Research Paper

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KEYWORDS :

Role of Fibrinolytic Therapy in Empyema Thoracis – A Hospital Based one year Cross Sectional Study

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ABSTRACT

AIM: This study was carried to study the safety and efficacy of fibrinolytic therapy in Indian patients with empyema thoraces.

MATERIALS AND METHODS: A total of 67 patients studied in a tertiary care hospital over a period of one year. The patients with empyema or Para pneumonic effusions were included in the study. The patients were then divided in to two groups in 2:3 randomly Group I (control) who received ICTD (Intercoastal Drainage Tube) alone with instillation of normal saline for 5 days, Group II (study) receive ICTD (Intercoastal Drainage Tube) alone with instillation of streptokinase (STK) 2.5 L Units daily for 5 days, all the patients in both groups received antibiotics irrespective of the culture and sensitivity reports.

RESULTS: Majority of the patients were in the age group of 31-40 years (27 cases) and total numbers of males included were 45 and total numbers of females included were 17. The major complains of the patients included are fever (88 %), chest pain (75%) dyspnea (56.4%) and weakness (79%) other minor symptoms are cough (22.5), productive cough (51.6%), shoulder pain (17.7 %). It is clear from this study that streptokinase treatment reduced the necessary for surgical intervention, so overall safety of intrapleural streptokinase infusion is safe and decreases the need for surgical intervention.

CONCLUSION:

In conclusion, this study has shown that the intrapleural streptokinase at a dose of 2.5 lakh I U daily for five days is safe and effective in improving the catheter drainage of infected pleural effusions, without any obvious systemic effects.

INTRODUCTION

Light1 defined empyema as "the presence of thick purulent fluid in the pleural cavity". Empyema's occur most commonly as a result of direct extension of infections from the adjacent site, mainly lung. All empyema's may become localized to one part of the pleural cavity or involve whole of the pleural space. Such empyema's may become loculated in to smaller collections by the development of fibrinous bands and is associated with significant morbidity and occasional mortality. Pulmonary infections with secondary pleural involvement lead to considerable morbidity and even mortality2-4.

Empyemas may arise with or without associated pneumonic process13-14, 3. Early drainage of pus from the pleural cavity along with broad-spectrum antibiotics is the cornerstone of treatment. Intercostal tube drainage (ICTD) is the usual mode of pus drainage. But ICTD is hampered by the presence of either thick pus, which tends to block the tube or the presence of multiple loculations that cannot be drained by a single chest tube. To overcome such problems surgical procedures like rib resection and open drainage were done in the past. These surgical procedures have been supplemented by safer and less invasive surgical procedures like video assisted thoracoscopic surgery (VATS) 15. Although these surgical procedures have been a major step forward in search of lesser invasive approach for management of empyema thoraces, they still carry the risk of significant morbidity, lack free availability and costs involved remain prohibitive 16. Use of fibrinolytic agents for intra pleural instillation has provided an option of managing these patients without subjecting them to surgical procedures. This therapeutic modality helps to break the loculations by virtue of its fibrinolytic property 17. .

Data from India on utility of Intra pleural Streptokinase Treatment in empyema thoraces is only limited to a few case reports 23-25. The objective of the study was to find out the clinical outcome with streptokinase therapy in patients with empyema, to find out the effect of streptokinase therapy in reducing the duration of hospitalization and also the need for surgical intervention in patients with empyema.

MATERIALS AND METHODS

The study was done at a a tertiary care hospital. The patients with empyema or Para pneumonic effusion at stage 6 and stage 7 were included in the study Details see Table 1). The following investigations were carried out in all the patients: CBC (complete blood picture), Chest PA View, FBSL, PPBSL, BLOOD UREA, SERUM CREATININE.

