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Title of the article: INTRAPLEURAL FIBRINOLYSIS WITH UROKINASE VERSUS ALTEPLASE IN COMPLICATED PLEURAL EFFUSIONS AND EMPYEMA: A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

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INTRAPLEURAL FIBRINOLYSIS WITH UROKINASE VERSUS ALTEPLASE IN COMPLICATED PLEURAL EFFUSIONS AND EMPYEMA: A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

Abstract

Introduction

Intrapleural fibrinolytic therapy is being used as an effective agent since 1949 in managing complicated pleural effusion and empyema. Several agents like streptokinase (STK), urokinase (UK), and recombinant tissue plasminogen activator (rt-PA) are found to be effective with variable effectiveness. However, head-to-head controlled trial to compare the efficacy of the most frequently used i.e., UK and rt-PA (alteplase) in managing complicated pleural effusion has rarely been reported.

Methodology

50 patients were randomized in two intervention groups i.e., UK and rt-PA. The dose of rt-PA was 10 mg, and that of UK was 1.0 lac unit. UK was given thrice daily for two days, followed by clamping to allow the drugs to retain in the pleural space for 2 hrs. rt-PA was instilled in the pleural space twice daily for two days, and the intercostal drainage was clamped for 1 hour.

Results

A total of 50 patients were enrolled for the study out of which 84% (n=42) were males and 16% (n=8) were females. Among them, 30 (60%) patients received UK, and 20 (40%) patients received alteplase as IPFT agents. The mean changes in the pleural opacity in the UK group was -33.0 % (SD +/- 9.9) and -41.0 % (SD +/- 14.9) in the alteplase group (P-value 0.014). Pain was the most common adverse side effect, occurring in 60% (n=18) of the patients in the UK group and 40% (n=8) in the alteplase group (P-value 0.24) while fever was the second most common side effect. Patients who reported early (within 6 weeks of onset of symptoms) have shown greater response than who reported late for intervention.

Conclusion
IPFT is a safe and effective option in managing complicated pleural effusion or empyema, and newer agents like alteplase have greater efficacy and similar adverse effects effect profile when compared with conventional agents like UK.

**Keywords:** Complicated Pleural effusion, Empyema, Intrapleural fibrinolysis, Urokinase, Recombinant tissue plasminogen activator (rt-PA), Alteplase

**Introduction**

Thoracic empyema continues to be a significant cause of morbidity, especially in developing countries. Pulmonary infections, including community-acquired pneumonia, bronchiectasis, and lung abscess, are the most prevalent cause of thoracic empyema in developed countries, followed by surgical trauma. In contrast, studies from India reveal that tuberculosis accounts for a large number of empyema cases (38.6%)

In empyema and complicated parapneumonic effusions (CPE), leucocytes sequestrate to the infected pleural space and secrete several permeable factors causing fibrinogen to spill into the pleural space. The fibrinogen is then converted to fibrin, which adheres to the tissue surface, which will trap the pathogenic microorganism. However, this entrapment will prevent host defence mechanisms and antibiotics from reaching the site of infection. Infected pleural fluid has been shown to have low fibrinolytic activity and increased concentrations of plasminogen activator inhibitors.

Tillet and Sherry first demonstrated the use of fibrinolytic in 1949 as a treatment for empyema. Fibrinolytic therapy was reintroduced by Bergh et al. in 1977, and they used a more refined form of streptokinase. Many trials and reports have shown the effectiveness of fibrinolytic agents in the treatment of empyema/CPE. Still, these were small trials and case series with success rates ranging from 38% to 100%.

Intrapleural fibrinolytic is frequently administered to patients with complicated parapneumonic effusion or empyema who fail antibiotic therapy and initial drainage. It is also a suitable option for patients who are not candidates for or do not want surgery. The rationale for this approach is that this strategy reduces the need for surgery and shortens the duration of hospitalization.

Urokinase was effective in a randomized trial of patients with multiloculated pleural effusions. Patients in the intervention group with UK drained significantly more volume of pleural fluid, required less surgical referral, and required fewer days in the
hospital. Intrapleural rt-PA has been successfully administered in patients with complicated parapneumonic pleural effusion and empyema.

