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ORIGINAL RESEARCH

Study of intrapleural fibrinolytictherapy in loculated pleural collections

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ABSTRACT

Aim: *To study of intrapleural fibrinolytictherapy in loculated pleural collections*

Material and methods: *All 50 patients of parapneumonic effusions with persistent pleural fluid and poor chest-tube drainage (less than 150ml/day) despite an appropriately positioned and patent drain; multiple loculi or fibrin strands in pleura as depicted by ultrasonography or CT scan chest were included in the study. Imaging studies with either chest radiography, ultrasonography (USG) or computed tomography (CT) were performed before the initiation of IPFT to assess the quantification of fluid the site and size of loculations and the extent of associated pleural thickening, marking of chest wall for site of insertion of chest drain.*

Results: *In 52% (n=26) of patients, the pleural effusion is caused by tuberculosis since these patients are primarily from rural areas and have low socioeconomic level. However, there were 10% (n=5) cases of malignant pleural effusion and 20% (n=10) cases of pneumonia with complex parapneumonic effusion. 6% of cases (n=3) involved hemothorax, while 12% involved empyema. 54% of the group under investigation needed three cycles of IPFT, followed by 46% who needed just two cycles and 10% who needed three cycles. 25 participants were found to have had a 10% improvement in FVC, while 19 patients had a 20% improvement. Only six patients saw the maximal FVC improvement of 30%. After IPFT, the FVC might reach a maximum of 70%. According to USG chest imaging, 86% of subjects had effusionsresolve to residual fluid less than 50 ml.*

Conclusion: *Studies have demonstrated that using intrapleural fibrinolytics is a good substitute for risky surgical treatments including VATS (video-assisted thoracoscopic surgery), thoracotomy, and decortication.*

Keywords: *VATS, Pleural effusion, Tuberculosis*

Introduction

Lower respiratory tract infections can become complicated by pleural infection, causing parapneumonic effusions and thoracic empyema. Due to their heterogeneity, pleural empyema and parapneumonic pleural effusions are clinically difficult disorders to treat and diagnose. They range from small, uncomplicated, pleural effusions that do not require specific treatment to multiloculated effusions and empyema with pleural fibrosis, systemic sepsis, trapped lung, metastatic infection, and respiratory failure.[1-3]

To start with, parapneumonic effusion starts with exudative stage, which consists of clear, sterile fluid which resolves with antibiotics alone. When antibiotics are started improperly or slowly, the exudative stage develops into the fibrinopurulent stage, where the fluid becomes more viscous and loculations form. If the infection is not controlled and drainage of the pleural space is not started, frank empyema with thick loculations and significant pleural thickening develops. Clinical terms for the three stages include simple parapneumonic effusion (SPE), complex parapneumonic effusion (CPE), and pleural empyema. Contrary to CPE and empyema, simple parapneumonic effusion

typically disappears with antibiotic treatment alone. The most common causes of failed drainage when there is a considerable volume of pleural fluid, and the chest tube is correctly positioned as shown by the postero-anterior and lateral chest radiographs are multiple pleural space loculations or tube obstruction by thick and viscous fluid. Pleural fluid loculations can have different etilologies such as complicated parapneumonic effusion (CPE), tubercular effusion, empyema, traumatic hemothorax and malignant effusion.[4,5]

Saline flushes, inserting one or more catheters into loculi while operating under image guidance, video aided thoracoscopic surgery (VATS), and traditional thoracotomy with empyema drainage and decortication are some of the therapeutic options for loculated pleural effusion. The first two modalities don't really help drainage that much. The last two surgical options are more intrusive, less common, and, if they are available, are not affordable for most patients in developing countries like India.[6] Drainage of pleural pus by tube thoracostomy has traditionally been thought to be the key to effective management, but modern methods including image guided small bore catheter insertion, intrapleural fibrinolytic instillation, and medical thoracoscopy are now readily accessible to practitioners. Loculated pleural effusions usually occur as a result of adhesions and sequelae of complicated tuberculosis, parapneumonic effusion, empyema, hemothorax and malignant effusions. Due to delayed treatment initiation, incorrect antibiotic usage, and longstanding pleural effusion, loculations develop. Adults with these collections typically receive antibiotic therapy, efficient drainage of infected fluid, and surgical intervention if conservative treatment is unsuccessful.[7] It has been suggested that intrapleural fibrinolytic medications, such as streptokinase, could enhance fluid evacuation in difficult parapneumonic effusions and empyemas, improve therapeutic results, and avoid the need for thoracic surgical intervention.[8]