Patients with empyema who were included in the study were having one or more of the following characteristics:

- Purulent pleural fluid
- Culture positive for bacteria
- Gram positive and negative organisms isolated from pleural fluid
- Glucose < 40 mg/dl
- Multiloculations demonstrated by CT or ultrasound images were included in the study

Exclusion of those patients with the following disorders were excluded i.e Bronchopleural fistula, Bleeding disorders, hemorrhage, or stroke; or anticoagulant therapy, Patients having tubercular pleural effusion and Pregnant women. CT scan of the thorax was carried out if the chest radiography findings were inconclusive.

Diagnostic pleural aspiration was done for the following investigations to detect Proteins, Sugars, LDH (lactate dehydrogenase);, ADA(adenosine deaminase), Fluid cytology for malignant cells, Total cell count, Differential cell count, Gram staining and Culture and sensitivity testing:

Chart 1. Classification and Treatment Scheme for Parapneumonic Effusions and Empyema.

Class 1	Non significant pleural effusion	Small <10 mm thick on decubitus x-ray study No thoracentesis indicated
Class 2	Typical parapneumonic pleural effusion	>10 mm thick Glucose >40 mg/dL, pH >7.2 LDH <3 times the upper limit normal for serumGram's stain and culture negative Antibiotics alone

Class 3	Borderline complicated pleural effusion	7.0 <pH <7.20 and/or LDH >3 times the upper limit normal and glucose >40 mg/dL Gram's stain and culture negative Antibiotics plus serial thoracentesis
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 Â± decortication
Class 7	Complex empyema	Frank pus present Multiple locules Tube thoracostomy Â± fibrinolytics Often require thoracoscopy or decortication

INTERCOASTAL DRAINAGE PROCEDURE:
Inter coastal tube procedure using Standard 28 F or 32 F Polymed thoracic chest tubes was done in a standard technique under local anesthesia .For local anesthesia 10-20 ml of 2 % xylocaine was used.1-2 ml atropine was given before the procedure. The chest tube was placed (on the correct side) in the mid- or anterior- axillary line. The area is prepared and draped appropriately An incision was made along the upper border of the rib below the intercostal space to be used. The drain track was directed over the top of the lower rib to avoid the intercostal vessels lying below each rib. The incision should easily accommodate the operator's finger. Using a curved clamp the track was developed by blunt dissection only. The clamp was inserted into muscle tissue and spread to split the fibers. The track was developed with the operator's finger. Once the track comes onto the rib, the clamp was angled just over the rib and dissection continued until the pleural is entered. A large-bore (28 or 32F) chest tube was passed along the track into the pleural cavity. The tube was connected to an underwater seal and sutured / secured in place.

A repeat chest radiograph was obtained after 24 hours of I.C.D procedure.\The patients were then divided in to two groups in 2:3 randomly

- Group I (control) received ICTD (Intercoastal Drainage Tube)alone with instillation of normal saline for 5 days
- Group II (study)receive ICTD (Intercoastal Drainage Tube) alone with instillation of streptokinase (STK) 2.5 L Units daily for 5 days

All the patients in both groups received antibiotics irrespective of the culture and sensitivity reports and follwed by antibiotics coverage. Broad spectrum β lactum, Aminoglycosides (gentamycin/amikacin) for anerobic organisms metronidazole/clindamycin, Intrapleural streptokinase instillation was given in the study group for 5days and control group received standard therapy with out streptokinase infusion. The standard therapy consists of intercoastal drainage procedure, antibiotics and supportive treatment and plain normal saline intrapleural infusion.

Procedure of streptokinase infusion
Patients were given streptokinase infusion in a standard dose of 250,000 IU of streptokinase which was instilled intrapleurally after diluting in 100 ml of sterile normal saline. Infusion was given slowly for one hour through the inter coastal tube after clamping the tube. Inter coastal tube was clamped for four hours following the infusion. The clamp was removed after four hours and total drainage was measured. The streptokinase instillation was repeated for a total duration of five days and the total drainage was measured. Repeat chest radiography was obtained after five days and after two weeks, during the follow up period.

