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Respiratory Medicine

UTILITY OF INTRAPLEURAL STREPTOKINASE IN THE MANAGEMENT OF COMPLICATED PLEURAL EFFUSION IN PATIENTS ATTENDING RESPIRATORY DISEASE HOSPITAL, BIKANER.

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ABSTRACT

Aim: To compare the success rate of Intrapleural Streptokinase with Saline flush in the management of Complex Complicated Pleural Effusion

Methods: Among 100 patients,50 patients are instilled Intrapleural Streptokinase and 50 patients are instilled normal saline(0.9%).Streptokinase,250,000 IU,diluted in 100 ml of saline solution is administered through the chest tube and clamped for 4 hours and patient rotated in several positions.After 4 hours,clamp removed and drained material measured subtracting injected volume.The procedure to be repeated twice a day for 3 days.In Saline group,100 ml of normal saline without Streptokinase is administered and repeated for 3 days. The criteria for improvement in chest radiograph (PA View) is defined as: maximum (normal or near-normal chest radiograph); moderate (a clearance of 50 to 80% of pleural opacities); minimal (<50% of clearance); or none (no change).The amount of fluid drained is quantified.

Results: In Saline group,only 6 %(3 patients) had radiological improvement which was minimal.Among Streptokinase group, 8% (4 patients) had maximum improvement, 46% (23 patients) had moderate improvement, 24% (12 patients) had minimal improvement and 22% (11 patients) with no change.Overall success rate of Streptokinase was 78% when compared to saline which was 6% which was statistically significant (p value <0.001).

Conclusion: We concluded that Intrapleural Streptokinase attains success in more than 3/4th (78%) patients reducing the use of video assisted thoracic surgery (VATS) and more invasive conventional thoracotomy.

KEYWORDS :

INTRODUCTION

Pneumonia remains one of the most common community and hospital acquired infection despite the advent of potent anti-microbial agents. It is estimated that at least 40% of hospitalized patients with pneumonia develop parapneumonic effusion, which is associated with an increased morbidity and a mortality of 15% [1-3].

To start with, parapneumonic effusion consists of clear, sterile fluid which resolves with antibiotics alone. A significant number of patients with pneumonia develop para-pneumonic effusions. Parapneumonic effusions may be "Simple" consisting of free flowing, clear exudative fluid which almost resolves completely with antibiotics alone. In case of delayed or inappropriate treatment, some of these simple effusions progress to "Complicated" para-pneumonic effusions. The management of these types of effusions with intercostal tube drainage and antibiotics fails most of the time due to thick viscous fluid and multiple pleural space loculations. Intrapleural adhesions and septated effusions remain a common and troublesome clinical entity. The presence of adhesions carries a poor prognostic factor in patients with exudative pleural effusions[4].The presence of loculations and thick viscous fluid leads to failed pleural space drainage in spite of tube being patent and correctly positioned.

In complicated parapneumonic effusions (CPE), white blood cells migrate to the infected pleural space and release permeable factors causing fibrinogen to spill into the pleural space. The fibrinogen is then converted to fibrin. Fibrin causes tissue surfaces to adhere and this will trap the causative microorganism [5].This entrapment will prevent host defence mechanisms and antibiotics from reaching the site of infection[6]. Infected effusions have been shown to have low fibrinolytic activity and elevated concentrations of plasminogen activator inhibitors[7-9].

Appropriate therapy varies depending on clinical circumstances and includes antibiotic therapy alone for uncomplicated effusions, chest tube or surgical drainage for complicated effusions and surgical drainage for established, organized empyemas.

The management options in complicated parapneumonic effusion consist of either use of minimally invasive video assisted thoracic surgery (VATS) or more invasive conventional thoracotomy[10]. In spite of being effective, VATS is not easily accessible and affordable in developing countries like India.

In dealing with this problem, intrapleural fibrinolytics may be a safe, easy, cost effective management option. The purpose of our study is to assess the safety and efficacy of streptokinase for intrapleural fibrinolysis in patients with septated pleural effusion.

DEFINITION

Parapneumonic pleural effusions are pleural effusions that develop as a consequence of bacterial pneumonia, lung abscess or bronchiectasis [11,12]. An uncomplicated PPE are usually small in volume, free-flowing without loculations and inflammatory in nature without the presence of detectable pathogens. Most often, uncomplicated parapneumonic pleural effusion resolve with antibiotic therapy of the underlying pneumonia. A complicated parapneumonic pleural effusion usually results from pleural infection and requires at least catheter drainage of pleural fluid and possibly surgical intervention.

PATHOPHYSIOLOGY

The increased rate of pleural fluid formation results from increased lung interstitial fluid in regions of the pneumonia and increased permeability of pleural capillaries and the pleural mesothelial monolayer barrier [13]. When the amount of pleural fluid entering the pleural space exceeds the capacity of the pleural lymphatics to reabsorb the fluid, a pleural effusion develops.

Exudative Stage

The pleural fluid at this stage is free flowing, non-turbid and sterile. Pleural fluid analysis shows pH greater than 7.2, glucose greater than 40 mg/dl and pleural fluid lactic acid dehydrogenase (LDH) levels less than three times the upper limit of serum LDH.[14]

Fibropurulent Stage

In the absence of early diagnosis or appropriate therapy, the fibrinopurulent stage ensues. The pleural fluid becomes clottable due to leakage of plasma proteins, increased formation of procoagulants and loss of fibrinolytic activity in pleural space resulting in the formation of a thick layer of fibrin over the parietal and visceral pleura and loculations within the fluid. Eventual deposition of fibrin along pleural membranes may occlude lymphatic stomata decreasing the reabsorption capacity of the pleural space for fluid.Mesothelial cells play a pivotal regulatory role in the development of the intrapleural inflammatory cascade. Mesothelial cells act as phagocytes and trigger an inflammatory response when activated by bacteria, with the release of a battery of chemokines (C-X-C group), cytokines (IL-1, IL-6, IL-8, TNF- α, MCP-1), oxidants and proteases. Activated mesothelial cells also regulate the recruitment of neutrophils and mononuclear phagocytes to the pleural space [15-18].The pleural fluid at this stage is invariably turbid but may be clear. The pleural fluid pH is less than 7.2, glucose level is less than 40 mg/dl and LDH levels are more than three times the upper limit of serum LDH.[14]

Organization Stage

In the absence of inadequate or delayed pleural space drainage and inappropriate antibiotics, the stage of empyema ensues over a period of

two to several weeks. Empyema is characterized by viscous, whitish-yellow and turbid to opaque fluid. Empyema fluid consists of fibrin, cellular debris and viable or dead bacteria[11,12]. There is a proliferation of fibroblasts leading to formation of solid fibrous peel, preventing the reexpansion of lung and creating a persistent pleural space with continuing potential for infection. The empyema is either in the form of single locule or can be multiloculated.

