

Use of fibrinolytic agents in the management of complicated parapneumonic effusions and empyemas

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Introductory article

Randomised controlled trial of intrapleural streptokinase in community acquired pleural infection

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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 14F 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 2.9 cm, 95% CI 0.3 to 4.4; $p < 0.05$) and the overall reduction in pleural fluid collection size ($p < 0.05$, 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. (Thorax 1997;52:416–421)

Scope of the problem

Pneumonia, one of the most common community acquired and nosocomial infections, is associated with a high incidence of pleural effusions.¹ The 36–57% incidence of parapneumonic effusions translates into approximately one million persons per year in the United States with effusions associated with pneumonia.^{2–4} These parapneumonic effusions usually resolve spontaneously if patients are treated with appropriate antibiotics shortly after the initial symptoms of pneumonia. However, a small percentage of parapneumonic effu-

sions will become complicated, either loculated non-purulent fluid or an empyema (frank pus). Empyema thoracis has a high likelihood to occur in individuals who delay seeking medical attention and those with co-morbid conditions such as alcoholism or chronic lung disease.⁴ In a few cases complicated parapneumonic effusions are caused by delayed or inappropriate treatment by the physician.^{5,6}

The natural history of a complicated parapneumonic effusion is to develop a single loculus or multiple loculations and to progress to an empyema cavity. Em-

pyema, from the Greek meaning accumulation of pus in a body cavity, represents the end stage of a complicated parapneumonic effusion. The optimal approach to the diagnosis and management of complicated parapneumonic effusions is controversial because of the paucity of prospective randomised trials. The availability of new options for management of these effusions further confounds clinical decision making.⁷ A 1992 interactive session of an American College of Chest Physicians' meeting on management of pleural space infections showed non-uniformity of opinions on treatment.⁸

Pathophysiology of parapneumonic effusions

The clinical features of the patient with a parapneumonic effusion depends on the stage of the effusion at presentation and can vary from symptoms of pneumonia only with a small, free flowing, non-purulent, non-infected effusion to severe chest pain, high fever and systemic symptoms with a classic empyema. The stage of the effusion at presentation correlates directly with the time interval between the onset of pneumonia and physician contact.

A parapneumonic effusion is formed when permeability pulmonary oedema fluid moves into the pleural space at a rate exceeding the lymphatic drainage capacity of the parietal pleura. The increased production of pleural fluid results from neutrophil induced endothelial injury of the parenchymal, subpleural and pleural vessels. The proteinaceous fluid that moves from the intravascular to extravascular space increases the parenchymal interstitial pressure and drives fluid between visceral pleural mesothelial cells into the pleural space. Presumably in most pneumonias pleural fluid production increases, but the excess fluid produced is removed rapidly by normal functioning parietal pleural lymphatics not allowing a clinical pleural effusion to form. It is probable that only when the parietal pleural stoma become dysfunctional or non-functional because of mesothelial cell swelling or fibrin occlusion does fluid accumulate to a degree that allows clinical detection.⁹ The earliest parapneumonic effusion, typical of the exudative (capillary leak) stage, is characterised clinically by an ipsilateral, small, free flowing, turbid exudate with a moderate number of neutrophils. The biochemistry of this effusion is a reflection of the pneumonia *per se* and not pleural space infection. Therefore, the pleural fluid pH is typically >7.30, the glucose level is >60 mg/dl, and the lactate dehydrogenase (LDH) concentration is <500 IU/l.^{2,10,11} If the pneumonia is treated with appropriate antibiotics at this stage the effusion is unlikely to progress to the second or fibrinopurulent stage.

However, if the pneumonia remains untreated, most commonly due to delayed patient presentation, endothelial injury becomes more severe and widespread and a larger volume of pleural fluid is formed. Without the inhibition of antimicrobial agents, bacterial multiplication in the lung is unchecked and bacteria move from the lung interstitium into the pleural space and eventually overwhelm the capacity of the intrapleural phagocytes (neutrophils and macrophages) and parietal pleural lymphatics and become persistent, resulting in a positive pleural fluid Gram stain and culture. This fibrinopurulent (bacterial invasion) stage typically occurs several days following the initial pleural fluid formation and is characterized by an absolute increase in pleural fluid neutrophils, which have an increased burst in metabolic activity during phagocytosis, resulting in increased glucose utilisation and increased production of glucose end products, carbon dioxide and lactic acid,

