Controlled Trial of Intrapleural Streptokinase in the Treatment of Pleural Empyema and Complicated Parapneumonic Effusions*

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Objective: To compare the efficacy of adjunctive intrapleural streptokinase (SK) with simple closed chest tube drainage (Drain) in the treatment of empyemas and complicated parapneumonic effusions.

Method: This was a controlled study of 52 patients (mean age, 57 years; 41 men) with pleura space sepsis. Forty patients (77%) had empyema and 12 had complicated parapneumonic effusions. Twenty-nine patients were treated with Drain only while 23 received, in addition, repeated daily SK, 250,000 U in saline solution (mean, 5.3 days).

Results: The two groups of patients had comparable degrees of peripheral blood leukocytosis, frequency of loculated effusions, pleural fluid pH, and lactate dehydrogenase levels. Infective organisms were isolated in 54% of which 32% were anaerobic and 21% were polymicrobial infections. The incidence of surgical decortication was 17% and mortality was 15%. A significantly larger volume of pleural fluid was drained from patients in the SK treatment group (2.0 [1.5] L) than those in the Drain treatment group (1.0 [1.01] L). There were no significant differences, however, between the two treatment groups in terms of duration before defervescence, duration of hospital stay, the need for surgical intervention, or mortality rates.

Conclusion: We conclude that thrombolytic therapy increased the volume of fluid drained from pleural empyemas but did not markedly reduce morbidity and mortality.

(CHEST 1997; 111:275-79)

Key words: decortication; empyema; parapneumonic; pleural effusion; streptokinase; thoracoscopy

Abbreviations: Drain=simple tube drainage; LDH=lactate dehydrogenase; SK=streptokinase

Pleural empyema is a serious complication of pneumonia associated with substantial morbidity and mortality.1-3 Treatment of pleural empyemas is based on early diagnosis and prompt evacuation of the pleural cavity.1,3-7 Failure to empty the infected pleural cavity may result in deposition of fibrin with formation of multiple pleural loculations. This very often leads to delayed resolution, further pleural suppuration, and a prolonged hospital stay with the need for costly and risky surgical intervention.2,7

The intrapleural administration of thrombolytic agents has been used to treat empyema for more than 40 years.8 It may prevent pleural fibrogenesis and facilitate drainage of pleural collections. This approach did not receive wide acceptance until the recent introduction of newer thrombolytic formulas with better safety profiles.9,10 This has resulted in renewed interest in these agents as an adjunctive treatment modality for empyema. A large number of reports have attested to the safety and efficacy of intrapleural thrombolysis in the treatment of thoracic empyema.9,16 None of these studies, however, has directly compared pleural thrombolysis with simple tube thoracotomy in the treatment of patients with pleural empyema. Since the management of empyema requires a multidisciplinary approach with key contributions from interventional radiologists and thoracic surgeons whose skills and expertise may vary between different hospitals, studies comparing different treatment regimens should recruit patients from the same institution.

We report a controlled study that compared intrapleural streptokinase (SK) with simple tube drainage (Drain) in the treatment of 52 patients with complicated parapneumonic pleural effusions and frank empyema.
Table 1—Clinical and Demographic Information:* Mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>SK Group</th>
<th>Drain Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>Age, yr</td>
<td>50 (19)</td>
<td>63 (14)</td>
</tr>
<tr>
<td>Sex ratio, M/F</td>
<td>18/5</td>
<td>23/6</td>
</tr>
<tr>
<td>Underlying disease, %</td>
<td>48</td>
<td>59</td>
</tr>
<tr>
<td>Blood TWBC, ×10⁹/L</td>
<td>18,200 (8,360)</td>
<td>16,210 (8,400)</td>
</tr>
</tbody>
</table>

*Underlying disease: frequency of occurrence of diabetes mellitus and chronic lung diseases. TWBC=total WBC count. There were no statistically significant differences between the two groups.

Materials and Methods

This was a 5-year (1990 to 1995), prospective study of 52 consecutive patients admitted to the hospital with community-acquired empyema and complicated (high-risk) parapneumonic effusions.³ Empyema (40 patients) was defined according to one or more of the following criteria: (1) grossly purulent fluid; (2) positive fluid culture; and (3) positive Gram stain for bacteria.³ Complicated parapneumonic effusions (12 patients) were defined according to Light¹ viz (1) pH < 7.00 or (2) lactate dehydrogenase (LDH) level > 1,000 U/L. Patients with tuberculous, hospital-acquired, posttraumatic, and postoperative empyemas were excluded.

