Role of Intrapleural Streptokinase treatment in children with empyema

Dr.(Col)D.Y. Shrikhande* , Dr. Anuj Kumar**, Dr. Abhijit Singh**, Dr. Ekta Singh**, Dr. Saurabh Shelke**

Introduction :

Pneumonias are often associated with pleural effusions and a small proportion of them progress to empyema i.e. "the presence of thick purulent fluid in the pleural cavity" Staphylococcus aureus, Streptococcus pneumoniae and Kleibsella are the organisms most commonly implicated. Our aim was to compare intrapleural streptokinase (SK) treatment and simple tube drainage in the treatment of children with complicated para-pneumonic pleural effusion and to established the role of intrapleuralfibrinolytic agents in the treatment of childhood empyema.

Materials and Methodology:

23 patients with empyema in whom ICD was inserted in our hospital in a span of 1 year (01/01/2015 to 31/12/2015), 15 were given intrapleural Urokinase and 8 were not given.+/-

Results:

Number of days for which the chest tube was kept in situ and number of days of hospital stay was found be less in patients who received intrapleural urokinase. There were significant differences in terms of clinical outcomes between the two groups.

Conclusion:

In the treatment of complicated parapneumonic effusions or empyema, the adjunctive treatment with Intrapleural Streptokinase does significantly reduced urations of fever, chest tube drainage and hospital stay, and the need for surgery regardless of the stage of the disease, compared to simple closed tube drainage without intrapleural streptokinase.

Introduction

Parapneumonic effusion usually develops in up to 30 % of patients with community-acquired pneumonia.Empyema is a collection of purulent material in the pleural space which occurs as a serious complication. The optimal management remains controversial regarding a variety of treatment options, such as antibiotics in combination with thoracocentesis, tube thoracostomy, fibrinolytic agents, debridement and decortication. Intrapleural injection of fibrinolytic agents such as streptokinase(SK) and urokinase(UK) are increasingly being used in the management of these conditions.

Our aim was to examine whether the addition of early intrapleural streptokinase therapy to conventional medical management would decrease the duration of chest tube drainage, fever and hospital stay and reduce the need for further surgical procedures. We report a study comparing intrapleural streptokinase with simple tube drainage in the treatment of 23 patients with complicated parapneumonic pleural effusions or empyema.

* Professor and Head, ** Senior Resident, *** Resident
Dept. Paediatrics

Corresponding Author:
Dr. Abhijit Singh
Department of Pediatrics
Rural Medical College, Loni, Tal- Rahata, Dist- Ahmednagar, Maharashtra

Materials And Methods

This was a 1 year (2015 Jan- Dec) observational retrospective study of 23 consecutive patients admitted to the university hospital of Rural Medical College with community-acquired complicated parapneumonic effusions or empyema.

Parapneumonic effusions were classified as a spectrum of disease, with three stages of progression.

Stage 1 ('Exudative'): Collection of free-flowing fluid with pH higher than 7.2, lactate dehydrogenase levels less than 1,000 IU/I, glucose levels higher than 60 mg/dl and negative cultures within the pleural cavity without the presence of loculations.

Stage2 ('Fibropurulent'): pH less than 7.2, lactate dehydrogen as levels higher than 1,000IU/L glucose levels less than 60 mg/dl and fibrin deposition within the pleural space giving rise to loculations or positive cultures; presence of pus (empyema).

Stage3 ('Organizing'): in addition to stage 2, organized multiloculated parapneumonic effusions with lung entrapment and pleural ring formation.

Stage	Name	Fluid Type	Ph	Fluid Ldh Levels	Fluid Glucose Levels	Culture	Loculations In Pleural Cavity
Stage 1	Exudative	Free-Flowing Fluid	>7.2	<1,000 Iu/l	>60 Mg/Dl	Neg	Not Present
Stage 2	Fibro-Purulent	Fibrin StrandsOrPus	< 7.2	>1,000 Iu/l	<60 Mg/Dl	Positive Or	Present
Stage 3	Organizing	Organized Multiloculated Parapneumonic Effusions With Lung Entrapment And Pleural Ring Formation	< 7.2	>1,000 Iu/l	<60 Mg/Dl	Positive	Present

Inclusion Criteria:

1. Age group: 3 months to 12 years
2. Patients who gave their consent

Exclusion Criteria:

1. Patients with underlying lung disease, tuberculosis
2. Patients with post-traumatic and post-operative parapneumonic effusions

A diagnosis of parapneumonic effusion was initially madeon the basisof clinical examination,chest radiography, ultrasound thorax and/or computedtomography(CT) scan, and the presenceof a complicatedparapneumonic effusion or empyemawas confirmed by pleural fluid culture and analysis.