ultimately leading to cell death. These pathophysiological changes result in pleural fluid acidosis, a low glucose concentration, and an increased LDH concentration.^{12,13} Thus, the typical pleural fluid triad of the fibrinopurulent stage of a parapneumonic effusion is a pH of <7.20, a glucose level of <40 mg/dl, and an LDH level of >1000 IU/l.^{2,10,11} In addition, pleural fluid becomes clottable as plasma proteins leak into the pleural space in conjunction with a loss of the fibrinolytic activity of the inflamed pleura resulting in pleural fibrin deposition.^{14,15} Fibroblasts migrate from the sub-mesothelial connective tissue into the pleural fluid, unimpeded by the injured mesothelial cell barrier. The secretion of glycosaminoglycan and collagen, in concert with fibrin deposition, compartmentalise the fluid into loculations by bridging the two pleural surfaces and limiting lung expansion.¹⁵ At some unknown point during the fibrinopurulent stage the clinician loses the ability to treat the patient with antibiotics alone and pleural space drainage becomes necessary to prevent pleural sepsis.

The natural progression of the parapneumonic effusion leads to the final stage, the organisational or empyema stage, over a period of at least two weeks to several weeks that results in the formation of either a single thick walled cavity or multiple loculations due to the continued fibroblast migration and growth into the coagulable pleural fluid matrix. An inelastic pleural "peel" inhibits pleural space drainage as well as lung expansion. The fluid that is found at thoracentesis in this stage is classic empyema fluid which is pus (a thick, whitish-yellow, opaque coagulum) that always requires drainage. Pus assumes its specific character because of coagulability of pleural fluid, the abundance of cellular debris, and fibrin and collagen deposition. Bacteria tend to persist in empyema fluid because of the decreased bacterial opsonisation from complement depletion and pleural fluid acidosis.¹⁶ An empyema rarely resolves spontaneously; it may herald its presence by draining through the chest wall (empyema necessitatis) or into the lung (bronchopleural fistula).

Pleural fluid in the exudative stage does not need drainage while an empyema always needs to be evacuated. The real dilemma facing the clinician is how best to manage the patient in the fibrinopurulent stage of a parapneumonic effusion. Some of these patients can be managed with antibiotics alone, while others require pleural space drainage which can be accomplished by several methods including serial therapeutic thoracenteses, standard chest tubes, or image guided small bore catheters with or without fibrinolytic agents, empyectomy and decortication by thoracoscopy or standard thoracotomy, or open drainage.

Features that suggest the need for pleural space drainage

The rapid identification of patients likely to develop complicated parapneumonic effusions should improve clinical outcome by allowing early pleural space drainage. It is unlikely that common clinical parameters such as the patient's age, peripheral blood leucocyte count, peak temperature, presence or absence of pleuritic chest pain, or number of lobes involved with pneumonia can differentiate between those parapneumonic effusions that would benefit from pleural space drainage and those that can be treated with antibiotics alone.^{2,17}

There are, however, clinical features, chest radiographic, ultrasound, and chest CT findings, and pleural fluid characteristics that suggest that a parapneumonic

effusion has a high likelihood of requiring drainage. The clinical features that suggest the need for pleural space drainage include prolonged symptoms prior to presentation, anaerobic infection,¹⁸ the combination of leucocytosis, anaemia and hypoalbuminaemia,¹⁹ failure of clinical response to antibiotic therapy,²⁰ and virulence of the pathogen.^{4,21,22} Chest radiographic and CT findings that suggest the need for pleural space drainage include an effusion of >40% of the hemithorax,¹⁹ the presence of an air fluid level,¹⁸ loculation,^{2,11,17,23} multiple loculations, the size of the loculations, pleural enhancement or pleural thickening on contrast CT scan,^{24,25} and septations, fibrin strands, and necrotic debris^{26,27} on ultrasonography. Pleural fluid characteristics that suggest an increased likelihood that a parapneumonic effusion requires drainage include purulent fluid (always requires drainage), a positive Gram stain or culture,¹⁸ a low pleural fluid pH (<7.30 or 7.20), low pleural fluid glucose (<40mg/dl), and a high LDH concentration (>1000 IU/l).^{2,10,11,17,28-30}

Methods of pleural space drainage

The pleural space can be drained by standard chest tubes, small bore, radiologically guided catheters (usually 8–14 F), thoracoscopic debridement, pleural irrigation and chest tube placement, standard thoracotomy with empyectomy and decortication, and open drainage with rib resection. It would be advantageous to the patient with a complicated parapneumonic effusion or empyema from the standpoint of morbidity and cost to be treated by closed drainage with either a standard chest tube or small catheter, in lieu of a more invasive surgical procedure such as thoracoscopy, standard thoracotomy, or open drainage. The major reasons for failure of tube drainage are tube malposition, tube obstruction by viscous fluid, and multiple pleural space loculations. Both tube obstruction and a multiloculated pleural space has generated interest in intrapleural fibrinolytic treatment of complicated parapneumonic effusions during the past half century.

