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Outcome of Intrapleural Streptokinase in Parapneumonic Loculated Pleural Effusion

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ABSTRACT

Background: Parapneumonic pleural effusion needs drainage by small drain or chest tube, but when becomes loculated it needs surgery, which can be avoided by using intrapleural streptokinase (SK).

Objectives: This study aimed to assess the outcome, efficacy and safety of intrapleural streptokinase in management of parapneumonic loculated pleural effusion.

Methods: A prospective study through the period from May 2020 to May 2024 included 45 patients presented with parapneumonic pleural effusion in which chest tubes were inserted. Effusion was not fully drained because of septations. Streptokinase was tried in these patients. Our protocol was using 250,000IU in 50 ml normal saline injected intrapleural. The same dose can be repeated every 48 hours to maximum of ten trials. Close observation for pain, anaphylaxis, fever or any complication.

Results: There was a highly significant increase in intercostal chest tube (ICT) drainage (p=0.003) after streptokinase injection. Patients had average doses of 4-10 (7.5 ± 1.94). Resolution occurred in 36 patients (80%). Patients under the age of 40 years showed a significantly higher success rate than older patients (p=0.03). There was significant association between starting streptokinase treatment from the beginning of symptoms and resolution (p=0.001).

Conclusion: Streptokinase had safe, efficient and good outcome in parapneumonic loculated pleural effusion. The outcome was significantly better in young patients (< 40 years) and in patients started streptokinase in the first ten days of their symptoms.

Keywords: loculated pleural effusion, Parapneumonic pleural effusion, Streptokinase.

INTRODUCTION

Para-pneumonic effusion occurs in up to 40 % of patients with pneumonia [1], it can be simple exudation or complicated para-pneumonic effusion [2].

The outcome is usually good but complications can occur like chronic empyema, loculation, sepsis, multi-organ failure or death [3, 4] so proper drainage should be done [5, 6].

Loculated effusion is diagnosed by chest US or CT where septations are dividing the pleural space into multiple loculi [7]. Simple effusions can be managed medically, but thick ones need ICT when free. Loculated effusions management ranges from ICT in the biggest loculus, Fibrinolytic injection, US/CT guided drainage, and video assisted thoracoscopic surgery (VATS) or thoracotomy [8].

First fibrinolytic was used in 1949 for management of post-pneumonic effusion, but stopped because of allergic reactions [9, 10]. Later, purified streptokinase became available that encouraged its usage for intrapleural fibrinolysis [11- 13].

Recently, multiple fibrinolytic agents like urokinase, streptokinase and alteplase have been used for drainage of loculated effusion [14, 15]. Thus the aim of the study was to assess the outcome, efficacy and safety of intrapleural streptokinase in management of parapneumonic loculated pleural effusion.

METHODS

This multicenter prospective study included 45 patients presented to Asser Central Hospital, Khamis Mushait General Hospital, KSA and Cardiothoracic Surgery Department, Menoufia University Hospitals, Egypt, between May 2020 and May 2024 with parapneumonic loculated pleural effusion.

Inclusion criteria: All patients with para-pneumonic loculated pleural effusions with failed complete drainage by ICT after 48 hours from insertion.

Exclusion criteria: Patients on anticoagulants or with active bleeding, bleeding disorders, abnormal coagulation profile, severe trauma, cerebrovascular accident or stroke within the past two months.

All patients had intercostal chest tube (ICT) but it does not drain all the effusion after 48 hours of insertion because of the pleural septations, so streptokinase was tried in these patients.

Detailed history was taken and complete examination, X-ray, chest US and CT were done before and 48 hours after ICT insertion. Streptokinase 250,000 IU in 50 ml of normal saline was injected in the pleural cavity through the ICT, then the ICT was clamped for 4 hours, during which the patient was kept in bed with position changing every half an hour. The same dose was

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repeated every 48 hours to a maximum of 10 doses. Daily follow up of the amount of drainage and radiological changes were done. Close observation for pain, anaphylaxis, fever or any other complication related to streptokinase injection.