Material and methods

After obtaining approval from Institutional Ethical Committee (Index Medical College Hospital and Research Centre) and written informed consent from the patients, all 50 patients of parapneumonic effusions with persistent pleural fluid and poor chest-tube drainage (less than 150ml/day) despite an appropriately positioned and patent drain; multiple loculi or fibrin strands in pleura as depicted by ultrasonography or CT scan chest were included in the study. Imaging studies with either chest radiography, ultrasonography (USG) or computed tomography (CT) were performed before the initiation of IPFT to assess the quantification of fluid the site and size of loculations and the extent of associated pleural thickening, marking of chest wall for site of insertion of chest drain. Chest tube was inserted using strict aseptic precautions and fluid drained daily was noted. Patients with persistent fluid and poor tube drainage despite an ultrasonography-confirmed appropriately positioned and patent drain or multiple loculi or fibrin strands, depicted by ultrasonography or CT scan of chest, were included in the study for IPFT. Three doses of streptokinase (2.5 lakh IU in 50 ml normal saline) was instilled in the chest tube at 8 hours interval with flushing by 20ml saline every time. Tube was clamped for 2 hours after instillation of each dose. Clinical response along with daily and cumulative drainage of the tube was noted. X-ray and ultrasonography of chest was done after 48 hours after the instillation of last dose of streptokinase. The criteria used for radiological resolution were as described by Sanchez et al. These were: maximum (normal or near normal chest radiograph); moderate (a clearance of 50% to 80% of pleural fluid); minimal (<50% clearance); none (no change). Treatment was discontinued if 48 hours after first cycle (3 doses) of STK, the cumulative drainage was less than 100mL and there was no radiological improvement. Responders to IPFT were defined as patients who had more than 500mL of cumulative drainage and maximum radiological resolution after one or two cycles of IPFT. The rest of the cases were defined as non-responders. Patients with insignificant drainage and insignificant reduction in amount of fluid less than 50% radiologically were subjected to a repeat cycle of 3 doses. Chest tube was removed when both daily drainage of clear pleural fluid was less than 50 mL and ultrasonography chest showed presence of less than 50 mL of fluid in pleural cavity. Expansion of the lung was assessed radiologically by chest x-ray taken before and after the administration of streptokinase. The reduction in the amount of pleural fluid by ultrasonography after IPFT was calculated. After the chest tube was removed for 48 hours, spirometry was performed. By removing fluid, using ultrasound, chest radiography, and forced vital capacity, pre- and post-IPFT clinical and radiological response were evaluated. Streptokinase is naturally produced by bacteria Streptococci Lancefield group C. As a member of the class of drugs known as

fibrinolytics, streptokinase interacts with human plasminogen to form complexes that hydrolytically activate additional unbound plasminogen by activating by bond cleavage to produce plasmin, a major fibriolysin that breaks down fibrin. Adverse reaction to Streptokinase range from fever, headache, nausea, coughing, sweating, itching, chest pain, bronchospasm, bleeding from multiple sites, hemoptysis,hematuria, gastrointestinal bleed, pulmonary edema and stroke.

INCLUSION CRITERIA

- Patients giving valid consent.
- Patients of age 18 to 100 years.
- Patients of pleural effusion with persistent fluid and poor chest tube drainage despite an appropriately positioned and patent chest tube.
- Patients with clotted hemothorax (provided there is no active bleeding) or loculated empyema, or malignant loculated pleural effusion.
- Multiple loculi or fibrin strands in pleura as depicted by Ultrasonography or CT scan chest.

EXCLUSION CRITERIA

- Known sensitivity to streptokinase.
- Contraindication to thrombolytic therapy - haemorrhagic stroke, intracranial neoplasm, cranial surgery or head trauma within 14 days, major thoracic or abdominal surgery within 14 days and PT INR > 2.
- Patients with h/o pneumonectomy, prior or present bronchopleural fistula.
- Uncontrollable hypertension with systolic values above 200 mm Hg and/or diastolic values above 100 mm Hg.

Results

16 (32%) of the patients were female, whereas 34 (68%) were male. This study's skewed distribution is caused by the hospital's increased admittance of male patients. (Table 1).

Table 1. Gender wise distribution of patients

Gender	Number ofpatients	Percentage(%)	MEAN ± SD
Male	34	68	41.97 ± 14.49
Female	16	32	43.06 ± 16.35
Total	50	100	42.32 ± 14.95

Patients ranged in age from 18 to 75. There are 13 patients (26%) who are older than 50. Patients under 30 and those between 30 and 50 are represented by 28% and 46%, respectively. (Table 2).

