

Intrapleural Streptokinase for Empyema and Complicated Parapneumonic Effusions

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We conducted a single-center, randomized, placebo-controlled trial to determine whether streptokinase instillations adjunctive to chest tube drainage reduce the need for surgery and improve outcome in patients with pleural empyema. Fifty-three patients (frank pus aspirated, 81%; microbiological agent cultured, 62%; mean effusion pH, 6.6 ± 0.4) received antibiotic treatment, chest tube drainage, and once-daily pleural rinses with either normal saline or normal saline with streptokinase (250,000 IU). Nine patients were excluded for various reasons before pleural rinses were started. Streptokinase ($n = 22$) was instilled over 4.5 ± 2 days and saline ($n = 22$) was instilled over 3 ± 1.3 days. One patient in each group died during treatment. Clinical treatment success and need for referral to surgery were the main outcome measures. No difference was observed after 3 days. After 7 days, streptokinase-treated patients had a higher clinical success rate (82 vs. 48%, $p = 0.01$) and fewer referrals for surgery (45 vs. 9%, $p = 0.02$). No significant radiologic or functional differences were observed between groups during follow-up over 6 months. We conclude that intrapleural streptokinase adjunctive to chest tube drainage reduces the need for surgery and improves the clinical treatment success in patients with pleural empyema.

Keywords: fibrinolysis; pleural effusion; pleural empyema; streptokinase

Pulmonary infections with secondary pleural involvement lead to considerable morbidity and even mortality (1–3). Bacterial and white cell metabolism can rapidly turn a simple exudative parapneumonic effusion into a multiloculated purulent empyema with low pH and high lactate dehydrogenase levels. This progressive process involves alterations in fibrin turnover, which leads to the formation of fibrinous deposits and membranes with sequestration of infected fluid (4, 5). Accepted management consists of systemic antibiotics and drainage of the pleural cavity, which is achieved by either medical chest tube drainage or surgery. Open thoracotomy or video-assisted thoracoscopic surgery (VATS) achieve the best drainage in gross empyema or loculated effusions, but are limited by operative risk, cost, and local availability (6).

Intrapleural instillation of fibrinolytic agents is undertaken to dissolve fibrinous clots and membranes, to prevent fluid sequestration, and hence to improve drainage. The technique was first described more than 50 years ago (7). Numerous case series

and a few controlled trials have since shown that urokinase or streptokinase (SK) used intrapleurally is safe, increases fluid drainage, and improves some clinical and radiologic outcome parameters (8–16). However, no controlled trial study addressed treatment success expressed as need for surgery, which is the outcome measure of primary interest for the clinician (11). Furthermore, it has never been evaluated whether better clearance of fibrinous material translates into quicker recovery of chest mechanics and better long-term functional outcome.

We hypothesized that fibrinolytic therapy reduces the need for surgery and improves long-term functional outcome in patients with complicated parapneumonic effusions and empyema. The article presented here, to our knowledge, reports the first randomized study designed to directly evaluate these clinically important end points. The results have also been presented in abstract form (17).

METHODS

Patients

Patients admitted to Tygerberg Academic Hospital (tertiary hospital; catchment area, 1.5 million) with lung infection and concomitant pleural effusion were included if pleural fluid aspiration revealed an empyema (frank pus) or a complicated parapneumonic effusion (pH less than 7.0 or pH less than 7.2 and evidence of fluid loculation on the chest radiograph [CXR] or ultrasonography). Exclusion criteria were as follows: age less than 16 years; recent severe trauma, hemorrhage, or stroke; bleeding disorder or anticoagulant therapy; administration of SK in the previous 2 years; and likely survival of less than 6 months. Patients with preceding drainage procedures were not included. Pleural fluid pH was measured on site with a blood gas analyzer (865 Rapidlab; Chiron, Corning, UK). All other biochemical parameters were processed within the hospital's laboratory routine service.

Treatment Protocol

Standard 24F or 28F Argyle chest tubes were inserted by J.T. or A.H.D. with ultrasound guidance (SAL77-A; Toshiba, Johannesburg, South Africa). Rinse therapy started the following day and was continued once daily for up to 7 days or until net drainage was less than 100 ml/day. Rinse solutions contained 100 ml of normal saline with or without 250,000 IU of dissolved SK (Aventis, Midrand, South Africa). After injection, the chest drain was flushed with 20 ml of saline and clamped for 2 hours. All patients received standardized broad-spectrum antibiotics initially that were later adjusted to the microbiological culture result.