The landmark MIST2 trial published in 2011 included a comparison with intrapleural recombinant human DNase, a potential treatment for pleural infection that may help prevent the septate formation and decreased viscosity by destroying extracellular DNA.\textsuperscript{10} The blinded 2-by-2 factorial trial randomly assigned 210 patients with pleural disease to receive a 3-day study treatment using double placebo, rt-PA and placebo, DNase and placebo, or rt-PA and DNase. The combined intrapleural rt-PA and DNase therapy reduced hospital stay length, decreased the need for thoracic surgery, and produced a more considerable improvement in pleural opacity on day seven relative to double placebo.\textsuperscript{15}

After the MIST2 study, no other randomized trial has been performed in this field. In our study, we aim to compare the efficacy of UK versus recombinant tissue plasminogen activator (alteplase) as intrapleural fibrinolytic agents in the management of complicated pleural effusion.

\textbf{AIM}

To evaluate the efficacy of UK versus recombinant tissue plasminogen activator (alteplase) as intrapleural fibrinolytic agents in the management of complicated pleural effusion.

\textbf{OBJECTIVES}

(a) \textbf{Primary Objective}

To compare the outcomes of Urokinase versus recombinant tissue plasminogen activator as intrapleural fibrinolytic agents at tertiary care Respiratory Center in Western Maharashtra

(b) \textbf{Secondary Objective}

To evaluate the safety profile of intrapleural fibrinolytic agents

\textbf{METHODOLOGY}

\textbf{STUDY DESIGN}

This randomized trial was conducted at our centers from December 2019 to June 2021. Ethical and regulatory approval was obtained before the recruitment of the subjects.
PATIENTS
Eligibility criteria were clinical and radiological evidence of infection and loculated pleural effusion that was either macroscopically purulent, positive on culture for bacterial infection, or positive for bacteria on Gram's staining, or pleural fluid that had a LDH level of more than one thousand on biochemical evaluation. The empyema in the study group included both Tuberculous and bacterial empyema. Exclusion criteria were age less than 18 years, previously treated with IPFT, known sensitivity to UK or rt-PA, any history of bleeding diathesis, pregnancy or lactation, broncho-pleural fistula, and life expectancy of fewer than three months.

RANDOMIZATION
After obtaining written informed consent from the patients, they were assigned to a study group using randomization by the date of admission. The patients admitted on an odd date were assigned to the first group, and the rest were assigned to the second group. We followed a double blinding method as neither the patient nor the doctor knew the drug allocated to the patients. The measured dose of t-PA or UK was issued to the physician in unmarked 50 ml syringes. The two study treatments groups were t-PA and Urokinase. Placebo groups were not included as both the drugs had proven efficacy compared to placebo, which was demonstrated in the previous studies.

The dose of rt-PA was 10 mg, and that of UK was 1.0 lac unit. UK was given thrice daily for two days, followed by clamping to allow the drugs to retain in the pleural space for 2 hrs. rt-PA was instilled in the pleural space twice daily for two days, and the intercostal drainage was clamped for 1 hour.

The relevant independent variables were collected during the study period and were stored as raw data sheets in Excel, word.doc, and PDF format. Later, the data were refined and analyzed during the analysis phase, and co-relation, association, and significance were calculated using STATA software (version 3). The results were then represented in the tables below.
A total of 50 patients were enrolled for the study. Among them 84% (n=42) was male and the female patients were 16% (n=08). The majority of the patients belonged to the young age group (between 20 to 30), which led to skewing the age distribution graph to the right. However, this was an expected phenomenon as a majority of the clientele of our hospital are young individual.

The cause of empyema included tuberculous (60%) and bacterial empyema (40%). Among them, 30 (60%) patients received UK, and 20 (40%) patients received alteplase as IPFT agents. The baseline demography, radiological and biochemical parameters are summarized in table-1.

The parameters like pre-intervention radiological features, the initial volume of the pleural fluid, and pleural fluid lactate dehydrogenase were similar across both groups. The median value of age and interval of symptoms to the intervention were comparable.

**PRIMARY ENDPOINTS**
The primary outcome was the change in pleural opacity, measured as the percentage of the areas of pre-treatment hemithorax occupied by effusion, on chest radiography and on completion of the therapy. The area of pleural opacity and the hemithorax was measured digitally and the response was quantified as maximum (near normal chest radiograph), moderate (50-80% clearance of pleural opacities) and minimal (<50% clearance of pleural opacities) or none (no response). The of mean changes in the pleural opacity in the UK group was –33.0 % (SD +/- 9.9) and -41.0 % (SD +/- 14.9) in the alteplase group. On applying the Wilcoxon Rank sum test, there was a significant difference in clearance of pleural opacities between the two drugs (p=0.014) which was statistically significant, favouring alteplase over urokinase (P-value – 0.014) (Table-2).