Fibrinolytic therapy

Tillet and Sherry³¹ in 1949 first reported the use of fibrinolytic agents in 23 patients who had either acute fibrinous pleurisy, bacterial empyema, or haemothorax. Their patients received intrapleural instillation of both streptokinase and desoxyribonuclease that resulted in transient pleural fluid fibrinolysis and proteolysis. They also demonstrated depolymerisation of the nucleoprotein in the exudate. When toxic manifestations of the drug occurred they were limited to transient febrile reactions and malaise. Subsequent investigations in small numbers of patients with complicated parapneumonic effusions reported improvement in clinical outcome. However, the initial enthusiasm for intrapleural fibrinolytics waned because of significant systemic adverse effects until Bergh and colleagues,³² using a purified streptokinase, reported chest radiographic improvement in 10 of 12 patients with empyemas without the need for thoracotomy and without significant adverse effects. Since that time there have been a plethora of case series using streptokinase and urokinase for initial drainage of the pleural space and for treatment of failed chest tube or small catheter drainage, obviating the need for surgical intervention.

CASE STUDIES

All studies with three or more patients using streptokinase or urokinase in the treatment of complicated parapneumonic effusions and empyemas are shown in tables 1 and 2, respectively (virtually all of the studies cited are uncontrolled case series). In general the studies show a "good success" rate in the treatment of these complicated parapneumonic effusions in the pleural space. However, the assessment of treatment in these uncontrolled case series is largely determined by patient selection, especially the timing of the initiation of therapy to the stage of evolution of the parapneumonic effusion. As can be stated for all treatment modalities of parapneumonic effusions, the earlier that a specific treatment is instituted the more likely the outcome will be successful. For example, early antibiotic therapy will not only tend to prevent a parapneumonic effusion but will tend to prevent the progress from a simple uncomplicated effusion to a complicated parapneumonic effusion or empyema. Furthermore, early drainage of a free-flowing, complicated parapneumonic effusion (by biochemical parameters) will tend to prevent loculation and progression to an empyema. Likewise, thoracoscopy is likely to be effective if used early in the fibrinopurulent stage of a parapneumonic effusion and less likely to be effective in a chronic empyema. Fibrinolytic therapy is also more likely to be successful early in the fibrinopurulent stage of parapneumonic effusion and unlikely to be successful in an organised empyema cavity when mature fibrin adhesions and a visceral pleural peel have developed.

The key to successful fibrinolytic drainage of complicated parapneumonic effusions is correct placement of tubes or catheters with radiological guidance early in the evolution of the parapneumonic effusion, followed by frequent monitoring (more than once daily) of tube placement and fibrinolytic effectiveness by assessing the volume of tube drainage and immediate re-instillation of the fibrinolytic agent if necessary. In the properly selected patient, attention to detail using a strict protocol will be critical in determining a successful outcome.

RANDOMISED CONTROLLED AND COMPARATIVE STUDIES

There has only been one randomised controlled trial evaluating an intrapleural fibrinolytic in the management of complicated parapneumonic effusions which forms the index article of this review. In this study Davies and associates⁴⁷ studied 24 patients with community acquired pneumonia and parapneumonic effusions (13 of the 24 patients had either frank pus or culture or Gram stain positivity (empyema), while the other 11 cases had a pleural fluid pH of <7.10, LDH concentration of >1000 IU/l, and pleural fluid/blood glucose ratio of <0.25 with loculation or septation of pleural fluid on chest CT scanning and ultrasonography, respectively (complicated parapneumonic); tables 1 and 3). Pleural fluid was drained with a 14 F catheter and antibiotics were given as a standard antibiotic regimen or guided by culture. Twelve patients were randomised to receive intrapleural streptokinase, 250 000 U daily, and 12 patients were randomised to receive the same volume of saline daily for three days. The authors found that the streptokinase group drained more pleural fluid both during the three days of treatment and during the overall drainage period. In addition, the streptokinase group showed a greater improvement on the chest radiograph and overall reduction in pleural fluid collection size at discharge. There was no biochemical or clinical evidence of systemic fibrinolysis. Surgery was required in three

Table 1 Intrapleural streptokinase in the treatment of complicated parapneumonic effusions (CPE) and pneumonic empyemas