Outcome Measures

Death, response to treatment, and need for surgery were the main outcome measures. On a daily basis, A.H.D. or J.T. assessed the patients and decided on tube management, termination of rinses, and discharge. Response to treatment was evaluated daily with a structured protocol, which is described in detail in the online supplement. Briefly, *therapy success* was defined as subjective and objective clinical improvement with control of systemic infection, adequate pleural drainage, and radiologic clearance. Criteria for *referral to surgery* were ongoing or progressive sepsis syndrome in combination with a substantial residual pleural collection or lack of satisfactory clinical or radiologic improvement beyond 7 days after chest drain insertion. All physicians involved in decision making were blinded to the treatment allocation until the end of the study.

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Secondary end points were amount of fluid drained, number of rinses received, number of days on chest drainage, days spent in hospital, as well as radiologic and functional outcome on follow-up. CXR and lung function testing with spirometry and plethysmography were performed at discharge and at 4, 12, and 26 weeks. Radiographs were reviewed by an independent radiologist blinded to treatment allocation and outcome parameters. For CXR scoring, we used the erect postero-anterior CXR film and determined (1) the largest lateral linear dimension of pleural effusion or thickening (in millimeters) and (2) the estimated overall percentage of shadowing present in the hemithorax.

Statistical and Ethical Aspects

The study was designed as a randomized controlled trial and analyzed according to the intention-to-treat principle. Patients were randomized in blocks of four, using a computer-generated table. Further details about statistical analysis, sample size calculation, and randomization are reported in the online supplement.

RESULTS

Patients and Treatment

We randomized 53 patients from December 2000 to March 2003. All had prolonged fever, shortness of breath, cough, and purulent sputum, and most patients had felt ill for more than 2 weeks. Nine patients were withdrawn from the study before rinsing was initiated (Figure 1). One patient died from overwhelming sepsis. Only consolidated lung with minimal or no effusion was found on sonography in two patients despite diagnostic aspiration of pus at another institution before inclusion. We assume that pus was aspirated from a necrotic area of the lung. Three patients were excluded with conditions technically not suitable for the study rinses: one had an infected hemothorax due to an actively bleeding arteriovenous fistula following a stab wound, one showed signs of aspiration of a test saline rinse into the lung via a severe air leak, and one had a trapped lung with a large pneumothorax. From the latter two effusions *Mycobacterium tuberculosis* was later cultured.

Forty-four patients received pleural rinse treatment. The groups were well matched for biographics, social background, characteristics of preexisting and acute illness, pleural effusion parameters, and CXR features (Table 1). C-reactive protein values were higher in the SK group, but white cell counts were not different. Less than one-third had septic temperatures at randomization, which was probably due to antibiotic treatment

initiated by the referring institution. Most effusions had features predictive of bad outcome such as frank pus on aspiration, low pH, high lactate dehydrogenase, and positive microbiological culture (3, 19). *M. tuberculosis* was cultured from three effusions, which all presented with pus on drainage, a neutrophilic cell count, and pH less than 7.2 (tuberculous empyema). No other bacteria were cultured in these effusions.

Main Outcome Measures

All patients who received at least one rinse were analyzed for outcome measures (Table 2). One patient in each group died during hospitalization because of overwhelming sepsis (saline group) and newly diagnosed small-cell lung cancer (SK group). Treatment success showed no difference after 3 days. On Day 7 and at discharge from hospital, however, a higher proportion of SK-treated patients were scored as successful, and more saline-treated patients were referred for surgery. Both these differences were statistically significant. Of the patients with tuberculous empyema, one was referred to surgery and two were scored as treatment successes (one after 3 days and one after 7 days). Clinical details of the patients referred to surgery are displayed in the online supplement.

Secondary Outcome Measures

No allergic or hemorrhagic complications occurred. The amounts of fluid drained were not significantly different between groups for the first day of drainage and in total (Table 2). SK-treated patients, however, had higher pleural drainage during the rinse period, carried the drain longer, and received more rinses. The median duration of hospital stay was longer with SK, 10.5 days versus 9 days with saline (difference not statistically significant). This is at least partly explained by two SK-treated patients with prolonged hospitalizations for reasons unrelated to empyema therapy (pulmonary tuberculosis with acute respiratory distress syndrome, 51 days; neurologic complications from alcohol withdrawal, 29 days).

Follow-up Period

Because death and referral for surgery resulted in withdrawal from the study, only 29 patients entered the follow-up period. Over 6 months, two more patients died from causes unrelated to the study and three could not be traced (Figure 1). All patients followed up improved clinically over time, and late recurrences or secondary referrals to surgery did not occur. CXR scores and functional residual capacity as well as total lung capacity gradually improved in both groups without statistically significant differences at any point of time (Table 2 and Figure 2). The mild remaining functional defects probably represent preexisting pathology such as chronic obstructive pulmonary disease rather than late sequelae of empyema. The data available do not support the hypothesis that SK is beneficial for the radiologic or functional outcome beyond the acute phase of disease, but the number of patients followed up to 6 months was relatively small.

