

To Study the Role of Intrapleural Streptokinase in The Treatment of Loculated Pleural Effusions - A Randomized Controlled Trial

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Abstract

Background: Loculated pleural effusions respond poorly to simple tube drainage, and surgical options are invasive and not widely available in resource-limited settings. Intrapleural fibrinolysis may be a practical alternative. We compared intrapleural streptokinase with saline irrigation in loculated pleural effusions. **Material and Methods:** In this randomised controlled trial at a tertiary care hospital in Mumbai, 50 adults with ultrasound-confirmed loculated pleural effusion were allocated by block randomisation to streptokinase (n = 25; 2.5 lakh IU in 100 mL saline per wash) or normal saline (n = 25) instilled through an intercostal drain or pigtail catheter, clamped for 2 hours, for 3 to 4 consecutive days. All patients received antitubercular therapy when indicated. Drain output, serial chest radiographs, post-wash ultrasonography, catheter duration, hospital stay, need for surgery and adverse reactions were recorded, with follow-up at 2 weeks, 2 months and 6 months. Success was defined as complete radiological resolution without surgery. **Results:** Tubercular effusion accounted for 86% of cases. Mean daily drain output was significantly higher with streptokinase on every wash day (day 1: 310.8 vs 202.0 mL, $p < 0.001$). Complete radiographic resolution on day 3 was 84% vs 44% ($p = 0.003$) and was sustained at 6 months. Complete dissolution of adhesions on ultrasonography was 60% vs 36% ($p = 0.030$). Catheter duration (14.4 vs 23.1 days) and hospital stay (16.5 vs 28.4 days) were shorter with streptokinase (both $p < 0.001$). Overall success was 84% vs 44% ($p = 0.003$). Surgery was needed in 1 (4%) vs 4 (16%) patients ($p = 0.35$, not significant). Fever with chills occurred in 16% of each group. **Conclusion:** Intrapleural streptokinase improved drainage, radiological resolution and hospital stay compared with saline in loculated pleural effusions, mostly of tubercular origin, with acceptable tolerability. It is an affordable option where thoracoscopic surgery is not readily available; larger, blinded multicentre trials are needed.

Keywords: Loculated Pleural Effusion, Streptokinase, Intrapleural Fibrinolysis, Tubercular Pleural Effusion, Randomised Controlled Trial.

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INTRODUCTION

Loculated pleural effusion, in which fibrin septa partition the pleural space into non-communicating compartments, is a frequent complication of pleural infection and tuberculous pleurisy and a common reason for failed tube drainage.^[1] Local inflammation and impaired fibrinolysis drive the evolution from a free-flowing exudate to a fibrinopurulent stage and finally to organized, thickened pleura, so that delayed drainage increases morbidity and the likelihood of surgery.^[2] Saline flushes and catheter placement alone seldom break down established septations, whereas video-assisted thoracoscopic surgery and decortication, although effective, are invasive, costly and unavailable in many resource-limited settings.^[3] Intrapleural fibrinolytics such as streptokinase lyse fibrin strands, improve catheter drainage and may spare patients an operation.^[4] Controlled trials in empyema and complicated parapneumonic effusion have supported this approach.^[5] but comparatively few randomised data come from settings where tuberculosis is a common cause of loculation. We therefore conducted a randomized controlled trial at a tertiary care centre in Mumbai to compare intrapleural streptokinase with saline irrigation in loculated pleural effusions, with radiological resolution without surgery as the primary outcome and

drainage volume, catheter duration, hospital stay and safety as secondary outcomes.

MATERIALS AND METHODS

Study design and setting: This was a parallel-group, two-arm randomized controlled trial conducted in the Department of Pulmonary Medicine, Grant Government Medical College and Sir J.J. Hospital, Mumbai. The protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants in English, Hindi or Marathi.