Reference	Study design	Number of patients/disease	Streptokinase dose (U)	Success criteria	Success rate (%)	Complications	Comments
Bergh (1977) ³²	Retrospective case series	12 empyemas	250 000 in 100 ml NS daily; clamped 4 h	Volume of fluid drainage; CXR improvement	83	1 fever 1 decreased Hgb	Failed conventional drainage; chest tubes 10–12 mm; 2–10 instillations
Lysy (1989) ³³	Retrospective case series	3 empyemas	250 000 in 100 ml NS daily; clamped 4 h	Clinical and CXR improvement	100	None	Failed chest tube drainage; 4–10 instillations
Mitchell (1989) ³⁴	Retrospective case series	9 5 CPE 4 empyemas	100 000–250 000 in 100 ml NS daily; clamped 2–4 h; patient rotation	Increased drainage; CXR improvement; no further surgery	44	2 fever 1 chest pain	1–3 instillations; successful only in CPE
Willie-Ediger (1990) ³⁵	Retrospective case series	3 empyemas	240 000 in 100 ml NS daily; clamped 4 h	Increased drainage; CXR improvement	100	None	Failed chest tube drainage; 1–10 instillations
Aye (1991) ³⁶	Retrospective case series	9 empyemas	250 000 in 100 ml NS daily; clamped 4 h	Increased drainage; CXR improvement; resolution of fever	89	3 temp to 38.9°C; 2 chest wall erythema & oedema	Failed chest tube drainage; 1–4 instillations
Henke (1992) ³⁷	Retrospective case series	12 CPE	250 000 in 30–60 ml NS daily; clamped 2 h	Increased drainage; CXR improvement; clinical improvement	67	None	Failed chest tube drainage; 1–7 instillations
Alfageme (1993) ³⁸	Retrospective case series	8 empyemas	250 000 daily	Complete CXR improvement	100	None	Failed chest tube drainage; none required surgery
Rosen (1993) ³⁸	Retrospective case series	5 empyemas	12 300–136 000/kg in 50 ml NS daily; clamped 2 h; rotate patient	Clinical improvement	100	1 high fever	Failed chest tube drainage; 2–5 instillations; paediatric cases
Bouros (1994) ³⁹	Prospective case series	20 15 CPE 5 empyemas	250 000 in 100 ml NS daily; clamped 3 h	Clinical and radiologic improvement	95	1 high fever	Failed chest tube drainage; 3–10 instillations
Taylor (1994) ⁴⁰	Retrospective case series	11 empyemas	250 000 in 100 ml NS daily; clamped 4 h	Clinical outcome; pleural drainage; US + CXR assessment	73	None	Failed chest tube drainage; 2–6 instillations; 8–12 F catheters
Chin (1996) ⁴¹	Prospective case series	13 CPE and empyemas	250 000 in 100 ml NS daily; clamped 4 h	Clinical and radiological resolution; pleural drainage <50 ml	69	None	Failed chest tube drainage; 1–10 instillations
Jerjes-Sanchez (1996) ⁴²	Prospective multicentre case series	30 empyemas	250 000 in 100 ml NS daily; clamped 4 h; patient rotation	Pleural drainage; CXR improvement; pulm function improvement	93	2 transient AMS 3 pleuritic pain 1 low grade fever 1 rash	Failed chest tube drainage; 2–10 instillations
Laisaar (1996) ⁴³	Retrospective case series	22 21 empyemas 1 CPE	250 000 in 100 ml NS daily; clamped 3 h	Increased pleural drainage; CXR improvement; clinical improvement	68	Chest pain fever bleeding	Failed chest tube drainage; 2–8 instillations
Roupie (1996) ⁴⁴	Retrospective case series	16 empyemas	250 000 in 30–50 ml NS daily; clamped 2 h; or via needle under CT guidance	Increased pleural drainage; CT improvement	88	1 chills and fever	Failed chest tube drainage; 1–3 instillations
Chin (1977) ⁴⁵	Prospective case series; sequential SK vs tube	23 17 empyemas 6 CPE	250 000 in 100 ml NS daily; clamped 4 h	Pleural drainage <50 ml; clinical & radiologic resolution	78	None	1–10 instillations
Bouros (1997) ⁴⁶	Prospective randomised double blind SK vs UK	25 20 CPE 5 empyemas	250 000 in 100 ml NS daily; clamped 3 h	Clinical outcome; fluid drainage; CXR, US, or CT improvement	92	2 high fever	Failed chest tube drainage; 3–10 instillations
Davies (1997) ⁴⁷	Randomised controlled SK vs saline	12 7 empyemas 5 CPE	250 000 in 20 ml NS daily × 3	Pleural drainage; CXR improvement	100	None	14 F catheter; none required surgery; systemic fibrinolysis or bleeding did not occur
Wait (1997) ⁴⁸	Prospective randomised SK vs VATS	9 loculated effusions or pH ≤ 7.20	250 000 in 100 ml NS daily × 3; clamped 3 h	>50% of original fluid volume drained; T <38°C; WBC <11 K;	44	Not reported	36 F chest tube; SK failures salvaged with VATS

NS = normal saline; SK = streptokinase; VATS = video-assisted thorascopic surgery; US = ultrasound; CXR = chest radiography.

patients in the control group and in none of the patients in the streptokinase group.

