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Intra Pleural Streptokinase in Management of Empyema, Is It Beneficial?

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ABSTRACT

Background: Around 15-20 % of patients suffering from parapneumonic effusion their condition is complicated by empyema. Despite treatment using aggressive antibiotics, it is associated with significant morbidity and mortality. Drainage of the collection in early stage by intercostal tube with administration of proper antibiotics according to the culture and sensitivity is considered the cornerstone of treatment. Intrapleural fibrinolytics as streptokinase is gaining more popularity.

Objective: This study aimed to show the advantages of adding streptokinase to the protocol of conservative management of empyema by studying its effectiveness and safety.

Patients and Methods: Our study was conducted on 58 patients on retrospective analytical manner through the period from December 2017 to March 2021 at Kasr Alainy Hospitals. All patients in this study were complaining of empyema following pneumonia. The diagnosis was based on frank pus aspiration from the pleural collection appeared on chest radiography (X-ray, ultrasonography or CT), confirmed by the results of bacteriological culture and gram staining of retrieved samples. Those patients received intrapleural instillation of streptokinase.

Results: Mean age of patients was 49. 2 years. The majority of them were males (n=42, 72. 4 %) and females were 16(27. 6 %). According to the causative organisms, Staphylococcus aureus was the commonest (n=31), kleibsiella (n=6), E. coli (n=5), pseudomonas (n=3), mixed (n=2) and others (n=2). Successful treatment occurred in 43 patients (74.1%), partial success in 13 patients (22.4%) and failure of treatment in 2 patients (3.5 %).

Conclusion: In our study, intrapleural instillation of fibrinolytics was a safe and effective procedure in management of empyema with decreased incidence of surgical referral.

Keywords: Empyema, Intrapleural instillation of streptokinase, Para pneumonic effusion.

INTRODUCTION

Empyema refers to the accumulation of pus in the pleural space, around 15-20 % of patients suffering from parapneumonic effusion post pneumonia suffer from empyema[(1)]. Empyema is classified into three stages according to the American Thoracic Society; Exudative phase (stage I) at which fibrin deposits on both pleural surfaces as reaction to infectious agent, fibrinopurulant phase (stage II) is an intermediate phase characterized by fibrous septations and loculations and organizing phase (stage III) is alate stage characterized by spider web and thick pleurae preventing lung expansion due to prolonged enhancement of fibroblastic activity[(1)].

Despite treatment using aggressive antibiotics, it is associated with significant morbidity and mortality[(2, 3)]. Drainage of the collection in early stage by intercostal tube with administration of proper antibiotics according to the culture and sensitivity is considered the cornerstone of treatment[(4)].

Septations and fibrous pleural loculation are common radiological signs, which carry a bad prognosis in management of empyema and make drainage of pleural collection more difficult[(5, 6)]. To overcome this problem there is many surgical techniques used to treat such condition as conventional rib resection and drainage or video assisted thoracoscopic evacuation[(7)].

In recent era, intrapleural fibrinolytics as streptokinase are gaining more popularity. Streptokinase can help in destruction of pleural fibrin bands and open the other difficult loculi, which makes better drainage [(8, 9)]. Three studies emphasized the positive effectiveness of using fibrinolytics in treatment of empyema, which had an impact both on the clinical and radiological parameters [(10, 11, 12)]. The use of intrapleural injection of streptokinase can decrease the period of hospital stay and intensity of fever and improve drainage of the collection [(11, 12)]. In this study we aimed to investigate the advantages of adding streptokinase to the protocol of conservative management of empyema by studying of its effectiveness and safety.

PATIENTS AND METHODS

Our study was conducted on 58 patients on retrospective manner through the period from December 2017 to March 2021 at Kasr Alainy Hospitals. All patients in this study were complaining of empyema following pneumonia. The diagnosis was based on frank pus aspiration from the pleural collection that appeared on chest radiography (X-ray, ultrasonography or CT), which was confirmed by the results of bacteriological culture and gram staining of retrieved samples. Those patients received intrapleural instillation of streptokinase.

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Exclusion criteria: Patients with long standing empyema, bleeding tendency, recent trauma, recent operation and on anticoagulation. In addition, patients that suffered from allergy from streptokinase, coma, severe hypertension, peptic ulcer, aortic aneurysm, aortic dissection, infective endocarditis and terminal malignancy.