Participants: Consecutive adult patients of either sex, from the outpatient and inpatient services, with confirmed loculated pleural effusion were eligible. Exclusion criteria were bleeding

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diathesis, known hypersensitivity to streptokinase, contraindications to thrombolysis (haemorrhagic stroke, cranial surgery or head trauma within 14 days, major thoracic or abdominal surgery within 10 days, PT-INR above 2) and pregnancy.

Sample size and randomisation: Assuming a favourable outcome in 82% with streptokinase and 48% with conventional therapy, based on the trial of Diacon et al. [6], with 95% confidence and 80% power (OpenEpi 3.01), 25 patients per arm (n = 50) were required. Participants were allocated 1:1 by block randomisation to the streptokinase or saline group.

Baseline work-up. All patients had a structured clinical assessment, complete blood count, serology, chest radiograph, thoracic ultrasonography, CT thorax, sputum and pleural fluid GeneXpert, and pleural fluid analysis. An intercostal drain (ICD) or pigtail catheter was placed under aseptic precautions. Antitubercular therapy was started according to investigation results, with adequate nutrition.

Intervention. In the streptokinase group, a 15-lakh IU vial was reconstituted and diluted, and a 0.1 mL intradermal test dose was given first. The catheter was flushed with 20 to 50 mL of normal saline, then 2.5 lakh IU of streptokinase diluted in 100 mL of saline was instilled, followed by a 20 mL saline flush. The catheter was clamped for 2 hours with changes in patient position to aid dispersion, then released. The control group received the same procedure with normal saline alone. Three to four washes were given on consecutive days according to drain output and clinical and radiological response. Antihistamines and antipyretics were used for infusion reactions.

Outcomes and follow-up: The primary outcome was success, defined as complete radiological resolution without surgical intervention. Secondary outcomes were daily drain output, serial chest radiograph resolution (graded as none, partial, near-complete or complete), post-wash ultrasonographic dissolution of adhesions, ICD or pigtail duration, length of hospital stay, need for surgery and adverse reactions. Patients were reviewed every 24 hours during washes, 3 days after catheter removal, and at 2 weeks, 2 months and 6 months.

Statistical analysis: Data were entered in Microsoft Excel and analysed with SPSS version 20. Continuous variables are presented as mean (SD) and compared with the independent-samples t-test. Categorical variables are presented as number (%) and compared with Pearson's chi-square test, or Fisher's exact test when expected counts were below 5 in a 2 x 2 comparison. A two-sided p value below

0.05 was considered significant.

RESULTS

Baseline characteristics: Fifty patients were randomised and analysed (25 per group). Baseline features are shown in [Table 1]. Mean age was similar (39.4 vs 35.2 years, $p = 0.20$), but the streptokinase group had more men (84% vs 52%, $p = 0.015$) and fewer patients with a past history of tuberculosis (24% vs 52%, $p = 0.041$). Symptom frequencies, comorbidities, laterality and pre-wash fluid volume (821.6 vs 724.8 mL, $p = 0.09$) were comparable. Tubercular effusion was the commonest diagnosis in both arms (86% overall), followed by parapneumonic (10%) and malignant effusion (4%).

Drain output: The mean number of washes was 3.68 (SD 0.48) with streptokinase and 3.32 (SD 0.48) with saline. Post-wash drain output was significantly greater with streptokinase on each of the four days [Table 2; Figure 1]. The summed mean output over four days was about 725 mL with streptokinase (88% of pre-wash volume) and 413 mL with saline (57%).

Radiological resolution: On day 1 there was no significant difference in chest radiograph response ($p = 0.25$). From day 2 onward, streptokinase produced better resolution [Table 3; Figure 2]. On day 3, complete resolution was seen in 84% vs 44% ($p = 0.003$), and this difference persisted unchanged at 2 weeks, 2 months and 6 months. Day 4 films also favoured streptokinase (complete resolution 56% vs 16%, $p = 0.013$), although these categories were recorded differently from earlier days and are not directly comparable. Post-wash ultrasonography showed complete dissolution of adhesions in 60% of the streptokinase group vs 36% of the saline group, with incomplete dissolution in 4% vs 32% [$p = 0.030$; Table 3].

