injection procedure in the treatment of empyema, which resulted in a lower incidence of surgical referral. Important questions about their routine administration, the ideal dose schedule, and potential severe adverse effects are still needed to be answered.

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