CLASSIFICATION AND TREATMENT SCHEME FOR COMPLICATED PLEURAL EFFUSION AND EMPYEMA[19]

Class 1 Nonsignificant Pleural Effusion
Small <10 mm thick on decubitus x-ray study
No thoracocentesis indicated

Class 2 Typical Parapneumonic Pleural Effusion
>10 mm thick
Glucose >40 mg/dl, pH >7.2
LDH <3x upper limit normal for serum
Gram's stain and culture negative
Antibiotics alone

Class 3 Borderline complicated pleural effusion
7.0 <pH <7.20 and/or
LDH >3 x upper limit normal and glucose >40 mg/dl
Gram's stain and culture negative
Antibiotics plus serial thoracocentesis

Class 4 Simple Complicated Pleural Effusion
pH <7.0 or glucose <40 mg/dl or
Gram's stain or culture positive
Not loculated not frank pus
Tube thoracostomy plus antibiotics

Class 5 Complex Complicated Pleural Effusion
pH <7.0 and/or glucose <40 mg/dl or
Gram's stain or culture positive
Multiloculated
Tube thoracostomy plus fibrinolytics (rarely require thoracoscopy or decortication)

Class 6 Simple Empyema
Frank pus present
Single locule or free flowing
Tube thoracostomy ± decortication

Class 7 Complex Empyema
Frank pus present
Multiple locules
Tube thoracostomy
Often require thoracoscopy or decortication

DIAGNOSIS

The possibility of a parapneumonic effusion should be considered during the initial evaluation of every patient with a bacterial pneumonia. At this evaluation, it is important to determine whether a complicated parapneumonic effusion is present because a delay in instituting proper pleural drainage in such patients substantially increases morbidity. The possibility of a parapneumonic effusion should also be suspected in patients who do not respond to antimicrobial therapy [20].

The patients first manifest an acute febrile illness with chest pain, sputum production and leukocytosis. In contrast to patients with aerobic bacterial pneumonias, patients with anaerobic bacterial infections involving the pleural space are usually first seen with subacute illnesses. Many patients have a history of alcoholism, an episode of unconsciousness or another factor that predisposes them to aspiration. Most patients also have poor oral hygiene. On examination, there will be shift of trachea to opposite side, decreased breathing movements, vocal resonance and breath sounds on the affected side.

Radiological:
The presence of D- shaped opacity or absence of typical sickle- shaped opacity in postero-anterior and lateral chest radiographs is suggestive of Complicated Parapneumonic effusion (CPE) or empyema which is loculated. Ultrasonography (USG) of chest is a useful and easily accessible test for detecting the presence of fibrin strands, septations or necrotic debris, the presence of which suggest the development of CPE. Contrast Enhanced Computed Tomography (CECT) of chest can reliably detect loculations, their number, sizes and pleural thickening.

MANAGEMENT OF PARAPNEUMONIC EFFUSIONS AND EMPYEMA

Early, appropriate antibiotic therapy represents the cornerstone of therapy for pneumonia and PPE. When PPE advances beyond the exudative stage and becomes complicated, early drainage of pleural fluid becomes necessary for a good clinical outcome. The choice of drainage technique depends on multiple factors that include the viscosity, location, volume and extent of loculations in combination with the general condition of the patient.

Antibiotic Selection
All patients with parapneumonic effusions or empyema should be treated with antibiotics. If the Gram's stain of the pleural fluid is positive, it should guide the selection of an antibiotic. The initial antibiotic selection is usually based on whether the pneumonia is community-acquired or hospital-acquired and on how sick the patient is. Metronidazole penetrated most easily, followed by penicillin, clindamycin, vancomycin, ceftriaxone and gentamicin[21][22]. For patients hospitalized with community-acquired pneumonias that are not severe, the recommended agents are a fluoroquinolone alone, such as levofloxacin, moxifloxacin, gatifloxacin or gemifloxacin, or a β-lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam or ertapenem). There is no reason to add a macrolide because atypical pathogens rarely cause a pleural effusion. If a pseudomonas infection is suspected, an antipseudomonas antibiotic such as piperacillin, piperacillin-tazobactam, imipenem, meropenem or cefepime should be included.

Options For Management Of Pleural Fluid
There are several treatment options available for the management of the pleural fluid in patients with parapneumonic effusion and these include observation, therapeutic thoracentesis, tube thoracostomy, intrapleural instillation of fibrinolytics, VATS with the breakdown of adhesions and possible decortication, thoracotomy with decortication and the breakdown of adhesions and open drainage.

Observation
Observation is the appropriate course if the patient has a Class 1 parapneumonic effusion, that is, the effusion is less than 10 mm in thickness on the decubitus chest radiograph.

Therapeutic Thoracocentesis
Therapeutic Thoracocentesis is indicated for borderline complicated pleural effusion (class 3).

Tube Thoracostomy
For the past several decades, the initial drainage modality for most patients with complicated parapneumonic effusions has been tube thoracostomy. The chest tube should be positioned in a dependent part of the pleural effusion. Initially, the chest tube should be connected to an underwater seal drainage system. If the visceral pleura is covered with a fibrinous peel, the application of negative pressure to the chest tube may help expand the underlying lung and hasten the obliteration of the empyema cavity.

The most common reason for failure of pleural drainage among patients with an appropriately positioned catheter is occlusion of the catheter by viscous, fibrin-rich fluid and cellular debris or the existence of fibrin strands that form pleural loculations that prevent sequestered fluid from reaching the chest tube [23-27]. Fibrinolytic agents have the potential to lyse fibrin clots and adhesions to promote pleural fluid drainage.

Video-Assisted Thoracoscopy with Lysis of Adhesions and/or Decortication
Another option for the patient with an incompletely drained parapneumonic effusion is VATS. Although medical thoracoscopy is occasionally used in this situation, VATS is usually preferred because if the lung cannot be expanded, the VATS can be converted to a full thoracotomy. With VATS, the loculi in the pleural space can be disrupted, the pleural space can be completely drained and the chest tube can be optimally placed[28]. In addition, if the lung is trapped, an attempt can be made to perform a decortication.

Decortication
With decortication, all the fibrous tissue is removed from the visceral and parietal pleura and all pus is evacuated from the pleural space.

Decortication eliminates the pleural sepsis and allows the underlying lung to expand. Decortication can be performed with VATS or with a full thoracotomy.

Open Drainage

Chronic drainage of the pleural space can be achieved with open drainage procedures. The procedure involves resecting segments of one to three ribs overlying the lower part of the empyema cavity and inserting one or more short, large-bore tubes into the empyema cavity. Following this procedure, the tubes are irrigated daily with a mild antiseptic solution. The drainage from the tubes can be collected in a colostomy bag placed over the tubes. The advantage of this method over closed-tube drainage is that drainage is more complete and the patient is freed from attachment to the chest tube bottles.

History Of Intrapleural Fibrinolytics

Tillet and Sherry[29-31] were the first ones to use fibrinolytic agents in 1949 in 23 patients who had loculated empyema or haemothorax. Their patients received intrapleural instillation of both streptokinase and streptodornase, which was extracted from concentrated filtrates of streptococci of Lancefield group C. There was significant improvement in drainage of fluid. However, the initial enthusiasm waned because of significant systemic adverse effects in the form of fever, leukocytosis and general malaise. These side effects were due to immunological reaction caused by impurities in the preparation of agents. There was not much of use of this therapy until Bergh and colleagues[32] in 1977 used purified streptokinase and reported significant improvement in 10 of 12 patients with empyema without the need for any major surgical intervention and without any significant adverse effects. In the last 25 years there has been numerous case series and randomized controlled trials using streptokinase (STK) and urokinase (UK) in complicated parapneumonic effusion and empyema with encouraging results.

Pharmacology of Fibrinolytics

Streptokinase is a non-enzymatic protein produced by the Lancefield group C strain of β-hemolytic streptococci (exotoxin), which activates the fibrinolytic system indirectly [33]. Streptokinase forms a 1:1 stoichiometric complex with plasminogen, which then undergoes a transition and exposes an active site in the modified plasminogen moiety,whereby the complex becomes a potent plasminogen activator. This complex has protease activity and cleaves a second plasminogen molecule, resulting in plasmin. Plasmin, a trypsin-like enzyme, active at neutral pH, hydrolyses fibrin, fibrinogen and other coagulant factors, leading to lysis of fibrin coagula [33][34][35].