DISCUSSION

This prospective comparative study found that streptokinase adjunctive to chest tube drainage significantly improved the outcome of medically treated complicated parapneumonic effusions and empyema. The beneficial effect of streptokinase became evident between the fourth and seventh day after initiation of treatment and led to a significantly reduced need for surgical referral. Up to 6 months after discharge, all patients remaining in the study recovered similarly well in terms of radiologic appearance and lung function. No side effects of streptokinase were seen.

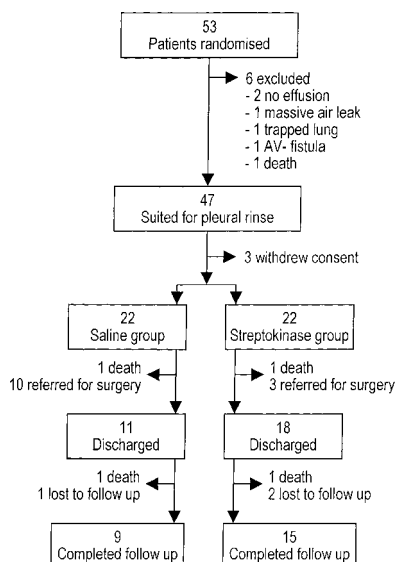


Figure 1. Study profile.

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS AND EFFUSIONS

Characteristic	All Patients	Saline	Streptokinase	p Value*
n	53	22	22	
Age, yr	39 ± 13 [†]	40 ± 14	40 ± 13	NS
Male, n (%)	38 (72)	15 (68)	18 (82)	NS
Unemployed, n (%)	22 (42)	8 (36)	8 (36)	NS
Preexisting conditions, n (%)				
HIV seropositive	9 (17)	3 (14)	1 (4)	NS
Diabetes	3 (6)	1 (4)	1 (4)	NS
Alcohol abuse	4 (8)	1 (4)	2 (9)	NS
Neoplastic disease	1 (2)	0	1 (4)	NS
Rheumatic disease	3 (6)	2 (9)	1 (4)	NS
Any comorbidity	20 (38)	8 (36)	6 (27)	NS
Acute illness				
Duration, d	31 ± 23	31 ± 25	30 ± 24	NS
Antibiotic treatment ≥ 3 d, n (%)	36 (68)	16 (73)	14 (64)	NS
Dyspnea grade (NYHA) [‡]	2.7 ± 1.0	2.6 ± 1.0	2.5 ± 1.1	NS
Fever > 38.5°C, n (%)	16 (30)	7 (32)	7 (32)	NS
C-reactive protein > 100 mg/L, n (%)	35 (66)	11 (50)	16 (73)	0.062
WBC > 20,000/ml, n (%)	13 (25)	4 (18)	4 (18)	NS
Pleural effusion				
Frank pus, n (%)	43 (81)	17 (77)	20 (91)	NS
pH	6.6 ± 0.4	6.7 ± 0.5	6.5 ± 0.4	NS
LDH > 1,000 U, n (%) [§]	30 (75)	14 (70)	11 (55)	NS
Adenosine deaminase, U	102 ± 67	102 ± 68	102 ± 74	NS
Positive microbiology, n (%)	32 (60)	14 (64)	13 (59)	NS
<i>Mycobacterium tuberculosis</i>	6 (11)	3 (14)	0	
<i>Streptococcus milleri</i>	6 (11)	3 (14)	3 (14)	
<i>Streptococcus pneumoniae</i>	3 (6)	2 (9)	1 (5)	
<i>Staphylococcus aureus</i>	5 (9)	2 (9)	2 (9)	
<i>Prevotella melaninogenicus</i>	5 (9)	2 (9)	3 (14)	
Others	7 (26)	2 (9)	4 (18)	
Chest radiograph (posteroanterior)				
Lateral effusion thickness, mm	73 ± 46	71 ± 47	83 ± 43	NS
Area of shadowing, %	53 ± 24	56 ± 22	54 ± 19	NS

Definition of abbreviations: HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; NS = not significant; NYHA = New York Heart Association; WBC = white blood cell count.

* p Values are for comparison of saline and streptokinase; p < 0.1 is displayed.

[†] Plus-minus values represent the standard deviation.

[‡] Dyspnea grading I-IV based on the New York Heart Association classification (18).

[§] Upper limit of normal, 190 U/L.