Diagnostic thoracentesis with a l4-gauge needle was performed for all patients on hospital admission. The pleural fluid samples were sent for biochemical analyses for glucose, protein, lactic dehydrogenase(LDH), pH, differential cell count, Gram's stain, and aerobic and anaerobic cultures.

All patients had closed tube thoracentesis. A size24F chest tube was used at the bedside in patients with large, dependent pleural collections. In patients with multiloculated effusions and / or in non - dependent areas 14F or 18F tube was inserted.

For treatment of community-acquired pneumonia, initially empirical treatment consisting of ampicillin-sulbactam plus cephalosporin was given. then the patients were switched to a more microorganism-specific treatment according to the results of bacterial culture and the sensitivity test. Ampicillin-sulbactam was changed to vancomycin if initial empirical antibiotic therapy had not been associated with a clinical response within 72 hours, i.e. the patient's disease failed to improve and deteriorated clinically, such as increase in tachypnoea. This was done because the possibility of highly penicillin-resistant pneumococcal infection or community-acquired methicillin-resistant Staphylococcus aureus (MRSA) infection could not be excluded(although not demonstrated by culture)in patients without a clinical response to the treatment despite the combination of

ampicillin-sulbactam and cefotaxime. The duration of antibiotic therapy was based on the response of the patient to the medical and surgical therapy.

In 2015, 13 patients additionally received intrapleural streptokinase(IP-SK). In the IAP-SK protocol, 250,000USKin100mlsalinewasinstilledintothepleural cavity on a daily basis starting within the first 24 h following tube placement.SK was left in the pleural cavity for about 4 h, after which fluid was manually aspirated and left to drain passively into a water-sealed chamber. Adverse effects of SK such as bleeding, chest pain, fever or allergy were noted.

CT examinations were made in all patients with suspected multiloculation and who failed to respond to treatment promptly. If there had been no response to treatment protocols and complicated parapneumonic effusions or empyema had formed a pleural peel visible on the CT further surgical evaluation was made. Video-assisted thoracoscopicsurgery (VATS) was the treatment modality of choicein thesecases.

Medical records were reviewed at the end of the study for demographic data, clinical presentation, chest tube drainage, use of fibrinolytic agents, type of surgical intervention, biochemical and microbial examinations of pleural effusion and radiographic evaluation.Patients who received conservative management with antibiotics and chest tube drainage (drainage group) were compared with the patients who received conservative treatment plus frbrinolytic agent(SK group). Reductions in the duration of chesttube drainage, fever, and hospital stay, a decrease in the need for further surgical procedures.

Collected data were entered into statistical program (SPSSversion7.0 for Windows 2007, SPSSInc., Chicago, IL,USA)for analysis. Results are expressed as mean* SD. The Mann-Whinrey U test was used for between-group comparisons; the chi square test was used for comparisons of group proportions with qualitative data. A p value less than0.05 was considered significant.

Results

During the 1 year period (2015), total of 23 children(13 M, 10 F) were complicated parapneumonic effusions or empyema were identified..The mean age at the time of presentation was 4.16+3.63 years (range: 5 months-11.6years).The left side was involved n 11(45%) cases and there were 2 cases with bilateral effusion. The mean duration of symptoms prior to admission was 11.4 days (range: 2-50 days).

At the time of sample collection for culture, Cough(87%), fever (85%) and decreased breath sounds(74%) were the most common symptoms. There were no significant difference sin terms of age, sex ratio, peripheral bloodleukocytosis, bacterial isolates and pleural biochemistrybetween the two groups. 5 patients (22.6%) had positive pleural fluid cultures: 3 (60%) Streptococcus pneumoniae, and 2 had (40%) Staphylococcus aureus. Leukocytosis, bacterial isolates and pleural biochemistrybetween the two groups. 5 patients (22.6%) had positive pleural fluid cultures: 3 (60%) Streptococcus pneumoniae, and 2 had (40%) Staphylococcus aureus.

14 ofthepatientshadstage2, and 7 had stage 3 empyema. The length of the hospital stay was 18.3 + 8.2 daysfor stage2 and 24.2+9.4for stage3 patients(p=0.02).The timetoafebrilestateafteradmissionwas5.3+3.9daysfor stage2 patientsand 9.3+8.4 days for stage3 patients(p: 0.04). The duration of chest tube placement was 7.5+ 6.9 days for stage2 patientsand.13.2+12.1 daysfor stage3 patients(p:0.05). The percentageof patients who eventuallyrequired VATS was 4.4% for stage 2 patients and 9.8%for stage3 patients (p>0.05).