The following outcome variables were studied.
Total duration of hospital stay, Total drain before streptokinase infusion and after 5 infusions, any change in the body temperature, Radiological improvement, Clinical improvement, Development of any adverse effects during the study period. The results were analyzed by statistical methods where t-tests were used in comparing the study and control group for the following outcome variables, total duration of hospital stay clinical and radiological improvement, total drainage, need for surgical intervention etc. were studied Therapy success was defined as subjective and objective clinical improvement with control of systemic infection, adequate pleural drainage, and radiologic clearance. Failure was defined as combination of residual pleural collection or lack of satisfactory clinical or radiologic improvement beyond 7 days after chest drain insertion. Criteria for referral to surgery or failure was defined as sepsis syndrome in combination with a substantial residual pleural collection or lack of satisfactory clinical or radiologic improvement beyond 7 days after chest drain insertion.

RESULTS.
A total of 67 patients in a tertiary care hospital over a period of one year. During the final analysis five patients were excluded due to the following reasons. Two patients were having tubercular pleural effusion proven by culture reports. Two patients were later proved to be malignancy (one endometrial carcinoma and one lung malignancy) and one patient died due to kidney failure secondary to diabetes. Thus 62 cases were analyzed in detail. These were 38 cases in the study group and 24 patients in the control group as shown in the Fig 2.

Fig 1. FLOW DIAGRAM DEPICTING PATIENT SELECTION

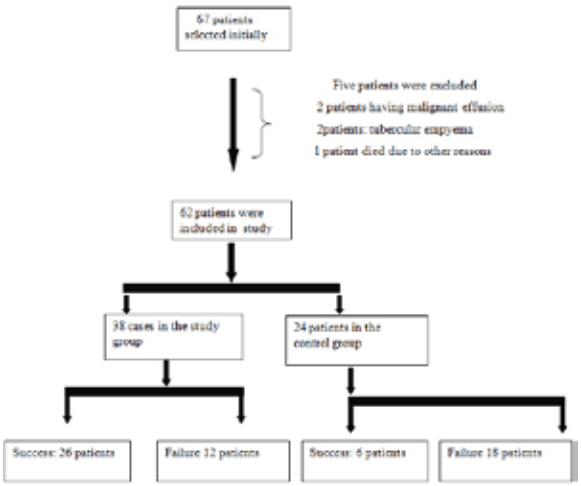

Table 1 and Graph 1 shows that majority of the patients were in the age group of 31-40 years (27 cases) and 17 patients belongs to the age group between 21-30 and 11 patients belongs to age group of 41-50. Total numbers of males included are 45 and total numbers of females included are 17. The male female ratio is 2.6:1.0 as shown in the Table 2. Table 3 shows that the major complains of the patients included are fever (88 %), chest pain (75%), dyspnea (56.4%) and weakness (79%) other minor symptoms are cough (22.5), productive cough (51.6%) and shoulder pain (17.7 %). Table 4 shows among the total population of 67 patients (later 5 cases excluded), in twenty two patients (35.5 %) cultures grew bacteria. Two patients (3.2%) cultures grew mycobacteria. Most of the culture reports show negative cultures (64.5%). Table 5 Shows Organisms isolated from pus culture where the gram positive organisms staphylococci (12.9%) and pneumococci (9.6%) are the commonest organisms isolated and among the gram negative organism's pseudomonas (6.4%) were the commonest organism isolated. Table 6 shows that it is observed that duration of hospitalization was less than 14 days in majority of patients (42.1%) in study group as compared to control group (4.1%). In the study group