Chin and Lim⁴⁵ reported on 52 patients (40 with empyema and 12 with complicated parapneumonic effusions) who were studied prospectively over a five year period (tables 1 and 3). The same criteria used to define empyema and complicated parapneumonic effusion were used as in the study by Davies and colleagues. In patients with large dependent pleural effusions, a 24 F chest tube was inserted at the bedside; in patients with multiloculated or non-dependent loculated effusions, a 7–12 F pigtail catheter was placed under ultrasound guidance. During the first 2.5 years of the study pleural space drainage alone was the treatment modality (29 patients) and during the last 2.5 years of

the study streptokinase (23 patients) was used. The same physicians were responsible for patient care during the entire study with a consistent approach to initial empiric antibiotics, indications for further intervention, and eventual hospital discharge. Streptokinase was administered intrapleurally in a dose of 250 000 U in 100 ml of normal saline daily with tube clamping for four hours. The total number of doses of streptokinase was determined by patient response. A significantly larger volume of pleural fluid was drained from patients in the streptokinase group (mean (SD) 2.0 (1.5) l) than in the drainage group (1.0 (1.0) l). There were no significant differences between the two treatment groups in time to defervescence, hospital stay, need for surgical intervention, or mortality.

Table 2 Intrapleural urokinase in the treatment of complicated parapneumonic effusions (CPE) and pneumonic empyemas

Reference	Study design	Number of patients/diseases	Urokinase dose (U)	Success criteria	Success (%)	Complications	Comments
Moulton (1989) ⁴⁹	Retrospective case series	11 8 positive Gram stain or culture 3 pH <7.00	80 000–150 000 several times daily, clamped 1–2 h	Clinical outcome; absence of residual fluid	91 complete 9 partial	None	Failed chest tube or catheter drainage; 3–8 instillations; 12–14 F catheters
Lee (1991) ⁵⁰	Prospective case series	10 empyemas	100 000 in 100 ml D ₅ W; clamping overnight	Complete drainage by CXR	90	None	8 F catheters; 1–7 instillations
Pollak (1994) ⁵¹	Retrospective case series	5 4 CPE 1 empyema	180 000–250 000 in 100–500 ml NS daily; clamped 30–180 min; rotated	Complete drainage; clinical improvement	80	None	Failed chest tube drainage; 1–2 instillations
Robinson (1994) ⁵²	Retrospective case series	10 CPE or empyemas	100 000 in 100 ml NS daily; clamped 6–12 h	Resolution by CT; clinical outcome	80	None	Two initially improved but subsequently required decortication; 1–14 instillations
Bouros (1996) ⁵³	Prospective case series	20 13 CPE 7 empyemas	50 000 in 100 ml NS daily; clamped 3 h	Volume of fluid drained; CXR; serial US/CT	95	None	Failed chest tube drainage; 10–12 F catheters; 3–7 instillations
Park (1996) ⁵⁴	Retrospective case series	10 empyemas	Total 250 000 daily in 3 doses; clamped 1–2 h	Lung expansion on CXR	60 complete 30 partial	None	US with linear septations and honeycombing associated with failure; 10–12 F catheters
Kornecki (1997) ⁵⁵	Retrospective case series	5 empyemas	100 000 in 100 ml NS daily; clamped 12 h, suction 12 h	US vol of daily fluid drained	80	None	Children (1.5–12 y); failure of tube drainage and large loculations; a single UK failure due to late treatment
Bouros (1997) ⁴⁶	Prospective randomized double blind	25 19 CPE 6 empyema	100 000 in 100 ml NS daily; clamped 3 h	Clinical outcome; fluid drainage; CXR; US and CT	92	None	Failure of CT drainage; 2 UK patients required surgery; 3–12 instillations

CXR = chest radiography; US = ultrasound; CT = computed tomography; NS = normal saline.

