European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 06, 2022

Original Research Article

Study of empyema and intrapleural streptokinase in management of paediatric empyema in resource limited settings

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Abstract

In empyema, white blood cells migrate to infected pleural space causing release of fibrinogen and its conversion to fibrin, which causes tissue surfaces to adhere and this will trap micro-organisms and prevent host defence mechanisms and antibiotics from reaching the site of infection. ICTD with antibiotics remains the cornerstone in management of pediatric empyema. But ICTD is hampered by presence of either thick pus which tends to block tube or fibrin deposition causing multiple loculations that cannot be drained by single chest tube. Decision for insertion of ICD was taken depending upon clinical condition of the patient, radiological and laboratory evidence. Single dose of Inj. Streptokinase, 15,000 IU/kg body wt. was dissolved in 100ml normal saline and instilled in pleural cavity through ICD over a period of 1 hour and tube was clamped for 4 hours. Patient was asked to frequently change position, so that Streptokinase could thoroughly spread in pleural cavity. 25/27 (92.5%) in ICD group had good lung expansion on follow-up. Two had persistent collapse who improved further on physiotherapy. All patients in ICD with SK group had good lung expansion.

Keywords: Empyema, intrapleural streptokinase, paediatric empyema

Introduction

Incidence of pediatric empyema is 0.7-3.3 per 100000 population world-wide and 1-3% in Indian population [1, 2].
In empyema, white blood cells migrate to infected pleural space causing release of fibrinogen and its conversion to fibrin, which causes tissue surfaces to adhere and this will trap micro-organisms and prevent host defence mechanisms and antibiotics from reaching the site of infection.
ICTD with antibiotics remains the cornerstone in management of pediatric empyema but ICTD is hampered by presence of either thick pus which tends to block tube or fibrin deposition causing multiple loculations that cannot be drained by single chest tube [3, 4].
Enzymatic debridement with Intra Pleural Instillation of Streptokinase (IPSK) is non-invasive management in loculated empyema, which obviates need of surgery.
It is unclear whether optimal management is closed tube drainage or video assisted thoraco-scopic surgery (VATS) followed by chest tube drainage [5].

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In our country VATS is not widely available, so on failure of medical treatment, open decortication is often needed and open decortication is associated with high mortality.
ICDT alone is not recommended in paediatric empyema, but streptokinase is not used as much as explained in the literature because of questionable safety of streptokinase.
Injection of various fibrinolytic agents like streptokinase, urokinase in the intrapleural space are increasingly being used for the management of such conditions [6-9].
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 [10].
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 [11, 12].
In another study conducted by Davies *et al*., [13] amongst 24 patients in whom streptokinase and placebo was administered through chest tube, there was significant improvement in the volume of pleural fluid drained and radiographs in the group that was administered with streptokinase.
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 [14-16].
In a study conducted by Ulku *et al*., [17] 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.
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 [18].
In a study conducted by Ekta Singh, *et al*., (19) addition of intrapleural streptokinase along with the conventional therapy provides no additional advantage in the outcome variables.
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 thoracentesis [20].
Ekingen *et al*., [21] showed success of medical management of 96% in early phase and 72.2% in late phase.
This study was carried out with goal of studying the safety and efficacy of IPSK in paediatric empyema management.

Aims and Objectives

1. To study the clinical and bacteriological profile of children with empyema in a tertiary care hospital.
2. To evaluate various therapeutic options in management of pediatric empyema cases in resource limited setting.
3. To assess clinical and radiological improvement with safety profile of intrapleural streptokinase

Materials and Methods

- Prospective study 50 children of less than 12 years.
- Presented to surgical and pediatric emergency department in VIMS, Ballari.
- Duration-20 months CXR and USG thorax or CT thorax were done to look for loculations in addition to basic blood investigations along with coagulation profile and blood grouping.
- All patients were treated with ICTD and broad-spectrum antibiotics.

- Those children who had loculations on ultrasonography were given Intra Pleural Strepto Kinase (IPSK) injection through ICD.

Inclusion criteria

Children of age less than 12 years with diagnosis of Empyema thoracis with loculations on USG.
Empyema thoracis was diagnosed based on diagnostic thoracentesis.

- pH <7.2.
- Cell count >10,000/micro L.
- glucose less than 40.
- Chest X Ray.
- Ultrasonography (USG) Thorax}.
- Organism on gram staining.

Exclusion criteria

1) Tuberculous empyema.
2) Post-surgical empyema.
3) Immunocompromised state.
4) Presence of broncho-pleural fistula.
5) Patients not willing for study.

