Utility of Intrathoracic Strepokinas in Management of Chronic Empyemas

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Abstract

Background : The nonsurgical medical approach with use of fibrinolytic agent is an alternative modality in management of chronic empyemas. With the introduction of purer forms of streptokinase, there has been renewed interest generated in the use of intrapleural thrombolytics with documented successful drainage of difficult to drain chronic empyemas. To evaluate the utility of streptokinase in the management of chronic difficult to drain empyemas in a single blind randomized case control study.

Material and Methods : Twenty four cases of chronic/multiloculated empyema were included which had cases preferred having loculations or multiloculations and failure of drainage via thoracostomies for less than 100 ml during last 24 hours. Cases were randomized into two groups as 12 cases of streptokinases group and 12 cases of placebo group. Streptokinase given as 2.5 lac units in 100 ml of normal saline instilled intrapleurally for 6 consecutive days. In control group, 100 ml of normal saline without streptokinase was instilled intrapleurally through intercostal drain for 6 days. They were assessed by amount of drainage through intercostal drain for six days after instillation of streptokinase/placebo, duration of intercostal drainage in situ, and radiological improvement by standard x-ray chest.

Results : The study revealed increased drainage through intercostal drain in streptokinase group compared to control group. The mean duration of intercostal drainage in situ was shorter in streptokinase group compared to control group. Radiologically, streptokinase group revealed score 3 improvement in eight out of twelve cases and score 2 improvement in rest of the four cases. In control group, score 1 improvement was seen in two out of twelve cases and no improvement was seen in rest of the 10 cases. The observation difference is found to be highly significant statistically (p <0.001). No major adverse effects were noted in the streptokinase group.

Conclusion : The study concludes the safety, efficacy, reduced hospital stay and decreased morbidity in patients treated with intrapleural streptokinase as compared to control group.

INTRODUCTION

The management of empyema was revolutionised in second half of this century by better understanding of its pathophysiology, bacteriology, advent of newer antibiotics and the ability to perform major thoracic surgery safely. The failure of first line of conventional therapy i.e., intercostal tube drainage and use of antibiotics occur when pleural fluid no longer flows freely. Multiloculations take place by formation of fibrin strands. Such types of patients with multiloculated effusion may not be amenable to antibiotics and tube drainage alone. Streptokinase dissolves loculations and septations permitting free flow of pleural fluid. Many authors have suggested the use of streptokinase for avoiding major thoracotomies.

The present study is undertaken to evaluate the utility of streptokinase in empyemas, chiefly with the understanding that drug would help in averting surgical interventions like decortication and prevent development of restrictive lung disease by breaking fibrinous septae in pleural space.

METHODS AND MATERIAL

Twenty four patients with multiloculated empyema were studied at Dept. of Medicine, Govt. Medical College and Hospital, Aurangabad.

Cases were randomized into two.
Group A - Streptokinase group - twelve cases
Group B - Control group - twelve cases.

All patients of empyema were diagnosed on pleural fluid cytology and radiology. Pleural fluid analysis included pH, glucose, proteins, lactate dehydrogenase (LDH), total and differential leucocyte count, microscopic examination, Gram’s staining and Ziehl-Neelson staining and culture. All patients were subjected for standard posteroanterior (PA) and lateral x-ray chest. Ultrasonography of chest/abdomen was carried out in all cases. Additional CT scan thorax in four cases were carried out in all cases. Additional CT scan thorax in four cases were carried out. The decision to insert chest tube followed the recommendations of Light.6

Following were the criteria’s for the selection of cases for intercostal drainage and streptokinase instillation.

1. Exudative pleural effusion as described by Light in 1991.
2. Pleural fluid with atleast one of the following:
   a. Total proteins >5 g/dl, grossly purulent.
   b. WBC count >20,000/microliter.
   c. Positive Gram’s stain/growth on culture
   d. pH <7.2
   e. Glucose <40 mg%
   f. LDH > 100 IU/L

Cases preferred having loculation or multiloculations and failure of drainage via thoracostomies for less than 100 ml during last 24 hours without radiological improvement. Drainage output was recorded after insertion of catheter and during last 24 hours. The etiology of empyema was presumed tuberculous origin. The diagnosis of tuberculous empyema was made using the following criteria.

1. Family history of tuberculosis
2. Biochemical criteria of exudative pleural effusion as described by Light.
3. Sputum or pleural fluid analysis for acid fast bacilli.
4. Associated lung parenchymal lesions consistent with radiological diagnosis of tuberculosis.
5. Negative routine bacteriological smear and culture.

