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MANAGEMENT OF PEDIATRIC EMPYEMA WITH INTRAPLEURAL STREPTOKINASE : RANDOMISED CONTROL TRIAL

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ABSTRACT

Parapneumonic pleural effusions may occur in 36–57% of patients with pneumonia and about 15–20% of this accumulated fluid becomes infected resulting in empyema [1,2)]Empyema generally occurs in children after pneumonia of acute bacterial origin and it is generally associated with significant morbidity and mortality.Injection of various fibrinolytic agents like streptokinase, urokinase in the intrpleural space are increasingly being used for the management of such conditions.(7-10)The main aim of this study was analysing role of adding intrapleural streptokinase in the management of childhood empyema.**Methodology:**The present retrospective study was conducted in our Institute during a period of 2 years. The study consisted of 20 subjects that were admitted to the hospital with the complaint of pneumonia complicated by empyema.. Chest tube placement were done by pediatricians.Half of the patients received intrapleural streptokinase. The dose of streptokinase was 2,50,000 U in 100 ml of saline.The criteria for comparison were - duration of chest tube drainage, stay in hospital, fever and decrease in incidence of hospital stay were considered as successful treatment.All the data was arranged in a tabulated form and was analysed using Epi info software version 7.1.2. Chi square test and student t test was used for comparison. Probability value of less than 0.05 was considered significant. **RESULT:** The study enrolled total of 20 subjects, out of these 10 belonged to conventional group and 10 were administered intrapleuralstreptokinase.Both groups compared &There was no significant difference in the variables between the two groups as the p value was more than 0.05. **CONCLUSION:** From this study it is clear that addition of intrapleural streptokinase along with the conventional therapy provides no special benefit.In complicated cases fibrinolytics can be used as additional therapy.

Key Words : Empyema, Intrapleural, Streptokinase, fibrinolytics, effusion

INTRODUCTION

Parapneumonic pleural effusions may occur in 36–57% of patients with pneumonia and about 15–20% of this accumulated fluid becomes infected resulting in empyema [1,2]. Here is the classification of the American Thoracic Society which has expanded the definition of empyema into three stages [3]. In this classification, initial reaction to the infectious agent is fibrin deposition on both pleural surfaces known as the early exudative phase (stage I). This is followed by an intermediate fibrino-purulent phase characterized by fibrinous septations forming loculations within the pleural space (stage II). Prolonged enhanced fibroblastic activity prevents lung re-expansion by covering the pleural space as a spider web and this is called the late organizing phase (stage III) [1,4,5].

Empyema generally occurs in children after pneumonia of acute bacterial origin and it is generally associated with significant morbidity and mortality. The major problems of concern are recurring episodes of fever and collection of fluid in pleural space. There is a controversy regarding the appropriate management of these cases. The management option include use of antibiotics either alone or in combination with thoracocentesis or thoracostomy, use of fibrinolytic agents, debridement followed by decortications, thoracoscopy etc.(6) Injection of various fibrinolytic agents like streptokinase, urokinase in the intrpleural space are increasingly being used for the management of such conditions.(7-10) Previous studies that were conducted were generally uncontrolled.(11-13) The use of these fibrinolytic agents for managing cases of childhood empyema resulted in reduced hospital stay, increased chest tube drainage and decrease in intensity of

fever.(14-15)

Three randomised studies have recently described the use of streptokinase and urokinase amongst adults for managing empyema cases.(16-18) They have shown that benefits occur both clinically and radiographically in all the cases. As per a recent review by Cameron et al, there is lack of sufficient data and evidences to support the use of fibrinolytic therapy for managing cases of empyema and parapneumonic effusion.(19)

The main aim of this study was analysing role of adding intrapleural streptokinase in the management of childhood empyema.

MATERIALS & METHODS

The present retrospective study was conducted in our Institute during a period of 2 years. The study consisted of 20 subjects that were admitted to the hospital with the complaint of pneumonia complicated by empyema.Patients with lung cancer, tuberculosis, post traumatic or post operative pneumonia were excluded from the study. Diagnosis of effusion was established on the basis of clinical and radiological examination. All patients clinically examined & were diagnosed as empyema. Chest radiograph, ultrasound or CT scan was performed as required based on the patients conditions. Pleural fluid culture and analysis was done in empyema cases. Initial diagnostic thoracocentesis was performed amongst all the patients on admission to hospital. Further biochemical analysis of the sample was done. Levels of LDH, glucose and protein were determined. Differential leukocyte count was also

