Intrapleural Fibrinolytic Agents for Empyema and Complicated Parapneumonic Effusions*
A Meta-analysis

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**Background:** Randomized controlled trials have shown conflicting findings about the role of intrapleural fibrinolytic therapy for the treatment of empyema and complicated parapneumonic effusions in adult patients.

**Objectives:** To assess the clinical efficacy and summarize the current evidence of intrapleural fibrinolytic use in patients with empyema and complicated parapneumonic effusions in adult patients.

**Methods:** We performed a meta-analysis of all properly randomized trials comparing intrapleural fibrinolytic agents with placebo in adult patients with empyema and complicated parapneumonic effusions. Outcome of primary interest was the reduction of death and surgical intervention.

**Results:** We included five trials totaling 575 patients. The number of enrolled patients for each trial was small, except for the recent trial by Multicenter Intrapleural Sepsis Trial (MIST1) group. Compared with placebo, intrapleural fibrinolytic therapy was associated with a nonsignificant reduction in death and need for surgery (27.6% of the treatment group vs 32.8% of the control group; random-effects pooled risk ratio, 0.55; 95% confidence interval, 0.28 to 1.07; heterogeneity, \( p = 0.023 \)). A separate analysis for outcomes on either death or need for surgery also showed nonsignificant results.

**Conclusion:** Our meta-analysis does not support the routine use of fibrinolytic therapy for all patients who require chest tube drainage for empyema or complicated parapneumonic effusions. However, there was significant heterogeneity of the treatment effects among the trials. Selected patients might benefit from the treatment.

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Key words: empyema; fibrinolysis; pleural effusion

Abbreviations: CI = confidence interval; MIST1 = Multicenter Intrapleural Sepsis Trial; RCT = randomized controlled trial; RR = risk ratio

Learning Objectives: 1. Identify that current available data does not support the routine use of intrapleural fibrinolytic therapy for all patients who require chest tube drainage for empyema or complicated parapneumonic effusions. 2. Assess the significant heterogeneity of treatment effects among the trials. The possibility that selected patients might benefit from fibrinolytic therapy cannot be excluded.

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Empyema and complicated parapneumonic effusions cause considerable morbidity and mortality, with an estimated case-fatality rate of 15%.1 Many patients require surgical intervention to drain the infected pleural space.1,2 The established medical treatment for this pleural infection is systemic antibiotics and the closed chest tube drainage of the infected pleural fluid.3 Intrapleural administration of
fibrinolytic agents such as urokinase and streptokinase has also been widely employed to lyse the fibrinous structures of multiloculated pleural space.4

Previous small trials have suggested the benefits of fibrinolytic agents in terms of reduction of surgical intervention,5 radiologic improvement,6 and effective drainage of infected pleural fluid.7 However, the recent Multicenter Intrapleural Sepsis Trial (MIST1),8 the largest trial to date, revealed no improvements in terms of death, rate of surgery, radiographic outcome, and duration of hospital stay. Consequently, the findings of this trial prompted debate about the role of intrapleural fibrinolysis.9 To clarify the current role of intrapleural administration of fibrinolytic agents for the treatment of empyema and complicated parapneumonic effusions, we performed the first meta-analysis of all properly randomized trials comparing fibrinolytic agents with placebo.

**Materials and Methods**

We performed literature searches to identify all relevant published and unpublished randomized controlled trials (RCTs) comparing intrapleural fibrinolytic agents with placebo for the treatment of pleural infection (empyema and complicated parapneumonic effusions). We searched electronic databases (MEDLINE and EMBASE) from January 1980 to March 2005, and the Cochrane Central Register of Controlled Trials (first quarter 2005), using the terms empyema OR parapneumonic OR pleural effusion OR pleural infection OR intrapleural fibrinolysis OR fibrinolytic OR streptokinase OR urokinase OR tissue plasminogen activator in combination with randomized controlled trial OR controlled clinical trial. We also performed hand search for bibliographies of journal articles and abstracts from major international meetings. We tried to extend our search to any languages of publication and limited our search to studies involved with only human.