Table 3 Trials of streptokinase versus tube drainage, saline, VATS, and urokinase in complicated parapneumonic effusions (CPE) and pneumonic empyemas

Reference	Study design	Number of patients	Dose of SK or UK (U)	Results	Comments	
Chin (1977) ⁴⁵	Sequential Consecutive SK vs. tube drainage	52 (29 drainage only vs 23 SK)	SK 250 000 in 100 ml NS daily via 24 F chest tube or 7–12 F catheter; Clamped 4 h	SK Hospital days 22 (11) Time to afebrile (d) 10.6 (7) Volume of fluid (l) 2 (1.5) Surg (%) 22 Mortality (%) 9 Failure (%) 30	Tube drainage 21 (12) 7.7 (5) 1 (1)* 14 24 34	40 empyema 12 CPE Larger volume drained in SK group; No differences in duration of fever, hospital stay, need for surgery, or mortality
Davies (1997) ⁴⁷	Randomised SK vs saline	24 (12 saline vs 12 SK)	SK 250 000 in 20 ml NS daily for 3 days; Clamped 2 h vs Control 20 ml of saline daily for 3 days	SK Hospital days 16 (13) Duration of drainage (d) 9 (5) Time to afebrile (d) 6 (6) Vol of drainage during Rx (ml) 391 (200) Vol of drainage overall (ml) 2564 (1663) CXR improvement (cm fluid collections) 6 (2.7)	Tube drainage 13 (8) 9 (3) 8 (6) 124 (267)* 1059 (502)* 3.4 (2.7)*	13 empyema 11 CPE 3 saline patients required surgery 0 SK patients required surgery
Wait (1977) ⁴⁸	Randomised SK vs VATS	20 (11 VATS vs 9 SK)	SK 250 000 in 100 ml NS daily for 3 days via 36 F chest tube; Clamped 4 h vs Immediate VATS	SK Hospital days 12.1 (1.1) Chest tube days 9.8 (1.3) Mortality (%) 11 Complications (%) 9 Success (%) 44 Cost 16K	VATS 8.7 (1.1)* 5.8 (1.1)* 9 0 91* 24K	Loculated effusion or <7.20 Failure in SK group determined at 3 days by <50% of fluid drained, temp ≥ 38 °C, and WBC >11 000/μl
Bouros (1997) ⁴⁶	Randomised SK vs UK	50 (25 UK vs 25 SK)	SK 250 000 in 100 ml NS daily vs UK 100 000 in 100 ml NS daily; Clamped 3 h. Re-instilled in persistent effusion and drainage <50 ml/24 h	SK Instillations (n) 6 (2.2) CXR improvement 2.5 (0.7) Fluid drainage before lytics (ml/24 h) 48 (23) Fluid drainage after lytics (ml/24 h) 380 (99) Fluid drainage (total ml) 1596 (68) Cost (\$/daily) 122	UK 5.9 (2.1) 2.7 (0.8) 56 (31) 421 (110) 1510 (55) 212	SK 20 CPE and 5 empyemas UK 19 CPE and 6 empyemas SK 7 transient fever; 2 with temp 39–40 °C SK 2 failures requiring surgery UK 2 failures requiring surgery

* Significant difference
UK = urokinase; SK = streptokinase; NS = normal saline; CXR = chest radiography; VATS = video-assisted thoracoscopic surgery.

A small randomised trial compared chest tube drainage with intrapleural streptokinase and video-assisted thoracoscopic surgery (VATS) for the treatment of complicated effusions or parapneumonic empyemas⁴⁸ (tables

1 and 3). Eligible patients had to have either loculated pleural effusions or a pleural fluid pH of <7.20. Twelve of the 20 patients had positive bacterial cultures, most of which were anaerobic or microaerophilic organisms.

Patients were randomised to receive either chest tube drainage with streptokinase (n=9) or VATS (n=11). Patients randomised to tube thoracostomy with streptokinase had a 36 F chest tube placed under the supervision of a pulmonary fellow or attending and appropriate placement confirmed by chest radiography. Streptokinase (250 000 U in 100 ml of normal saline) was instilled intrapleurally and the tube clamped for four hours. Each patient received three daily doses of streptokinase. Following the last dose of streptokinase the patients were evaluated for success using the following criteria: adequate drainage was defined as the resolution of >50% of the original volume of pleural fluid on chest radiography; defervescence to a temperature <38°C; and a peripheral leucocyte count of <11 000/ μ l. The streptokinase failures were referred to thoracic surgery for additional treatment. The streptokinase successes were followed until chest drainage was <100 ml per day, at which time tubes were removed and the patient discharged. Patients randomised to VATS went immediately to surgery without prior chest tube placement.

Based on the study criteria, the VATS group had a significantly higher primary treatment success, fewer days on chest tube drainage, and shorter hospital stays. There was a trend for a lower hospital cost in the VATS group. All streptokinase treatment failures were salvaged by VATS and none required thoracotomy. The problems with this study are the small sample size, the question of adequate chest tube placement by house officers at the bedside, uncertainty of chest tube position judged only by standard chest radiography, the short duration of streptokinase treatment, and the strict radiographic criteria for success. It is possible that more frequent or prolonged use of streptokinase would have resulted in a better outcome. It appears that the "deck was stacked" against the streptokinase group because of the aforementioned problems. The cost trend was greater for the streptokinase group because of the addition of the five VATS procedures.