Diagnostic thoracentesis with a 14-gauge venula was performed for all patients on hospital admission. The pleural fluid samples were sent for biochemical analysis (sugar, protein, pH, LDH); for differential cell counts; Gram stain; and aerobic, anaerobic, and mycobacterial cultures. Closed tube thoracentesis with a size 24 chest tube was performed at the bedside in patients with large, dependent pleural collections. In patients with effusions that were multiloculated and/or were in nondependent areas, 7 to 12F pigtail catheters were placed under ultrasound guidance. All patients were seen at least daily to assess progress. The need for further imaging and drainage was decided on an individual basis. CT examinations were made in all patients with suspected multiloculation and who failed to respond promptly.

The two treatment protocols, Drain and tube drainage with adjunctive intrapleural SK, were instituted in a sequential manner with Drain utilized for the first 2.5 years and SK used exclusively in the last 2.5 years of the study. The same team of chest physicians was responsible for patient care over the whole study period with a consistent approach to the initial choice of empiric antibiotics, the indications for further intervention (including open or thoracoscopic surgical drainage and decortication), and eventual discharge from hospital.

In the SK protocol, we administered 250,000 U of SK in 100 mL of saline solution into the pleural cavity on a daily basis. Each dose of SK was left in the pleura for 4 h with the chest tube clamped following which the fluid was manually aspirated and then released into an underwater seal for passive drainage. The total number of doses was determined by patient response. Contraindications to the use of SK were known allergy or a history of bleeding ulcer disease.

The chest drains were removed when the daily drainage had fallen below 50 mL with clinical and radiologic resolution of the pleural collection. Either thoracoscopic or open surgical drainage and decortication was performed only if there had been no response to either treatment protocols and the empyema had organized itself into a pleural peel visible on the CT.

We prospectively evaluated the effect of the two different treatment protocols on the following clinical outcomes: (1) volume of pleural fluid drained on a daily and cumulative basis; (2) duration from the day of hospital admission to defervescence; (3) duration of hospital stay; (4) need for surgical intervention; and (5) mortality.

All results were expressed as mean (SD) values. Continuous variables were compared with paired and unpaired Student’s t tests where appropriate while the χ² was used to test for differences between proportions.

Results

There were 52 patients (41 men and 11 women) with a mean (SD) age of 57 (17) years, range between 16 and 18 years. Most patients (75%) had some underlying disease, with diabetes in 41% and chronic lung diseases in 31%. There were no significant differences in age, sex ratio, frequency of underlying disease, and degrees of peripheral blood leukocytosis between patients on the SK and Drain treatment protocols (Table 1).

Forty patients (77%) had frank empyema and the rest had complicated parapneumonic effusions. Twenty-eight (54%) patients had positive pleural fluid cultures, of which 32% were anaerobic and 21% were polymicrobial. The most common aerobic isolates were Klebsiella pneumoniae and Staphylococcus aureus while the most frequently isolated anaerobe was Bacillus fragilis. There was no significance difference between the two treatment groups in the frequency of gross empyema, bacterial isolates, pleural fluid loculations, and biochemical abnormalities (Table 2).

The mean (SD) duration of tube drainage on the Drain protocol was 12 (SD=8) days (n=29) with five patients requiring more than one tube insertion (Table 3). Four patients (14%) did not respond to the treatment and required surgical decortication. Two patients in this group stayed more than 60 days in hospital. They developed complications (end-stage renal failure in one and postanoxic encephalopathy in another) not related to the pleural sepsis that had resolved after 12 and 15 days of tube drainage. If

Table 2—Pleural Fluid Characteristics:* Mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>SK Group</th>
<th>Drain Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empyema, %</td>
<td>74</td>
<td>79</td>
</tr>
<tr>
<td>Positive cultures, %</td>
<td>48</td>
<td>59</td>
</tr>
<tr>
<td>Multiloculation, %</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>pH</td>
<td>7.2 (0.2)</td>
<td>6.96 (0.6)</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>14,580 (10,000)</td>
<td>16,700 (18,000)</td>
</tr>
</tbody>
</table>