Two investigators (Y.T., D.M.) independently evaluated studies for inclusion. The disagreements were referred to a third investigator (G.H.S. or S.M.). Criteria for inclusion were as follows: (1) randomization; (2) allocation concealment; (3) objectively diagnosed empyema or complicated parapneumonic effusions; (4) comparison of fibrinolytic agents with placebo; and (5) objective methods to assess clinical outcomes. We excluded trials for patients who had prior surgical intervention, posttraumatic infection, and trials for children (≥14 years old).

We adopted the criteria for study quality outlined by Schulz et al10 and Eikelboom et al11 in the evaluation for the studies. These criteria include the following: (1) adequate generation of the allocation sequence; (2) adequate concealment of the allocation sequence; (3) blinding of patient and investigator assessing clinical outcomes; and (4) completeness of follow-up.

We chose the reduction in both mortality and the need for thoracic surgery as the primary outcome. The secondary outcomes were the individual components of primary outcome, the duration of the hospital stay, and improvement in chest radiography. We did not consider pleural fluid drainage volume since fibrinolytic itself will increase pleural fluid. We also analyzed side effects of the treatment including adverse reactions. Two investigators (Y.T., D.M.) independently extracted data by study design, study quality, and the outcomes. Where further information was required, we contacted authors of each trial for necessary details.

We used a fixed-effects model unless there was significant heterogeneity, in which case we applied a random-effects model.12 We assessed binary outcomes as risk ratios (RRs) with 95% confidence interval (CI) and continuous outcomes as effect sizes with 95% CI. Pooled estimation was performed using Mantel-Haenszel method for fixed effects model and the DerSimonian and Laird method for random-effects model.13

We conducted sensitivity analysis to identify any trial that may have exerted a disproportionate influence on the summary treatment effect; we deleted trials one at a time. For the Q statistic test for heterogeneity, we used p = 0.10 for statistical significance.

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**Figure 1. Study selection of RCTs.**
Results

Study Selection

Figure 1 outlines the trial flow diagram for study selection. We identified 356 potentially eligible studies. After we selected 50 studies by scanning of the titles and the abstracts, we identified and retained 9 studies for further evaluation. Subsequently, we excluded two studies that used nonrandomization allocation. Furthermore, we excluded additional two studies due to no relevant data (different end point use). Thus, we finally retained a total of 5 RCTs for our meta-analysis.

Study Design

Table 1 summarizes the design of studies included in the meta-analysis. Inclusion criteria of four studies satisfied the definitions of empyema or complicated parapneumonic effusions based on Light. Inclusion criteria for entry to the trial of Davies et al were purulent pleural fluid; pleural fluid Gram stain or culture positive for bacteria; pH of pleural fluid < 7.1; pleural fluid glucose < 40 mg/dL; lactate dehydrogenase > 1,000 IU/L; and multiloculations demonstrated by CT or ultrasound images. In the trial of Bouros et al, patients were included if pleural fluid aspiration revealed an empyema (frank pus) or complicated parapneumonic effusions (pH < 7.0 or pH < 7.2 and evidence of fluid loculation on the chest radiograph or ultrasound images); this trial also included patients with tuberculous pleuritis (n = 3; 7%). In MIST1, inclusion criteria were purulent pleural fluid, positive culture or Gram stain of pleural fluid for bacterial infection, or pH of pleural fluid < 7.2 in patients with clinical evidence of infection; clinical evidence of infection was assessed by the recruiting physician on the basis of the clinical indicators such as fever, an elevated WBC count, and an elevated serum level of C-reactive protein. However, the trial of Bouros et al preferentially selected patients in whom pleural effusion did not resolve with chest tube drainage. Their diagnosis was based on categories 7 and 5 of Light’s classification for empyema and complicated parapneumonic effusions, respectively. However, Bouros et al did not provide explicit criteria as “failure of resolution” with chest tube drainage.

