

# Intrapleural Streptokinase in Management of Complicated Parapneumonic Effusion and Empyema

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## ABSTRACT

We report our study of the use of intrapleural streptokinase (IPSK) in ten patients with multiloculated complicated parapneumonic effusion & empyema who had failure of conservative first line of treatment with antibiotics and intercostal tube drainage. In order to break the multiple loculi and facilitate tube drainage, we instilled intrapleurally streptokinase 250,000 units diluted in 100 ml of 0.9% saline. All our patients showed improved fluid drainage after IPSK. Five patients experienced clinical and radiological resolution. IPSK therapy was unsuccessful in the remaining five, who then underwent successful surgical intervention.

**Key words:** Streptokinase, Empyema, Parapneumonic effusion, Intrapleural.

## INTRODUCTION

Parapneumonic effusions are a common problem in patients hospitalized with pneumonia. Most of these effusions resolve with antibiotics alone. Some of them also require intercostal tube (ICT) drainage along with antibiotics. Unfortunately, a few of these develop fibrinous loculations which make their drainage difficult, demanding further intervention. Adequate management requires the use of effective antibiotics along with ensuring complete pleural drainage. Intrapleural fibrinolytic drugs are widely used to lyse the fibrinous septations within the infected pleural effusion, in an attempt to reduce the need for surgery to achieve this drainage.

Our study attempts to investigate the efficacy and safety of IPSK, used as an adjunct to intercostal tube drainage, in the management of ten patients with multiloculated complicated parapneumonic effusion & empyema.

## MATERIAL AND METHODS

The records of ten consecutive patients admitted to Al-Noor Specialist Hospital, Holy Makkah, with the diagnosis of multiloculated

complicated parapneumonic effusion & empyema were retrospectively reviewed. Patients' charts were analyzed for demographic data, results of thoracentesis, chest radiographs, CT scans and for possible causes of treatment failure.

All patients underwent pleural aspiration which was analyzed for pH, leukocyte count, biochemical and microbiological analysis. While empyema was defined as presence of "frank pus"; the diagnostic criteria for complicated parapneumonic effusion requiring ICT insertion, was one or more of the following: a pleural fluid pH of < 7.20, glucose <40mg/dl, LDH >1000 IU/L, positive gram stain or culture. All patients showed evidence of loculations on chest X-ray or thoracic CT scan.

All patients were initially managed by antibiotics and intercostal tube drainage, but they failed to improve clinically or radiologically (inadequate lung expansion). Persistence of loculations was confirmed by CT scan, prior to instillation of IPSK.

Our protocol of use of IPSK was as follows: documentation of normal coagulation profile and preparation of streptokinase solution by diluting 250,000 units of streptokinase in 100 ml of 0.9%

saline. Site of instillation was guided by the CT scan. We used ICT for the IPSK instillation in four cases, while in remaining six cases 18 gauge Abbocath needle with catheter was used at the site of the largest loculation. Thereafter, ICT was clamped for six hours and the patient rotated every half an hour. ICT was then unclamped and connected to negative suction. Patient was monitored for fever, chest pain, anaphylaxis and bleeding tendency. Daily recordings of ICT drainage were kept. The procedure was repeated on a daily basis over a period of up to one week. Success was indicated by improvement in symptoms and resolution of chest X-ray pleural opacity with complete expansion of the underlying lung. Failure to do so defined failure of the IPSK therapy. Those who failed were referred to thoracic surgeons for thoracoscopy / thoracotomy.

## RESULTS

A total of ten cases with a diagnosis of loculated complicated parapneumonic effusion & empyema, who underwent IPSK treatment were reviewed. Age distribution was 20—70 years, with a male to female ratio of 7:3. All patients were febrile and had chest pain. Seven of the ten effusions were right sided. Table 1 summarizes the clinical information.

Five patients experienced marked improvement of their empyema with 3—6 doses of IPSK. The volume of ICT drainage ranged between 100—600 ml/day after IPSK. This was accompanied by clinical recovery & resolution of chest X-ray abnormality. They were discharged without further intervention. The remaining five patients, also had increased pleural drainage, but failed to show clinical & radiological resolution. They underwent successful decortication.