Table 2. Distribution of patients on the basis of age

Age (in years)	Numberof patients	Gender	Frequency	Percentage(%)	MEAN ± SD
<= 30	14	Male	10	20	23.46 ± 4.05
		Female	04	08	
31-50	23	Male	14	28	42.63 ± 6.55
		Female	09	18	
>50	13	Male	10	20	60.62 ± 8.09
		Female	03	06	
Total	50	50		100	42.32 ±14.95

Pleural effusion location 29 patients had pleural effusions on the right side (58%) and 21 patients had pleural effusions on the left (42%). (Table 3)

Table 3. Distribution of patients on the basis of side of pleural effusion

Side of effusion	Frequency	Percentage (%)
Right	29	58
Left	21	42
TOTAL	50	100

Patients were separated into three groups based on the amount of pleural fluid determined by chest ultrasonography prior to the implantation of an ICD (Table 4) Massive (>1500ml n=16), Mild (500ml n=11), and Moderate (500ml-1500mln=23) (Table 4).

Table 4. Distribution of patients on the basis of quantity of pleural fluid

Quantity of fluid	No. of patients	Gender	Frequency	Percentage (%)
Mild (<500ml)	11	Male	9	18
		Female	2	4
Moderate (500ml-1500ml)	23	Male	14	28
		Female	9	18
Massive (>1500ml)	16	Male	11	22
		Female	5	10
Total	50		50	100

In 52% (n=26) of patients, the pleural effusion is caused by tuberculosis since these patients are primarily from rural areas and have low socioeconomic level. However, there were 10% (n=5) cases of malignant pleural effusion and 20% (n=10) cases of pneumonia with complex parapneumonic effusion (Table 5). 6% of cases (n=3) involved hemothorax, while 12% involved empyema. (Table 5).

Table 5. Gender wise association of etiological types of effusion

Type of effusion	Gender	Frequency	Percentage %	Total Percentage
Tubercular	Male	18	36	52
	Female	8	16	
Malignant	Male	3	6	10
	Female	2	4	
Hemothorax	Male	2	4	6
	Female	1	2	
Empyema	Male	5	10	12
	Female	1	2	
Parapneumonic	Male	6	12	20
	Female	4	8	
TOTAL	50		100	

54% of the group under investigation needed three cycles of IPFT, followed by 46% who needed just two cycles and 10% who needed three cycles. (Table 6).

Table 6. Distribution of patients on the basis of number of cycles done of ipft

Number ofcycles	Number ofpatients	Gender	Frequency	Percentage(%)
2	23	Male	20	40
		Female	3	6
3	27	Male	14	28

Three cycles of IPFT were necessary in nearly all patients (94%) of large effusions. Only two cycles of IPFT were necessary toresolve all mild effusion cases.

Table 7. Association of quantity of effusion and number of cyclesdone of IPFT

Quantity of Effusion	Cycles done for IPFT	
	2 cycles	3 cycles
Massive	1 6%	15 94%
Moderate	11 48%	12 52%
Mild	11 100%	0 0%

On the IPFT, 56% of patients reported no negative effects. When streptokinase was administered, the most frequently reported side effects were tachycardia (20%), chest discomfort (14%) and fever (8%) at the site of the ICD. 2% (n=1) of patients with substantial tubercular effusion and haemorrhage were male (Table 8).

Table 8. Distribution of patients on the basis of frequency of adverse effects of IPFT

Adverse effect	Number of patients	Gender	Frequency	Percentage (%)	Total percentage
Fever	4	Male	4	8	8
		Female	0	0	
Tachycardia	10	Male	8	16	20
		Female	2	4	
Pain	7	Male	5	10	14
		Female	2	4	
Bleeding	1	Male	1	2	2
		Female	0	0	
NIL (No Adverse effect)	28	Male/Female	28	56	
TOTAL	50		50	100	

25 participants were found to have had a 10% improvement in FVC, while 19 patients had a 20% improvement. Only six patients saw the maximal FVC improvement of 30%. (Table 9). After IPFT, the FVC might reach a maximum of 70%.

Table 9. Distribution of patients on the basis of improvement in fvc after ipft

Improvement in FVC	Number ofpatients	Gender	Frequency	Percentage(%)
+10%	25	Male	15	30
		Female	10	20
+20%	19	Male	14	28
		Female	5	10
+30%	6	Male	5	10
		Female	1	2
Total	50		50	100

Table 10. Comparison of quantity of effusion with improvement in FVC

Quantity ofeffusion	Improvementin FVC	Frequency	Percentage (%)
Mild (<500ml)	+10%	3	6
	+20%	6	12
	+30%	2	4
Moderate (500ml-1500ml)	+10%	15	30
	+20%	7	14

	+30%	1	2
Massive (>1500ml)	+10%	7	14
	+20%	6	12
	+30%	3	6
Total		50	100

These were maximum (chest radiograph that was normal or almost normal), moderate (a pleural fluid clearance of 50% to 80%), and minimal (less than 50%). Following IPFT delivery, apparent chest X-ray resolution was visible in all 50 patients. Chest X-ray resolution before and after IPFT is significantly improved by employing paired t-test with p-value 0.05.