According to the residual pleural collection and septations together with improvement in chest X-ray (CXR), chest US and CT, the degree of improvement was classified as follow: 0: No improvement, 1: Less than 1/3 improvement, 2: Between 1/3 and 2/3 improvement, 3: More than 2/3 improvement, 4: Total improvement without any residual effusion, and according to this the patients were divided into three groups:

- **Group (A):** (Failed group) aborted due to ICT drainage less than 100 ml after two frequent doses or no radiological improvement (degree 0) or occurrence of severe complications like sever pain, severe anaphylaxis or hemodynamic instability.
- **Group (B): (**Partial Responders) completed the protocol with partial radiological improvement (degree 1and 2). **Group (C):** (Responders) complete or nearly complete radiological improvement with marked clinical improvement (degree 3 and 4). Failed and partially responders groups were assessed for the feasibility, risk and benefits of surgical intervention. In the responders group, ICT removed and medical treatment continued with radiological follow up.

Ethical approval: This investigation received ethical clearance from The Research Ethics Committee, Faculty of Medicine, Menoufia University. All subjects provided written informed consents prior to their participation. The consent process included explicit information about data use and publication, with guarantees of privacy and confidentiality. The study conformed to the principles of the World Medical Association's Declaration of Helsinki.

Statistical Analysis

Results were collected, tabulated, and statistically analysed by an IBM compatible personal computer with statistical package of the social sciences, version 20 (SPSS Inc. released 2011, IBM SPSS statistics for windows, version 20.0; IBM Corp., Armonk, New York, USA). Data were expressed as mean ± SD for continuous variables, and as percentages for categorical variables. Chi- squared test (χ^2) was used to check for significance and p value $\leq$ 0.05 was considered significant. Independent sample t test was applied to look for mean drain output before and after SK.

RESULTS

Our study included 45 patients presented with loculated parapneumonic pleural effusion, their demographic data, clinical characteristics and risk factors were demonstrated in table (**1**).

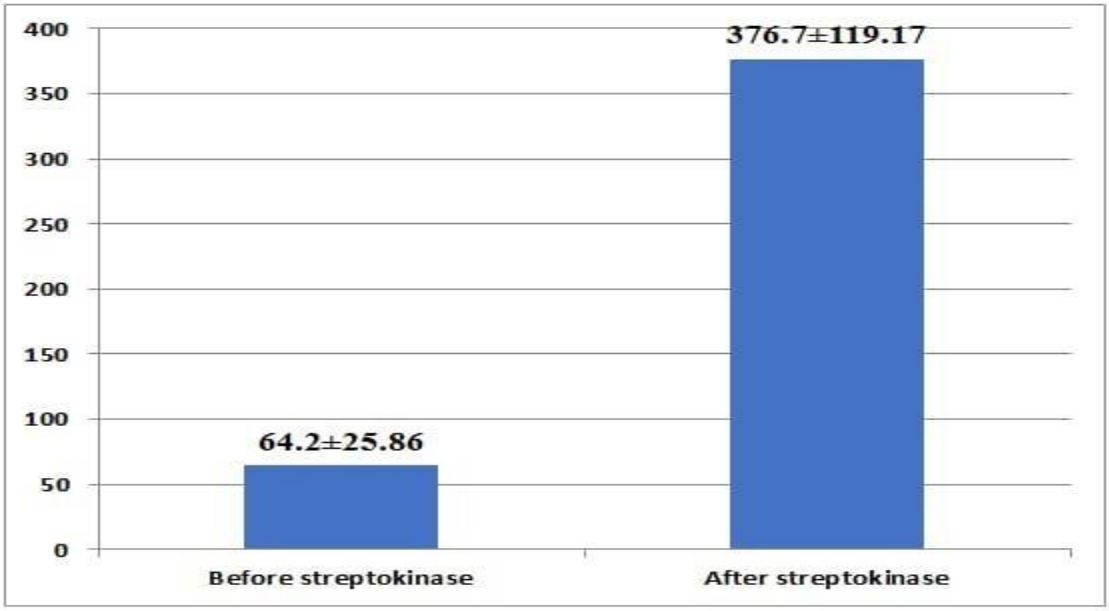
Table (1): Demographics and clinical data

Variable		Value	Percentage
age (Years)	Range	16-78	
	Mean ± SD	36 ± 16.79	
sex	male	34	75.56%
	female	11	24.44%
DM	Diabetic	16	35.56%
	Non diabetic	29	64.44%
Duration of symptoms (Days)	First 10 days	32	71.11%
	After 10 days	13	28.89%

DM, diabetes mellitus; SD, standard deviation.