only 25% of patients had a hospital stay of more than one month when compared to control group (33.1%).In the control group majority of the patients (62.5%) had more than two weeks of hospital stay when compared to the study group (36.8%). Days taken for the improvement is shown in the Table 7, it is observed that there was significant clinical improvement with in 14 days in the study group (36%) when compared to the control group (4.1%), while another 7 patients (18.4%) showed good clinical improvement with in another 15 days, when compared to control group (4.1%).and only 3 patients (7.8%) required more than twenty eight days for the clinical improvement. In the control group only 6 cases (25%) showed good clinical improvement with majority (75%) showing clinical improvement after 28 days. Thus the overall successful therapy was observed in 26 cases(68.4%) in study group with 12(31.5%) failure cases, while the successful therapy was observed in only 6 cases (25%) in the control group with 18 cases(75%) having treatment failure rates. Total duration of the inter coastal drain is shown in the Table 8, it is observed that duration of ICTD was less than 14 days in majority of the patients(71%) while only five patients(13.5%) required ICTD more than 28 days. In the control group the majority of patients (15 cases-62.5%) had ICD from 15-28 days while 8 patients (33.3%) required ICTD for more than 28 days. Thus the overall success with ICD was observed in 26 cases (68.4%) in study group and failure rate of 12 cases (31.5). While in the control group the success rate was 25.0 % (6cases) and failure with ICD was observed in (18 cases) 75% in the study group. Table 9 Shows amount of drain after Streptokinase Infusion. Table 10 shows Radiological Improvement after Streptokinase Infusion(44.7%) when compared to the study group (12.5%) and the occurrence of pleural thickening (23.6%) and relapse (23.6%) is less when compared to the study group. Table 11 Complications of Streptokinase Therapy and Patients Referred for Surgery. Surgery is required only for 2 patients (5.26%) among streptokinase treated group where as 6 patients (25.0%) required surgery in the control group and the complications with streptokinase treatment includes fever (29.9%), chest pain (13.1%), giddiness and weakness (10.5%) and hypersensitivity reactions (5.26%). From the above it is clear that streptokinase treatment reduced the necessary for surgical intervention, so overall safety of intrapleural streptokinase infusion is safe and decreases the need for surgical intervention.

DISCUSSION

The high incidence of empyema in the productive age group of 21-40 years in this study consistent with the findings in the earlier study by Acharya, Behra and Tandon 96,106,107.According to acharya the mean age was 33.12 years and majority of the patients ,i.e.,42% were in the age group of 21-40 years .This may be due to the common occurrence of pulmonary infections in this age group, particularly in the developing countries.

Two other studies shown the incidence of empyema to be higher after the age 40 108,109.This may be attributed to the fact that the above studies were carried out in the developed countries, where the overall prevalence of respiratory infections are relatively low; in contrast to the present study, which was undertaken in India.

In the present study, males to female ratio ratio was 2.6:1.0 ,which is consistent with acharya 96 study .The male female ratio in the acharya study was 3.4:1.0. Males in general are more prone to mechanical stresses due to their tall stature and strenuous work. Smoking is a more frequent habit, and tuberculosis and COPD 110 are more frequent in males and hence lung infections are more common in males.

The major complains of the patients included in this study are fever(88 %) ,chest pain(75%), dyspnea (56.4%) weakness(79%) and cough with expectoration (51.6%)which was similar to other study reported by acharya et al .According to Acharya 115 cough (92.5%) , dyspnea (92.5) ,fever (87.5%), and chest pain (80 %) to be the most common complaints .

The clinical manifestations of an empyema can vary widely, depending on both the nature of the infecting organism and the competence of the patient's immune system.

In the present study, pleural fluid positive culture was obtained in 22 patients (35.4%).Usually Rates of microbiological diagnosis in the earlier studies have been in the range of 31-72%19,112. Staphylococcus aureus was the commonest (12.9%) amongst the microbiological isolates which was similar to study done by banga et al113 where Staphylococcus aureus was the commonest organism (46.2%) isolated from the pleural pus. Many earlier reports from the West have indicated the rising incidence of Staphylococcus aureus as a cause of empyema thoracis 11 and the same seems to be true for patients from India as well. Gram-negative organisms were isolated in 22.7% of the patients in the present study. This is in concurrence with the reports of various workers who have emphasized the emergence of gram-negative bacilli as predominant pathogen 114,108 .In our study pleural fluid was sterile in 55% cases. This high negative culture results are due to the fact that the study was conducted in a tertiary care hospital and most of the patients had already received antibiotics before admitting to the hospital.