Contraindications:

Patients allergic to Streptokinase, hemodynamically unstable patients, known patients of bleeding disorders and patients having abnormal coagulation profile and liver function tests are the contraindications for intrapleural streptokinase therapy.

Adverse Effects:

The obscuring effects of systemic responses to the underlying pneumonia prevent a reliable estimate of the frequency of adverse effects from these agents[34][27][36]. Immunologic reactions to streptokinase, however, represent the most commonly reported adverse effects. The initial use of nonpurified solutions of streptokinase resulted in frequent febrile reactions, general malaise and leukocytosis. Current preparations cause far fewer allergic reactions with fever occurring in 0 to 20% of patients. A prospective study by Maskell and coworkers[37] observed only a trend toward more commonly occurring serious adverse events (chest pain, fever or allergy) with streptokinase as compared with placebo. Rare reports exist of local and systemic hemorrhage with intrapleural fibrinolytic therapy [25][39]. One case study reported that 500,000 units of intrapleural streptokinase caused systemic hemorrhage with a mild-moderate disturbance of clotting indices [26]. Additionally, Temes et al. reported in a case series a patient of significant local bleeding that required thoracotomy [38].

AIM AND OBJECTIVE

To compare the success rate of Intrapleural Streptokinase with Saline flush in the management of Complex Complicated Pleural Effusion.

REVIEW OF LITERATURE

A study conducted by **Saleh Abu-Daff** in which IPFT was used in 237 patients with pleural effusions; 163 with empyema/complicated parapneumonic effusions, 32 malignant effusions and 23 with haemothorax. With Streptokinase, resolution was achieved in 73.1% cases. Failure occurred in 46 (20%) cases. Multivariate analysis revealed that failure was associated with the presence of pleural thickening (>2 mm) on CT scan (p=0.0031, OR 3, 95% CI 1.46 to 6.57).[40-42]

A study conducted by **SH Talib** revealed increased drainage through intercostal drain in streptokinase group compared to control group. The mean duration of intercostal drainage was shorter in streptokinase group compared to control group. Radiologically, streptokinase group revealed improvement in 8/12 cases and less improvement in rest of the 4 cases. In control group, less improvement was seen in 2/12 cases and no improvement was seen in rest of the 10 cases. The observation difference is found to be highly significant statistically ($p < 0.001$).[43-45]

A study conducted by **Surider Jinda in** 801 patients comparing fibrinolytic therapy with placebo. Fibrinolytic therapy was beneficial for the outcomes of treatment failure (surgical intervention or death) (risk ratio [RR],0.50; 95% CI, 0.28-0.87) and surgical intervention alone (RR,0.61;95% CI,0.45-0.82).[46-48]

A study conducted by **Antonio Padua** in 48 patients; there were 30 patients with empyema, 14 with hemothorax and 4 patients with malignant pleural effusions without lung trapping. Successful fibrinolysis was obtained in 44 patients, with complete resolution of the pleural collection and adequate radiologic and spirometric improvement. In ¾ patients with multiloculated malignant hemothorax with high-yielding pleural drainage, IPSK allowed successful lysis of loci and an adequate pleurodesis was achieved. Only 4 patients required surgical treatment. The overall success rate was 92%.[49-52]

A study conducted by **Donna E Maziak** in which IPFT was used in 237 patients with pleural effusions; 163 with empyema/complicated parapneumonic effusions, 32 malignant effusions and 23 with haemothorax. Overall, resolution achieved was 80%.Failure occurred in 46 (20%) cases. Multivariate analysis revealed that failure was associated with the presence of pleural thickening (>2 mm) on CT scan (p=0.0031, OR 3, 95% CI 1.46 to 6.57).[53-55]

A study conducted by **Bergh** in which purified streptokinase reported significant improvement in 10 of 12 patients with empyema without the need for any major surgical intervention. Treatment success criteria included increased volume of fluid drainage and clinical and radiological resolution of CPE or empyema. Success rate was 67-100% in these studies. The majority (>90%) of patients had no complications and 5-10% had transient fever, pleuritic chest pain and chest wall erythema.[56-58]

A study conducted by **Diacon** and coworkers is a single-center, placebo-controlled RCT to determine whether streptokinase instillations adjunctive to chest tube drainage reduce the need for surgery and improve outcome in 53 patients who had frank pleural pus (81%), positive pleural fluid cultures (62%), or low pleural fluid pH values (mean pH 6.60) [59]. The study is important because it is the first RCT of intrapleural streptokinase that evaluated the clinical outcomes of a need for surgery and clinical success as primary endpoints [59] [60]. After seven days, streptokinase treated patients had a higher clinical success rate (82% vs. 48%, p=0.01) and fewer referrals for surgery (43% vs. 9%, p=0.02). Furthermore, no significant radiological or functional differences were observed between groups during follow-up over six months.

A study conducted by **Davies** and colleagues [61] conducted a RCT of streptokinase versus saline placebo administered from the second to fifth hospital days and enrolled 24 patients with parapneumonic effusions that appeared frankly purulent or fulfilled biochemical criteria for infected pleural fluid. Primary endpoints included the 1) total volume of pleural fluid drainage; 2) volume of fluid drainage during the interval of streptokinase administration; and 3) improvement of chest radiographs from baseline to hospital discharge. Streptokinase caused an increased rate of fluid drainage and greater improvement of chest radiographs.

Systemic fibrinolysis or hemorrhagic complications did not occur. Although surgical drainage was required in three placebo-treated patients and none in the streptokinase group, differences in this and other clinical endpoints did not reach statistical differences.

After publication of this, small RCTs with and without placebo control,[62-65] a Cochrane Collaboration systematic review assessed the evidence for efficacy of fibrinolytic therapy [66]. The reviewers concluded that the aggregate data demonstrated that fibrinolytic therapy provided significant benefits in terms of hospital stay, duration of fever, radiographic improvement and need for surgical drainage without serious side effects of therapy, but study results were not consistent across the investigations. Because of the small sample sizes and heterogeneous study designs, the reviewers could not recommend routine use of fibrinolytic therapy.

A study conducted by **Yousef Ahmed, Sahar Refaat** revealed increased drainage of pleural fluid through intercostal tube after streptokinase instillation. The observation difference in fluid volume before and after streptokinase instillation is found to be highly significant statistically ($p< 0.001$). Outcome was defined according to scoring of changes in X-ray and ultrasound with success rate of 60%. Chance of success increases when the adhesions are fine based on the sonographic features[67]. No major adverse effects were noted.

A study conducted by **Aruna Talattam** in which 75 complicated parapneumonic effusion patients were studied. Streptokinase was administrated in 3 dosage variants; 25 patients with 2,50,000 IU in 50 ml NS once a day for 1 week, 25 patients with 5,00,000 IU in 50 ml NS once a day for 1 week, & 25 patients with 7,50,000 IU in 50 ml NS once a day for 3 to 5 days. There was significant drainage of 1,500 ml in patients treated with 7,50,000 IU and around 1,000 ml in patients treated with 5,00,000 IU and 300 to 500 ml in patients treated with 2,50,000 IU. Clinical, radiological resolution and volume of pleural fluid drained were assessed for final outcome. Chest pain was reported in 7 patients (9.3%), fever in 5 patients (6.6%) and haemoptysis in 3 patients (4%).There was no allergic reaction in any patient[68].