After streptokinase injection, there was a highly significant increase in the drainage amount (p=0.003) as the mean drain output before streptokinase was 64.2 ± 25.86 (range 10 - 100 ml) versus 376.7 ± 112.17 (range 100 – 500 ml) after streptokinase injection (Figure 1).

Figure (1): Mean amount of pleural fluid drainage



P=0.003

Complications happened in 7 patients in the form of pain (4) patients, hypersensitivity reaction (2) patients (One of them was very severe so no more doses were given and the other was mild and managed by one dose of IV steroids and antihistamine), and low-grade fever (1) patient. None of our patients had any bleeding complication. There was no mortality in our study group. With radiological follow up after streptokinase injection, three patients (6.67%) showed no improvement (class 0), 2 patients (4.44%) showed class 1, 4 patients (8.89%) showed class 2, 17 patients (37.78%) showed class 3 and 19 patients (42.22%) showed class 4 improvement according to pleural effusion amount, septations and loculi improvement (Table 2).

Table (2): Complications and Radiological follow up after Streptokinase

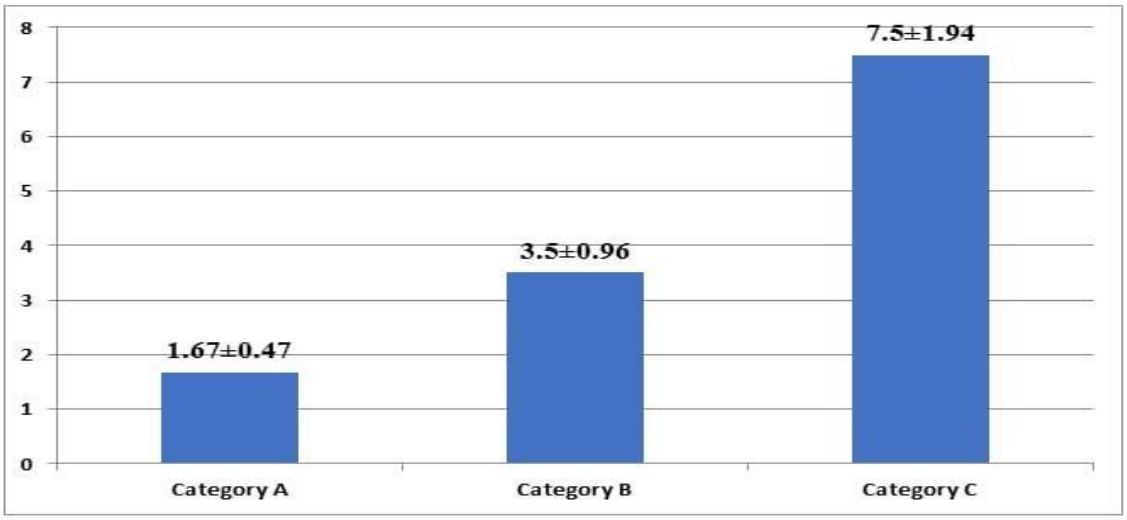
Variable		Number	Percentage
Complications	**Pain**	**4**	**8.89%**
	Hypersensitivity **- Mild** **- Severe**	**2** **1** **1**	**4.44%** **2.22%** **2.22%**
	Fever	**1**	**2.22%**
	Bleeding	**0**	**0%**
Degree of Radiological improvement	**0**	**3**	**6.67%**
	1	**2**	**4.44%**
	2	**4**	**8.89%**
	3	**17**	**37.78%**
	4	**19**	**42.22%**

Patients were divided into three groups:

- **Group A** (failed group): Included three patients, two of them did not show any clinical or radiological improvement after 2 doses (degree 0) and in the third patient streptokinase was discontinued due to severe hypersensitivity reaction.
- **Group B** (partial responders): Included six patients of our study group and they did not show significant clinical or radiological improvement (degree 1, 2). **Group C** (responders): Included 36 patients and they had complete or nearly complete radiological improvement (degree 3 & 4) with marked clinical improvement. The average number of doses of streptokinase used in every group were documented in figure (2), the average duration taken till improvement and chest tube removal was 11-25 days with mean 17± 4 days and the difference between succeeded (Group C) and non-succeeded (Group A and B) was very highly significant (p=0.004) (Figure 2).

