Randomised controlled trial of intrapleural streptokinase in community acquired pleural infection

Robert J O Davies, Zoe C Traill, Fergus V Gleeson

Abstract

Background — Standard treatment for pleural infection includes catheter drainage and antibiotics. Tube drainage often fails if the fluid is loculated by fibrinous adhesions when surgical drainage is needed. Streptokinase may aid the process of pleural drainage, but there have been no controlled trials to assess its efficacy.

Methods — Twenty four patients with infected community acquired parapneumonic effusions were studied. All had either frankly purulent/culture or Gram stain positive pleural fluid (13 cases; 54%) or fluid which fulfilled the biochemical criteria for pleural infection. Fluid was drained with a 14 F catheter. The antibiotics used were cefuroxime and metronidazole or were guided by culture. Subjects were randomly assigned to receive intrapleural streptokinase, 250 000 IU daily, or control saline flushes for three days. The primary end points related to the efficacy of pleural drainage — namely, the volume of pleural fluid drained and the chest radiographic response to treatment. Other end points were the number of pleural procedures needed and blood indices of inflammation.

Results — The streptokinase group drained more pleural fluid both during the days of streptokinase/control treatment (mean (SD) 391 (200) ml versus 124 (44) ml; difference 267 ml, 95% confidence interval (CI) 144 to 390; p<0.001) and overall (2564 (1663) ml versus 1059 (502) ml; difference 1505 ml, 95% CI 465 to 2545; p<0.01). They showed greater improvement on the chest radiograph at discharge, measured as the fall in the maximum dimension of the pleural collection (6.0 (2.7) cm versus 3.4 (2.7) cm; difference 2.7 cm, 95% CI 0.3 to 4.4; p<0.05, two-tailed Fisher’s exact test). Systemic fibrinolysis and bleeding complications did not occur. Surgery was required by three control patients but none in the streptokinase group.

Conclusions — Intrapleural streptokinase probably aids the treatment of pleural infections by improving pleural drainage without causing systemic fibrinolysis or local haemorrhage.

(Torax 1997;52:416–421)

Keywords: pneumonia, pleural empyema, streptokinase, fibrinolysis, pleural effusion.

Secondary pleural infection is an important complication of pneumonia. Over 40% of patients with community acquired pneumonia develop an associated pleural effusion and about 15% of these become secondarily infected. In the UK pleural infection has a mortality of about 20%. The transition of a simple effusion to the infected state is heralded by fibrin deposition in the pleural cavity and by indicators of white cell and bacterial metabolism within the effusion fluid (falling pH and glucose levels and rising levels of lactate dehydrogenase). Once secondary infection of the pleural space has occurred, the mainstay of management is effective drainage of the pleural collection. Traditionally, drainage of the pleural space has been achieved by simple aspiration, catheter drainage, or thoracotomy with decortication or rib resection. Of these approaches, surgical procedures achieve the best drainage but carry an obvious morbidity. Less invasive drainage techniques are often limited by the loculation of pleural fluid by fibrinous septae, the presence of fibrinous clots within the empyema fluid which may block chest drains, and the development of an infected fibrinous pleural “rind”.

Uncontrolled studies have suggested that intrapleural streptokinase may improve the drainage of infected pleural effusions by lysis of the intrapleural fibrinous adhesions. None of these series includes a control group which makes interpretation of their results difficult. The weaknesses of these series means that this form of treatment is still controversial and the need for a controlled study which assesses the early use of streptokinase has been emphasised. This paper reports the results of a randomised comparison of intrapleural streptokinase given at diagnosis with control saline flushes in patients with complicated parapneumonic effusion and empyema.

Methods

Subjects

Twenty four subjects (17 men) were studied. All presented to one unit over three years with community acquired pneumonia associated with features of systemic sepsis (fever, raised white blood cell count, and C reactive protein) and a pleural effusion requiring drainage.

Inclusion criteria for entry to the study were purulent pleural fluid, pleural fluid Gram stain or culture positive for bacteria, pH of pleural fluid of <7.1, pleural fluid concentrations of...
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20 cm H₂O (except during saline or streptokinase injection). This was connected to an underwater seal and linked to a one-way valve. The catheter was positioned in either the most dependent portion of the lung or the area with the largest locule under ultrasound guidance. The catheter was inserted by two radiologists who were unaware of the study design. The catheter was connected to an underwater seal and kept on continuous suction at −20 cm H₂O (except during saline or streptokinase injection) until removal. All catheters were flushed six-hourly with 20 ml of saline to maintain their patency.²¹

The primary end points of the study related to the efficiency of pleural fluid drainage and were as follows: (1) volume of pleural fluid drained in total; (2) volume of pleural fluid drained during days 2–5 of pleural drainage (first dose of streptokinase injection/control given on day 2); and (3) improvement in chest radiograph from baseline to discharge. Secondary end points were (1) change in INR from baseline to its average over days 2–5; (2) total number of pleural procedures for fluid drainage; (3) time until white blood cell count was <12 × 10⁹/l, C reactive protein levels were <8 mg/l (normal range <8 mg/l), and the patient was consistently afebrile; and (4) duration of stay in hospital.

