Randomizing patients to surgical versus non-surgical management of pleural infections, can it be done?

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The clinical question

Is it feasible to conduct a phase III randomized control trial that randomizes participants to early surgical (video-assisted thoracoscopic surgery) versus early non-surgical intervention (intrapleural enzyme therapy) for the treatment of non-resolving pleural infections?

AABIP Take home message

Based on the results of MIST-3, it would be feasible to conduct a definitive phase III randomized control trial to compare surgical vs non-surgical treatment for pleural infections that do not resolve with standard medical management alone. Several questions remain unanswered, including the optimal timing of advanced treatment with intrapleural enzyme therapy (IET) or video-assisted thoracoscopic surgery (VATS) after the initial diagnosis of a pleural infection. Given the large proportion of cross-over in the standard care arm to more advanced treatments (IET or VATS), it is reasonable to conduct a phase III trial that does not include a standard care arm for a more direct comparison of these advanced interventions.

Study Background

Despite advancements in therapy, pleural infections in the US and the UK continue to have high rates of 30-day and 1-year mortality. Standard care of pleural infections based on British Thoracic Society guidelines recommend initial treatment with antibiotics and chest tube insertion. However, studies such as the large international multicenter prospective PILOT study have demonstrated a failure rate of 33.5% of cases with chest tube and antibiotics alone. For these cases, the combination of intrapleural enzyme therapy with tissue plasminogen activator (tPA) and DNase, as well as surgical drainage with VATS, are well-established techniques to manage non-resolving pleural infections in adults....

... Specifically, the MIST-2 trial has advanced standard practice by demonstrating clinical benefit and a reduction in hospital length of stay with the use of combined tPA-DNase therapy as compared with placebo. However, due to the lack of supporting evidence, early IET and early surgical drainage with VATS are not recommended by society guidelines.

Study Design

- **Study design:** Multicenter three-arm randomized feasibility trial.
- **Primary outcome:** Feasibility of randomization and treatment compliance.
- **Secondary Outcome(s):** Hospital length of stay, mortality, Hospital Anxiety and Depression Scale (HADS), EuroQol five-dimension health utility index (EQ-5D), and pain score.
- **Intervention(s)**: A total of 60 participants were randomized to
- (1) Standard care per British Thoracic Society treatment guidelines
- (2) Early IET with tPA (10mg twice daily) and DNase (5mg twice daily) for a maximum of 6 doses over 72 hours or
- (3) Early VATS surgical evaluation.

Randomization was stratified by center and baseline RAPID risk scores.

Population

Inclusion criteria: Age >18 years with clinical presentation of pleural infection, a pleural collection with a chest drain in place, and pleural sampling consistent with infection (positive gram stain or culture for bacterial infection or pH<7.2). Patients were eligible for randomization if there was evidence of medical treatment failure after 24-hours of initial drainage as defined by

1. The presence of residual or clinically significant pleural collection and
2. At least one of the following:
    - a) clinical evidence of ongoing sepsis
    - b) serum c-reactive protein that fails to fall by more than 50% peak
    - c) persistently elevated leukocytosis

Exclusion criteria: Resolution of pleural infection within 24 hours of chest tube insertion, previous treatment with tPA or Dnase, major hemorrhage, or major surgery in the previous 5 days.

Baseline characteristics: Out of 178 screened patients, 110 patients met initial eligibility criteria. Of those, 11.8% (n=13) of patients had resolution of pleural infection within 24 hours and were excluded from randomization. Of the remaining 97 eligible participants, 60 were randomized to the three study arms. The majority of participants were male, with ages ranging from 51-74 years.

Outcomes

Primary outcome:

- *Feasibility* was pre-defined as (1) >50% of eligible patients are successfully randomized, (2) >95% of randomized participants are retained to discharge and (3) >80% of randomized participants are retained at 2-week follow up. The results of this study met feasibility criteria with the randomization of 62% of eligible participants, 100% retention rate to hospital discharge and 85% retention at 2-week follow up.
- Overall *treatment compliance* was 47.6% in the standard care arm, 73.6% in the IET arm and 50% in the VATS arm. 11 patients in the standard care arm received IET or VATS due to clinical concern that the patient required further intervention.

Secondary outcomes:

- There was no statistically significant difference in median length of stay, the need for further interventions post-discharge, mortality or HADS score between the three study arms.
- The IET group had a statistically favorable change in mean EQ-5D health utility index score from baseline to 2-months when compared to VATS (p=0.023).
- The IET group had a statistically favorable change in the participant's perception of overall health from baseline to 2 months when compared to standard care (p=0.027).
- There was no difference in pain scores amongst the three study arms, however the IET group had the largest observed improvement in pain score with the highest average pain scores during hospitalizations followed by the lowest pain scores at 2-month follow-up.

Adverse events:

- There was one death associated with post-surgical hemorrhage in the VATS study arm. The most common non-serious adverse event was pain.

Commentary

The key strength of this study is that it is the first randomized control trial that directly compares early IET versus early VATS in the treatment of non-resolving pleural infections. The high randomization rate of 62% of eligible participants demonstrates that patients with pleural infections and clinicians are amenable to early escalation of treatment to more invasive therapies...

...There are several limitations in this study design. While patients were randomized to a specific intervention, there were high rates of treatment non-compliance and cross-over to other interventions, particularly in the VATS and standard care groups. The decision to proceed with surgery was at the discretion of the local surgical team which introduces bias and unmeasured confounders. Sites were also able to reduce dosages of tPA on an individual case basis which may have had an impact on secondary outcomes.

This study was underpowered, which unfortunately resulted in several trends in secondary outcomes with non-significant results. For instance, length of stay was lower in both the VATS and IET groups as compared to the standard care arm, however, due to the low sample size, no significant difference was detected. That said, MIST-3 is still quite informative and suggests that a larger definitive phase III trial comparing early IET versus early VATS in the treatment of pleural infections is feasible, and with sufficient power may yield clinically significant results to inform and advance standard treatment guidelines.

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Suggested reading

1. Corcoran JP, Psallidas I, Gerry S, Piccolo F, Koegelenberg CF, Saba T, et al. Prospective validation of the RAPID clinical risk prediction score in adult patients with pleural infection: the PILOT study. Eur Respir J 2020; 56:2000130.
2. Rahman NM, Maskell NA, West A, Teoh R, Arnold A, Mackinlay C, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection (MIST-2). N Engl J Med 2011; 365:518–526.
3. Roberts ME, Rahman NM, Maskell NA, Bibby AC, Blyth KG, Corcoran JP, et al. British Thoracic Society guideline for pleural disease. Thorax 2023; 78:1143–1156.

Article citation

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