There was difference of the enrollment number and the chest tube size among these five trials. The number of enrolled patients was small in four trials, while the most recent trial (MIST1) enrolled the large number of patients (n = 427) based on multi-institution design. Furthermore, MIST1 used a relatively small-sized chest tube for pleural drainage (median, 12Fr; interquartile range, 12 to 20Fr).

Three trials specified patients with serious illness of limited survival expectation for their exclusion criteria. Davies et al excluded patients with survival at 2 months unlikely. In the trial by Diacon et al, exclusion criteria contained likely survival of < 6 months. MIST1 excluded patients with survival at 3 months unlikely.

Table 1—Design of Trials Included in the Meta-analysis*

<table>
<thead>
<tr>
<th>Trial, Year</th>
<th>Patients Eligibility</th>
<th>Enrolled, No.</th>
<th>Male, %</th>
<th>Mean Age ± SD, yr</th>
<th>Chest Tube Size, Fr</th>
<th>Fibrinolytics</th>
<th>Treatment Dose per Day, IU</th>
<th>Duration, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies et al, 1997</td>
<td>PE or CPE</td>
<td>12</td>
<td>12</td>
<td>75</td>
<td>62 ± 23</td>
<td>60 ± 23</td>
<td>Streptokinase</td>
<td>250,000</td>
</tr>
<tr>
<td>Bouros et al, 1999</td>
<td>PE or CPE</td>
<td>15</td>
<td>16</td>
<td>73</td>
<td>54</td>
<td>57</td>
<td>Urokinase</td>
<td>100,000</td>
</tr>
<tr>
<td>Tuncozgur et al, 2001</td>
<td>PE stage II</td>
<td>24</td>
<td>25</td>
<td>83</td>
<td>34</td>
<td>33</td>
<td>Urokinase</td>
<td>100,000</td>
</tr>
<tr>
<td>Diacon et al, 2004</td>
<td>PE or CPE</td>
<td>22</td>
<td>22</td>
<td>82</td>
<td>40</td>
<td>40</td>
<td>Streptokinase</td>
<td>250,000</td>
</tr>
<tr>
<td>MIST1, 2005</td>
<td>PE or CPE</td>
<td>208</td>
<td>222</td>
<td>67</td>
<td>62</td>
<td>61</td>
<td>Streptokinase</td>
<td>500,000</td>
</tr>
</tbody>
</table>

*TG = treatment group; CG = control group; PE = pleural empyema; CPE = complicated parapneumonic effusion.
†Defined by Light’s classification.15
‡Defined by the American Thoracic Society.19
¶Median values.
||Or until net drainage was <100 mL/d.
¶¶Median (interquartile range).
Study Quality

Table 2 presents the analysis of study quality in these five trials. Four trials provided information about proper concealment of the treatment allocation. Investigators assessing the outcomes were blinded to treatment allocation in four trials, while one trial²⁰ did not provide this information. There were no patient attritions in three trials, whereas two trials, Diacon et al⁵ and MIST1,⁸ reported three patients not available for follow-up at the time of outcome assessment, respectively. Diacon et al⁵ used the intent-to-treat principle for an outcome analysis. In MIST1,⁸ these three patients were included in the analysis of the duration of hospital stay but were excluded from the other analyses.

Decisions for the need of surgical intervention were based on clinical judgment in all trials, although each study provided the criteria of decisions for referral for surgery. In the trials of Davies et al⁶ and Bouros et al⁷, the criteria were progressive or unresponsive (persistent) sepsis syndrome in the presence of a substantial residual pleural fluid collection. The trial of Tuncozgur et al¹⁹ suggested that the decision for surgery was made if a successful response to treatment was not obtained or drainage and expansion were not complete. In the trial of Diacon et al⁵ the criteria were ongoing sepsis syndrome in combination with a substantial residual pleural fluid collection or lack of satisfactory clinical or radiologic improvement beyond 7 days after chest tube insertion. Finally, MIST1⁸ suggested that referral for surgical drainage was made by the recruiting physician on the basis of a substantial residual pleural fluid collection and evidence of persistent infection.