The study end point was discharge from hospital. Withdrawal before this point occurred in two circumstances – death of the patient or refusal for surgery. Criteria for refusal for surgery consisted of a progressive or unresponsive sepsis syndrome in the presence of a substantial residual pleural fluid collection.

STRAWY EN POINTS AND WITHDRAWAL

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STATISTICAL ANALYSIS

Statistical analysis was performed with the SAS statistical software package (SAS Institute, Cary, NC, USA). Unpaired t testing was used unless otherwise stated.

Results

All the data analysis was performed after the end of data collection. Twenty-four patients entered the study and were randomly assigned in an age stratified manner into the two study groups. The clinical and radiological baseline characteristics of the studied groups are presented in table 1. The two groups were well matched by all the criteria examined.
Table 1 Mean (SD) clinical characteristics of the study groups at randomisation

<table>
<thead>
<tr>
<th></th>
<th>Streptokinase (n=12)</th>
<th>Control (n=12)</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>62 (23)</td>
<td>60 (23)</td>
</tr>
<tr>
<td>M:F</td>
<td>9:3</td>
<td>8:4</td>
</tr>
<tr>
<td>Maximal linear dimension of pleural collection on thoracic CT scan (cm)</td>
<td>8.3 (2.6)</td>
<td>6.6 (2.1)</td>
</tr>
<tr>
<td>% hemithorax occupied by pleural collection on PA chest radiograph</td>
<td>35 (22)</td>
<td>28 (19)</td>
</tr>
<tr>
<td>Admission temperature (°C)</td>
<td>37.8 (0.20)</td>
<td>37.6 (0.40)</td>
</tr>
<tr>
<td>Total white blood cell count (× 109)</td>
<td>17.9 (8.0)</td>
<td>12.2 (6.8)</td>
</tr>
<tr>
<td>Prothrombin ratio (INR)</td>
<td>1.25 (0.13)</td>
<td>1.18 (0.9)</td>
</tr>
<tr>
<td>C reactive protein (mg/l) (normal &lt;6 mg/l)</td>
<td>194 (83)</td>
<td>206 (107)</td>
</tr>
<tr>
<td>Pre-diagnosis symptom duration (days)</td>
<td>27 (17)</td>
<td>35 (26)</td>
</tr>
<tr>
<td>Number with frankly purulent fluid</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Pleural pH</td>
<td>6.95 (0.32)</td>
<td>6.97 (0.32)</td>
</tr>
<tr>
<td>Pleural LDH (IU/l)</td>
<td>2397 (2296)</td>
<td>4667 (7847)</td>
</tr>
<tr>
<td>Pleural fluid to blood glucose ratio</td>
<td>0.30 (0.32)</td>
<td>0.21 (0.26)</td>
</tr>
<tr>
<td>Blood or pleural fluid Gram stain or culture positive</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

The differences between the groups were all non-significant.

MICROBIOLOGY
In 13 of the 24 subjects a microbiological diagnosis was established from pleural fluid Gram stain and culture or from blood culture. Streptococcus pneumoniae was identified in seven cases and Streptococcus milleri in three cases, in one of which the culture was mixed and included Arcanobacterium haemolyticum and Fusobacterium Haemophilus influenzae, enterococci, and haemolytic streptococci Lancefield’s group A were identified in one case each.

PLEURAL FLUID DRAINAGE
Two of the primary study end points related to the volume of pleural fluid drainage. Both of these showed highly significant differences between control and active treatment. The streptokinase treated group drained more pleural fluid during days 2–5 (streptokinase, mean (SD) 391 (200) ml versus control, 124 (44) ml; difference 267, 95% confidence interval (CI) 144 to 390; p<0.001) and more pleural fluid in total (2564 (1663) ml versus 1059 (502) ml; difference 1505 ml, 95% CI 465 to 2545; p<0.01; fig 1). Of the secondary end points relating to pleural drainage, the number of pleural procedures required to control the fluid (streptokinase median 1, 95% range 1–2; control median 2, 95% range 1–3; p<0.05, Mann-Whitney U test) and the total duration of pleural drainage in the two groups were similar (streptokinase 8.9 (4.7) days versus control 8.72 (2.6) days; difference 0.1, 95% CI -3.04 to 3.4, p=NS).