Catheter duration and hospital stay: Mean catheter dwell time was 14.4 (SD 6.0) days with streptokinase and 23.1 (SD 4.2) days with saline ($t = -5.91$, $p < 0.001$). Mean hospital stay was 16.5 (SD 7.4) vs 28.4 (SD 4.8) days ($t = -6.76$, $p < 0.001$) [Table 4; Figure 3].

Overall outcome and safety: Treatment succeeded in 21 of 25 patients (84%) given streptokinase and 11 of 25 (44%) given saline (chi-square 8.68, $p = 0.003$) [Figure 4]. Across the three outcome categories (success, failure, surgery) the distribution differed significantly (chi-square 8.69, $p = 0.013$). Surgery was required in 1 patient (4%) in the streptokinase group and 4 patients (16%) in the saline group; this difference was not statistically significant (Fisher's exact $p = 0.35$). Fever with chills occurred in 4 patients (16%) in each arm and was managed with antipyretics and antihistamines; no other adverse reactions were recorded.

Table 1: Baseline characteristics of the study participants

Characteristic	Streptokinase (n = 25)	Saline (n = 25)
Age, years, mean (SD)	39.4 (12.0)	35.2 (10.9)
Male sex, n (%)	21 (84)	13 (52)
Fever, n (%)	15 (60)	15 (60)
Chest pain, n (%)	14 (56)	14 (56)
Cough, n (%)	12 (48)	13 (52)
Breathlessness, n (%)	10 (40)	11 (44)
Loss of weight or appetite, n (%)	10 (40)	15 (60)
Diabetes mellitus, n (%)	5 (20)	6 (24)
Hypertension, n (%)	5 (20)	2 (8)

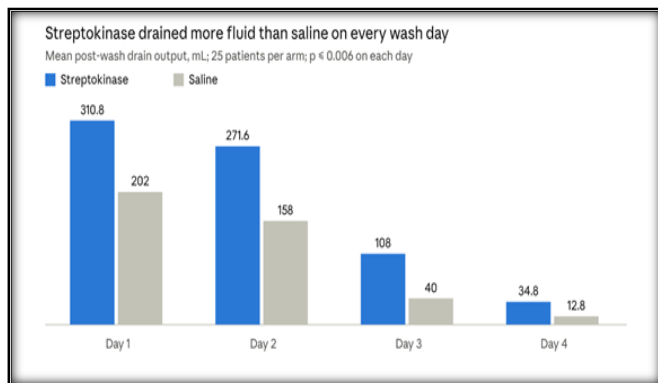
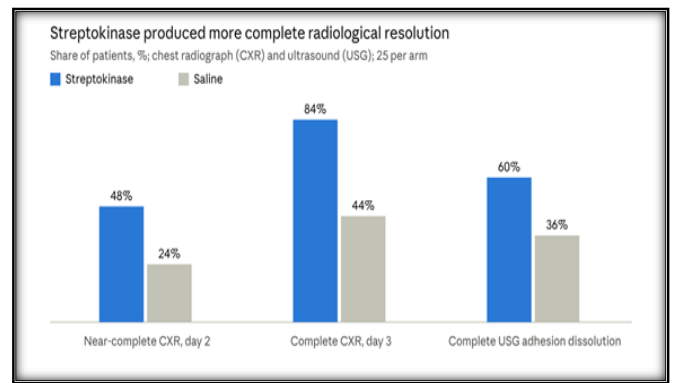
Chronic kidney disease, n (%)	1 (4)	0 (0)
Past history of tuberculosis, n (%)	6 (24)	13 (52)
Right-sided effusion, n (%)	14 (56)	11 (44)
Multiloculated effusion on ultrasound (any type), n (%)	21 (84)	22 (88)
Pleural fluid GeneXpert positive (rifampicin sensitive), n (%)	3 (12)	7 (28)
Pre-wash pleural fluid volume, mL, mean (SD)	821.6 (209.9)	724.8 (184.6)
Final diagnosis: tubercular / parapneumonic / malignant, n	21 / 3 / 1	22 / 2 / 1
ICD / pigtail catheter, n	14 / 11	17 / 8