Table 11. Distribution of patients on the basis of amount of chest x-ray resolution

Chest x-ray resolution	Number of patients	Gender	Frequency	Percentage(%)	Total Percentage
Maximum	37	Male	23	46	74
		Female	14	28	
Moderate	10	Male	9	18	20
		Female	1	2	
Minimal	3	Male	2	4	6
		Female	1	2	
TOTAL	50		50	50	

Table 12. Comparison of Quantity of effusion with amount of chest x rayresolution

Quantity ofeffusion	Chest x ray resolution	Frequency	Percentage
Mild	Maximum	6	12
	Moderate	3	6
	Minimal	2	4
Moderate	Maximum	16	32
	Moderate	6	12
	Minimal	1	2
Massive	Maximum	15	30
	Moderate	1	2
	Minimal	0	0
Total		50	100

According to USG chest imaging, 86% of subjects had effusions resolve to residual fluid less than 50 ml.

Table 13. Comparison of drained fluid before IPFT & after IPFT

Quantity ofFluid	No. of Patients	MEAN ± SD		p-value
		Before IPFT	After IPFT	
Mild (<= 500ml)	11	260.91 ± 46.36	179.09 ± 25.48	0.0001
Moderate (501– 1500ml)	23	1218.70 ± 1308.79	392.61 ± 108.09	0.0042
Massive (> 1500ml)	16	1794.38 ± 389.97	436.88 ± 74.27	0.0000

Discussion

This research details a clinical trial of intrapleural fibrinolytic therapy (IPFT). These patients stand for those people who ordinarily do not react to conventional forms of therapy for tubercular, parapneumonic, or malignant pleural effusion.

Intra-pleural streptokinase is clearly safe and effective in enhancing chest-tube drainage and shortening the hospital stay of patients with complicated parapneumonic effusion and empyema, according to the initial study by Bergh et al. and subsequent studies by Taylor et al. and Sanchez et al. According to the aforementioned research[9–11], individuals who get intra-pleural Streptokinase require less hospitalization and less additional surgery. Therefore, these findings are consistent with the idea that streptokinase acts via lysis of pleural adhesions rather than by the volume of injected fluid. This served as the basis for the loculated pleural effusion intra-pleural fibrinolysis using streptokinase.

This investigation, which involved 50 patients, was conducted on hospital patients regardless of the cause of the effusion. Patients were hospitalized, and the effectiveness of fibrinolytic therapy was monitored. Patients ranged in age from 18 to 75. Thirteen patients (or 26%) are over the age of 50. Since this study, there were fewer patients in the study with extremes of age. The study involved 50 consecutive individuals who met the inclusion criteria and had a diagnosis of loculated pleural effusion. Out of 50 patients, 34 (68%) were men, despite the fact that female gender and traits were not excluded. This study's skewed distribution is caused by the hospital's increased admittance of male patients.

Due to the majority of patients at this hospital being from rural areas and having poor socioeconomic position, TB is the cause of pleural effusion in 52% of cases. However, there were 5 cases of malignant pleural effusion, 3 cases of hemothorax, and 10 cases of pneumonia with parapneumonic effusion. In each case, the purpose of inserting an ICD was to alleviate the symptoms and stop any further pleural thickening in patients who had loculated pleural effusions. The malignant pleural effusion patients were older than 40 years old. To confirm the malignant pleural effusion diagnosis in two of the patients, a diagnostic thoracoscopy was performed. One patient had metastasized carcinoma of the breast, whereas the other had original carcinoma of the lung. All of the study participants had unilateral effusions, either on the right or left. pleural effusion location 29 patients (58% of them) had pleural effusions on the right side, compared to 21 individuals (42% on the left).

The fluid was drained from a total of 50 patients who were included in the trial and underwent ICD installation. However, more than 200 ml of intrapleural fluid was seen in 39 patients' pleura. After the operation, a chest ultrasonography showed that the loculi were still present. Streptokinase was used to break up the loculi, and IPFT was performed in accordance with procedure once the tube was repositioned.

