Intrapleural Fibrinolytic Therapy in Loculated Effusions

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Loculated pleural effusions are most commonly due to complicated parapneumonic effusions and empyema followed by tubercular pleural effusions and empyema, hemothorax and malignant effusions. Loculations develop due to delayed initiation and inappropriate use of antibiotics and, delayed initiation of pleural space drainage. The presence of loculations and thick viscous fluid leads to failed pleural space drainage in spite of tube being patent and correctly positioned. The management options in such cases consist of either use of minimally invasive video assisted thoracic surgery (VATS) or more invasive conventional thoracotomy. In spite of being effective, VATS is not easily accessible and affordable in developing countries like India. The use of intrapleural fibrinolytics is a safer, easier and cost effective option and various uncontrolled and small randomized studies have shown it to be a useful alternative. However, a recent large multicenter randomised trial using intrapleural streptokinase in cases of pleural infection and using mortality and need for surgery as primary outcomes found no significant difference between patients receiving streptokinase or placebo. This study met with serious criticism with regard to the selection of primary outcomes and methodology. This article discusses the parapneumonic effusions, which are the most common cause of loculated effusions, rationale of this therapy, its indications and treatment protocols and the present status of this therapy especially in a developing country like ours.

CLASSIFICATION OF PARAPNEUMONIC EFFUSION

It is important to know the various stages of parapneumonic effusions since the management differs for each stage. A new classification has been proposed by expert panel from American College of Chest Physicians and is based on anatomic characteristics of the fluid, bacteriology and the chemistry of pleural fluid. This classification is not practical in our kind of set up since it requires the measurement of pleural fluid pH, which is not available in most of the hospitals in our country. A more practical classification as suggested by British Thoracic Society is as follows:-

Simple Parapneumonic Effusion
Simple Parapneumonic Effusion corresponds to exudative stage of parapneumonic effusion and it almost always resolves with antibiotics alone.

Complicated Parapneumonic Effusion
Complicated Parapneumonic Effusion (CPE) corresponds to late fibrinopurulent stage. The pleural fluid is usually clear or turbid, but is nonpurulent. Fibrin strands with or without loculations may be evident on Ultrasoundography (USG) or computed tomography (CT). This stage requires pleural space drainage along with either instillations of intrapleural fibrinolytics or VATS apart from appropriate antibiotics.

Empyema
Empyema is a condition of frank pus with a single or multiple loculations. The management of empyema is always by chest tube drainage with or without fibrinolytics or by surgical drainage.

Diagnosing Parapneumonic Effusions
The diagnosis of simple parapneumonic effusion and empyema is quite straightforward. The diagnosis of CPE is not so straightforward especially in the presence of
clear pleural fluid and it is very essential to diagnose CPE at earliest so that timely pleural space drainage can be initiated. Furthermore, in case intercostal tube drainage fails due to presence of loculations, intrapleural instillation of fibrinolytics may be helpful. If tube drainage is delayed the CPE progress to empyema stage. In a multicenter trial\(^1\), no attempt was made to identify this important subset of patients with CPE and this may be one of the reasons why intrapleural streptokinase was found to be ineffective in this trial. There are no definite clinical, radiological or biochemical parameters, which suggest CPE. However, following parameters suggest the development of CPE.

**Clinical:**
Prolonged symptoms prior to presentation, combination of leukocytosis, anemia and hypoaluminaemia and failure of clinical response to antibiotics may suggest CPE\(^4\).

**Radiological:**
The presence of D-shaped opacity or absence of typical sickle-shaped opacity in postero-anterior and lateral chest radiographs is suggestive of CPE or empyema which is loculated. Ultrasoundography (USG) of chest is a useful and easily accessible test for detecting the presence of fibrin strands, septations or necrotic debris, the presence of which suggest the development of CPE. Contrast Enhanced Computed Tomography (CECT) of chest can reliably detect loculations, their number, sizes, and pleural thickening.

**Pleural fluid characteristics:**
The pleural fluid may be clear, cloudy or turbid. In case of clear or slightly turbid fluid, pH can be measured using blood gas analyzer and heparinised sample. The biochemical analysis, apart from routinely done protein estimation must include sugar and LDH estimation. Pleural fluid pH less than 7.20; glucose less than 60mg/dl and LDH level more than three times the upper limit of serum LDH suggest the diagnosis of CPE. The positive gram stain or bacterial culture further confirms CPE. If pH testing is not possible because of lack of facility or turbid fluid, then finding of low glucose and high LDH along with presence of fibrin strands or septations on ultrasonography of chest practically confirms the presence of CPE and is an indication for intercostal tube drainage.