Analysis of Outcomes

Table 3 presents data for death, surgery, and a combination of these two outcomes in each trial. Table 3 also provides a pooled relative risk with Q statistics calculated by combining these outcomes. The pooled relative risk for death was estimated using two trials (Diacon et al⁵ and MIST1⁸), since the other three trials showed no mortality in the fibrinolysis group and the placebo group.

Figure 2 shows data on outcome of mortality and the need for surgical intervention. Four trials suggested a reduction in mortality or the need for surgical intervention by intrapleural fibrinolysis compared with placebo. However, the pooled estimate of

### Table 2—Quality of Trials Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Trial, Year</th>
<th>Concealment of Treatment Allocation</th>
<th>Blinding of Outcome Assessment</th>
<th>Patient Attrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies et al⁶ 1997</td>
<td>Yes</td>
<td>Yes</td>
<td>No attrition</td>
</tr>
<tr>
<td>Bouros et al⁷ 1999</td>
<td>Yes</td>
<td>Yes</td>
<td>No attrition</td>
</tr>
<tr>
<td>Tuncozgur et al⁸ 2001</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No attrition</td>
</tr>
<tr>
<td>Diacon et al⁵ 2004</td>
<td>Yes</td>
<td>Yes</td>
<td>3 (6.8%) unavailable for follow-up*</td>
</tr>
<tr>
<td>MIST1,⁸ 2005</td>
<td>Yes</td>
<td>Yes</td>
<td>3 (1%) unavailable for follow-up†</td>
</tr>
</tbody>
</table>

*Intent-to-treat principle was used for handling of patient attrition.
†These three patients were included in analysis of the duration of hospital stay but excluded from other analyses.

### Table 3—Outcomes of the Individual Trials and Pooled RR*s*

<table>
<thead>
<tr>
<th>Trial, Year</th>
<th>Surgery or Death</th>
<th>Surgery</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fibrinolysis</td>
<td>Placebo</td>
<td>Fibrinolysis</td>
</tr>
<tr>
<td>Davies et al⁶ 1997</td>
<td>0/12 (0)</td>
<td>3/12 (25)</td>
<td>0/12 (0)</td>
</tr>
<tr>
<td>Bouros et al⁷ 1999</td>
<td>2/15 (13.3)</td>
<td>6/16 (37.5)</td>
<td>2/15 (13.3)</td>
</tr>
<tr>
<td>Tuncozgur et al⁸ 2001</td>
<td>7/24 (29.2)</td>
<td>15/25 (60)</td>
<td>7/24 (29.2)</td>
</tr>
<tr>
<td>Diacon et al⁵ 2004</td>
<td>4/22 (18.2)</td>
<td>11/22 (50)</td>
<td>3/22 (13.6)</td>
</tr>
<tr>
<td>MIST1,⁸ 2005</td>
<td>64/206 (31.1)</td>
<td>62/221 (28.1)</td>
<td>32/206 (15.5)</td>
</tr>
</tbody>
</table>

Total | 77/279 (27.6) | 97/296 (32.8) | 44/279 (15.8) | 66/296 (22.3) | 33/279 (11.8) | 31/296 (10.5) |

Pooled RR (95% CI) | 0.55 (0.28–1.07)† | 0.71 (0.28–1.02)† | 1.14 (0.72–1.79)‡ |
Q statistic (p value) | 11.4 (0.023) | 8.60 (0.072) | 0.01 (0.923) |

*Data are presented as No. of patients/total patients (%) unless otherwise indicated.
†Pooled estimation was performed using DerSimonian & Laird method.
‡Pooled estimation was calculated using 2 studies by Diacon et al and MIST1.
RR from all of the five trials was not statistically significant (treatment group, 27.6%; vs control group; 32.8%; RR, 0.55; 95% CI, 0.28 to 1.07). We calculated this estimate using random-effects model since test for heterogeneity Q statistic was 11.4 (4° of freedom) which was statistically significant (p = 0.023).