N	Stage	Duration Of Hospital Stay	Duration To Afebrile State	Duration Of Chest Tube In Situ	Culture Report Positive	Vats
14	Stage 2	18.3 +/- 8.2	5.3 +/- 3.9	7.5 +/- 6.9	1 Strep Pneumonia	4.4%
7	Stage 3	24.2 +/- 9.4	9.3 +/- 8.4	13.2 +/12.1	42 - Strep Pneumonia 2 – Staph Aureus	9.8%

8 patients received conservative management (antibiotics with chest tube drainage), and 15 patients received conservative treatment plus fibrinolytic agents. No adverse effect of SK was noted. The two groups were compared with respect to meanage, sex ratio, length of hospital stay, total number of days with fever after admission, time to afebrile state after chesttube insertion or fibrinolytic therapy and duration of chest tube placement . The length of hospital stay was 19.1+5.5days for the drainage group and 24.9+11.2 for the SK group. The time to afebrile state aftera dmission was 7.8+4.1days for the drainagegroup and 5.6+7.5 days for the SK group. The duration of antibiotic therapy was 24.70+5.18days (10-32) in the drainage group and 19.62+5.90 days(7-33) in the SK group (p=0.16). Ampicillin-sulbactam was changed to vancornycin in five cases (three casesin the SK group and two cases in the drainage group). The percentageofpatientswho eventually required VATS was 24.3%(n:2) for the drainage group and 8% (n=1) for the SK Group.

	SK group	Non – SK group	Test of significance (P Value)
n	15	8	
Duration of hospital stay	19.1 +/- 5.5	24.1 +/- 11.2	P<0.05
Duration to afebrile state	5.6 +/- 7.5	7.8 +/- 4.1	P<0.05
Duration of antibiotics	19.6 +/- 5.9	24.7 +/- 5.18	P<0.05
Reqiurement surgical intervention (VATS)	8%n=1	24%n=2	P<0.05

Disscussion

The present study was conducted in paediatric patients with complicated parapneumonic effusion or empyema and demonstrated that intrapleural streptokinase reduced the duration of fever, duration of chest tube drainage,length of hospital stay and the need for surgery.

Parapneumonicpleural effusions are mostly very simple, small, uncomplicated pleural effusions that do not require specific treatment. But they may sometimes progress to life-threatening conditions such as multiloculated effusions, pleural fibrosis, systemicsepsis, respiratory failure and metastatic infection. In the face of newer treatment modalities, several management algorithms and guidelines have been published,but there are still many unanswered questions about treatment. Although intrapleural administrafion of thrombolytic agents has been used to treat empyema for more than 50 years , one of the most controversial issues is regarding the use of fibrinolytics. It is not yet clear whether intrapleural fibrinolytic therapyis beneficialin empyema, and if so, at which stageand at what time it should be administered.

Five small randomized controlled trials have been reported in adult patients. ln 1991, a double-blind trial comparing streptokinase and urokinase in 50 patients found that both were equally effective although urokinase was safer .In the sameyear, another randomized contolled study compared streptokinase and saline (as placebo) administered through a chest tube in 24 patients .Clinical endpoints did not show any significant difference befween the intervention and the control groups,though the volume of pleural fluid drained and the improvement in the chest radiograph were significantly greater in the SK group. Two and four years thereafter, two subsequent randomized trials compared urokinase and normal saline. In the first trial, a successful pleural drainage was obtained with urokinase and the second trial showed a reduced need for decortications with urokinase treatment.

In paediatric patients,the experience with fibrinolyticsand their actual efficacy are still limited. There have been severalsmall case series with streptokinase, urokinase or tissue plasminogen activator with a successful outcome without surgery and one randomized controlled trial of 60 children comparing urokinase and normal saline with a shortened hospital stay. As reportedin a recent meta-analysis in most of the paediatric studies fibrinolytic therapy was used for children who failed to exhibit improvement with non-operativetherapy (antibiotics and

thoracentesis and/or tube thoracostomy) alone . Three studies of primary fibrinolytic therapy were evaluated in this review: the above mentioned ran- domized controlled trial, one study with a historicalcontrol group comparing streptokinase and saline in 42 patients and one retrospective case note review of intrapleural urokinasein 48 patients. Overall, a reduction in failure rate but a higher reported complication rate was obtained compared to primary non-operative therapy.Our results do support the use of intrapleural fibrinolytic therapy in paediatric empyema cases as shown for adults in a large multicenter randomizedtrial.

Conclusion

In the treatment of empyema, the adjunctive treatment with intrapleural SK does significantly reduce durations of fever, chesttube drain ,ageand hospital stay, and the need for surgery regardless of the stageof the disease, compared to simple closed tube drainage. Further there is significant improvement of peak expiratory flow rates observed 3 months after discharge in SK group as compared to non streptokinase given group.

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