SECONDARY OBJECTIVES

ADVERSE SIDE EFFECTS

Various side effects were also monitored and compared between the two study groups. The most reported side effects were fever and pain in the affected hemithorax. Pain was the commonest adverse side effect, occurring in 60% (n=18) of the patients in the UK group and 40% (n=8) in the alteplase group. Chi-square test with Fischer correction was applied. There was no significant difference in secondary outcome in the form of fever (Chi-square value- 0.292, with a P-value of 0.740) and pain (Chi-square value-1.923, P-value of 0.248) as adverse reactions between the two groups. The difference was not statistically significant (P-value 0.24) (Table-3).

Fever was the second most common side effect. The incidence of fever among the UK group was 26.7% (n=8) and 20% (n=4) in the group that received alteplase. However, similar to the side effect profile of pain, there is no significant statistical difference of incidence of fever in the two study groups (P-value 0.74). (Table-3) 02 patients developed severe adverse reactions in the alteplase group. They developed severe bleeding, and there was a drop of hemoglobin by more than one gm%. The therapy was terminated after first cycle. However, none of the patients required resuscitation or component transfusion. There was no incidence of severe adverse reaction in the UK group.

Association between the interval of symptoms to intervention with the response

There is also a statistically significant association between the interval of symptoms to intervention with the outcome of the IPFT. Patients who had reported within six weeks of
symptoms were compared with those who reported relatively late, i.e., more than six weeks. More than 20% of X-ray clearance was taken as a cut-off for a significant response to IPFT. 100% of patients (n=40) had shown an excellent response to the therapy. In contrast, only 60% (n=6) patients had a significant response in the group when they reported more than six weeks after the onset of symptoms. Chi-square test with Fischer correction was applied. There was a significant difference in outcome when presentation was less than 6 weeks as compared to when it was more than 6 weeks of duration (Chi-square) (Table-4)

DISCUSSION
Tillet and Sherry first demonstrated the use of fibrinolytic in 1949 as a treatment for empyema.3 A group of 23 patients with loculated empyema or hemothorax received intrapleural instillation of STK and streptodornase through an intercostal drain. Several reports emerged thereafter, showing the effectiveness of fibrinolytic agents in the management of loculated pleural effusion.4 However, the initial enthusiasm waned due to severe systemic side effects like fever, leucocytosis caused by various impurities in the enzyme mixture.). The success rates of fibrinolytic agents still ranges from 38% to 100%.3,13-14

The patients with complicated parapneumonic effusion or empyema who fail antibiotic therapy and initial drainage are generally administered IPFT.9,10 It is also a suitable option for patients who are not candidates for or do not want surgery. The rationale for this approach is that this strategy reduces the need for surgery and shortens the duration of hospitalization3.

UK was effective in a randomized trial of patients with multiloculated pleural effusions.13-14 Patients in the intervention group with UK drained significantly more volume of pleural fluid, required less surgical referral, and required fewer days in the hospital. However, a RCT by Bouros et al. in 1997 showed that UK had more fluid drainage after 24 hours than (STK).16 The drain in the first 24 hours was 380 +/- 99 ml for the STK group (p < 0.001) and 420.8 +/- 110 ml for the UK group (p < 0.001), but the total drain at the end of the therapy was not statistically significant. The total volume (mean +/- SD) of fluid drained after treatment was 1,596 +/- 68 ml for the STK group, and 1,510 +/- 55 ml for the UK group (p > 0.05). An odds ratio of death or referral for surgery of STK versus UK was not significantly different. (OR 1.00 ,95% CI 0.13 to 7.72). Severe adverse reaction in the form of fever and an allergic reaction was significantly more in the STK group. The author concluded that intrapleural STK or UK is an equally effective adjunct in managing complicated parapneumonic effusion and may reduce the need for referral for surgery in some cases. Despite the comparable efficacy,
the UK could be the thrombolytic of choice due to the potentially dangerous allergic reactions to STK and relatively little higher cost of the UK.\(^\text{16}\)