All of our patients were subjected to the following:

1. Full history.
2. Full clinical examination.
3. Routine laboratory investigations including bleeding profile.
4. Pleural fluid PH and chemistry (LDH, protein, glucose).
5. Chest X-ray or CT.

All patients were admitted to hospitals at which intercostal tube inserted with large size 34-36F. Pus samples were used for bacteriological culture and sensitivity and gram stain. Following the intercostal tube insertion the amount of drainage was estimated and daily chest X-ray was done. Routine CT chest every three days and before discharge. We started giving a combination of antibiotics empirically at first then according to culture and sensitivity once results appeared. If the inserted tube was not in the proper position it can be reinserted again under sonographic guidance.

Streptokinase can be administrated at least 24 hours after intercostal tube insertion. The daily dose was 250,000IU diluted with 50-100 ml normal saline. It can be repeated up to 14 days. Streptokinase was administrated on lateral position to be sure that the whole volume entered the chest, then clamping the tube very proximal as we can. Clamping of the tube for 2-4 hours and then reopen again. During the period of clamping ask the patient to change his position between supine, prone, right lateral, left lateral and sitting position. Administration of streptokinase slowly over 5 minutes. At any time of occurrence of severe complications from this maneuver we can stop the procedure. Follow up amount of daily drainage, fever, pain, number of doses of streptokinase and duration of hospital stay.

Good results were defined from the adequate pleural drainage, reasonable radiological picture with subjective and objective improvement of the clinical condition and controlling of systemic infection. Criteria of failure and surgical intervention is presence of residual space or collection on chest-X ray or CT with progressive deterioration of the clinical condition beyond 2 weeks of insertion. In group of patients with good response to streptokinase chest tube was removed and we continued to treat the underlying etiology. In the other group with failure or incomplete response to streptokinase, surgical interference was decided either by conventional method or video assisted thoracoscopy (VATS) according to surgeon preference.

Ethical approval:

The study was approved by the Ethics Board of Cairo University and an informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were collected and entered on a 'Microsoft Excel' spreadsheet. Analysis was performed with SPSS version 20.0 software. Continuous variables were summarized by mean and standard deviation, where categorical variables were described by number and percent. Student's t-test was used to compare between volume drained before and after streptokinase instillation. A two-tailed p <0.05 was considered statistically significant. Statistical significance for the present study was considered at $P \leq 0.05$ (only two tailed).

RESULTS

Patients and clinical profile:

Age of patients ranged from 25 to 68 years with mean of 49.2 years. The majority of them were males (n=42, 72.4 %). Females were 16 (27.6 %). Table (1) showed preoperative clinical variables.

Table (1): Clinical variables

Age (years)	
Range	25 – 68 years
Mean ± SD	49. 2 ± 12.7
Sex:	
Male	n = 42 (72.4%)
Female	n = 16 (27.6%)
Duration of Illness	14 – 78
Mean ± SD (days)	35. 6 ± 7.2
Comorbidities:	
Cardiac disease	n=3
Respiratory disease	n=2
Kidney disease	n=1
Liver disease	n=2

Microbiological and laboratory characteristics:

Exudative effusion in empyema characterized by: PH< 7.2. Specific gravity > 1018 Kg/L. Pleural to serum protein > 0.5. Pleural to serum LDH > 0.6. Pleural LDH > Two thirds of upper limit of serum LDH.

According to the causative organisms, Staphylococcus aureus was the commonest (n=31), kleibsiella (n=6), E.coli (n=5), pseudomonas (n=3), mixed (n=2) and others (n=2) (Table 2).

Table (2): Causative organism

Bacteria	Number	Percent
Staph. aurious	31	53.45 %
Kleibsiella	6	10.34 %
E. coli	5	8.62 %
Pseudomonas	3	5.2 %
Mixed	2	3.44 %
Others	2	3.44 %
Negative culture	9	15.51 %

Radiological imaging:

Chest X-ray and CT scan were done for all patients. Chest ultrasonography was done for repositioning of the site of chest tube or in reinsertion of new dependent one. All of them had residual collection with pleural septations or loculation. The amount of drained fluid collected daily was calculated. The results of streptokinase was evaluated according to the amount of daily fluid drained and the picture of the chest X-ray and CT scan. Successful results meant complete lung expansion with decreased amount of drainage to less than 100 ml/day. In partial response there was partial decrease in the amount of collection and more improvement of lung expansion but not a complete expansion. In failed group there was still presence of residual large loculi and large amount of drainage as shown in table (3).