*Empyema=percentage of patients with empyema as defined in the "Materials and Methods" section; positive cultures=percentage of patients with positive bacterial isolates; multiloculation=percentage of patients with two or more pleural locules. There were no statistically significant differences between the two groups.
Table 3—Clinical Outcomes: * Mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>SK Group</th>
<th>Drain Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of hospitalization, d</td>
<td>22 (11)</td>
<td>21 (12)</td>
</tr>
<tr>
<td>Days before defervescence, d</td>
<td>10.6 (7)</td>
<td>7.7 (5)</td>
</tr>
<tr>
<td>Total volume of fluid drained, L</td>
<td>2.0 (1.5)</td>
<td>1.0 (1.01)</td>
</tr>
<tr>
<td>Days with chest tube</td>
<td>12 (5)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Surgical procedures, %</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Failure rate, %</td>
<td>30</td>
<td>34</td>
</tr>
</tbody>
</table>

* Surgical procedures=percentage of patients who needed surgical drainage; failure rate=percentage of patients who either died or needed surgery.

† Only total volume of fluid drained was significantly different between the two groups (p=0.007). There were no significant differences in all other outcome indexes.

These two patients were excluded, the mean (SD) duration of stay in hospital for this group was 21 (12) days (n=27). One patient who stayed 21 days in hospital developed a persistent fistula following chest tube removal which resolved after 18 months of ambulatory care. Seven patients (24%) in this group died, six from septicemia (one of these patients died following open drainage and decortication) and one after an acute myocardial infarct.

The patients on the SK protocol received between 1 to 10 daily administrations of SK (mean [SD] 5.3 [2.7]). No adverse effect of SK was noted. Figure 1 shows the marked increase in pleural fluid drainage after SK instillation. The mean (SD) total cumulative volume of fluid drained in the SK group was 1,982 (1,500) mL. This was significantly higher than the cumulative volume of pleural fluid in the Drain group (1,007 [1,008] mL; p=0.007). Nine patients had more than one chest tube inserted. One patient who needed five tubes inserted into three locules over a 2-week period made a complete recovery. Five patients (22%) underwent thoracoscopic evacuation and pleurodesis; all survived. Two patients in the SK group died, one from myocardial infarction and the other from septicemia.

There were no significant differences in clinical outcomes between the two groups (Table 3). The duration of hospital stay was 22 (11) days for the SK group and 21 (12) for the Drain group (n=27, excluding the two patients described above who had long stays in hospital from complications not related to pleural sepsis); the duration from the day of hospital admission to defervescence was 10.6 (7) days for the SK protocol and 7.7 (5) days for the Drain protocol. The percentage of patients who eventually required surgical intervention was 22% for the SK group and 14% for the Drain group, and there was also no significant difference in the mortality, which was 9% in the SK group and 24% in the Drain group. The overall failure rate (defined as either surgical intervention or death) was 30% (7/23) in the SK group and 34% (10/29) in the Drain group.

**Discussion**

Previous reports on the use of intrapleural thrombolysis as an adjunctive modality in the treatment of empyema suggested that it may be highly effective with success rates ranging from about 50 to 100%.8-16 These include a multicenter report of 30 patients from Mexico by Jerjes-Sanchez et al16 (SK was used) and a large series of 84 patients with multiloculated effusions from Denver described by Moulton et al15 (urokinase was used). The overall success rate of 70% (SK group, n=23) in this study is comparable to that reported from elsewhere.8-16 None of these previous studies, however, directly compared the clinical outcomes of adjunctive thrombolysis with closed tube drainage alone. From the consistently encouraging comments in the literature, we had anticipated a clear improvement in patient outcome with the use of intrapleural SK. This was not the case.

The administration of SK did increase the volume of pleural fluid drained from our patients. In some cases, this increase was dramatic (Fig 1). However, this did not result in any significant improvement in the key measures of clinical outcome such as duration of hospital stay, the need for open surgical
drainage, or mortality (Table 3). Our results are very similar to those of another yet unpublished randomized controlled trial discussed by Davies et al18 at the American Thoracic Society meeting in May 1996. In 23 patients (10 with frank empyema), they compared three daily doses of intrapleural SK with chest tube drainage and found that while SK treatment drained more pleural fluid (cumulative volumes of 2.5 L vs 1.0 L, very similar to this study; see Table 3), it did not significantly affect duration of hospitalization and success rates. Thus, two separate controlled studies have confirmed that pleural fibrinolysis improves fluid drainage but not clinical outcome.