Intrapleural rt-PA in patients with complicated parapneumonic pleural effusion and empyema has shown significant response. \(^\text{17}\) The landmark MIST2 study evaluated the efficacy of rt-PA, DNase, rt-PA plus DNase, and placebo in the treatment of complicated parapneumonic effusions. \(^\text{18}\) Two hundred ten patients were randomized to one of the above four regimens. The interventions were given twice daily for three days (rt-PA 10 mg, DNase 5 mg). The primary outcome measure was the absolute change in the pleural opacity on the chest radiograph from the day of randomization until seven days post-randomization. \(^\text{18}\) The administration of the combination of rt-PA and DNase resulted in a more significant reduction in the pleural opacity (-29.5%) than did the administration of rt-PA (-17.2%), DNase (-14.7%), or placebo (-17.2%). \(^\text{18}\) There were no significant differences between rt-PA, DNase, and placebo. \(^\text{18}\) When the secondary endpoints were examined, the patients who received the combination had a significant decrease in surgical referrals and a significantly shorter hospital stay than did the patients who received a placebo. \(^\text{18}\) The rt-PA alone did not differ significantly from placebo on either of these secondary endpoints, while DNase alone was associated with more surgical referrals than was placebo. \(^\text{18}\)

Both Urokinase and rt-PA have been used as IPFT agents and have proven efficacy against placebo, which have been shown in several previous trials. \(^\text{17}-\text{19}\) However, data related to the comparative effectiveness of Urokinase and alteplase is not abundant. Carmen Aleman and colleagues conducted a double blinded RCT in 2015 and compared UK and alteplase's efficacy and adverse effect profile. A total of 99 patients were recruited, of whom 51 received alteplase and 48 UK. Success rates for UK and alteplase at 3 and 6 days were not significantly different, but when only the subgroup of CPE was considered, UK resulted in a high proportion of cures. There were no differences in mortality or surgical need (overall, 3 %). The odds ratio of death comparing alteplase (combining 10 mg and 20 mg groups) with UK at one year was 0.94 (95% CI 0.18 to 4.89). \(^\text{20,21}\) Five (28 %) patients receiving 20 mg of alteplase and 4 (12 %) receiving 10 mg presented severe bleeding events. The author recommended that if intrapleural fibrinolytic are required to be used, UK may be a more effective and safer agent than alteplase in patients with CPE. \(^\text{14}\)

Unlike the trial by Aleman and colleagues, our trial has demonstrated that as compared to UK, the newer fibrinolytic agents like alteplase improved the drainage of infected pleural fluid and
can lead to significant X-ray clearance (approximately 42% of the initial X-ray opacity compared to 33% in UK group) (Table-2).

Bleeding was the most severe adverse effect noticed by Aleman and colleagues. This study was at high risk of bias as several adverse events were identified in the 20 mg alteplase arm, which led to the breaking of the blind after an interim analysis by the drug safety and monitoring committee. The protocol was altered, and the dose of alteplase was reduced to 10 mg daily.20

Similar to the 2015 RCT, our trials also showed severe adverse reactions like bleeding in the newer fibrinolytic, i.e., alteplase group, which was not observed in the patients treated with UK. Two of our patients in the alteplase group developed bleeding in the affected hemithorax after the initial dose of alteplase, which led us to terminate the therapy after one cycle. However, the alteplase was associated with comparable side effect profiles when common side effects were taken into consideration. The odds of fever (20.0% vs. 26.7%) and pain (40% vs. 60%) was low in the alteplase group, but these difference in incidence was not statistically significant between the groups (Table-3). There is no incidence of life-threatening adverse reactions like severe bleeding and hypovolemic shock requiring blood transfusion or severe anaphylactic reaction in any intervention group. This again reiterates that both the drugs are safe when used as IPFT agents.

Our study also demonstrated that the early initiation of fibrinolytic therapy before the development of extensive pleural adhesion might lead to a favorable outcome and more pleural fluid drainage. A 5 year observational study from India reported that more than 75% of the non-responder presented more than six weeks after initiation of symptoms.3 On subgroup analysis, our study showed that 100 % of the patients (n=40), who had received IPFT within six weeks of initiation of symptoms, had shown an excellent radiological clearance, compared to only 60% patients (n=6) among those who presented late, i.e., six weeks after initiation of symptoms. This difference was also statistically significant (P-value 0.001) (Table-4).