^{||} Specimens unsuitable for analysis in 13 patients.

To our knowledge, this is the first randomized study to show SK to be effective on end points of primary practical interest. Previous randomized controlled trials demonstrated beneficial effects of SK on radiologic appearance and volume of pleural drainage, time to defervescence, and length of hospital stay (13, 15). However, the value of these end points is unclear for several reasons. It has been shown that radiologic change does not predict outcome (3), and that SK increases pleural drainage due to mechanisms independent of fibrinolysis (5), which makes the isolated use of these parameters unsuitable to determine the necessity of surgery. Moreover, underlying disease and comorbidities are difficult to control for and can extend the hospital stay well beyond the time needed for empyema treatment alone. In the present study, a consistent team of physicians blinded to the method of treatment throughout the study made decisions on the basis of predefined clinical, biochemical, and radiologic criteria. We believe that this is the best way to scientifically approach a complex clinical situation such as empyema treatment. The lack of recurrences and the similar functional recovery of the remaining patients in both groups lend further support to this strategy.

An interesting finding of this study is the relatively late manifestation of clinical success of SK between Days 3 and 7 after chest drain insertion. Previous studies demonstrated earlier ben-

efit of SK on radiologic findings and increased amounts of drainage (10, 13, 14). Increased drainage with SK was also observed in the present study and is probably due to direct interaction of the fibrinolytic agent with the biochemical processes involved in empyema formation (4). However, reaching the combined clinical-radiologic end point of clinical success required more than 3 days for most patients, which at least partly explains this discrepancy. Furthermore, most patients included in the present study had features of advanced empyema that might delay the effect of medical therapy. Frank pus as an established predictor of unfavorable outcome (3) was present in 81% of our patients. They were also younger than in comparable trials, which might explain the low mortality despite the severity of empyema. Apart from this, however, the patients included were comparable to other published case series or controlled trials, suggesting that the results are applicable to a global scale.

Some weaknesses of the study must also be addressed. The trial was designed to determine the value of intrapleural SK in a "real life" scenario with fairly broad inclusion criteria. Patients were included on the grounds of pleural fluid morphology and smell, pH, and evidence of loculation on either CXR or sonography before additional biochemical parameters were available. We did not anticipate the high rate of withdrawals before rinse treatment could be started. This affected the number of

TABLE 2. TREATMENT AND OUTCOMES

Parameter	Saline (n = 22)	Streptokinase (n = 22)	p Value*
Clinical outcome, n (%)			
Died	1 (5)	1 (5)	NS
Success at 3 d	7 (32)	5 (23)	NS
Success at 7 d	10 (45)	18 (82)	0.012
Success at discharge	11 (50)	18 (82)	0.024
Referred for surgery	10 (45)	3 (9)	0.018
Death or referral for surgery	11 (50)	4 (18)	0.026
Pleural drainage			
Drains replaced, n (%)	3 (14)	2 (9)	NS
Rinses applied, n	3.0 ± 1.3 [†]	4.5 ± 2.0	0.015
Fluid drained, L			
Initial drainage	0.92 ± 1.0	0.75 ± 0.5	NS
After first rinse (24 h)	0.18 ± 0.16	0.31 ± 0.19	0.006
After second rinse (24 h)	0.17 ± 0.16	0.26 ± 0.14	0.013
After third rinse (24 h)	0.17 ± 0.17	0.26 ± 0.19	0.083
Total after three rinses (72 h)	0.42 ± 0.39	0.84 ± 0.39	0.001
Total drainage	1.71 ± 1.6	2.07 ± 1.2	NS
Duration of chest drainage, d, median	6 ± 5.3	7 ± 3.7	0.082
Duration of hospitalization, d, median	9 ± 7.7	10.5 ± 10.6	NS
Follow-up			
FVC, % predicted			
Discharge	49.6 ± 19.7	50.3 ± 14.8	NS
6 mo	70.3 ± 11.2	77.4 ± 14.3	NS
TLC, % predicted			
Discharge	68.5 ± 21.5	70.2 ± 12.2	NS
6 mo	88.0 ± 16.6	86.9 ± 16.5	NS
Lateral pleural shadowing on CXR pa, mm			
Discharge	25.3 ± 25.2	17.5 ± 11.8	NS
6 mo	6.2 ± 10.7	4.7 ± 6.1	NS
Area of shadowing on CXR pa, %			
Discharge	22.8 ± 19.7	24.5 ± 15	NS
6 mo	6.8 ± 11.0	4.7 ± 5.2	NS

Definition of abbreviations: CXR = chest X-ray; NS = not significant; pa = posteroanterior; TLC = total lung capacity.