Table 2: Daily post-wash drains output (mL), mean (SD)

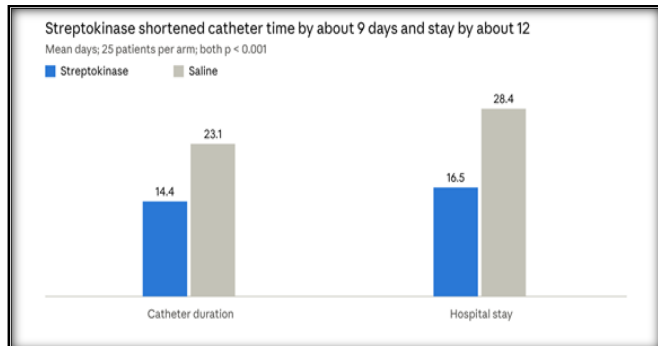
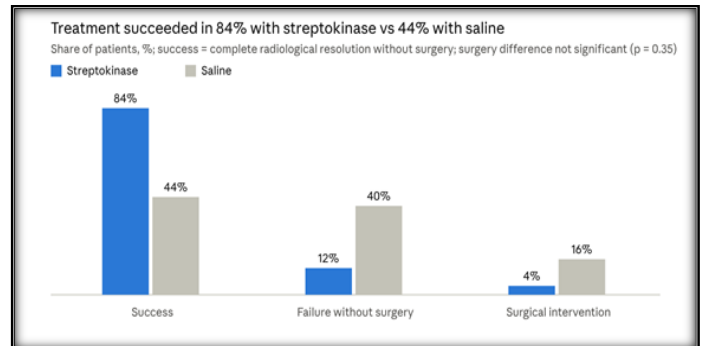
Post-wash day	Streptokinase	Saline	t	p
Day 1	310.8 (82.4)	202.0 (107.4)	4.018	< 0.001
Day 2	271.6 (114.1)	158.0 (132.9)	3.243	0.002
Day 3	108.0 (103.6)	40.0 (54.8)	2.900	0.006
Day 4	34.8 (22.9)	12.8 (21.7)	3.484	0.001

Table 3: Radiological response

Assessment	Streptokinase, n (%)	Saline, n (%)	p
Chest radiograph, day 1: none / partial	13 (52) / 12 (48)	9 (36) / 16 (64)	0.25
Chest radiograph, day 2: none / partial / near-complete	2 (8) / 11 (44) / 12 (48)	0 (0) / 19 (76) / 6 (24)	0.047
Chest radiograph, day 3: partial / complete	4 (16) / 21 (84)	14 (56) / 11 (44)	0.003
Chest radiograph at 2 weeks, 2 months and 6 months: partial / complete	4 (16) / 21 (84)	14 (56) / 11 (44)	0.003
Ultrasound adhesions: incomplete / partial / complete dissolution	1 (4) / 9 (36) / 15 (60)	8 (32) / 8 (32) / 9 (36)	0.030


Figure 1: Mean daily post-wash drain output by treatment arm. Trial data, n = 50 (25 per arm)

Figure 2: Radiological response on chest radiograph and ultrasonography. Trial data, n = 50 (25 per arm)
Table 4: Clinical outcomes and safety

Outcome	Streptokinase (n = 25)	Saline (n = 25)	p
Catheter duration, days, mean (SD)	14.4 (6.0)	23.1 (4.2)	< 0.001
Hospital stay, days, mean (SD)	16.5 (7.4)	28.4 (4.8)	< 0.001
Success (complete resolution without surgery), n (%)	21 (84)	11 (44)	0.003
Failure without surgery, n (%)	3 (12)	10 (40)	0.013 (3-category)
Surgical intervention, n (%)	1 (4)	4 (16)	0.35 (Fisher)
Fever with chills, n (%)	4 (16)	4 (16)	1.00