The outcome between males and females was non-significant. Thirty out of 32 patients under the age of 40 years showed complete resolution (93.75%) compared to 6 out of 13 above the age of 40 (46.15%) and the difference was statistically significant (p=0.03). Patients who started streptokinase early within the first ten days of symptoms showed statistically significant improvement than those who started it later after 10 days (p=0.001) (Table 3).

Figure (2): Mean doses of Streptokinase in group A, B and C



P = 0.004

Table (3): Outcome in Correlation to Gender, Age and Timing of management

	Responders (Group C)	Non responders (Group A&B)	Number of patients	P value
Gender:				
-Male	**27 (79.41%)**	**7 (20.59%)**	**34 (75.56%)**	**0.29**
-Female	**9 (81.82%)**	**2 (18.18%)**	**11 (24.44%)**	
Age:				
≤ 40	**30 (93.75%)**	**2 (6.25%)**	**32 (71.11%)**	
- >20	**8(88.89%)**	**1(11.11%)**	**9 (20%)**	
- 21-40	**22(95.65%)**	**1(4.35%)**	**23 (51.11%)**	
< 40	**6 (46.15)**	**7 (53.84%)**	**13(28.89%)**	**0.03***
-41-60	**4(50%)**	**4(50%)**	**8 (17.78%)**	
-61-80	**2(40%)**	**3(60%)**	**5 (11.11%)**	
Timing of management:				
-First 10 days	**31(96.88%)**	**1(3.12%)**	**32 (71.11%)**	
-After 10 days	**5(38.46%)**	**8(61.54%)**	**13 (28.89%)**	**0.001***

* Significant.

DISCUSSION

Tillet and Sherry [10] were the first who used fibrinolytics for treatment of complicated parapneumonic effusion and empyema in 1949 but stopped because of allergic reactions. In 1977, purified streptokinase was used by **Bergh *et al.*** [16]. Since that time studies had been done to evaluate its outcome in parapneumonic loculated effusion and empyema. Many studies stated that it might be a safer, easier and cost-effective option for management of loculated pleural adhesions [17].

In our study, the mean age of patients was 36 ± 16.79 and patients under the age of 40 years showed a significant improvement compared to those above the age of 40. The same was concluded by **Amit *et al.*** [18], and **Chin *et al.*** [19] who stated that the younger the age the better the resolution. This could be attributed to the better remoulding power, earlier presentation and less comorbidity in younger age group.

We used Streptokinase 250,000 IU in 50 ml of normal saline injected in the pleural cavity through the ICT and the same dose can be repeated every 48 hours to a maximum of ten doses and our success rate was 80%. This comes in agreement with what was reported by **Diacon *et al.*** [20], who recorded success of 82%. However, **Maskell *et al.*** [21] reached a maximum of 14 doses and the success rate was 65%.

In our study, 32 patients (71.11%) presented in the first 10 days from the beginning of symptoms while 13 patients (28.89%) presented after 10 days and there was a significant association between earlier presentation and improvement as 96.88% of patients presented early in the first 10 days were improved in comparison to 38.46% of patients presented late after 10 days, and this can be explained by the pathophysiology of the disease process in which streptokinase works best when the adhesions are at earlier stages where fibrosis has not yet developed. This is also noted by **Diacon *et al.*** [20] who also found that patients with earlier presentation have got high success rates and better outcome.

After streptokinase injection in the ICT the amount of drainage was closely observed daily and there was a highly significant increase in the drainage amount with a mean drainage of 64.2 ± 25.68 before versus 376.7 ± 119.17 after streptokinase injection. This significant difference was observed in most of the studies about intrapleural injection of streptokinase like those done by **Abu-Daff *et al.*** [17] and **Omar *et al.*** [22].

We reported complications in 7 out of the 45 patients (15.56%) of them only one showed a severe hypersensitivity reaction with no bleeding complication or mortality, so the procedure can be considered safe, which is similar to what is published by **Taylor *et al.*** [23] who stated that all patients tolerated intrapleural streptokinase well, but only one complained of mild chest discomfort shortly after each streptokinase instillation.

CONCLUSION

Streptokinase had a safe, efficient and good outcome in parapneumonic loculated pleural effusion patients with a success rate of eighty percent, the outcome was better in young patients less than 40 years and in patients presented in the first ten days of their symptoms.

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