A study conducted by **Lary A. Robinson** in which 13 consecutive patients presenting with a fibrinopurulent empyema were demonstrated to have incomplete drainage. To facilitate drainage, streptokinase, 250,000 units in 100 mL 0.9% saline solution (3 patients), or urokinase, 100,000 units in 100 mL 0.9% saline solution (10 patients), was instilled daily into the chest tube and the tube was clamped for 6 to 12 hours followed by suction. This routine was continued daily for a mean of 6.8 2 3.7 days (range, 1 to 14 days) until resolution of the pleural fluid collection was demonstrated by computed chest tomography and clinical indications. This regimen was completely successful in 10 of 13 patients (77%), who had resolution of the empyema, eventual withdrawal of chest tubes and no recurrence. Two patients, both pediatric liver transplant patients, had an initial good response but eventually required decortication[69,70].

A study conducted by **RJO Davies** in which twenty four patients with infected community acquired parapneumonic effusions were studied. 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 2.9cm, 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[71].

A study conducted by **Christopher W H Davies** in which eight patients received a single dose of 250,000 IU IPSK and a further eight received serial doses of 250,000 IU IPSK every 12 h for 3 d (total dose: 1.5 million IU). Each dose was retained in the pleural cavity for 2 h. Venous blood for prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen and D-dimers due to fibrin degradation were measured before any IPSK. These end points were then remeasured 24 h after IPSK in the single-dose group and after 24, 48 and 72 h in the group receiving serial doses. There were no physiologic or statistical differences in any of the indices after administration of IPSK. IPSK administered up to a dose of 1.5 million IU does not cause significant activation systemic fibrinolysis in humans[72].

MATERIALS AND METHODS

Study Design: Hospital based observational study

Study Place: Department of Respiratory Medicine, SP Medical College, Bikaner, Rajasthan.

Study Duration: From approval of plan to sample size acquirement

Study Population: Patients with Complex Complicated Pleural effusion admitted in Respiratory Disease Hospital, Bikaner

Sampling Technique: Consecutive sampling

Sample Size: 100 cases of Complex Complicated Pleural effusion admitted in Respiratory Disease Hospital, Bikaner.

Inclusion Criteria

1. Those who are giving informed consent.
2. Patients of Complex Complicated Pleural effusion (USG showing loculations) with tube thoracostomy in correct position having no radiological improvement/ minimum or no drainage over 24 hours.

Exclusion Criteria

1. Hemodynamically unstable patients.
2. Patients having previous history of Coronary artery disease, Stroke and significant hemorrhage in last 6 months.
3. Prior failed AST for Streptokinase.
4. Known patients of bleeding disorders and patients having abnormal coagulation profile and liver function tests.
5. Use of fibrinolytic agents in two years by any route.

Study Tool:

A pre tested, pre structured questionnaire with both open and close ended questions were used.

Data Collection & Analysis:

After obtaining permission from Ethical Committee and informed consent of study population selected by analyzed inclusion and exclusion criteria with help of consecutive sampling, the questionnaire was administered to study subjects by the researcher. All relevant information related to study subjects, socio demographic details, anthropometry, clinical profile were taken. The patients were explained in detail about the procedure to begin with.

Technique :

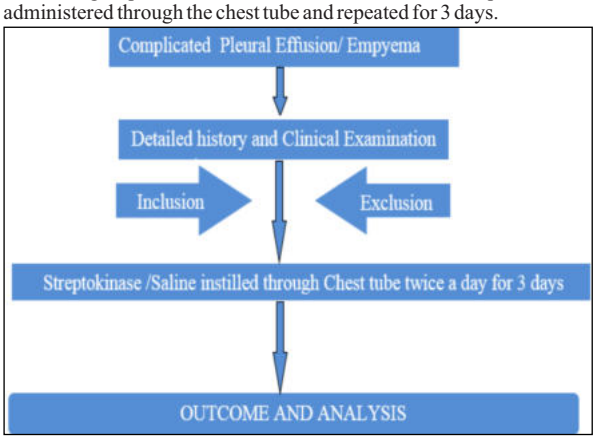
Patients will be explained in detail about the procedure to begin with.

Among 100 patients, 50 patients (Streptokinase group) are instilled Intrapleural Streptokinase and 50 patients (Saline group) are instilled normal saline (0.9%).

In Streptokinase group, AST for Streptokinase is done.

Using an aseptic technique, Streptokinase, 250,000 IU, diluted in 100 mL of saline solution is administered through the chest tube. The chest tube to be clamped for 4 hours and patient has to be rotated in several positions to allow a better distribution of Intrapleural Streptokinase. After 4 hours, the clamp to be removed and the drained material measured subtracting the injected volume. The procedure has to be repeated twice a day for 3 days.

In Saline group, 100 ml of normal saline without Streptokinase is administered through the chest tube and repeated for 3 days.



FLOW CHART

Criteria For Effectiveness:

The radiologic improvement after administration of Intrapleural Streptokinase is quantified. The criteria for improvement in chest radiograph (Postero-Anterior View) is defined as follows: maximum (normal or near-normal chest radiograph); moderate (a clearance of 50 to 80% of pleural opacities); minimal (<50% of clearance of pleural opacities); or none (no change).The amount of fluid drained is also quantified.

OBSERVATIONS

A Total 100 People Were Included In The Final Analysis.

Table 1: Descriptive Analysis Of Group In Study Population (N=100)

Group	Frequency	Percentage
Streptokinase	50	50%
Saline	50	50%
Total	100	100%

Table 2: Comparison Of Mean Age Between Two Group (N=100)

Parameter	Group		Total	Unpaired t test P value
	Streptokinase (N=50)	Saline (N=50)		
Age (Mean ± SD)	54.26 ± 14.49	53.28 ± 10.02	53.77 ± 12.40	0.695

Table 2 shows comparison of mean age between two groups. Mean age of streptokinase group observed was 54.26 ± 14.49 years and in saline group was 53.28 ± 10.02 years.

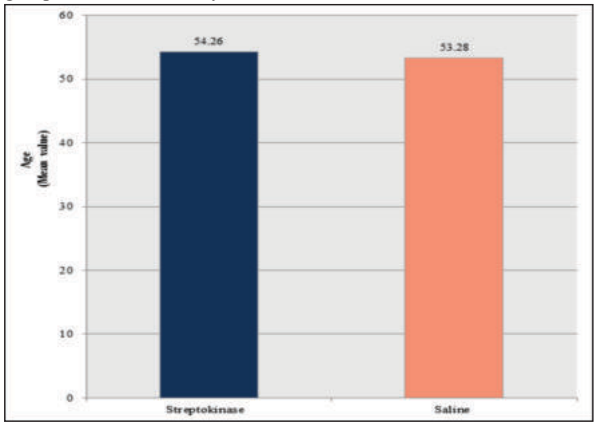


Table 3: Comparison Of Age Group Between Two Group (N=100)

Age group	Group		Total	Chi square	P value
	Streptokinase	Saline			
≤30	3 (6%)	0 (0%)	3 (3%)	9.171	0.102
31 to 40	6 (12%)	5 (10%)	11 (11%)		
41 to 50	9 (18%)	17 (34%)	26 (26%)		
51 to 60	16 (32%)	16 (32%)	32 (32%)		
61 to 70	10 (20%)	11 (22%)	21 (21%)		
>70	6 (12%)	1 (2%)	7 (7%)		
Total	50 (100%)	50 (100%)	100 (100%)		

Table 3 shows comparison of age group between two groups. In streptokinase group, maximum 32% were in 51-60 years and minimum 6% were in 0-30 whereas in saline group, maximum 34% were in 41-50 years. Both groups were statistically insignificant.