* p Values are for comparison of saline and streptokinase; p < 0.1 is displayed.

[†] Values presented are mean ± SD unless otherwise indicated.

participants in the trial but not the validity of the result, because the remaining patients were well matched. Further, the study was not large enough to show a difference in mortality, and surgical referrals, death, and failure to trace some patients weakened the study's ability to make strong conclusions for the follow-up period. The patients at highest risk for poor functional and radiologic recovery were referred to surgery and thus were excluded from follow-up. This might have introduced a selection bias against SK, and masked a potential long-term functional benefit of SK. However, the numbers are respectable for a single-center study and the reproducible clinical judgment provided by a small team is an advantage. The inclusion of patients with pleural tuberculosis also deserves comment, because classic tuberculous pleurisy features clear, straw-colored fluid, a pH greater than 7.2, negative culture, and a benign course under antituberculous treatment alone. However, all patients who later turned out culture positive for *M. tuberculosis* on pleural fluid effectively had empyema with neutrophilic effusions and were included and treated according to the study criteria.

It is commonplace that the earlier the best available treatment is instituted the more likely the outcome will be favorable. Early VATS has shown promising results in case series and one small controlled trial (10, 20). A potential advantage of early surgery is a shorter hospital stay, which could compensate for the increased initial cost (10, 20). General anesthesia and single-lung ventilation allow extensive debridement of loculations by VATS or limited thoracotomy, but the surgical risk might be prohibitive in critically ill patients (11). No data about functional and radiologic

long-term outcome after VATS are available, but a meaningful further improvement over successful medical therapy seems unlikely in the light of the present study's results. However, VATS is not universally available and its routine use is out of reach for the majority of health care systems worldwide. Moreover, there is no firm evidence from published trials that suggests that tube drainage with instillation of fibrinolytics could not be undertaken in the first instance (11). Streptokinase is generally safe and no side effects were observed in the present study (12). Nonanaphylactic allergic reactions to SK, but not to urokinase, have been reported and activation of systemic fibrinolysis is at least a theoretical risk, albeit doses of up to 1.5 million units of SK have been shown to be safe in humans (12, 13). Human recombinant fibrinolytic agents such as plasminogen activator or deoxyribonuclease are nonantigenic and have advantageous pharmacologic properties over those of urokinase and SK (21). Experimental results in rabbit models of pleural empyema and case reports are promising, but these agents still need evaluation in controlled studies in humans (22, 23).

In conclusion, it remains beyond doubt that treatment of empyema and complicated parapneumonic effusions is multidisciplinary. The results of the present study support a stepwise approach to empyema treatment with initial chest tube drainage and medical management. Instillation of streptokinase additional to chest tube drainage is safe, improves outcome, and reduces the rate of surgical referrals. Further research should aim to assess the value of new fibrinolytic agents and to determine the ideal timing and modality of empyema surgery.

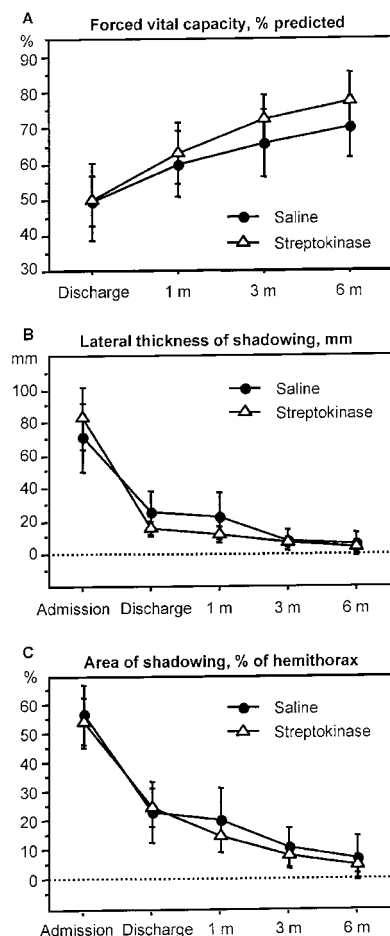


Figure 2. Forced vital capacity (A) and chest radiograph scores (B and C) over time. Consistent radiologic and functional improvement in both groups is observed. No statistically significant difference between groups was seen at any time point of follow-up. Patient numbers for saline/streptokinase were as follows: at admission, 22/22; at discharge, 11/18; after 1 month of follow-up, 10/18; after 3 months of follow-up, 9/17; after 6 months of follow-up, 9/15. Values represent means and error bars represent 95% confidence intervals. m = month.

Conflict of Interest Statement: A.H.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.M.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; B.W.V.d.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.T.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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