All the patients tolerated IPSK very well. We observed no complications, except mild ipsilateral chest pain in two patients which was relieved by oral analgesia.

## DISCUSSION

Approximately 20—40% of patients hospitalized with bacterial pneumonia have a co-

existing pleural effusion, a significant proportion of these develop into complicated parapneumonic effusion and empyema<sup>1</sup>. The presence of this complication adds to the morbidity and mortality of pneumonia. Adequate management requires the use of effective antibiotics along with ensuring complete pleural drainage. The latter objective can be achieved by a series of treatment options, which in order of increasing invasiveness, are therapeutic thoracentesis, tube thoracostomy, tube thoracostomy with thrombolytics, thoracoscopy and thoracotomy with decortication.

The evolution of a parapneumonic pleural effusion can be divided into three stages, which represent a continuous spectrum. In the first or the Exudative stage, there is accumulation of a sterile pleural effusion secondary to parenchymal focus of infection. The fluid in this stage has a normal glucose & pH. It responds to antibiotics and does not require tube drainage. In the second stage called the fibropurulent stage the pleural fluid gets infected with the offending bacteria. The fluid increases and contains many polymorphonuclear leucocytes, bacteria and cellular debris. Fibrin is laid down which tends to partition the fluid. The pleural fluid glucose and pH decrease and the LDH level progressively increase. In the last, Organization stage, fibroblasts grow into the exudate and produce an inelastic membrane, sometimes called a "pleural peel". This encases the lung and hinders its reexpansion. This may require surgical decortication in order to control the sepsis and for the expansion of the underlying lung.

Intercostal tube drainage is generally used as a first line of management if the pleural fluid is grossly purulent, has positive gram stain or culture, is loculated and has low pH < 7.20, low glucose (<40 mg/dl) and increased LDH (>1000 IU/L). Unfortunately, a significant number of these effusions develop fibrinous septations which defy complete evacuation of infected fluid by tube thoracostomy—often resulting in ongoing sepsis despite parenteral antibiotics.

IPSK has been in use since it was first described in 1949 by Tillet & Sherry<sup>2</sup>. Numerous case series and a few controlled trials have shown that intrapleural fibrinolytics are safe, increase fluid drainage, and improve some clinical and radiologic

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**Table 1: Patients' information and Outcomes.**

Pt No	Age (yrs)	Sex	Side of effusion	Pleural fluid Culture result	No of IPSK instillations	Fluid output 1 <sup>st</sup> 24 hr	Radiographic result	Outcome
1	20	Male	Right	No growth	5	400 ml	Full expansion	Success
2	30	Male	Right	No growth	6	300 ml	Thick cortex	Failure
3	35	Male	Right	No growth	5	600 ml	Full expansion	Success
4	39	Female	Right	No growth	6	600 ml	Thick cortex	Failure
5	71	Male	Right	No growth	6	250 ml	Full expansion	Success
6	35	Female	Left	Pseudomonas	4	500 ml	Full expansion	Success
7	28	Male	Left	No growth	7	300 ml	Thick cortex	Failure
8	40	Female	Left	Staph. Aureus	3	100 ml	Full expansion	Success
9	31	Male	Right	No growth	4	250 ml	Loculations	Failure
10	35	Male	Right	Staph. Aureus	3	100 ml	Loculations	Failure

**Table 2: Comparison of different studies on IPSK use.**

	Bouros et al. <sup>7</sup>	Taylor et al. <sup>8</sup>	Henke et al. <sup>9</sup>	Fraedrich et al. <sup>10</sup>	Rosen et al. <sup>11</sup>	Bergh et al. <sup>12</sup>	Hameed et al
No of Pts.	20	11	12	27	5	38	10
Success rate	19/20	8/11	9/12	12/27	5/5	30/38	5/10
Subseq. Surgery	1	3		15	0		5
Dose	250,000 U in 100 ml NS	250,000 U in 100 ml NS	250,000 U in 30-60 ml NS	200,000 to 1500,000 U in 50 ml NS		250,000 U in 100 ml NS	250,000 U in 100 ml NS
No of IPSK instillations	3-10	2-6	1-3	3-18	< 5	1-12	3-7
Adverse effects	1: high fever		Nil		Nil	Nil serious	2: chest pain