Thus the two basic principles for the successful management of thoracic empyema – namely, the control of infection with appropriate antimicrobial therapy and the adequate drainage of pus.

The main aim of this study was to show the utility of intra pleural streptokinase treatment in patients with empyema thoracis from a region where chronic empyema's was common. It was demonstrated that intra pleural streptokinase treatment was consistently associated with marked increase in the pleural fluid drainage, which was correlated with findings of Banga et al 113 According to Banga mean daily pleural fluid drainage was significantly higher for patients who received intrapleural streptokinase than those who did not (213 ml vs. 57 ml, p = 0.006). On the other hand, drainage of those patients who did not receive STK showed a gradual decline.

According to davies et al114 , pleural fluid during days 2–5 (streptokinase therapy), mean (SD) 391 (200) ml versus control, 124 (44)ml; difference 267, 95% confidence interval (CI) 144 to 390; p<0.001) ,showed more fluid drained after streptokinase infusion

For most of the patients (42.1%) in the streptokinase group the mean duration of hospitalization and the days taken for the clinical and radiological improvement were less than 2 weeks. These findings are similar to Davies et al114 in which mean duration of intra pleural drain in streptokinase group were nine days (9 days) and the mean duration of the clinical improvement seen were 16 days. These results differ in banga113 et al study, in which mean duration of hospital stay were 30 days and mean duration of inter coastal drain is more than 10 days.

In addition, requirement of a surgical procedure was reduced in patients who received STK (5.26 % vs 25.0%). Similar finding was also reported by Davies et al114 although Chin and Lim 21 did not find any such advantage.

The use of intra pleural streptokinase therapy at the dose used in the present study (average dose 250,000 IU /day for 5 days) was not associated with any obvious systemic effects,

Only two patients (5.26%) showed hypersensitivity reactions and minor population shown fever (29.9 %,chest pain(13.1%) and giddiness (10.5%) this can be compared with other studies done by Chin21 , Lysy116 ,Willsie-Edger.117

CONCLUSION

Empyema thoracis is associated with significant morbidity. Empyema is common in Indian setting but rates of isolation of bacteria from pus cultures are low. Corroborative evidence in the form of suggestive radiology is utilized for supporting the diagnosis. In conclusion, this study has shown that the intrapleural streptokinase at a dose of 2.5 lakh I U daily for five days is safe and effective in improving the catheter drainage of infected pleural effusions, without any obvious systemic effects.

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Table 1.AGE WISE DITRIBUTION OF THE PATIENTS

AGE GROUP	TOTAL	STUDY GROUP	CONTROL GROUP
< 20 YEARS	02	01	01
21-30 YEARS	17	10	07
31-40 YEARS	27	16	11
41-50 YEARS	11	07	04
> 51YEARS	05	04	01

GRAPH 1 AGE WISE DITRIBUTION

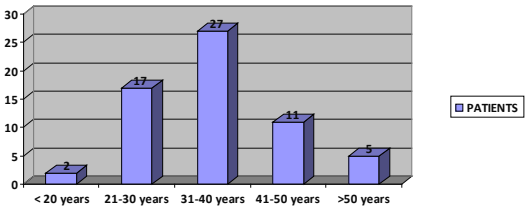
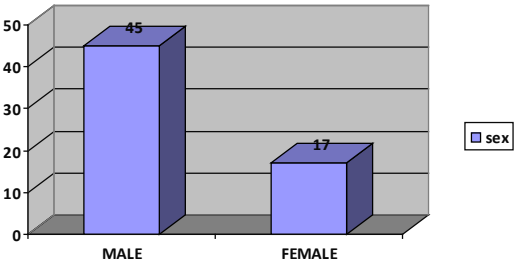