Procedure

- Decision for insertion of ICD was taken depending upon clinical condition of the patient, radiological and laboratory evidence.
- Single dose of Inj. Streptokinase, 15,000 IU/kg body wt. was dissolved in 100ml normal saline and instilled in pleural cavity through ICD over a period of 1 hour and tube was clamped for 4hours. Patient was asked to frequently change position, so that Streptokinase could thoroughly spread in pleural cavity.
- At the end of 4 hours, clamp was opened and amount of drainage in addition to saline instilled was recorded.
- All patients were closely noted for development of any side effects such as fever, chills, allergic reactions, bleeding, hypotension.
- Response was evaluated on basis of clinical outcome, drain output and need of surgical interventions.
- Study group was divided in to IPSK group (who received intrapleural streptokinase, n= 15) and non-IPSK group (who didn't receive streptokinase, n=20) and various parameters were compared between groups.
- IPSK group was further divided into early IPSK (<7 days of onset of symptom) and late IPSK (> 7 Days of onset of symptom).
- ICD was removed on clinical and radiological improvement when drain output was less than one mL/kg per day.

Following variables were assessed for the studying the outcome of treatment

1. Duration of hospital stay-total duration of hospital stay from the date of admission till the end point of the study (discharge).
2. Duration of chest tube *in situ*-total number of days a patient stays with the chest tube.
3. Duration of IV antibiotic treatment.
4. Treatment failure-Failure is defined as the need for surgical intervention.

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5. Side effects of intrapleural streptokinase.
6. Mortality.
7. Re-expansion of lung.

All the patients were advised for follow up at 1, 3 and 6 months. Those who came for follow up were assessed for lung expansion and deformities of the chest wall by clinical examination and chest x-ray.
Ethical clearance was obtained for this study.

Results

Table 1: Age distribution of empyema in children (n=50)

Age in years	No. of Patients	%
< 1 year	3	6
1-4 years	31	62
5-9 years	14	28
10-12 years	2	4
Total	50	100.0

31/50 (62%) of affected patients were between 1 to 4 years. 3 (6%) cases were seen in infancy. Youngest child was 1 months old and the oldest was 12 years old.

Table 2: Sex Wise Distribution of Cases

Gender	No. of cases	%
Male	27	54
Female	23	46
Total	50	100.0

27/50 were males and 23/50 were females. Male to female ratio was 1.17: 1.

Table 3: Clinical Presentation of the Cases at Admission

Clinical presentation	Number (n=50)	%
Fever	50	100
Cough	41	82
Hurried Breathing	39	78

All patients had fever. Cough and hurried breathing was seen in 41/50 (82%) and 39/50 (78%) cases respectively. Fever was the predominant symptom in 30 cases (60%) and cough in 10 cases (20%).

Table 4: Incidence of PEM (IAP Classification)

PEM	No. of Patients (n=50)	%
No PEM	22	44
Grade 1	13	26
Grade 2	8	16
Grade 3	6	12
Grade 4	1	2
Total	50	100.0

28/50 (56%) had PEM according to IAP classification. 13/50 (26%) had grade 1 PEM and 8/50(16%) had grade II PEM.

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Table 5: Respiratory findings

Respiratory Findings	No. of Patients (n=50)	%
Reduced air entry	50	100
Dullness	50	100
Mediastinal shift	15	30

All patients had reduced air entry on the respective side and dullness on percussion. 15/50 (30%) had mediastinal shift.

Table 6: Incidence of anemia

Haemoglobin	No. of Patients (n=50)	%
<7	11	22
7-10	28	56
>10	11	22
Total	50	100.0

39 out of 50 patients (78%) were anemic. Of which 11/60 (22%) had Hb less than 7 gm/dl.

Table 7: Macroscopy

Pleural Fluid Macroscopy	No. of Patients (n=50)	%
Pus	40	80
Seropurulent	10	20
Total	50	100.0

40/50 (80%) had pus on diagnostic thoracentesis and 10/50 (20%) had seropurulent effusion.

Table 8: Pleural Fluid-Biochemical parameters

Pleural fluid biochemical parameters	Criteria	No. of Patients (n=50)	%
Total count	<11000	23	46
	>11000	27	54
Glucose	<40	37	74
	>40	13	26
Protein	<3	46	92
	>3	4	8
LDH	<1000	6	12
	>1000	44	88
ADA	<60	26	52
	>60	24	48

37/50 (74%) had glucose value <40 mg/Dl. 46/50 (92%) had protein value more than 3 gm/dl. 44/50 (88%) had LDH >1000 IU/L. 24/50(48%) had ADA >60. Pleural fluid cell count was more than 11000 cells in 27/50 (54%) with polymorphonuclear predominance in all.

Table 9: Gram Staining of Pus Sample

Gram stain	No. of Patients (n=50)	%
Gram positive	16	32
Gram negative	8	16
No staining	26	52
Total	50	100.0

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Table 10: Treatment Modalities in Empyema

Treatment	No. of Patients	%
ICD	27	54
ICD with Fibrinolytics	23	46
Total	50	100.0

Results of comparative variables of main two treatment groups (i.e. ICD Vs ICD with fibrinolytics).