Likewise, when we separately analyzed the need for surgery (Fig 3), we also noted significant heterogeneity (Q statistic, 8.6; p = 0.072). Therefore, using a random-effects model, we obtained a non-significant treatment effect (treatment group, 15.8%; control group, 22.3%; RR, 0.71; 95% CI, 0.28 to 1.02). We analyzed the pooled estimation for mortality from only two trials since the remaining three trials showed no mortality identified in both groups. Only MIST18 provided subgroup analysis. None of their subgroups showed a benefit in reduction of mortality or the need for surgery in this study.

Three trials provided data for the mean duration of hospital stay with its SD, whereas the recent 2 trials (Diacon et al8 and MIST18) presented only median duration of hospital stay. Consequently, we could not calculate the pooled estimation for this outcome. Moreover, trials used the different criteria for improvement of chest radiography findings. Thus, we could also not perform the analysis for this outcome. No patients experienced side effects in four trials, except in MIST1,8 in which treatment group had serious adverse events in 7% and the control group in 3% (unpaired t test, p = 0.08 by their analysis).8

**Sensitivity Analysis**

Deletion of MIST18 significantly altered the primary outcome. Otherwise, no effect of deleting the other trials was noticed. Estimation of publication bias was not considered, since there were only five trials available for our meta-analysis and the pooled relative risk showed a negative result.

**Discussion**

Our meta-analysis provides no evidence of benefit of intrapleural fibrinolytic therapy for reduction of mortality and the need for surgery in adult patients with empyema and complicated parapneumonic effusions. There was significant heterogeneity of treatment effect on death and the need of surgery among the published trials. Moreover, the small sample-size RCTs suggested the positive benefits, while the recently published large trial with reasonable statistical power, MIST1,8 showed the negative result.

Sensitivity analysis identified a significant effect for reversing the pooled result by removing MIST1.8 There are several potential explanations for the dominance of this trial. First, it was possible that MIST18 had a different study quality. Our analysis of study quality showed that MIST1,8 had a good quality profile in terms of concealment of treatment allocation and blinding of treatment allocation in outcome assessment; the patient attrition of this trial was small (1%). However, referral for surgical drainage was
made by judgment of the recruiting physicians. Thus, there is still concern regarding study quality relating to the absence of management algorithms as standardized protocols.

Second, it was possible that MIST1\(^8\) had a different patient population compared to the other trials. It is common to notice a different treatment effect of a medical intervention when applied to a different study population. However, study inclusion criteria of MIST1\(^8\) were mostly similar to the other trials except for the trial of Bouros et al.\(^7\) Most trials, including MIST1,\(^8\) enrolled patients with objectively diagnosed empyema or complicated parapneumonic effusions. Bouros et al\(^7\) preferentially selected patients in whom pleural effusion did not resolve with chest tube drainage.

Third, MIST1\(^8\) used different intervention settings; streptokinase was mailed to study centers after randomization. This process may have delayed fibrinolytic treatment that might have been potentially effective when used in a timely manner. In addition, MIST1\(^8\) used relatively smaller chest tubes (median, 12F) without ultrasonographic guidance.\(^8\) Intrapleural fibrinolytic therapy leads to lysis of intrapleural fibrin adhesions.\(^21\) However, it does not reduce the viscosity of pleural pus.\(^22\) For effective drainage of highly viscous infective fluid, the placement of larger chest tubes with proper positioning may be required to obtain the benefit of intrapleural fibrinolytic therapy. However, the relative efficacy of using larger chest tubes was not investigated in RCTs.\(^9\)

For the final possible explanation for the dominance of MIST1,\(^8\) decisions for the need of surgical intervention were based on clinical judgment without objective protocols, adding a potential bias across all of the trials. The health-care system of the Great Britain may have limited availability of thoracic surgeons. Thus, variation in indication for surgery may have played a role in study outcome. Moreover, video-assisted thoracoscopic surgery is now being recommended as a well-tolerated procedure for pleural effusions that have failed to resolve with initial fibrinolytic treatment even in early stages of the effusion.\(^23\) Availability of this minimally invasive surgical technique may have influenced the threshold for surgical intervention at different institutions.