Strange and colleagues19,20 have shown, in a rabbit model of pleural sepsis, that intrapleural thrombolytic agents caused two clinically significant effects. They increased plasminogen-dependent fibrinolytic activity in the pleura and thus reduced the number of pleural adhesions. They also, for yet unknown reasons, increased the volume of pleural fluid independent of drainage (from 4.8 [1.7] mL to 18.8 [5.1] mL).19 We think that both these effects were important in our patients and accounted for the marked difference in volume of fluid drainage between the two groups of patients. The effect of SK in increasing pleural fluid production may not in itself be deleterious provided effective overall drainage is achieved and patients show rapid clinical and radiologic improvement. It is possible, however, that SK treatment could have been carried on for longer than appropriate in some patients. If the administration of SK were to result, each time, in a large volume of “positive” fluid drained, this might delay decisions regarding tube removal or the need for further intervention. The average number of doses of SK administered in this study (5.3 [2.7]) was comparable to most other series (4.9 in Moulton et al15 and 5.1 [2] in Jerjes-Sanchez et al16). This suggests that we were not unduly prolonging the SK regimen in our patients in comparison with current practice. Furthermore, Davies et al,18 who used three doses of SK (over 3 days) for all patients, achieved very similar patient outcomes. It is possible, however, as suggested by Moulton et al,15 that a better result might be achieved by administering two to three doses of the thrombolytic agent within 24 h. This might achieve a more intense fibrinolysis in the pleural cavity over a shorter time and avoid any tendency to delay. This approach will require more frequent clinical and radiologic review of the patients at closer intervals.

We think that while the use of intrapleural thrombolytic agents may not have a major impact on the clinical outcome in all patients with pleural empyema, it did facilitate the evacuation of loculated effusions and some patients did respond dramatically with prompt and complete clearance of the pleural infection. Failure of the empyema to resolve, both clinically and radiologically, within 48 to 72 h following the repeated use of intrapleural thrombolytic agents may be an indication for further intervention. We suggest that it may be appropriate, at this stage, to consider either early thoracoscopic debridement and evacuation or open surgical drainage in surgically fit patients with multiloculated empyemas.21,22 While results of thoracoscopic management of empyemas have been encouraging, no controlled studies have been reported (to our knowledge).21,23-25 The role of thoracoscopy in the management of empyema is thus, unclear. Randomized trials are needed to compare chest tube drainage with fibrinolytic agents vs either early thoracoscopic or open debridement and drainage.

This study has several limitations. It was not a formal randomized controlled trial since the different treatment regimens were not instituted in parallel but in series. The patients in the SK treatment group were younger and there were a larger number of patients with multiloculated empyemas than in the Drain protocol. These differences were not statistically significant, however, and we think overall, the two groups of patients had diseases of comparable severity. With regards to outcome, there were no marked differences between the two groups with failure rates (defined as either death or surgical intervention) of 30% and 34% (Table 3). Furthermore, the results of this study were very similar to those reported from the randomized controlled study by Davies et al.18 The higher mortality rate (especially death rates from septicemia which were also not significantly greater than in the SK group) in the group that did not receive SK may be related to older age rather than less effective treatment. It is possible that a randomized trial involving a larger number of patients may be needed to demonstrate the therapeutic impact of intrapleural fibrinolysis.

We conclude that, in the treatment of pleural empyema, in comparison with simple closed-tube drainage, the adjunctive treatment with daily administration of intrapleural SK significantly increased the volume of pleural fluid drainage, but did not markedly reduce mortality, morbidity, or the need for surgical intervention.

REFERENCES
7 Sahn SA, Light RW. The sun should never set on a parapneumonic effusion. Chest 1989; 95:945-47
11 Moulton JS, Moore PT, Mencini RA. Treatment of loculated pleural effusions with transluminal intracavitary urokinase. AJR 1989; 153:941-45