A randomised study compared the efficacy, safety profile, and cost of two fibrinolytic agents in the treatment of complicated parapneumonic effusions. Bouros and co-workers⁴⁶ studied 50 consecutive patients with complicated parapneumonic effusions³⁹ or empyema¹¹ who were randomly allocated to receive either streptokinase (25 patients) or urokinase in a double blind fashion (tables 1, 2 and 3). Criteria for inclusion included multiloculated complicated parapneumonic effusions or loculated empyemas confirmed by CT scanning, ultrasound, or both and failure of drainage via tube thoracostomy (<70 ml during the previous 24 hours).

All patients had pleural space drainage with a 28 to 32 F chest tube. Twenty five patients received 250 000 U streptokinase in 100 ml of normal saline and 25 received urokinase 100 000 U in 100 ml normal saline. Chest tubes in both groups were clamped for three hours following instillation and re-opened to suction. Streptokinase or urokinase was re-instilled if, on ultrasound or CT scanning, a persistent pleural effusion was seen and the amount of pleural fluid drainage was <50 ml during the previous 24 hours. Clinical and radiological improvement was noted in all but two patients in each group who required surgical intervention. Mean (SD) instillations were 6 (2.7) in the streptokinase group and 5.9 (2.1) in the urokinase group. The chest radiographic improvement score was the same in both groups. The mean volume of pleural fluid drained during the first 24 hours after instillation was significantly increased in both groups compared with the volume drained in the

24 hours prior to instillation. A significant increase in the mean daily pleural fluid drainage was seen after either drug instillation compared with the volume drained in the 24 hours prior to treatment; however, there was no difference between streptokinase and urokinase. High fever (39–40°C) was seen in two of the patients on streptokinase. The cost of the urokinase was twice that of streptokinase, with the mean hospital stay being about 10 days in both groups. In this comparative study both fibrinolytic agents were effective adjuncts in the management of parapneumonic effusions.

Intrapleural streptokinase in experimental empyema

Strange and colleagues⁵⁶ studied the effect of intrapleural streptokinase compared to saline control in a rabbit model of empyema. Streptokinase or saline was instilled daily for a total of three days immediately after bacterial inoculation of the pleural space. At day 4 following bacterial inoculation the streptokinase treated animals had a significantly increased amount of pleural fluid and fewer pleural adhesions than the saline treated control animals but comparable amounts of visceral and parietal pleural thickening. No evidence of systemic fibrinolysis was observed one hour after intrapleural streptokinase instillation. The investigators attempted to prevent fibrin deposition before a pleural peel was established, yet failed to completely prevent pleural adhesion formation, although the number of adhesions was significantly less than in the control group.

A possible explanation for the failure to completely prevent pleural adhesions is the rapid binding of streptokinase within an inflamed pleural space. While the half life of streptokinase intravascularly is 15–30 minutes,⁵⁷ it is probably shorter in the inflammatory pleural space. Streptokinase normally binds to plasminogen and the modified plasminogen complex is autocatalytically converted to plasmin. The proteolytic activity of plasmin on fibrin, however, can be blocked by a number of protease inhibitors such as α_2 -macroglobulin and α_2 -antiplasmin found in high concentrations in the inflamed pleural space.¹⁴ The increased procoagulant activity and high concentrations of plasminogen activator inhibitor 1 and plasminogen activator inhibitor 2, which have been found in empyema fluid,¹⁴ may explain the progressive fibrin deposition that can occur between 24 hour streptokinase dosing. It is possible that an increased frequency of dosing would increase the success of fibrinolytic agents.

It is unclear, in the experimental study, why streptokinase produced an increased volume of pleural fluid. Streptokinase alone did not produce demonstrable effusions while streptokinase, in the setting of a non-infected inflammatory pleurisy, did produce large effusions. The possibility that pleural fibrinolysis resulted in an increased volume of inflammatory fluid entering the pleural space from the visceral or parietal pleura while not affecting the patency of the pleural stoma might explain these findings.