**INTRAPLEURAL FIBRINOLYTIC THERAPY**
When the chest tube is correctly positioned (as evidenced by chest radiography postero-anterior and lateral chest radiographs) and there is significant amount of pleural fluid, the major reasons for failed drainage are multiple pleural space loculations or tube obstruction by thick and viscous fluid\(^5\). The various modalities of treatment available at this stage are; saline flushes, placing one or more catheters in loculi under image guidance, thoracoscopic debridement, standard thoracotomy with drainage of empyema and decortication. The first two modalities are not so effective in improving drainage. The last two surgical modalities are more invasive, not easily available and, if available, are not affordable by majority of patients in developing countries like India. The fibrinolytic agents, if used early in the CPE, break loculations and early pleural peel thereby facilitating pleural space drainage. These agents possibly do not have significant liquefying effect on pus and hence may not be effective in empyema stage\(^6\). Tillet and Sherry\(^8\) were the first ones to use fibrinolytic agents in 1949 in 23 patients who had loculated empyema or haemothorax. Their patients received intrapleural instillation of both streptokinase and streptodornase, which was extracted from concentrated filtrates of streptococci of Lancefield group C. There was significant improvement in drainage of fluid. However, the initial enthusiasm waned because of significant systemic adverse effects in the form of fever, leukocytosis and general malaise. These side effects were due to immunological reaction caused by impurities in the preparation of agents. There was not much of use of this therapy until Bergh and colleagues\(^11\) in 1977 used purified streptokinase and reported significant improvement in 10 of 12 patients with empyema without the need for any major surgical intervention and without any significant adverse effects. In the last 25 years there has been numerous case series and randomized controlled trials using streptokinase (STK) and urokinase (UK) in complicated parapneumonic effusion and empyema with encouraging results. There are about 25 uncontrolled case series\(^12\) using intrapleural fibrinolitics (STK/UK). The number of patients in these case series varied from 3-30 and the indication for initiating fibrinolytic therapy was failed chest tube drainage in presence of patent and adequately positioned tube or catheter. STK dose used was 2,50,000 IU in 50-100 ml of saline daily and the tube was clamped for 2-4 hrs. The dosage of urokinase used in these studies has been in the range of 50,000-1,00,000 IU. Number of installations used was 2-10. Treatment success criteria included increased volume of fluid drainage and clinical and radiological resolution of CPE or empyema. Success rate was 67-100% in these studies. The majority (>90%) of patients had no complications and 5-10% had transient fever, pleuritic chest pain and chest
Till date, there are five small randomized trials on the use of fibrinolytic agents. In the first trial\(^{13}\), three doses of intrapleural STK (2, 50,000 IU/day) was compared with saline flushes in 24 patients (13 with empyema and 11 with CPE). The STK group had significantly greater drainage of pleural fluid and radiological resolution. The second study\(^{14}\) compared urokinase in 15 patients (11 with CPE and 4 with empyema) with normal saline in 16 patients (13 with CPE and 3 with empyema) with pleural infection resulting in significantly more fluid drainage in urokinase group. In another study which was not a formal randomized trial but sequential trial in which only chest tube drainage was used during first half of study and intrapleural STK was administered during later half of study. The study\(^{15}\) included 52 patients who were treated with drainage (n=29) and intrapleural STK (n=23) with more number with empyema (n=40) than with CPE (n=12). A significantly larger volume of pleural fluid drained in STK group but there was no difference in the need for surgery or in the mortality rate.