The study included patients who also had loculations and residual fluid, and majority of these patients had significant reductions in residual pleural effusion, with 43 patients (86%) demonstrating less than 50 ml after IPFT.

Before the trial, there was an average with standard deviation of (mild 260.91 ± 46.36) (moderate 1218.70 ± 1308.79) (massive 1794.38 ± 389.97) ml of intrapleural fluid. Streptokinase treatment resulted in an average intrapleural fluid volume of 57.84 ml, with a standard variation of 53.14; earlier research revealed similar results. The mean intrapleural fluid level before and after IPFT differs significantly with improvement. Therefore, the residual amount of intra pleural fluid is statistically significantly reduced (p value 0.001) when IPFT and streptokinase are used to treat loculated pleural effusion. IPFT helped patients with malignant pleural effusions recover more quickly for chemical pleurodesis before having their ICDs removed by reducing their respiratory symptoms.

Few patients experienced less than ideal pleural fluid drainage as a result of using streptokinase in the recommended six doses. Reduced pleural fluid drainage was observed in instances with numerous loculi on ultrasonography and increased pleural fluid viscosity. IPFT was given to these individuals twice or three times to help break up loculi and promote drainage. As indicated before, each cycle included 6 doses of streptokinase that were given at intervals of 8 hours. It was discovered, however, that patients didn't need more than three cycles of streptokinase to get rid of the fluid. 54% of patients, or 27 out of 50 subjects, required 3 cycles of IPFT. Among them, 6 cases of empyema, 5 cases of parapneumonic effusion, 5 cases of malignant pleural effusion, 11 cases of tubercular pleural effusion. Following IPFT delivery, apparent chest X-ray resolution was visible in all patients. Chest X- ray resolution before and after IPFT is significantly improved using the paired t-test with p- value 0.05.[12,13]

To measure the functional response to IPFT, the patients underwent the FVC manoeuvre. After IPFT, the FVC might reach a maximum of 70%. Prior to IPFT, the mean FVC was 46% with an 11.5%

standard deviation. The mean FVC after IPFT increased from 46% to 70%, a statistically significant increase (p-value 0.05).

The majority of patients (56%) reported no observable negative effects from the fibrinolytic therapy with streptokinase. The side effects noted were brand-new after fibrinolytic therapy, not concerns that existed prior to streptokinase therapy. However, only those individuals whose new-onset chest discomfort (14%) or fever (8%) were considered to be a side effect of streptokinase. All patients experienced pain at the site of the ICD. The majority of them (20%) had tachycardia at the location of the ICD. In the literature, the prevalence of bleeding following IPFT ranged from 2% to 15% [14–17], which was equivalent to the current study. Rahman et al[18] and Maskell et al[19] report on five instances of bleeding in the MIST II trial, including two instances of intrapleural haemorrhage and one instance of hemoptysis that happened in the tPA and DNase arm (5.76%). Cumulative dosages of IPSK may also have reduced plasma fibrinogen levels due to streptokinase's ability to decrease plasma fibrinogen levels in addition to fibrinolysis, which could result in a predisposition to bleed. In line with this, the negative effects of using intra-pleural streptokinase were minimal and short-lived Usually, surgery is required for acute multiloculated thoracic empyemas that cannot be fully drained by tube thoracostomy. Intrapleural fibrinolytic medicines were used to manage this complex issue without performing a thoracotomy.

Davies and colleagues[20], who examined the systemic fibrinolytic activity of two intrapleural streptokinase regimens, recently released the most thorough investigation of the intrapleural streptokinase's effects on systemic fibrinolysis. Intrapleural streptokinase was administered to eight patients in a single dosage of 250 000 U, then to eight more in a series of doses of 250000 IU every 12 hours for three days (total dose 1.5 million units). The streptokinase was left in the pleural cavity for two hours with each patient. Before administering streptokinase intravenously, levels of prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, and D-dimer were assessed. The single dosage group's end points were reassessed 24 hours after streptokinase, while the group receiving serial doses' end points were reassessed at 24, 48, and 72 hours. After intrapleural streptokinase injection, none of the indicators showed any physiological or statistical differences. Even at a dose of 1.5 million units, intra-pleural streptokinase did not significantly activate the systemic fibrinolytic system

Conclusion

Studies have demonstrated that using intrapleural fibrinolytics is a good substitute for risky surgical treatments including VATS (video-assisted thoracoscopic surgery), thoracotomy, and decortication. It is also a safer, simpler, and more affordable approach. If the intercostal drainage tube is properly positioned and there still appears to be pleural fluid in the cavity, then loculated pleural fluid collection ortube obstruction from viscous fluid are the likely causes of unsuccessful drainage.

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