Pleural biopsy was not carried out. Cases fulfilling above criteria were taken for the study as presumed tuberculous origin. Streptokinase was given as daily doses 2.5 lac units dissolved in 100 ml of normal saline instilled intrapleurally for six days through intercostals drain. Ultrasonography of chest abdomen was carried out in all cases. Additional CT scan thorax in four cases were carried out in all cases. Additional CT scan thorax in four cases were carried out. The decision to insert chest tube followed the recommendations of Light.6

Radiological arbitrary scoring system was used as described by Bouros et al7 as follows.
0 - no change
1 - less than 1/3 improvement
2 - improvement between 1/3 and 2/3
3 - more than 2/3 improvement

Observations and Results

The study group and control group consisted of twelve patients in each. Both the groups had 10 males and 2 females. The age ranged from 15-60 years in both the groups. All 24 cases in study group received antituberculous treatment as the initial and continuation phase therapy after due investigations. Out of 12 cases in the study group, four cases were having fluid AFB positivity while fluid AFB was positive in three cases in the control group.

All 12 patients in streptokinase group remained well and did not need further surgical interventions. The volume of pleural fluid drained following streptokinase instillation (after subtracting 100 ml) ranged from 990 ml - 3500 ml with mean of 1829 ± 750.14 ml in 6 days. Streptokinase was well tolerated by all patients. The chest tube drainage over six days after placebo i.e. normal saline instillation in the control group ranged from 130 ml - 480 ml (mean 270 ± 98.62 ml)

The mean volume of fluid drained in group A was 1829 ± 750.14 ml. The observation revealed that there was significantly higher volume of fluid drained in study group A as compared to group B (S.E. of difference between two means = 72.50, RD = 21.62) (Table - 1).

The duration of intercostal drain in situ after streptokinase instillation in group A ranged from 10-80 days with a mean of 28.08 ± 18.45 days whereas in control group the duration of intercostal drain in situ after placebo instillation ranged from 40 - 162 days with a mean of 100.25 ± 43.99 days. The difference in mean duration of intercostal drain between the two groups found to be significantly statistically (RD >2) (Table 1).
Fig. 1: X-ray chest PA view of the patient before streptokinase instillation showing hydropneumothorax

Fig. 2: X-ray chest PA view of the same patient 18 days after streptokinase instillation showing complete clearance

The radiological observations in streptokinase group revealed score 3 response improvement in eight out of twelve cases (Fig. 1, 2) and score 2 improvement in the remaining four cases while in the control group score 1 improvement was seen in 2 cases and score 0 (no improvement) was seen in remaining 10 cases. The difference was found to be statistically highly significant (p < 0.001) (Table 1).

Adverse reactions to streptokinase therapy are shown in Table 2. All patients had rise in temperature by an average one degree after giving streptokinase for two consecutive days. Two cases had massive expectoration 100-150 cc, 20-30 mts after streptokinase instillation lasting for twenty minutes. Six patients had mild ipsilateral chest pain 20-30 mts after instillation lasted for one and half to two hours.

This chest pain was noticed daily after instillation. ECGs taken during this period and afterwards were within normal limits. Transient hypotension was seen in one patient lasted for twenty minutes. No specific therapy was given. There was no evidence of anaphylaxis or intrapulmonary hemorrhage in any of the patient.

**DISCUSSION**

In chronic empyemas, despite intercostal tube insertion as well as aggressive antibiotic therapy some patients fail to recover by intercostal drainage. Most patients progress of fibrinopurulent stage with multiple loculations and viscous pus. Aggressive surgical therapy has been developed ranging from resection, open flap drainage to thoracoplasty. The use of intrapleural fibrinolytic agent is consumed for the first time by Tillet and Sherry in 1949. It is considered as a viable alternative to facilitate drainage and lung expansion in empyemas inadequately treated by chest tube alone.

Streptokinase, the first fibrinolytic agent described by Aye

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**Table 1: Comparative assessment of different variables of efficacy in streptokinase (A) and control group (B)**

<table>
<thead>
<tr>
<th>Parameters used</th>
<th>Group A (n=12)</th>
<th>Group B (n=12)</th>
<th>Test of significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean volume of fluid drained (ml)</td>
<td>1829.16 ± 750.15</td>
<td>270 ± 98.62</td>
<td>RD &gt; 2</td>
</tr>
<tr>
<td>Mean duration of ICD in situ (days)</td>
<td>28.08 ± 18.45</td>
<td>100.25 ± 43.99</td>
<td>RD &gt; 2</td>
</tr>
<tr>
<td>Mean radiological scoring#</td>
<td>2.67</td>
<td>0.17</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

*Statistical error of difference between two means is used to find out the statistical significance of amount of fluid drained and duration of ICD institu between streptokinase group and control group (RD > 2, statistically significant). Unpaired t-test is used to find out the statistical significance of radiological scoring between streptokinase group and control group (p value < 0.05, statistically significant); #Radiological scoring system is adapted as per method described by Bouros et al in 1994