IMPROVEMENT IN THE CHEST RADIograph
The radiographic end points were also primary study end points. The reduction in the largest linear dimension of the pleural fluid collection was greater in the streptokinase treated group than in the control group (streptokinase 6.0 (2.7) cm versus control 3.4 (2.7) cm; difference 2.6, 95% CI 3.0 to 4.9, p<0.05). The reduction in the overall estimated size of the pleural collection on the chest radiograph was greater in the streptokinase treated group than in the control group. At discharge 10 of 12 streptokinase treated subjects showed a >75% improvement in the size of their pleural collection while only four of the nine assessable control

Figure 1 Volumes of pleural fluid drained by each subject in the two study groups. In (A) the volume of fluid drained during the days of treatment with streptokinase or control saline are compared and in (B) the total volumes of pleural fluid drained in the individual patients are shown. The differences between the groups are statistically and physiologically significant.

Figure 2 Percentage improvement in the size of the pleural opacity on the chest radiograph from entry into the study to discharge from hospital for all the subjects who completed the protocol. The improvement was consensus scored by two radiologists who were unaware of the subject’s randomisation status. The three empty circles represent the three control subjects withdrawn for surgery in whom pleural drainage was poor. The differences between the groups are statistically and physiologically significant.
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kinase/control therapy was performed in six subjects in each study group. During the days of streptokinase/control therapy the average prothrombin ratio (INR) was a little higher than at baseline in the control group. This rise was statistically but not physiologically significant (table 2). In the streptokinase group there was no rise in systemic INR, and no subject exhibited physiologically significant systemic fibrinolysis (highest INR = 1.5 in both groups). There were no local pleural or systemic haemorrhagic problems in either group.

**Table 2** Mean (SD) prothrombin ratios expressed as the International Normalised Ratio (INR) at entry into the study (baseline) and averaged over the period of treatment with intrapleural streptokinase or control therapy.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Streptokinase/control treatment period</th>
<th>Difference (95% CI)</th>
<th>p value (paired t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>1.25 (0.13)</td>
<td>1.29 (0.14)</td>
<td>0.08 (0.22)</td>
<td>NS</td>
</tr>
<tr>
<td>group (n = 6)</td>
<td></td>
<td></td>
<td>(−0.06 to 0.22)</td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>1.18 (0.08)</td>
<td>1.32 (0.14)</td>
<td>0.14 (0.12)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(n = 6)</td>
<td></td>
<td></td>
<td>(0.04 to 0.22)</td>
<td></td>
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</table>

**Figure 3** Thoracic CT scans of a subject with a multiloculated purulent empyema (A) at diagnosis and (B) after three days of treatment with intrapleural streptokinase.

subjects showed a >75% improvement (fig 2). Assuming that the three subjects withdrawn for surgery had not shown a >75% overall radiographic improvement (the definition of withdrawal for surgery included “the presence of a substantial residual pleural collection” – see protocol), the improvement in the streptokinase treated group was significantly greater than in the control group (p<0.05, two-tailed Fisher’s exact test). Resolution of a severely loculated empyema with intrapleural streptokinase is illustrated in fig 3.

**SYSTEMIC FIBRINOLYSIS AND HAEMORRHAGE**
Measurement of the blood prothrombin ratio (INR) at baseline and daily during streptokinase/control therapy was performed in six subjects in each study group. During the days of streptokinase/control therapy the average prothrombin ratio (INR) was a little higher than at baseline in the control group. This rise was statistically but not physiologically significant (table 2). In the streptokinase group there was no rise in systemic INR, and no subject exhibited physiologically significant systemic fibrinolysis (highest INR = 1.5 in both groups). There were no local pleural or systemic haemorrhagic problems in either group.

**Surgery and Clinical Progress**
In the control group three patients were withdrawn from the study and referred for surgery. In the streptokinase group no patients required surgery. Two patients (one in each treatment group) had an underlying bronchial carcinoma identified during later investigation.

The duration of the hospital stay among the patients completing the protocol and the time to normalisation of the total white blood cell count, blood levels of C reactive protein, and temperature were similar (table 3).