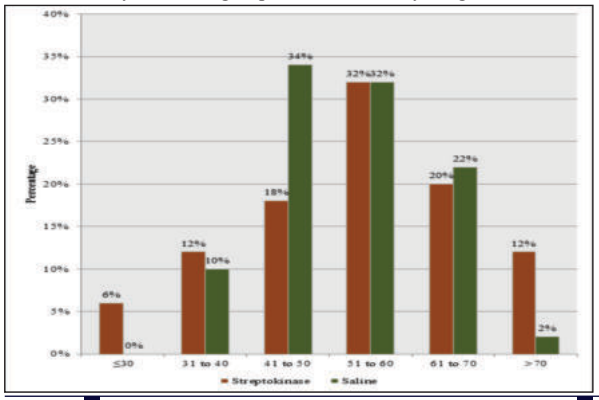


Table 4: Comparison Of Gender Between Two Group (N=100)

Gender	Group		Total	Chi square	P value
	Streptokinase	Saline			
Male	39 (78%)	38 (76%)	77 (77%)	0.056	0.812
Female	11 (22%)	12 (24%)	23 (23%)		
Total	50 (100%)	50 (100%)	100 (100%)		

Table 4 shows comparison of gender between two groups. Majority are males in both groups (78% in Streptokinase group and 76% in saline group).

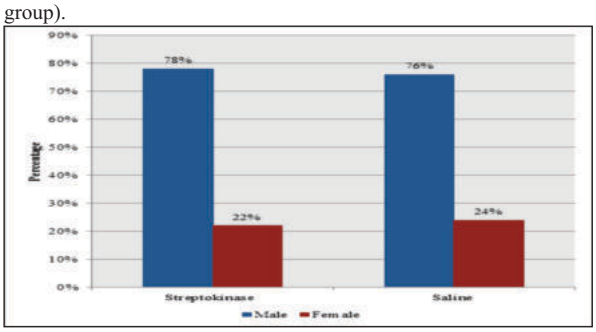


Table 5: Comparison Of Chief Complaints Between Two Group (N=100)

Chief Complaints	Group		Total	P value
	Streptokinase	Saline		
Cough	20 (40%)	19 (38%)	39 (39%)	0.838
Breathlessness	33 (66%)	40 (80%)	73 (73%)	0.115
Chest pain	37 (74%)	41 (82%)	78 (78%)	0.334
Fever	31 (62%)	39 (78%)	70 (70%)	0.081
Others	12 (24%)	9 (18%)	21 (21%)	0.461

Table 5 shows comparison of chief complaints between two groups. Maximum patients of both group had chest pain (74% in streptokinase group and 82% in saline group), breathlessness (66% in streptokinase group and 80% in saline group) and fever (62% in streptokinase group and 78% in saline group).

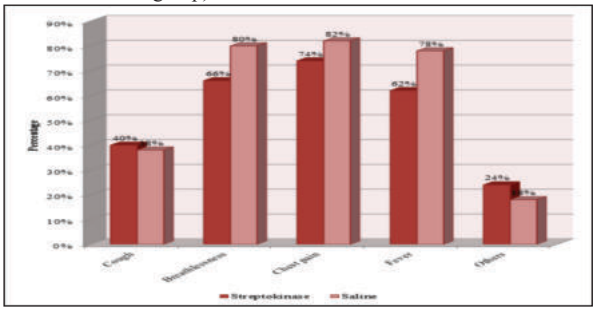


Table 6: Comparison Of Past History Between Two Group (N=100)

Past History	Group		Total	P value
	Streptokinase	Saline		
Nil	32 (64%)	42 (84%)	74 (74%)	0.084
Treated Tuberculosis	1 (2%)	2 (4%)	3 (3%)	
Treated Tuberculosis, Syst. Hypertension	0 (0%)	1 (2%)	1 (1%)	
Diabetes Mellitus	5 (10%)	0 (0%)	5 (5%)	
Syst. Hypertension	8 (16%)	3 (6%)	11 (11%)	
Syst. Hypertension, Others	1 (2%)	0 (0%)	1 (1%)	
Others	3 (6%)	2 (4%)	5 (5%)	

Table 6 shows comparison of past history between two groups. Both groups were statistically insignificant.

Table 7: Comparison Of Modified Past History Between Two Group

Past History	Group		Total
	Streptokinase	Saline	
Treated Tuberculosis	1 (2%)	3 (6%)	4 (4%)
Diabetes Mellitus	5 (10%)	0 (0%)	5 (5%)
Syst. Hypertension	9 (18%)	4 (8%)	13 (13%)
Others	4 (8%)	2 (4%)	6 (6%)

Table 7 shows comparison of past history between two groups. Both

group patients had maximum past history of systemic hypertension (18% in Streptokinase group and 8% in Saline group).

Table 8: Comparison Of Smoking Between Two Group (N=100)

Smoking	Group		Total	Chi square	P value
	Streptokinase	Saline			
No	31 (62%)	34 (68%)	65 (65%)	0.396	0.529
Yes	19 (38%)	16 (32%)	35 (35%)		
Total	50 (100%)	50 (100%)	100 (100%)		

Table 8 shows comparison of smoking between two groups. Majority are non smokers in both the groups. In Streptokinase group, 38% are smokers whereas in saline group 32% are smokers.

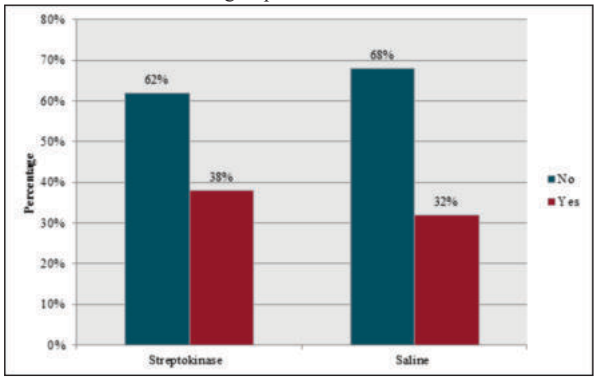


Table 9: Comparison Of Mean Anthropometric Between Gender And Two Group (N=100)

Anthropometric	Streptokinase (N=50)	Saline (N=50)	P value
Male			
Weight (Kg)	59.21 ± 9.38	61.84 ± 9.66	0.228
Female			
Weight (Kg)	64.55 ± 6.09	59.83 ± 7.86	0.061
Male			
Height (cm)	166.31 ± 10.97	167.13 ± 11.22	0.745
Female			
Height (cm)	171.55 ± 11.10	162.92 ± 10.41	0.068
Male			
BMI	21.34 ± 2.27	22.17 ± 3.20	0.191
Female			
BMI	21.99 ± 2.03	21.49 ± 2.65	0.616

Table 9 shows comparison of mean anthropometric between gender and two group. In Streptokinase group, mean BMI of male was (21.34 ± 2.27) whereas saline group was (22.17 ± 3.20). In Streptokinase group, mean BMI of female was (21.99 ± 2.03) whereas saline group was (21.49 ± 2.65).