**Table 2: Adverse reactions to intrapleural streptokinase therapy**

<table>
<thead>
<tr>
<th>Type of reaction</th>
<th>No. of pts.</th>
<th>Time from instillation</th>
<th>Duration of reaction</th>
<th>No. of days (out of 6 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain (Ipsilateral)</td>
<td>6</td>
<td>20-30 min.</td>
<td>1½-2 hrs.</td>
<td>First 2 days</td>
</tr>
<tr>
<td>Dry cough</td>
<td>2</td>
<td>20-30 min.</td>
<td>3-4 hrs.</td>
<td>First 3 days</td>
</tr>
<tr>
<td>Fever</td>
<td>12</td>
<td>4-6 hrs.</td>
<td>—</td>
<td>First 2 days</td>
</tr>
<tr>
<td>Hypotension (Reduction in systolic BP by 20-30 mm Hg)</td>
<td>1</td>
<td>5-10 min.</td>
<td>20-30 min.</td>
<td>First day only</td>
</tr>
<tr>
<td>Massive expectoration (100-150 cc)</td>
<td>2</td>
<td>20-30 min.</td>
<td>20 min.</td>
<td>First 2 days</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Nil</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>Nil</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Discussion**

In chronic empyemas, despite intercostal tube insertion as well as aggressive antibiotic therapy some patients fail to recover by intercostal drainage. Most patients progress of fibrinopurulent stage with multiple loculations and viscous pus. Aggressive surgical therapy has been developed ranging from resection, open flap drainage to thoracoplasty. The use of intrapleural fibrinolytic agent is consumed for the first time by Tillet and Sherry in 1949. It is considered as a viable alternative to facilitate drainage and lung expansion in empyemas inadequately treated by chest tube alone.

Streptokinase, the first fibrinolytic agent described by Aye.
et al. is a purified proteolytic enzyme derived from bacterial protein of group C beta hemolytic streptococci. Plasminogen is converted into proteolytic enzyme plasmin by streptokinase. Plasmin then degrades fibrin clots and fibrinogen.

The present study is undertaken making use of this purified streptokinase in management of multiloculated empyemas when the drainage even after intercostal tube placement is inadequate. Preferably we have chosen the cases belonging to one aetiology i.e. tuberculosis, to maintain infraposition alike in all cases. In the present study, radiological evaluation showed excellent improvement in eight out of twelve cases, moderate in four to twelve cases. Taylor et al. in 1994 found complete resolution in eight out of twelve patients. While, Sanchez et al. in 1996 found complete resolution in 44% with a success rate of 92%. Temes in 1996 in his study of 26 patients noted complete resolution in 44% with a success rate of 92%. Temes in 1996 in his study of 96 patients noted complete resolution in sixteen out of twenty six patients (62%), partial resolution in two out of twenty six patients (8%). Eight out of twenty six patients failed to improve radiologically or clinically in his series.

Various workers have used varied hours of clamping period after instillation of streptokinase intrapleurally. In practice, the clamping period after streptokinase instillation varied from 2 hours to 24 hours. It was suggested by Bergh et al. in 1977 that shorter instillation time of four hours combined with use of purified preparation contribute to lack of adverse reactions.

In our study, dose used was 2.5 lac of purified streptokinase with clamping period of three hours. Dose of 2.5 LU was prepared and given after re-constituting vial of 7.5 LU (the vials were preserved at 2-8°C). And the remaining streptokinase doses were given from the same re-constituted vial on subsequent days merely to minimize the cost of therapy. The advocacy for immediate use/use within 8 hours after re-constitution is made for the intravenous/intracoronary use, without any mention for intra pleural utility. Results, so achieve, with the same re-constituted vial for the usage for the purpose were excellent as assessed by daily enhancing pleural output without any major side effects. Sharma and colleagues (1998) reported a case on intrapleural streptokinase in multiloculated empyema thoracic used vial of 7,50,000 U utilizing 2.5 LU immediately after reconstitution and the next dose of 2.5 LU was withdrawn from the same vial after 12 hours merely to minimize the cost of therapy.

No major adverse reactions noted in the present study. Although bronchopleural fistula is considered a relative contraindication for instillation of streptokinase, the present studied cases signify the importance of instillation of this drug with relative beneficial outcome. One patient had profuse expectoration (owing to opening of obliterated bronchopleural fistula after streptokinase instillation) almost drowning in secretions due to drainage of empyema fluid through this path needed active attention for preventing asphyxia. Proper vigilant suction and throat toilet is required.

Intrapleural purified streptokinase may be used as an adjunct to initial chest tube drainage when there is residual collection of pleural fluid. Streptokinase enhances the drainage of fluid, which is loculated or too viscous to be drained by tube thoracostomy alone. Subsequent surgical intervention is not jeopardized by the prior use of streptokinase.

The study concludes the safety, cost effectiveness, efficacy, reduced hospital stay and decreased morbidity in patients treated with intrapleural streptokinase as compared to control group. However, each patient should be evaluated individually with consideration of stage, characteristics of empyema and condition of the patient.

**References**

14. Sanchez J, Rivera AR, Elizalde JJ, Delado R, et al. Intrapleural fibrinolysis with streptokinase as an adjunctive treatment in...


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