**Discussion**
This study reports the results of a randomised controlled trial to assess the efficacy of intrapleural streptokinase in the drainage of infected pleural effusions. Effective pleural drainage is a primary aim of treatment in this condition.10 The primary end points of this study show that streptokinase improves the catheter drainage of such pleural collections in terms of increased pleural fluid flow and improvement in the chest radiograph by discharge from hospital. This benefit was achieved without significant systemic fibrinolysis and was not associated with local or systemic haemorrhage.

The study groups did not differ significantly in any of their baseline characteristics (table 1). Despite this there is a trend towards more severe disease in the group receiving streptokinase (who ultimately had the better outcome). The streptokinase group included more patients with overtly purulent pleural fluid and their average baseline pleural collection size was larger. Since a larger pleural collection has a poorer prognosis than a smaller collection,3 this strengthens the evidence for the efficacy of streptokinase in this study.

We have studied a population with community acquired parapneumonic pleural effusions exhibiting the clinical, biochemical, and anatomical characteristics of secondary pleural infection.14 In 13 of the subjects (54%) the fluid was either frankly purulent or Gram stain or culture positive. In two of these the pleural fluid was Gram stain and/or culture positive but not overtly purulent, which confirms that frank purulence is a late feature of pleural sepsis9 and is insensitive if used as the only index of infection. In the other 11 cases the fluid was either loculated, confirming fibrinous pleurisy (and hence infection related inflammatory disturbance of pleural fibrin meta-
bolism), and/or met the biochemical criteria which indicate secondary infection and the need for pleural drainage. As well as indicating infection, fibrinous fluid loculation predicts failed catheter drainage since the loculation impedes free drainage and for this reason this was included as one of the study entry criteria. All the studied subjects fulfilled more than one of the entry criteria, and 17 of the 24 (71%) fulfilled three or more.

The accepted mainstay of the treatment of pleural infection is pleural drainage and this study was designed to assess the effect of streptokinase on this and not on overall mortality or the need for later surgery. Despite this there is a trend towards less surgery in the streptokinase group with none of these subjects, and three similar approach in several other clinical situations including ocular hyphaema, intra-cerebral haematoma, loculated pericardial effusion and various abscesses. The efficacy of intrapleural streptokinase in this study provides general support for this novel approach. Fibrinolytic “enzymatic debriement” may evolve to reduce the need for drainage surgery in many common situations.

In conclusion, this study has shown that intrapleural streptokinase at a dose of 250 000 IU daily for three days is safe and effective in improving the catheter drainage of infected pleural effusions. It suggests it may be a useful aid in the management of this disorder.

Table 3 Mean (SD) time to normalisation of the clinical end points, the total duration of hospital stay, and the total duration of pleural drainage in the two groups

<table>
<thead>
<tr>
<th></th>
<th>Streptokinase (n=12)</th>
<th>Control (n=12)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of pleural drainage (days)</td>
<td>9 (5)</td>
<td>9 (3)</td>
<td>0.0 (−3.49 to 3.49)</td>
</tr>
<tr>
<td>Duration of hospital stay (days)</td>
<td>16 (13)</td>
<td>13 (8)</td>
<td>3.0 (−6.14 to 12.1)</td>
</tr>
<tr>
<td>Time to normal white blood cell count (days)</td>
<td>9 (11)</td>
<td>5 (11.8)</td>
<td>4.0 (−3.81 to 11.8)</td>
</tr>
<tr>
<td>Time to normal blood C reactive protein (days)</td>
<td>34 (10)</td>
<td>27 (17)</td>
<td>7.0 (−4.81 to 18.8)</td>
</tr>
<tr>
<td>Time to temperature normal consistently (days)</td>
<td>6 (6)</td>
<td>8 (6)</td>
<td>−2.0 (−7.08 to 3.08)</td>
</tr>
</tbody>
</table>

The differences between the two groups were all non-significant.

Early treatment has both potential advantages and disadvantages. More effective pleural drainage might be achieved by intervening before severe pleural adhesions develop; animal work supports this hypothesis. On the other hand, early treatment could have been detrimental by increasing pleural fluid production in subjects who would have drained adequately without streptokinase. This study shows that overall there is an improvement in pleural drainage when streptokinase is used as early treatment.

This study is the first randomised controlled trial of the use of a fibrinolytic agent to drain an infected fluid collection (“enzymatic debriement”). Small case series have reported a similar approach in several other clinical situations including ocular hyphaema, intra-cerebral haematoma, loculated pericardial effusion, and various abscesses. The efficacy of intrapleural streptokinase in this study provides general support for this novel approach. Fibrinolytic “enzymatic debriement” may evolve to reduce the need for drainage surgery in many common situations.

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Thorax 1997 52: 416-421
doi: 10.1136/thx.52.5.416