Figure 3: Catheter duration and length of hospital stay. Trial data, n = 50 (25 per arm)

Figure 4: Final outcome by treatment arm. Trial data, n = 50 (25 per arm)

DISCUSSION

In this randomised trial of loculated pleural effusions, mostly tubercular, intrapleural streptokinase yielded greater drainage, faster and more complete radiological clearing, shorter catheter dwell time and hospital stay, and a higher overall success rate than saline irrigation, with a similar rate of infusion-related fever and chills. The success rate of 84% in the streptokinase arm closely matches the 82% assumed from the trial of Diacon et al,^[6] and the 44% in the control arm is consistent with the 48% assumed for conventional therapy.

Our population was young and predominantly male (68%), a pattern also reported by Sandeepa et al., who found 70% men in patients with tuberculous effusions treated with intrapleural streptokinase through a pigtail catheter. Mean age (39.4 and 35.2 years) was similar to that of Diacon et al., whose arms averaged about 40 years.^[6] Fever, chest pain and cough were the commonest presenting symptoms in our series, as in Sandeepa et al,^[7] whereas breathlessness predominated in the series of Saxena and Maturu.^[8] such differences probably reflect case mix. Baseline pre-wash fluid volumes in our patients were comparable with those reported by Saxena and Maturu.^[8]

The greater drainage with streptokinase is biologically plausible, because plasmin generated from streptokinase dissolves fibrin septa and allows communication between pockets. Cumulative drainage over the washes corresponded to roughly 88% of the initial volume with streptokinase compared with 57% with saline. Ultrasonography confirmed this mechanism: complete adhesion dissolution was seen in 60% of the streptokinase group against 36% of controls. The streptokinase group received slightly more washes (3.68 vs 3.32), possibly because patients with denser loculations were more likely to receive a fourth wash, and this should be considered when interpreting drainage figures.

Shorter catheter dwell time (14.4 vs 23.1 days) and hospital stay (16.5 vs 28.4 days) are clinically and economically meaningful where inpatient beds and surgical capacity are limited. Surgical comparators suggest the gap to surgery should not be overstated: Samancilar et al. reported a significantly shorter hospital stay after VATS decortication (about 6.8 days) than after intrapleural fibrinolysis (about 14.3 days).^[9] Fibrinolysis therefore does not replace thoracoscopic surgery where it is available and affordable, but it offers a lower-cost first-line option that may avoid operation. Surgery was required in 4% vs 16% of our patients, a trend in the expected direction that did not reach statistical significance with this sample size, so the claim that streptokinase reduces surgical referral requires confirmation in a larger study.

Tolerability was acceptable. Fever with chills affected 16% of both groups, which argues against a streptokinase-specific effect and suggests contributions from the underlying disease, antitubercular therapy or the procedure itself. Fever and chest pain have likewise been the reactions reported after intrapleural streptokinase in an Egyptian series.^[10] No bleeding events were recorded in our patients,

although exclusion of high-risk patients limits generalisation.

This study has limitations. It was a single-centre trial with 50 patients, and no blinding of clinicians or patients was described. Randomization left imbalances in sex and past tuberculosis history, and 86% of cases were tubercular, so results may not apply to bacterial empyema. Radiological grading was subjective, and day-4 chest radiograph categories were not harmonized with earlier days. Surgical outcome was underpowered. Strengths include the saline-controlled randomised design, standardised dosing and technique, objective drain volumes, and radiological follow-up to 6 months.

CONCLUSION

In adults with loculated pleural effusions, predominantly tubercular, intrapleural streptokinase given through an indwelling catheter improved drainage and radiological resolution, shortened catheter duration and hospital stay, and increased the proportion of successful outcomes compared with saline irrigation, with tolerability similar to the control. It is a simple, affordable alternative where thoracoscopic surgery is unavailable. The trend towards fewer surgical interventions needs confirmation in larger, blinded, multicentre trials.

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Conflicts of interest

There are no conflicts of interest.

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