In a fourth study\(^{16}\), 49 patients with parapneumonic empyema were randomly assigned to receive either intrapleural urokinase or normal saline for five consecutive days. The urokinase group had shorter time for defervescence, shorter need for hospitalization and a lower need for decortication. In a fifth randomized control trial\(^{17}\) 44 patients were randomized to receive either STK or normal saline. The primary outcome measures were taken as need for surgery, response to treatment and mortality. The significant beneficial effect of STK was seen between fourth and seventh day after initiation of treatment and there was reduced need for surgical referral in STK group. Most of these studies may be criticized for using the pleural fluid drainage and radiological improvement as primary outcome measures since it has been shown that radiological improvement does not reliably predict outcome\(^{18}\) and streptokinase can increase pleural fluid drainage due to mechanism independent of fibrinolysis\(^{19}\). At the same time using other primary outcome measures like need for surgery, mortality, hospital stay also may not be appropriate end points for assessing the effect of fibrinolytic therapy. This hypothesis will be explained later. During last five years or so, the intrapleural streptokinase has been used with encouraging results in our country as reflected in various case reports\(^{20,21}\), non-randomized trial\(^{22}\) and randomized trials\(^{23,24}\). However, the results of most recent and long awaited study\(^{1}\) on utility of intrapleural fibrinolytics have been negative. This was a multicenter, randomized, double blind study\(^{1}\) in which 427 patients with pleural infection were randomized to receive either intrapleural streptokinase or placebo. There were no significant differences between the two groups in terms of mortality, need for surgery, radiographic outcome or length of hospital stay and the authors concluded that intrapleural streptokinase should generally be avoided in pleural infection. Although this was a large multicenter trial, yet it had some significant flaws in selection of primary outcomes and methodology. Mortality in patients with parapneumonic effusions depends more upon the severity of underlying pneumonia, other co morbid conditions and age rather than facilitation of pleural space drainage with intrapleural fibrinolytics and it has been suggested that extent of pleural fluid drainage should not be considered as primary outcome measure\(^{25}\).

Moreover significant number of patients in this trial was more than 60 years of age and majority of them had co morbid diseases, which could have contributed in increasing mortality and hospital stay. The patient population was heterogeneous in this study and radiological investigations like USG or CT were not used to select patients with CPE or empyema with loculations without any significant pleural thickening, since this subgroup of patients is most likely to benefit from fibrinolytic therapy which breaks the loculations but possibly does have any significant effect in liquefying pus\(^{6,7,25}\). Althought in this trial subgroup analysis of patients with and without septations / loculations was carried out, yet it is difficult to select such patients only on the basis of chest radiography\(^{26,27}\). In a recent cochrane review\(^{28}\), intrapleural fibrinolytic therapy has been shown in the trials included in this review to confer significant benefit in reducing the requirement for surgical intervention for patients in the early studies included in this review but not in the more recently published Maskell\(^{1}\) study. The reasons for this difference are uncertain. Separate subgroup analysis of proven loculated/septated effusions from the available data in this meta-analysis suggests a potential overall treatment benefit with fibrinolytics, but these results should be treated with caution as the data are incomplete and the benefit is not significant in meta-analysis of the subgroup of the high quality trials (Cochrane Grade A). Intrapleural fibrinolytics have not been shown to significantly increase adverse events, but the confidence interval is too wide to firmly exclude this possibility. Hence more better designed trial are required with emphasis on proper selection of patients before we abandon this therapy as has also been...
suggested by other workers\textsuperscript{24,29}.

The above mentioned randomized controlled trials, except for multicenter trial, in spite of low number of patients and non-uniform selection criteria, have nevertheless shown that intrapleural fibrinolytic therapy with either STK or UK does facilitate the drainage of pleural fluid by breaking the loculations as in complicated parapneumonic effusion and empyema with loculations without any significant adverse effects. The most important prerequisite for initiating this therapy is early diagnosis of complicated parapneumonic effusion and empyema by means of ultrasonography or computed tomography. The use of video assisted thoracic surgery (VATS) in such effusions is undoubtedly a better option, as has been brought out by multicenter trial\textsuperscript{1}, but in a developing country like ours where VATS is both inaccessible and costlier option, the use of intrapleural fibrinolytics is definitely a cheaper, safer and effective option. The ACCP evidence based guidelines\textsuperscript{2} have also recommended fibrinolytic and VATS as acceptable options in CPE and empyema. The BTS guidelines\textsuperscript{3} have also recommended consideration of intrapleural fibrinolytics in failed drainage in CPE and empyema. There has been a problem in adopting daily dosage schedule of intrapleural STK or UK in our country due to non-availability of required dosage of STK or UK. The minimum strength of STK freely available in our country is 7, 50,000 IU per vial and once the vial is reconstituted the solution can be stored only for 8 hours at 2-8°C.