NS= 0.9% saline

outcome parameters<sup>3-12</sup>. Table 2, gives the comparison of our study with some of the earlier studies<sup>7-12</sup>. In the two controlled studies, with 24 patients<sup>3</sup> and 31 patients<sup>5</sup> the authors concluded that fibrinolytics were effective in facilitating the drainage of multiloculated parapneumonic effusions. In a recent randomized, placebo-controlled trial<sup>13</sup> that enrolled patients with empyema (i.e. frank pus) or loculated parapneumonic effusions, IPSK was compared to saline. The results showed that the patients in the IPSK group had a greater clinical success rate (82 vs. 48%,  $p = 0.01$ ) and fewer surgical referrals (45 vs. 9%,  $p = 0.02$ ). The authors concluded that intrapleural streptokinase adjunctive to chest tube drainage is safe, improves outcome, reduces the need for surgery and improves the clinical treatment success in patients with pleural empyema. It has been generally found that the best time to use IPSK

is before the onset of organization stage. In patients who show thickened cortex along with loculations, IPSK is less likely to be successful and early surgical intervention is preferred. In our series also, looking at the five patients who failed IPSK therapy (Table 1); three of them (patients 2, 4 & 7) showed evidence of thickened visceral pleura on CT scan, which was also confirmed intra-operatively when they underwent decortication. Retrospectively, we feel that such patients were probably not suitable for IPSK therapy. If we set aside these three patients, then in our study, five out of seven patients benefited from IPSK. CT scan is more sensitive than chest X-ray and is recommended for assessing loculations, thickened pleura and adequacy of pleural drainage.

Contrary to the studies favouring the use of IPSK, there are studies which did not find IPSK beneficial. This was best shown in a recent

multicentre, double-blind, placebo controlled trial, in which 454 patients with pleural infection (defined by the presence of purulent pleural fluid or pleural fluid with a pH below 7.2 with signs of infection or by proven bacterial invasion of the pleural space) were randomly assigned to receive either IPSK (250,000 IU twice daily for three days) or placebo. The conclusion of the study was that the intrapleural administration of streptokinase does not improve mortality, the rate of surgery, or the length of the hospital stay among patients with pleural infection<sup>14</sup>. However, the design of the study has been questioned, especially as the study enrolled all patients with pleural infection and not only those who had multiloculated effusion, the group in which IPSK is generally used<sup>15</sup>.

Our patients tolerated IPSK therapy very well. Only two required oral analgesia for chest pain. IPSK is considered to be a relatively safe procedure, although adverse effects have been encountered rarely. These include one reported case of major hemorrhage, intrapleural hemorrhage, fever and chest pain. Severe anaphylactic reactions have not been reported. Systemic fibrinolytic activity of intrapleural streptokinase is a theoretical concern, but IPSK administered up to a dose of 1.5 million IU does not cause significant activation of systemic fibrinolysis in humans. In the study by Maskell NA, there was a substantial systemic antistreptokinase-antibody response. Such a response might inhibit the efficiency of streptokinase given later for a myocardial infarction. Therefore, patients who have received intrapleural streptokinase and later require systemic fibrinolysis should receive a different fibrinolytic agent<sup>14</sup>. Urokinase is non-antigenic and has been used intrapleurally. It has been found to be of comparable efficacy to streptokinase, but is more expensive<sup>4,5</sup>.

In conclusion, we feel that IPSK is an effective adjunct to the management of loculated complicated pleural effusion and empyema. In patients who fail to drain adequately with ICT, the use of IPSK should be considered before surgical referral, especially in patients who present early before fibrosis and *pleural peel* sets in. This stepwise approach is likely to reduce the need for open thoracotomy or video-assisted thoracoscopic surgery (VATS) which although achieve the best

drainage in gross empyema or loculated effusions, are limited by operative risk, cost, and local availability<sup>16</sup>. IPSK is well tolerated by the patients, with minimal adverse effects. Although the use of IPSK is supported by management guidelines<sup>17, 18</sup>, there is conflicting evidence in medical literature regarding its efficacy. Despite widespread optimism, adjunctive intrapleural streptokinase has so far not become an established routine practice.

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