Table (3): Results, total dose of STK and drainage amount

Results: Successful Partially Successful Failure	(n=43, 74.14%) (n= 13, 22.41 %) (n= 2, 3.45 %)			
Amount of Streptokinase: Successful Group Partially Successful &Failure Group	(1, 000, 000 to 3, 250, 000 IU) (750, 000 to 1. 500. 000 IU)			
Amount of Drainage:				
	Mean	**SD**	**Mean Difference**	**P. value**
Before	264.6	158.2	897.8	<0. 001
After	1162.4	723.1		

In successful group the chest tube was removed and the patient was discharged or continued to treat the original pathology. In the groups with partial response or failure we started to arrange for operative intervention (decortication and evacuation). Patients were carefully assessed for complications. Transient chest pain occurred in 8 patients whereas fever and cough were less frequent (Table 4).

Table (4): Complications

Complications	Number	Percentage
Pain	8	18.3 %
Fever	2	3.4 %
Cough	1	1.7 %
Anaphylaxis	0	0 %
Death	0	0 %

DISCUSSION

Intrapleural infection carries high risk of morbidity and mortality among patients. Numerous management protocols have been designed for treating these cases. Till now there was no single standard guidelines followed for management of empyema[13].

Fibrinolytic agents first used for management of Para-pneumonic effusion and empyema in 1949. More purified streptokinase (SKT) was reintroduced in 1977, which carries less side effects of allergic reactions. STK can dissolve fibrin clots and membranes. Over 70 years of using of intrapleural streptokinase in management of empyema and loculated effusion, but the timing of best use and stage of empyema is still debatable [14].

This study was conducted on 58 patients suffering from empyema with residual collection or loculation. We tried to accumulate more data regarding the efficacy and safety of intrapleural instillation of fibrinolytics for management of such cases. Age of patients range from 25to68years (mean 49.2years).The majority of them were males (n=42, 72.4%). Regarding amount of drainage before and after streptokinase instillation, our study showed marked increase in drainage amount, which was statistically significant (P <0. 001).

The effect of streptokinase is evaluated by clinical, laboratory and radiological improvement. Successful improvement occurred in43 patients (74.14%), partially successful response occurred in 13 patients (22.41 %) and failure occurred in 2 patients (3. 45 %). Our results are in agreement with **Diacon *et al.*[15]** who recorded 82% success. **Taylor *et al.*[16]** recorded 67% success. **Sanchez *et al.*[17]** recorded 92% success. The variability of success cannot precisely explained, it may be related to many factors as selection of cases, experience and methods of evaluation of the results.

Regarding complications, there was transient chest pain (18.3 %), cough (1.7 %) and fever (3.4 %) detected in our study. No severe allergic reaction, severe bleeding or major adverse side effects. **Taylor *et al.*[16]** recorded only one case suffering from mild transient chest pain following streptokinase instillation.

The beneficial effect of streptokinase becomes evident between the fourth and seventh day after initiation of treatment. There was a significant reduction for surgical referral noticed. In a study conducted by **Diacon *et al.*[15]**, they found higher success rates in the streptokinase group with few referrals for surgery.

In a met analysis study conducted by **Cameron and Davies[14],** they concluded that streptokinase helps in decreasing the hospital stay along with observed

radiological improvements but these trials do not provide an insight to fibrinolytics effect in reducing the mortality and need for surgery.

In another study conducted by **Thomson *et al.*** [11] among 24 patients, comparison between streptokinase group and placebo group effect, they found that there was no significant difference between the two groups.

CONCLUSION

In our study, intrapleural instillation of fibrinolytics is safe and effective procedure in management of empyema with decreased incidence of surgical referral.

Table of abbreviations

CT	**Computed Tomography**
CXR	**Chest X Ray**
IU	**International Unit**
LDH	**Lactate Dehydrogenase**
n	**number**
Nacl	**Sodium chloride**
SD	**Standard Deviation**
STK	**Streptokinase**
VATS	**Video Assisted Thoracoscopy**

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