Table 2. GENDER WISE DISTRIBUTION

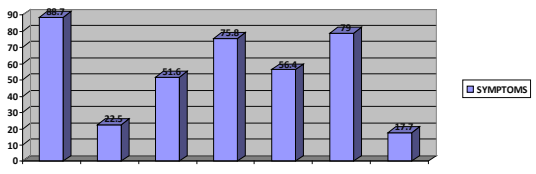
SEX	TOTAL	STUDY	CONTROL
MALE FEMALE	45 17	27 11	18 06



GRAPH 2 GENDER WISE DITRIBUTION OF PATIENTS

TABLE 3.MAJOR COMPLAINS OF THE PATIENTS NOTED IN OUR STUDY.

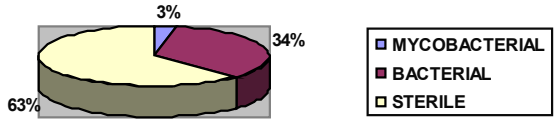
COMPLAINS	TOTAL PATIENTS(n-62)	PERCENTAGE
FEVER	55	88.7
DRY COUGH	14	22.5
PRODUCTIVE COUGH	31	51.6
CHEST PAIN	47	75.8
DYSPNEA	35	56.4
WEAKNESS	49	79
SHOULDER PAIN	11	17.7



GRAPH 3 SYMPTOMS OF THE PATIENTS

TABLE 4.PLEURAL PUS FOR THE CULTURE SHOWED THE FOLLOWING RESULTS.

PUS CULTURE	TOTAL PATIENTS	PERCENTAGE
BACTERIAL	22	35.4
MYCOBACTERIAL	02	03.2
STERILE	40	64.5



GRAPH 4 PLEURAL PUS MICROBIOLOGY

TABLE 5. BACTERIOLOGY OF THORACIC EMPYEMA

Various organisms isolated from the pus culture are shown in the Table 7

	Organism	Patients Number	Per-cent-age(%)
Gram Positive	Coagulase positive staphylococcus	8	12.9%
	Pneumococci	6	09.6%
	Streptococcus pyogenes	3	04.8%
Gram Negative	Pseudomonas	4	06.4%
	Enterobacteria	1	01.6%
	Sterile cultures	40	64.5%

GRAPH 5 ORGANISMS ISOLATED FROM THE CULTURE OF PUS

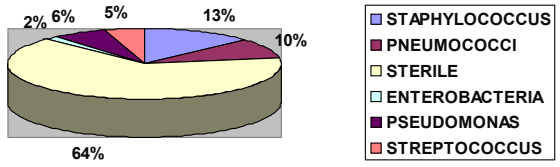


TABLE 6 DURATION OF HOSPITALIZATION

GROUPS	Duration of Hospitalization			Total
	<14 days	15-29 days	>30 days	
CONTROL GROUP	01(04.1%)	15(62.5%)	08(33.3%)	24
STUDY GROUP	16(42.1%)	14(36.8%)	08(25.0%)	38
TOTAL	17	29	16	62

P-VALUE

COMPARISION	P VALUE	INTERFERENCE
STUDY GROUP X CONTROL GROUP	0.005	Highly significant

TABLE 7. NUMBER OF DAYS TAKEN FOR THE SIGNIFICANT CLINICAL IMPROVEMENT

GROUPS	DAYS TAKEN FOR SIGNIFICANT IMPROVEMENT			SUCCESS	FAILURE
	<14 days	15-28 days	>28 days		
CONTROL GROUP	01(04.1%)	01(04.1%)	04(15.0%)	06(25.%)	18(75.0%)
STUDY GROUP	14(36.8%)	07(18.4%)	03(07.8%)	25(68.4)	12(31.5%)
TOTAL	17	08	07	32	30