Table 10: Comparison Of Mean Weight (kg) Between Two Group (N=100)

Parameter	Group		Total	Unpaired t test P value
	Streptokinase (N=50)	Saline (N=50)		
Weight (kg) (Mean ± SD)	60.38 ± 8.99	60.64 ± 9.43	60.51 ± 9.17	0.888

Table 10 shows comparison of mean weight (kg) between two groups. Mean weight (kg) in Streptokinase group was (60.38 ± 8.99) whereas saline group was (60.64 ± 9.43).

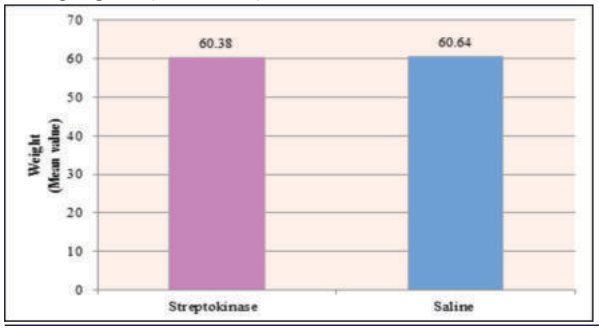


Table 11: Comparison Of Mean Height (cm) Between Two Group (N=100)

Parameter	Group		Total	Unpaired t test P value
	Streptokinase (N=50)	Saline (N=50)		
Height (cm) (Mean ± SD)	167.46 ± 11.10	166.12 ± 11.08	166.79 ± 11.05	0.547

Table 11 shows comparison of mean height (cms) between two groups. Mean height (cms) in Streptokinase group was (167.46 ± 11.10) whereas saline group was (166.12 ± 11.08).

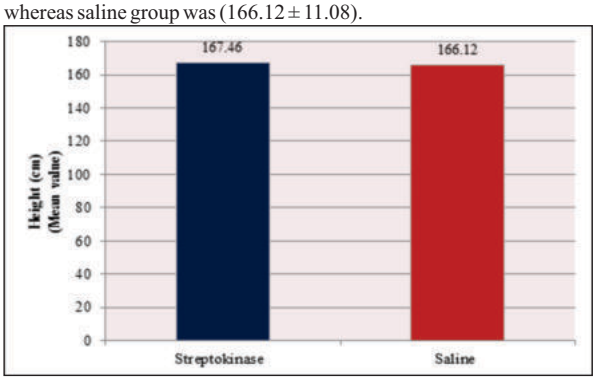


Table 12: Comparison Of Mean BMI Between Two Group (N=100)

Parameter	Group		Total	Unpaired t test P value
	Streptokinase (N=50)	Saline (N=50)		
BMI (Mean ± SD)	21.48 ± 2.22	22.01 ± 3.07	21.75 ± 2.68	0.329

Table 12 shows comparison of mean BMI between two groups. Mean BMI in Streptokinase group was (21.48 ± 2.22) whereas saline group was (22.01 ± 3.07).

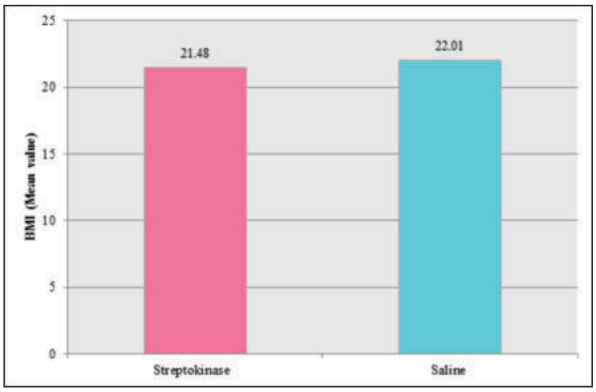


Table 13: Comparison Of Left Laterality Between Two Group (N=100)

left	Group		Total	Chi square	P value
	Streptokinase	Saline			
No	32 (64%)	25 (50%)	57 (57%)	1.999	0.157
Yes	18 (36%)	25 (50%)	43 (43%)		
Total	50 (100%)	50 (100%)	100 (100%)		

Table 13 shows comparison of left laterality between two groups. 36% in Streptokinase group and 50% in saline group had left laterality.

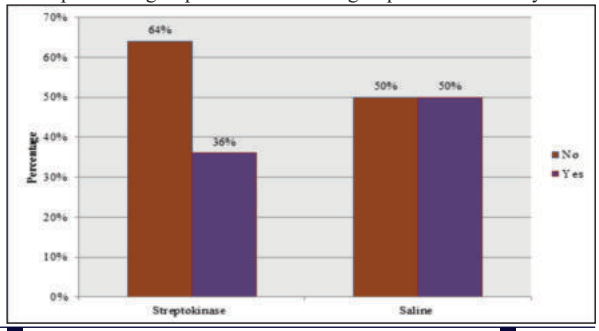


Table 14: Comparison Of Right Laterality Between Two Group (N=100)

Right	Group		Total	Chi square	P value
	Streptokinase	Saline			
No	18 (36%)	25 (50%)	43 (43%)	1.999	0.157
Yes	32 (64%)	25 (50%)	57 (57%)		
Total	50 (100%)	50 (100%)	100 (100%)		

Table 14 shows comparison of right laterality between two groups. 64 % in Streptokinase group and 50% in saline group had right laterality.

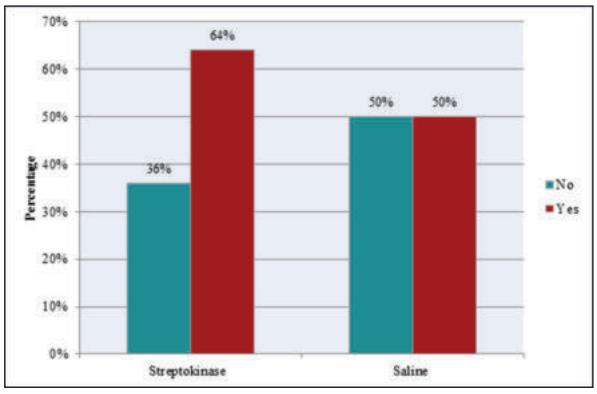


Table 15: Comparison Of Mean Pleural Fluid Glucose (mg/dl) Between Two Group (N=100)

Parameter	Group		Total	Unpaired t test P value
	Streptokinase (N=50)	Saline (N=50)		
Pleural fluid Glucose (mg/dl) (Mean value)	30.14 ± 6.96	32.02 ± 3.92	31.08 ± 5.70	0.100

Table 15 shows comparison of mean pleural fluid glucose (mg/dl) between two groups. Mean pleural fluid glucose levels (mg/dl) in streptokinase group was 30.14 ± 6.96 whereas in saline group was 32.02 ± 3.92.Both were statistically insignificant.

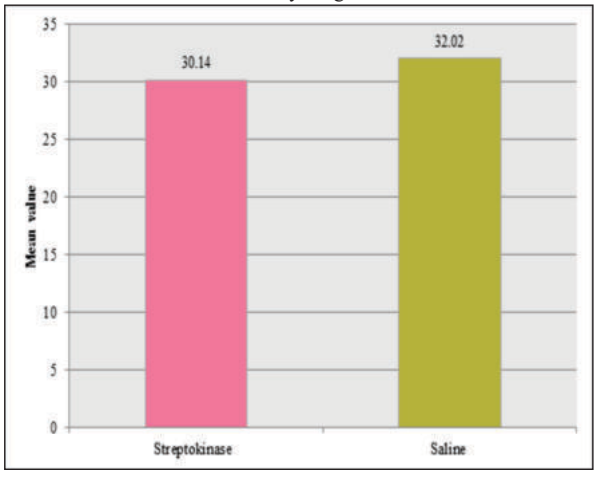


Table 16: Comparison Of Mean Amount Of Fluid Drained (ml) Between Two Groups (N=100)

Parameter	Group		Total	Unpaired t test P value
	Streptokinase (N=50)	Saline (N=50)		
Amount of fluid drained(ml) (Mean ± SD)	505.13 ± 259.50	133.33 ± 57.73	478.57 ± 268.27	0.019

Table 16 shows comparison of mean amount of fluid drained after streptokinase and after saline (ml). Mean pleural fluid amount drained in Streptokinase group was 505.13±259.50 ml whereas saline group was 133.33±57.73 ml which was statistically significant (p=0.019).