Our trial indicates that newer fibrinolytic agents like alteplase may have greater efficacy than UK, as it improves pleural fluid drainage and produces significant radiological clearance. Alteplase has marginally fewer side effects than UK, but the difference is not statistically significant. However, unlike the UK group, a severe adverse reaction like bleeding was seen in the alteplase group. Both the drugs have an excellent safety profile, as none of them were associated with a life-threatening adverse reaction.
Our study has few limitations. One of the limitations of our study was age group. The majority of the patients belonged to the young age group (between 20 to 30), which led to skewing the age distribution graph to the right. However, this was an expected phenomenon as a majority of the clientele of our hospital are young individuals. We administered only a fixed number (2 cycles) and dose of the drugs (UK 1,00,000 IU and alteplase 10 mg) for all the patients, irrespective of the extent and duration of the disease. Patients with extensive disease and those presenting late may require different doses and more cycles to show significant responses. Our study was a small single centre trial and further multicentric trials are necessary to determine the association of varying drug doses with the severity of the disease.

CONCLUSION

Our trial showed that rt-PA (Alteplase) has greater efficacy than and improves drainage and chest clearance when compared with UK. Though alteplase is associated with a higher incidence of bleeding, both the drugs were not associated with any life-threatening adverse event. Early initiation of fibrinolytic therapy before the development of severe loculation leads to better drainage and superior radiological clearance than those who presented late. From the previous studies and our trials, it may be concluded that IPFT is a safe and effective option in managing complicated pleural effusion or empyema, and newer agents like alteplase have greater efficacy and similar adverse effects effect profile when compared with conventional agents like UK.

Statements:

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References:


Table 1: Baseline characteristic of the patients according to the study group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>t-PA</th>
<th>Urokinase</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (no of subjects)</td>
<td>20 (40%)</td>
<td>30 (60%)</td>
</tr>
<tr>
<td>Male sex</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Age in Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Median</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>▪ (IQR)</td>
<td>(21,37)</td>
<td>(19,24)</td>
</tr>
<tr>
<td>% Of hemithorax occupied with pleural fluid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Mean</td>
<td>18.2</td>
<td>14.4</td>
</tr>
<tr>
<td>▪ Std Deviation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase in pleural fluid (IU/L)</td>
<td>2075</td>
<td>1730</td>
</tr>
<tr>
<td>▪ Mean (ml)</td>
<td>795</td>
<td>733</td>
</tr>
<tr>
<td>▪ Std Deviation (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial Volume of fluid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Mean (ml)</td>
<td>1758</td>
<td>1887</td>
</tr>
<tr>
<td>▪ Std deviation (ml)</td>
<td>995</td>
<td>1091</td>
</tr>
<tr>
<td>Duration of symptoms before intervention in weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Median</td>
<td>(1,6)</td>
<td>(3,7)</td>
</tr>
<tr>
<td>▪ (IQR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table-2: Table showing comparison of pleural fluid clearance in both the arms between Urokinase and alteplase

<table>
<thead>
<tr>
<th>Clearance</th>
<th>Drugs</th>
<th>N</th>
<th>Changes of hemithorax area occupied by pleural fluid (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UK</td>
<td>30</td>
<td>-33.00 (±/- 9.9)</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>rt-PA</td>
<td>20</td>
<td>-42.00 (±/- 14.9)</td>
<td></td>
</tr>
</tbody>
</table>

Plus-minus values are mean ± SD
Table-3: showing adverse side effects of both the drugs:

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Urokinase</th>
<th></th>
<th>rt-PA</th>
<th></th>
<th></th>
<th>Total</th>
<th></th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fever</td>
<td></td>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Count</td>
<td>8</td>
<td></td>
<td>18</td>
<td></td>
<td>12</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>% within</td>
<td>26.7%</td>
<td></td>
<td>60.0%</td>
<td></td>
<td>24.0%</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>within</td>
<td>drugs</td>
<td></td>
<td>drugs</td>
<td></td>
<td>drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P-Value</td>
<td>0.74</td>
<td></td>
<td>0.24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table-4: showing comparison between radiological clearance between both the drugs-

<table>
<thead>
<tr>
<th></th>
<th>Clearance type</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good clearance (&gt;20 % of the area on X-Ray)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early intervention</td>
<td>less than 6 weeks</td>
<td>40</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.0%</td>
</tr>
<tr>
<td>Late intervention</td>
<td>more than 6 weeks</td>
<td>6</td>
<td>60.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40.0%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>46</td>
<td>92.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8.0%</td>
</tr>
</tbody>
</table>

Chi-square test with Fischer correction was applied.
There was a significant difference in outcome between less than 6 weeks and more than 6 weeks of duration (Chi-square)