The duration for assessing outcomes was provided only in MIST1\(^8\); this length (3 months) may be relatively longer than the other trials to assess mortality. In fact, mortality in both groups in this trial was higher than that of the other trials. Thus, it is possible that this difference could have accounted, at least in part, by using the longer duration for outcome assessment in MIST1.\(^8\)

Inclusion criteria used by the trial of Bouros et al\(^7\) were different for those of the other trials. Bouros et al\(^7\) preferentially selected patients in whom pleural effusion did not resolve with chest tube drainage, although they did not specify explicit criteria in terms of “resolution” with chest tube drainage. In patients with improving clinical and laboratory sepsis markers, the small, residual, and loculated pleural
effusions, which are not drained completely by a chest tube, may be absorbed with antibiotic treatment alone for further follow-up. Therefore, the inclusion criteria used by the trial of Bouros et al7 may partly explain the favorable outcome associated with intrapleural fibrinolysis in their study.

Intrapleural fibrinolytic therapy may still have some roles. Previous studies6,7,20 that were conducted prior to MIST18 indicated that intrapleural fibrinolytic therapy reduced the volume of infected pleural-fluid collections. Therefore, it is still possible that fibrinolytic therapy might provide a benefit for symptomatic patients with a large volume of pleural fluid collection and resistance to chest tube drainage. In addition, the newly available drugs, such as deoxyribonuclease, reducing the viscosity of pleural pus and promote its drainage, may be a candidate for use in combination with fibrinolytic agents22; they may increase the potential effectiveness of these agents. Furthermore, fibrinolytic agents may be attempted in patients with persistent sepsis who are poor candidates for surgical drainage due to serious comorbidities.

RCTs have provided conflicting conclusions about the benefits of fibrinolytic therapy on the duration of the hospital stay. Bouros et al7 and Tuncozgur et al19 reported significant benefit for reducing the duration, whereas Davies et al6, Diacon et al5 and MIST18 reported nonsignificant results. Nevertheless, our meta-analysis could not address this outcome measure since two trials provided the data only as median values.

Our study has several limitations. First, despite analysis from all the available properly randomized trials including MIST1,8 the number of trials and the total number of enrolled patients were still modest. Consequently, our meta-analysis had little statistical power to reliably identify the cause of heterogeneity of the trials using meta-regression analysis, which we did not perform in this study.

Second, in analyzing the need of surgical intervention as a primary outcome measure, we may need to consider the source of bias derived from the use of clinical judgment. The need for surgical intervention was left to individual clinical judgment in these studies. Decisions for the need of surgical intervention may vary among the managing physicians; they may also be different among the trials. Although we aimed to include studies with objective methods to assess clinical outcome, decisions for the need of surgical intervention had the inherent variability of clinical judgment.

Third, meta-analysis is by definition retrospective research that is subject to methodologic deficiencies of the included trials. We attempted to minimize the likelihood of bias by developing a standard protocol before initiating our study, by performing an exhaustive search for trials, and by using an explicit method for study selection, data extraction, and data analysis. In addition, we considered the totality of the randomized evidence by including all properly randomized trials. Even so, the number of the available trials was small, and we identified significant heterogeneity of them.

In conclusion, the currently available data provide no evidence for a benefit of intrapleural fibrinolytic therapy for reducing mortality and the need for surgery of unselected adult patients with empyema and complicated parapneumonic effusion. Our meta-analysis does not support the routine use of fibrinolytic therapy for all patients who require chest tube drainage for empyema or complicated parapneumonic effusions. However, there was significant heterogeneity of the treatment effects among the trials. Selected patients could still have benefit from the treatment. Further evaluation may be needed for the efficacy of fibrinolytic therapy in subgroups with large fluid collection or in combination with a large size chest tube, viscosity-reducing drugs, and video-assisted thoracoscopic surgery.

**References**

11. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip surgery.