We have been using intrapleural STK in the dosage of 2, 50,000 IU 8 hourly. This way we can utilize two doses, thereby minimizing the wastage of this costly drug and at the same time maintaining its potency. The same dosing regimen was used in cases reported earlier from this country\textsuperscript{20,21} and in an uncontrolled study\textsuperscript{22}. The same problem exists with urokinase with the availability of only 2,5000 IU per vial as the minimum strength. We have been using it in the dosage of 100,000 IU 8 hourly for similar reasons as for STK. We had to resort to this increased dosage out of compulsion. However, Strange \textit{et al} \textsuperscript{19} in an experimental study demonstrated that increasing dosing interval might in fact increase the efficacy of fibrinolytic therapy. The possible explanation for this is that due to various protease inhibitors in the inflamed pleural space the half-life and, therefore, the proteolytic activity of STK is shortened and increasing dosing frequency can prolong the same. How much contribution to the successful outcome of this therapy can be attributed to increase dosing frequency needs to be further evaluated by a controlled trial. The intrapleural fibrinolytic therapy has also been used successfully in pediatric patients as reflected by various case reports\textsuperscript{30,31} and a randomized control trial\textsuperscript{32}. This therapy has also been used successfully in loculated effusions due to tuberculosis\textsuperscript{23} and in clotted traumatic hemothorax\textsuperscript{33}. Apart from STK or UK, other fibrinolytic agent like tissue plasminogen activator (tPA) has also been used with positive results in uncontrolled studies\textsuperscript{34, 35}. A wide range of doses has been used in these studies but a reasonable dose is 10mg \textsuperscript{35}. There has been no standardized protocol for using intrapleural fibrinolytics and the suggested protocol is as shown in Figure 1.

### ADVERSE EFFECTS OF FIBRINOLYTIC AGENTS

Fever, chest pain has been reported in <10% of patient. Major hemorrhage was reported in a single case report after 5, 00,000 IU of STK and dwell time of 6 hrs\textsuperscript{37}. There have been isolated case reports of ventricular fibrillation following urokinase\textsuperscript{38}. It is recommended not to exceed single dose of >2,50,000 of STK or 100,000 of UK and dwell time more than four hours. There is no significant activation of systemic fibrinolytic system with a total dose of 1.5 MIU given in a dose of 2, 50,000 IU 12 hourly and no monitoring of coagulation parameters is required\textsuperscript{39}.

### CONTRAINDICATIONS OF USING FIBRINOLYTIC THERAPY

H/O bleeding diathesis, stroke or significant hemorrhage in the preceding six months and use of STK by any route in the previous two years.

### FUTURE PROSPECTS

As mentioned previously, Tillet and Sherry\textsuperscript{8-10} used Varidase in patients with loculated empyema and haemothorax, which was a combination of unpurified preparation of STK (fibrinolytic) and streptodornase (DNase), extracted from group ‘C’ β-hemolytic streptococci.

The use of this therapy was based on the hypothesis that purulent exudates contain almost equal proportion of fibrin and deoxyribose nucleoprotein. Streptokinase or UK (fibrinolytics) liquefies fibrin and streptodornase (DNase) liquefy deoxyribose nucleoprotein. The results were good but further studies were abandoned because of adverse side effect like fever, malaise, and leukocytosis. The efficacy of Varidase has been demonstrated in an in vitro trial\textsuperscript{7} in which when thick empyema fluid from rabbits was incubated with STK or UK, there was no significant liquefaction of fluid. When the same fluid was incubated with Varidase, the fluid...
was completely liquefied in 4 hours. Varidase has now been replaced by recombinant DNase and a study by Simpson et al6 have demonstrated that recombinant DNase by itself is very effective in reducing the viscosity of human empyema fluid. There is another multicenter trial underway in United Kingdom in which patients with CPE are randomized to receive saline, 10mg tPA, 1mg recombinant Dnase or the combination of tPA and Dnase twice a day. Until the result of this trial are available or further well designed trials are done in carefully selected patients with CPE or loculated empyema and using clinical, radiological, drainage and need for surgery as primary outcomes, we should continue using intrapleural STK/UK in above mentioned classes of parapneumonic effusion.

REFERENCES


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