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P-VALUE

COMPARISION	P VALUE	INTERFERENCE
STUDY GROUP X CONTROL GROUP	0.018	Highly significant

P-VALUE

COMPARISION	P VALUE	INTERFERENCE
STUDY GROUP X CONTROL GROUP	0.0001	Highly significant

TABLE 8. DURATION OF THE INTERCOASTAL DRAIN

GROUPS	DURATION OF INTERCOASTAL DRAIN			SUCCESS	FAILURE
	<14 days	15-21 days	>21 days		
CONTROL GROUP	01(04.1%)	15(62.5%)	08(33.3%)	06(25.0%)	18(75.0%)
STUDY GROUP	27(71.0%)	06(15.7%)	05(13.5%)	26(68.4%)	12(31.5%)
TOTAL	28	21	13	32	30

TOTAL 9. TOTAL AMOUNT OF DRAIN AFTER STREPTOKINASE INFUSION

GROUP	DAY 1(ML)	DAY 2(ML)	DAY 3(ML)	DAY4(ML)	DAY5(ML)	TOTAL DRAIN(ML)
CONTROL GROUP	383.33+/- 29.16	254.16+/-94.79	375+/- 41.6	312+/- 63.95	125+/-45.83	1404+/- 205.55
STUDY GROUP	471.05+/- 83.1	1028.94+/- 163.43	543.24+/-113.95	409+/- 160.53	320+/- 172.11	2484.21+/- 280.60

TABLE 10 TOTAL AMOUNT OF PLEURAL FLUID DRAINED IN BOTH THE GROUPS AFTER STREPTOKINASE INFUSION

Streptokinase treated group drained more pleural fluid during days 2–5

On day 1 streptokinase group mean (SD) pleural drain is 471 (83) ml versus control, 383 (29) ml.

On day 2 streptokinase group mean (SD) pleural drain is 1028 (163) ml versus control, 254 (94) ml

On day 3 streptokinase group mean (SD) pleural drain is 543 (113) ml versus control, 375 (41) ml

On day 4 streptokinase group mean (SD) pleural drain is 409 (160) ml versus control, 312 (63) ml

On day 5 streptokinase group mean (SD) pleural drain is 320 (172) ml versus control, 125 (45) ml

TOTAL DRAIN in streptokinase group mean (SD) pleural drain is 2484 (280) ml versus control, 1404 (205) ml

Thus streptokinase group drained more fluid mean (SD): 2484 (280) ml when compared to control group mean (SD):1404 (205) ml.

It was demonstrated that Intra pleural streptokinase was consistently associated with marked increase in the pleural fluid drainage markedly from day 2 onwards. On the other hand, drainage of those patients who did not receive STK showed a gradual decline.

TABLE 10.RADIOLOGICAL IMPROVEMENT AFTER STREPTOKINASE INFUSION

	RADIOLOGICAL FEATURES AFTER STREPTOKINASE INFUSION				
GROUPS	CASES(n)	CHEST X RAY CLEAR	PLEURAL THICKENING	LOCULATIONS PRESENT	RELAPSE
CONTROL	24	3(12.5%)	21(87.5%)	18(75.0%)	11(45.8%)
STUDY	38	17(44.7%)	09(23.6%)	12(31.5%)	9(23.6%)
TOTAL	62	20	30	30	20

P VALUE

COMPARISION OF LOCULATION	P VALUE	INTERFERENCE
STUDY GROUP X CONTROL GROUP	0.001	Highly significant

P VALUE

COMPARISION OF RELAPSE	P VALUE	INTERFERENCE
STUDY GROUP X CONTROL GROUP	0.051	NO SIGNIFICANT

PRE TREATMENT CHEST RADIOGRAPHS

POST TREATMENT CHEST RADIOGRAPH

REFERENCE

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