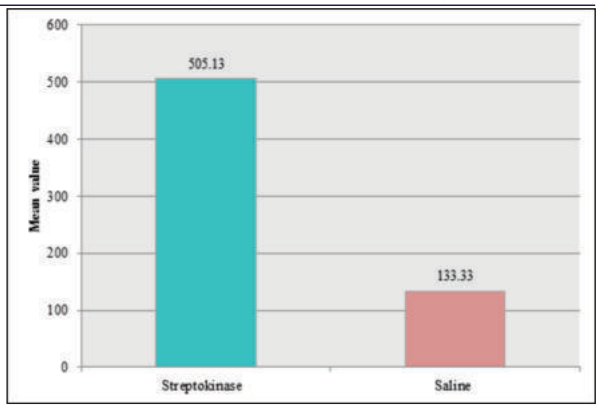


Table 17: Comparison Of Radiological Improvement Between Two Groups (N=100)

Radiological Improvement	Group		Total	Chi square	P value
	Streptokinase	Saline			
Minimum	12 (24%)	3 (6%)	15 (15%)	54.74	<0.001
Moderate	23 (46%)	0 (0%)	23 (23%)		
Maximum	4 (8%)	0 (0%)	4 (4%)		

Table 17 shows comparison of radiological improvement between streptokinase and saline. In Streptokinase group, 8% (4 patients) had maximum improvement, 46% (23 patients) had moderate improvement, 24% (12 patients) had minimal improvement and 22% (11 patients) with no change whereas in saline group, only 6% (3 patients) had mild radiological improvement.

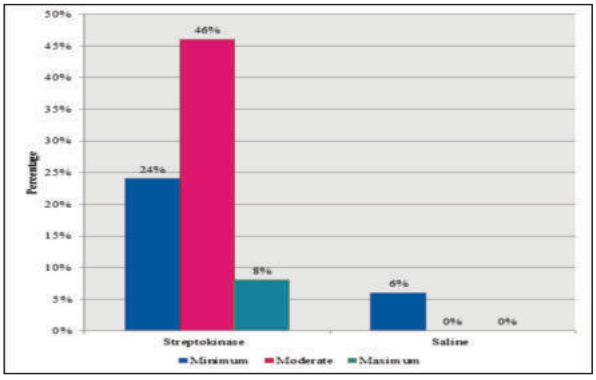
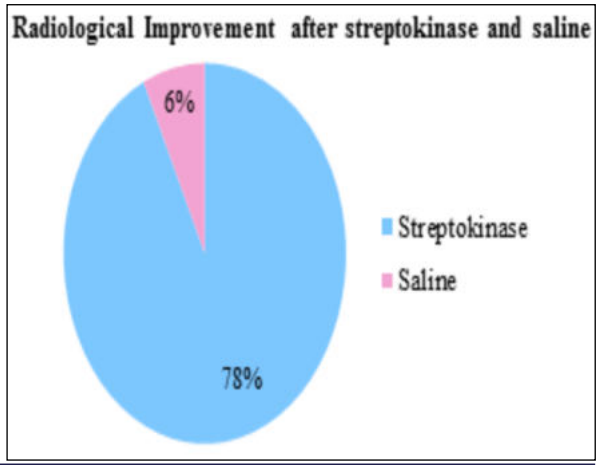


Table 18: Comparison Of Radiological Improvement Between Two Groups (N=100)

Parameter	Streptokinase	Saline	P value
Radiological Improvement	39 (78%)	3(6%)	<0.001

Table 18 shows comparison of radiological improvement between Streptokinase and Saline.78% (39 patients) had radiological improvement after Streptokinase whereas only 6% (3 patients) had radiological improvement after saline which was statistically significant (p value <0.001).



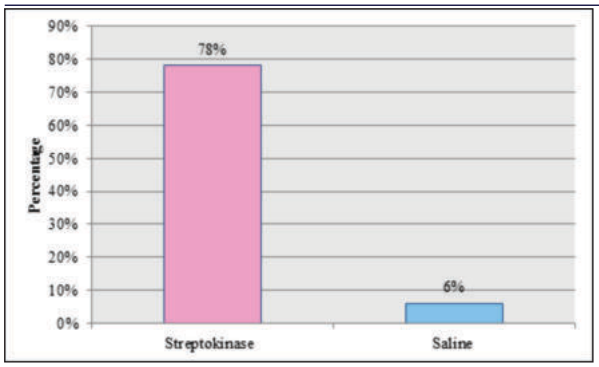
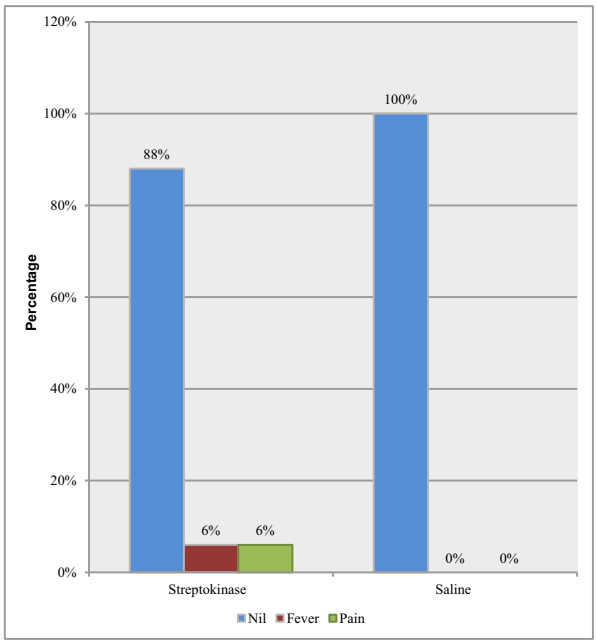


Table 19: Comparison Of Complications Between Two Group (N=100)

Complications	Group		Total	Chi square	P value
	Streptokinase	Saline			
Nil	44 (88%)	50 (100%)	94 (94%)	6.383	0.041
Fever	3 (6%)	0 (0%)	3 (3%)		
Chest Pain	3 (6%)	0 (0%)	3 (3%)		
Total	50 (100%)	50 (100%)	100 (100%)		

Table 19 shows comparison of complications between Streptokinase and Saline. 6% (3 patients) developed fever and 6% developed chest pain (3 patients) whereas saline group had no complications.



DISCUSSION

Despite the advent of potent antibiotics, bacterial pneumonia still results in significant morbidity and mortality. 40% of hospitalized patients with bacterial pneumonia have an accompanying pleural effusion. Para-Pneumonic Effusions (PPE) account for a large percentage of pleural effusions. The morbidity and mortality rates in patients with pneumonia and pleural effusions are higher than those in patients with pneumonia alone. The management of these types of effusions with intercostal tube drainage and antibiotics fails most of the time due to thick viscous fluid and multiple pleural space loculations. The presence of loculations and thick viscous fluid leads to failed pleural space drainage in spite of tube being patent and correctly positioned. In spite of VATS being effective, it is not easily accessible. In dealing with this problem, intrapleural fibrinolytics is a safe, cost effective management option.