performed. Both anaerobic and aerobic cultures were performed and Gram staining was also done. Using a chest tube, closed tube thoracocentesis was performed bedside amongst patients with large pleural collections. Chest tube placement were done by pediatricians. Initially patients were given empirical treatment with ampicillin and ceftriaxone. If there was no response during the initial 72 hours, i.e. failure to improvement or deterioration of the condition then this ampicillin was changed to vancomycin. Based on the type of response and medical and surgical condition, the duration of antibiotic therapy was decided. Half of the patients received intrapleural streptokinase. The dose of streptokinase was 2,50,000 U in 100 ml of saline. Streptokinase was started within initial 24 hours of admission. It was allowed to rest in the pleural cavity for 4 hours and later manual aspiration was done and passive drainage of fluid was done in a water sealed container. The procedure was done daily. Any adverse events associated with streptokinase administration were noted like allergy, pain or fever. Regular follow up of all the patients were performed by the same medical personnel. Medical records of all the patients were evaluated for demographic details, presentations, surgical method used, use of fibrinolytic agent, radiographic evaluation. Both the groups of patients were compared with each other, the one who received conservative treatment and the other receiving streptokinase therapy. The criteria for comparison were - duration of chest tube drainage, stay in hospital, fever and decrease in incidence of hospital stay were considered as successful treatment.

All the data was arranged in a tabulated form and was analysed using Epi info software version 7.1.2. Chi square test and student t test was used for comparison. Probability value of less than 0.05 was considered significant.

Approval for this study was taken from institutional ethical board.

RESULTS

The study enrolled total of 20 subjects, out of these 10 belonged to conventional group and 10 were administered intrapleural streptokinase. The mean age of the subjects in conventional group was 4.9 +/- 2.8 years and in the streptokinase group was 3.9 +/- 2.6 years. The male to female ration in conventional group was 2:3 and in the streptokinase group was 3:2. Cough was presented by 82% subjects in conventional group and 92% subjects in streptokinase group. Fever was seen in 94% subjects in conventional group and 94% subjects in streptokinase group. Dyspnea was seen amongst 75%subjects in conventional group and 85% subjects in streptokinase group. Chest pain was associated with 25% subjects in conventional group and 15% subjects in streptokinase group. GI symptoms were seen in 10% subjects in conventional and 20% in streptokinase group. Oxygen saturation in conventional group was 91.9 +/- 5.2 and 89.7 +/-4.8 in streptokinase group. Positive blood cultures were seen in 13% subjects of conventional group and 23% subjects of streptokinase group. Pleural effusion culture was positive in 45% Subjects and 25% subjects of conventional group and streptokinase group respectively. The mean haemoglobin levels in convention group and streptokinase group was 11.2 +/-2.6 and 9.6+/-1.6 respectively. The mean platelets count in conventional group and streptokinase group was 393,423 +/- 34,554 and 453,332 +/- 30,643 respectively. The mean LDH level in pleural fluid was 3226 +/-3230 and in streptokinase group was 4331+/- 2887. The mean glucose levels were 33.9 +/- 23.4 and 27.4 +/- 18.7 in

conventional and streptokinase group respectively. There was no significant difference between the groups (table-1).

The mean hospital stay in conventional group was 19.6 +/- 5.9 days and in streptokinase group was 18.7 +/-4.6. The mean duration of hospital stay after surgery was 9.8 +/-2.3 and 8.8 +/- 3.7 in the conventional and streptokinase group respectively. Duration of afebrile state after surgery was 6.6 +/- 2.5 and 5.6 +/- 4.7 in the conventional and streptokinase groups respectively. The mean duration of chest tube drainage in conventional group was 5.6 +/- 4.7 days and in streptokinase group was 9.3 +/- 8.9 days. There were 12% in drainage group and 22% in streptokinase group that resorted to surgery. Pneumothorax as a complication was seen in 22% subjects in conventional group and 12% subjects in streptokinase group. There was no significant difference in the variables between the two groups as the p value was more than 0.05 (Table-2).

Charactrstics	**Conventional Group** (n=10)	**Streptokinase Group** (n=10)	**P value**
Age	4.9 +/- 2.8 years	3.9 +/- 2.6 years	>0.05
Male: Female	2:3	3:2	>0.05
Presenting Signs And Symptoms			
Cough	82%	92%	>0.05
Fever	94%	94%	>0.05
Dyspnea	75%	85%	>0.05
Chest pain	25%	15%	>0.05
GI Symptoms	10%	20%	>0.05
Oxygen Saturation	91.9 +/- 5.2	89.7 +/- 4.8	>0.05
Lung Affected (R/L)	5/5	7/3	>0.05
Blood Culture (positive)	13%	23%	>0.05
Pleural effusion Culture (positive)	45%	25%	>0.05
Blood tests			
WBC(/uL)	14,487 +/- 6223	15,104 +/- 6321	>0.05
Hb(g/dl)	11.2+/- 2.6	9.6 +/- 1.6	>0.05
Platelets (/cumm)	393,423 +/- 34,554	453,332 +/- 30,643	>0.05
Pleural Results			
LDH (U/L)	3226 +/- 3230	4331 +/- 2887	>0.05
Protein(g/dl)	4.3 +/- 3.2	3.8 +/- 2.7	>0.05
Glucose(mg/dl)	33.9 +/- 23.4	27.4 +/- 18.7	>0.05