Systemic fibrinolytic activity of intrapleural streptokinase

The most comprehensive study of the systemic fibrinolytic effect of intrapleural streptokinase was recently published by Davies and colleagues⁵⁸ who studied the systemic fibrinolytic activity of two intrapleural streptokinase regimens. Eight patients received a single dose of 250 000 U of intrapleural streptokinase and an ad-

ditional eight received serial doses of 250 000 U every 12 hours for three days (total dose 1.5 million units). Each patient had the streptokinase retained in the pleural cavity for two hours. Prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen and D-dimer levels were measured before intrapleural administration of streptokinase. These end points were then re-measured 24 hours after streptokinase in the single dose group and at 24, 48 and 72 hours in the group receiving serial doses. There were no physiological or statistical differences in any of the indices after administration of intrapleural streptokinase. Intrapleural streptokinase, even in a dose of 1.5 million units, did not cause significant activation of the systemic fibrinolytic system.

Adverse effects of fibrinolytics

Streptokinase has been reported to be antigenic and leads to antibody formation. Re-exposing patients to these agents may cause hypersensitivity or anaphylactoid reactions. These would be more likely to occur following intravenous administration but could conceivably occur following intrapleural administration. Lee and colleagues⁵⁹ found that antibodies to streptokinase were raised from four days to at least 54 months following the initial administration of streptokinase intravenously. The potential for serious adverse effects would therefore exist following re-exposure to streptokinase during this time period.

Major haemorrhage has been reported in a 36 year old man following instillation of 500 000 U of streptokinase intrapleurally and clamping of the chest tube for six hours.⁶⁰ This patient drained 1500 ml of bloody fluid, developed haematuria, gastrointestinal bleeding, pulmonary haemorrhage and epistaxis, in addition to oozing from puncture sites. Eleven hours after streptokinase the PT and PTT were 28% and 14% greater than before streptokinase. A single patient developed severe pleural space haemorrhage following intrapleural streptokinase (exact dose not recorded) one month following rib fractures.⁶¹

Frye and colleagues⁶² reported acute hypoxic respiratory failure following both streptokinase and urokinase given 24 hours apart for treatment of a loculated haemothorax. The streptokinase dose was 250 000 U

and the urokinase dose was 450 000 U. It is possible that the patient's severe hypoxaemia resulted from the effect of the products of fibrinolysis on the pulmonary circulation leading to a capillary leak pulmonary oedema. Alfageme and Vaquez⁶³ reported a patient who developed ventricular fibrillation following intrapleural urokinase. Mild anaphylactoid reactions after intravenous urokinase have been reported but occasionally these reactions may be severe.^{64,65} Urokinase has not been found to be antigenic but urokinase can directly stimulate mast cells and basophils to release histamine and serotonin, causing vasodilatation and vascular permeability which can lead to hypotension and shock.⁶⁴ Histamine is involved in the enhanced arrhythmogenicity seen during experimental anaphylaxis by decreasing the threshold for ventricular fibrillation and could have resulted from an anaphylactoid reaction. It is possible that a high single dose and prolonged dwell time might increase the risk of excess systemic absorption and systemic fibrinolysis. It would appear prudent not to use a single dose of streptokinase of >250 000 U or a single dose of urokinase of >100 000 U and to keep dwell times to below four hours. It may also be advisable to pretreat patients with acetaminophen and diphenhydramine prior to intrapleural fibrinolytics as has been recommended prior to intravenous urokinase.⁶⁴

Conclusion

A single randomised controlled trial of intrapleural streptokinase has shown that pleural drainage was enhanced, the chest radiograph was improved, and surgery was avoided with streptokinase without causing local haemorrhage or systemic fibrinolysis. Intrapleural streptokinase and urokinase are equally efficacious in treating complicated parapneumonic effusions and empyemas and may reduce the need for more invasive surgical procedures. Streptokinase can be associated with high fever and allergic reactions, while urokinase has rarely been associated with severe adverse effects. However, urokinase is approximately twice the cost of streptokinase. There has not been a randomised trial of intrapleural fibrinolytic therapy versus VATS with an adequate number of patients. A large multicentre trial

LEARNING POINTS

- * Fibrinolytic agents are a useful adjunct in the management of complicated parapneumonic effusions.
- * Both streptokinase and urokinase are equally effective.
- * Systemic fibrinolysis and bleeding complications are rare events.
- * In the only randomised controlled trial, in which streptokinase was compared with saline control, the streptokinase group showed an increased volume of pleural fluid drainage during the treatment phase and, overall, an improved chest radiograph and no need for surgery.
- * Intrapleural fibrinolytics, if used early in the fibrinopurulent stage of a parapneumonic effusion, may obviate the need for VATS or thoracotomy.
- * A large multicentre randomised trial comparing a fibrinolytic and VATS early in the fibrinopurulent stage of a parapneumonic effusion is needed to determine the optimal management of these patients.

with a meticulous study design comparing these modalities is needed.

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