The present prospective, hospital based, observational study was done in department of Respiratory Medicine, S P Medical college, Bikaner, Rajasthan including 100 patients with Complex complicated pleural effusion fulfilling inclusion and exclusion criteria were included. 50 patients received Streptokinase whereas other 50 patients received normal Saline. Success rate of Intrapleural Streptokinase based on radiological improvement has been compared with Normal Saline.

In our study, patients were of all ages. In streptokinase group, maximum 32% were in 51-60 years and minimum 6% were in 0-30 whereas in saline group, maximum 34% were in 41-50 years.

Mean age of streptokinase group observed was 54.26 ± 14.49 years and in saline group was 53.28 ± 10.02 years.

In our study, majority were males in both groups (78% in Streptokinase group and 76% in saline group) whereas 22% in streptokinase group and 24% in saline group were females.

In our study, we observed that maximum patients of both group had chest pain (74% in streptokinase group and 82% in saline group), breathlessness (66% in streptokinase group and 80% in saline group) and fever (62% in streptokinase group and 78% in saline group).

We observed that, both group patients had maximum past history of systemic hypertension (18% in Streptokinase group and 8% in Saline group).

We also observed that majority were non smokers in both the groups. In Streptokinase group, 38% were smokers whereas in saline group 32% were smokers.

In our study, we observed that in streptokinase group, mean BMI of male was (21.34 ± 2.27) whereas saline group was (22.17 ± 3.20). In Streptokinase group, mean BMI of female was (21.99 ± 2.03) whereas saline group was (21.49 ± 2.65).Both groups were statistically insignificant.

We observed that mean weight (kg) in Streptokinase group was (60.38 ± 8.99) whereas saline group was (60.64 ± 9.43).

Mean height (cms) in Streptokinase group was (167.46 ± 11.10) whereas saline group was (166.12 ± 11.08).

Mean BMI in Streptokinase group was (21.48 ± 2.22) whereas saline group was (22.01 ± 3.07).

We observed that 36% in Streptokinase group and 50% in saline group had left laterality. 64 % in Streptokinase group and 50% in saline group had right laterality.

We observed that that the mean pleural fluid glucose levels (mg/dl) in Streptokinase group was 30.14 ± 6.96 whereas in saline group was 32.02 ± 3.92.Both were statistically insignificant.

In our study, we observed that the mean pleural fluid amount drained in Streptokinase group was 505.13±259.50 ml whereas saline group was 133.33±57.73 ml which was statistically significant (p = 0.019). A study done by Jose J. Elizalde et al[77] in which the mean pleural fluid drained was 380.67±204.07 ml after 2 doses (250,000 IU/dose) which is lower than our study probably because of reduced number of doses.

In our study, we observed that among Streptokinase group, 78% (39 patients) had radiological improvement. Similar results were found in studies done by Saleh Abu-Daff et al[73] with a success rate of 73.1% and Diacon et al[74] with a success rate of 82%. On contrary, study done by Yousef Ahmed et al and Sahar Refaat et al[76] had success rate of 60%.

We observed that, among Streptokinase group 8% (4 patients) had maximum improvement, 46% (23 patients) had moderate improvement,24% (12 patients) had minimal improvement and 22% (11 patients) with no change. Overall success rate was 78% when compared to saline which was 6%, hence statistically significant (p value <0.001).

In our study, we observed that 6% (3 patients) developed fever (>38°c) which was mild and subsided by antipyretic. 6%(3 patients) developed Chest pain which was mild, subsided by analgesics. No major adverse effects were noted in our study. Similarly a study done by M S Barthwal et al[75] had complications of Chest pain and fever of 6-10%. The Saline group in our study had no complications.

SUMMARY AND CONCLUSION

SUMMARY

This study was a prospective study conducted in the Department of Respiratory Medicine, S P Medical college, Bikaner, Rajasthan including 100 patients in which Intrapleural Streptokinase has been

compared with saline flush in the management of Complex complicated pleural effusion.

The Following Observations Were Noted:

- In our study, patients were of all ages. In streptokinase group, maximum 32% were in 51-60 years whereas in saline group, maximum 34% were in 41-50 years.
- Mean age of streptokinase group observed was 54.26 ± 14.49 years and in saline group was 53.28 ± 10.02 years.
- Majority were males in both groups (78% in Streptokinase group and 76% in saline group).
- Maximum patients of both group had chest pain (74% in streptokinase group and 82% in saline group) followed by breathlessness (66% in streptokinase group and 80% in saline group).
- Both group patients had maximum past history of systemic hypertension (18% in Streptokinase group and 8% in Saline group).
- Majority were non smokers in both the groups. In Streptokinase group, 38% were smokers whereas in saline group 32% were smokers.
- Mean weight (kg) in Streptokinase group was (60.38 ± 8.99) whereas saline group was (60.64 ± 9.43).
- Mean height (cms) in Streptokinase group was (167.46 ± 11.10) whereas saline group was (166.12 ± 11.08).
- Mean BMI in Streptokinase group was (21.48 ± 2.22) whereas saline group was (22.01 ± 3.07).
- On chest X ray, 36% in Streptokinase group and 50% in saline group had left laterality. 64 % in Streptokinase group and 50% in saline group had right laterality.
- All patients had loculations/septations on ultrasonography.
- Mean pleural fluid glucose levels (mg/dl) in Streptokinase group was 30.14 ± 6.96 whereas in saline group was 32.02 ± 3.92, which was statistically insignificant.
- Mean value of amount of pleural fluid drained in Streptokinase group was 505.13 259.50 ml whereas Saline group was 133.33 57.73 ml which was statistically significant (p value =0.019).
- In Saline group, only 6 % (3 patients) had radiological improvement which was minimal.
- Among Streptokinase group, 78% (39 patients) had radiological improvement in which 8% (4 patients) had maximum improvement, 46% (23 patients) had moderate improvement, 24% (12 patients) had minimal improvement and 22% (11 patients) with no change.
- Overall success rate of Streptokinase was 78% when compared to saline which was 6%, hence statistically significant (p value <0.001).
- In Streptokinase group, 6% (3 patients) developed fever and 6% developed Chest pain (3 patients) whereas Saline group had no complications.

CONCLUSION

In present study we concluded that Intrapleural Streptokinase attains success in more than 3/4th (78%) patients reducing the use of minimally invasive video assisted thoracic surgery (VATS) and more invasive conventional thoracotomy.

No major side effects were noted in our study, making it a safe procedure.

Since VATS is not easily accessible and affordable in developing countries like India, intrapleural streptokinase would be a safe, easy, cost effective management option.

LIMITATIONS

This study was able to evaluate the efficacy of Intrapleural Streptokinase in Complex complicated pleural effusion based on the radiological improvement after Streptokinase instillation. Nevertheless, there had been certain limitations.

1) In criteria for radiological improvement after Streptokinase instillation, maximum has been set as normal or near normal chest radiograph whereas observation of moderate (a clearance of 50 to 80% of pleural opacities) and minimal radiological improvement (<50% of clearance of pleural opacities) were subjective and could not be separated perfectly.

2) Although the amount of pleural fluid drained is considered positive response to streptokinase, segregation into mild, moderate and maximum improvement could not be made out.

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