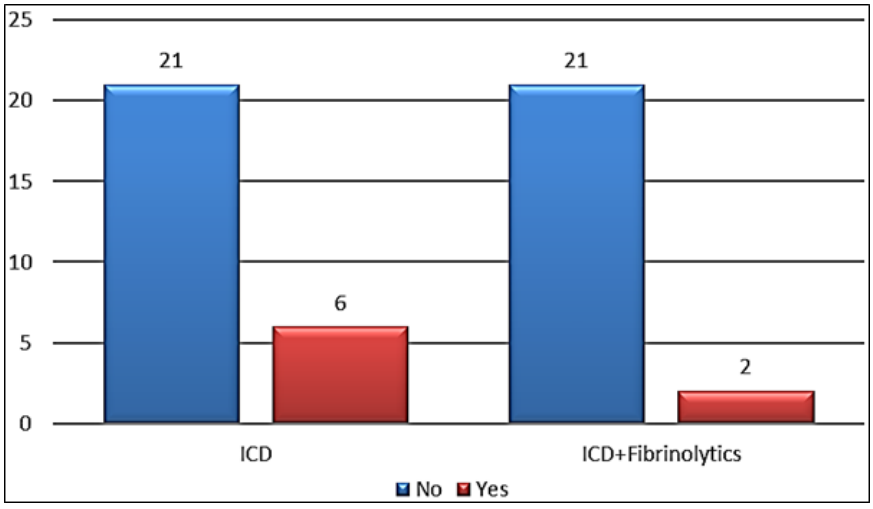
Table 11: Duration of hospital stay-mean and standard deviation

Treatment group	No. of Patients	Mean no. of days	Standard deviation	Std. Error Mean
ICD	27	17.3	4.772	0.909
ICD with fibrinolytics	23	11.6	4.979	1.038

Table 12: Duration of hospital stay-t test for equality of means

t-test for Equality of Means				
	t	Df	Significance (2 tailed)	Mean Difference
Duration of hospital stay	4.14	48	0.00014	5.6876

The mean duration of hospital stay in ICD group was 17.3 days whereas in ICD with fibrinolytics group it was only 11.6 days, which was statistically significant ($p<0.05$).
The failure rate in ICD group was 22.2% (6/27) compared to only 8.6% (2/23) in that ICD with Fibrinolytics group, but it was not statistically significant ($p>0.05$).



Graph 1: Failure rate

Table 13: Complications after administration of IPSK

Complications	Number	Percentage
Pain	5	21.7%
Dyspnoea	3	13.04%
Fever	5	21.7%
Tachycardia	15	65.21%
Hypotension	0	0
Chills	8	18.4%
Bleeding	0	0

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Table 14: Follow-Up

Outcome	ICD Group (n=27)	ICD with SK group (n=23)
Good Lung Expansion	25	23
Collapse	2	0
Pleural Thickening	0	0

25/27 (92.5%) in ICD group had good lung expansion on follow-up. Two had persistent collapse who improved further on physiotherapy. All patients in ICD with SK group had good lung expansion.

Discussion

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] Empyema thoracis consists of three stages-exudative phase (fibrinous exudates forms on pleural surfaces), fibrinopurulent phase (fibrinous septa form, causing lobulation and thickening of parietal pleura), and organization phase. Though empyema thoracis in children caries very little (20%) mortality as compared to adults, it causes lots of morbidity and complications. In some studies VATS or surgery was preferred choice in late (> 7 days) phase but we are showing that medical management can reduce surgery even in late phase.

Although in our study we did not face any major complication related to insertion of intercostal tube or administration of streptokinase, coagulopathy, intra-pleural hemorrhage, hemothorax, anemia and shock were rarely reported [23].

The advantages of the study are

- Primary and secondary aim (clinical and radiological improvement) of this study is proved.
- No significant adverse effects were noted during administration which has to be further confirmed by extending the study over a larger sample size.
- Failure rates in our study is less than in other studies. In other few studies it was 19.44% and 8.1% [24, 25].
- Statistical significance of medical management is proved.
- Streptokinase is easily available and is cost effective.
- This study could also compare the outcome of Early vs Late use of IPSK, because tertiary care hospital receive patients after a significant duration of onset of symptoms.

The drawbacks of the study are

- As the sample size is relatively small in this study, the result need to be substantiated by larger trial.
- Proper randomization of cases for comparison was not possible as each case of empyema differed in their clinical spectrum.
- Blinding has not been done and as a result bias could not be completely eliminated.

Conclusion

- Paediatric empyema has a better prognosis unlike adult empyema as there is no underlying pulmonary pathology. Empyema causes significant morbidity and rarely mortality
- In children with diagnosis of empyema thoracis with loculations, either early or late stage, IPSK appears to be a useful and safe modality.

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- This results in maximum preservation of lung function and it obviates the need for surgical intervention in places where VATS is not easily available.

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