Table no 1 : Showing the details of study population

Characterstics	**Drainage group**	**Streptokinase**	**P value**

	(n=10)	**group(n=10)**	
Length of hospital stay (days)	19.6 +/- 5.9	18.7 +/- 4.6	>0.05
Duration of hospital stay after surgery(days)	9.8+/- 2.3	8.8 +/- 3.7	>0.05
Time of afebrile state after treatment (days)	6.6+/- 2.5	5.5+/- 4.4	>0.05
Duration of chest drainage(days)	5.6+/- 4.7	9.3 +/- 8.9	>0.05
Surgical Therapy	12%	22%	>0.05
Complication (pneumothorax)	22%	12%	>0.05

Table no. 2 :Comparision between two groups

DISCUSSIONS

Empyema thoracis is an accumulation of pus in pleural space. It is most often associated with pneumonia due to Streptococcus pneumoniae, although Staphylococcus aureus is most common in developing nations and Asia [(22)]. Haemophilus influenzae, group A Streptococcus, gram negative organisms, tuberculosis, fungi, malignancy and trauma are other causes. Though empyema thoracis in children caries very little (20%) mortality as compared to adults, it causes lots of morbidity and complications. If the pus is not drained in second phase it may dissect through pleura into lung parenchyma leading to bronchopleural fistula (BPF), pyopneumothorax, in abdominal cavity or through chest wal l (empyaemanecessitans). If organized lung may collapse and become surrounded by thick inelastic peel. Option for drainage is controversial. Some experts are in favor of VATS followed by chest tube drainage, some experts opine in favor of closed tube drainage with or without fibrinolytics, some think of early decortication [(23)].

Various management protocols have been put forward for the management of cases of effusion and emypema.[(22)] but there is still no standard guidelines that should be followed in all the cases. Since more than 50 years the intrapleural thrombolytic agents are in use for the management of empyema cases but the stage and time of action of these agents is still controversial.[(24)] There have been few randomised trials in literature that report the use of these agents amongst adults. In a study conducted by Buoros et al in the year 1991 found that both urokinase and streptokinase are equally effective in managing empyema cases but urokinase was found to be much safe.[(13)] In another study conducted by Davies et al amongst 24 patients in whom streptokinase and placebo was administered through chest tube, found that there was no significant difference between the case and control group. But there was significant improvement in the volume of pleural fluid drained and radiographs in the group that was administered with streptokinase.[(17)] In a study conducted by Diacon et al in the year 2004 found higher success rates in the streptokinase group with few indications for surgery. However during a follow up period of 6 months, there were no significant radiological differences observed in the placebo and the intervention group.[(25)] In a metanalysis conducted by Cameron et R, they concluded that although streptokinase helps in reducing the hospital stay along with visible radiological improvements but these trials do not provide an insight to

the efficacy of fibrinolytics in reducing the mortality and need for surgery.[26] The use of these fibrinolytics amongst children is still limited such that their actual efficacy cannot be established. There has been various case series evaluating the use of streptokinase, urokinase or tissue plasminogen, all of them have shown successful results without the use of surgery.[27-30] In a randomised controlled trial conducted by Thompson et al amongst 60 children, they found that use of urokinase resulted in shortened hospital stay compared to placebo.[14] In a study conducted by ulku et al[10] amongst 78 children to determine the efficacy of intrapleural fibrinolytic agents like streptokinase and urokinase in different stages of effusion or empyema, they concluded that treatment with fibrinolytics provides significant benefit in patients of stage 2 empyema but no significant effect was observed amongst stage 3 cases.

According to the present study, the mean hospital stay in conventional group was 19.3 +/-5.7 days and in streptokinase group was 18.9 +/-4.8. The mean duration of hospital stay after surgery was 9.6 +/-2.1 and 8.5 +/- 3.5 in the conventional and streptokinase group respectively. Duration of afebrile state after surgery was 6.4 +/- 2.3 and 5.2 +/- 4.1 in the conventional and streptokinase groups respectively. The mean duration of chest tube drainage in conventional group was 5.8 +/- 4.5 days and in streptokinase group was 9.2 +/- 8.8 days. There were 4% in drainage group and 8% in streptokinase group that resorted to surgery. Pneumothorax as a complication was seen in 8% subjects in conventional group and 4% subjects in streptokinase group. There was no significant difference in the variables between the two groups as the p value was more than 0.05. In another retrospective study conducted by Barnes et al, amongst 100 subjects suffering from stage 2 or stage 3 empyema found that surgical intervention was required only in 2% of the cases.[31] In a meta analysis reported by Avansino et al, the use of fibrinolytics provided with no added advantage over the non operative conventional therapy of using antibiotics and thoracocentesis.[32] The major limitations of our study was the retrospective design and smaller sample size.

CONCLUSION

From this study it is clear that addition of intrapleural streptokinase along with the conventional therapy provides no special benefit. Fibrinolytics can be used as an adjunctive therapy without any significant advantage over the conventional group. In complicated cases fibrinolytics can be used as additional therapy.

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