ADAPT-ing the tPA dose for pleural infection: How low can we go?

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The clinical question

Does a starting dose of 2.5mg intrapleural alteplase (tPA) in combination with 5mg deoxyribonuclease (DNase) effectively treat pleural infections?

AABIP take home message

Lower starting dose of tPA at 2.5mg (in combination with usual dose of DNase) appears to safely and effectively treat pleural infections. This warrants further study with direct comparison with usual care (using a starting dose of tPA at 10mg) to assess relative benefit.

Background

MIST-2 demonstrated that intrapleural treatment of tPA (10mg) and DNase (5mg) for pleural infection reduced the frequency of surgical referral and hospital length of stay. A worrisome adverse effect of intrapleural tPA is pleural bleeding, with an overall risk of around 4%. Lower doses of tPA have been associated with lower risk of pleural bleeding; however, evidence for using lower doses of tPA is limited. This trial (ADAPT-2) aims to find whether lower doses of tPA can be effectively used for pleural infections, with the hypothesis that lower doses should also lower risk of pleural bleeding. The ADAPT group demonstrated the safety and effectiveness of using 5mg as the starting dose for intrapleural treatment of pleural infection.

Study Design

Study Design

- **Type of trial:** Multi-center retrospective observational cohort (single arm)
- **N:** 69
- **Study groups:** Adult patients with pleural infection
- **Settings:** Sir Charles Gairdner Hospital (SCGH), Australia; Guy's and St Thomas' Hospital (GSTT), UK
- **Treatment period:** 6/2016-10/2017 at SCGH, 12/2016-10/2017 at GSTT
- **Follow up:** 90 days

- **Primary outcome:** Survival to hospital discharge and without the need for surgical intervention within 90 days following the initial dose of tPA/DNase.
- **Secondary Outcome(s):** tPA dose escalation, hospital length of stay, change in area of hemithorax covered by pleural opacity on chest x-ray from before and 72 hours after the first dose of intrapleural therapy, duration of antibiotic therapy, frequency of adverse events
- **Intervention:** 2.5mg tPA and 5mg DNase as starting doses for intrapleural therapy.

Population

Inclusion criteria
Adult patients admitted with pleural infection. Pleural infection was defined as any of the following: (1) purulent macroscopically; (2) presence of bacteria by Gram staining or microbial culture; and (3) pleural fluid pH ≤ 7.20 and/or glucose ≤ 3.0 mmol/L.

Exclusion criteria
At discretion of treating physician.

Baseline Characteristics
69 patients. 40.6% female, mean age 61 years. 51 patients at SCGH, 18 at GSTT. Majority of pleural infections were community-acquired pneumonia (47.8%) or hospital-acquired pneumonia (13.0%); 13.0% had indwelling pleural catheter related infections. Most patients (76.8%) had at least 1 significant comorbidity. Two-thirds of patients were current or ex-smokers.

Outcomes

Primary outcomes:
- 61 of 69 patients (88.4%) were successfully treated without surgical intervention.
- 2 patients required surgery within 90 days.
- Six patients died during the hospital admission.

Secondary outcomes:
- 17 patients (24.6%) were given higher tPA doses (2 received 5mg, 15 received 10mg). This was done after an average of 3.3 doses of 2.5mg tPA. Dose-escalation was performed to target persistent loculated disease in 12 patients and for persistent infection in 5 patients. 13 of these 17 patients were successfully treated with dose escalation.
- Median hospital length of stay was 8 days [IQR 5-15].
- Median area of hemithorax occupied by pleural opacity decreased from 27.0% [IQR 17.1-44.5] before therapy to 11.0% [IQR 6.4-23.3] ($p < 0.0001$) after 72 hours from initiation of therapy.
- Median volume of pleural fluid drained in the 24 hours prior to starting intrapleural therapy was 183ml [IQR 58-313]. In the 24 hours after therapy, median volume of

output was 980ml [IQR 729-1544]. Median cumulative total of output after 72 hours was 1975ml [IQR 1381-2684].
- As compared to baseline, CRP levels decreased by 22.3% on day 3 and by 45% on day 5 of intrapleural therapy.

Adverse events:
- 2 patients developed a pleural bleed.
- 4 other patients required blood transfusions, though without evidence of pleural bleeding.
- Pain with instillations was reported in 37.7% of patients.

Article critique

Study Strengths

The comorbidity burden in the study population mirrors real-world patient populations, improving the external validity of the study. Also, clinicians were given the option of escalating doses at any time, though most patients did not require dose escalation.

Study Limitations and Potential for Bias
- There was no comparison group, which limits conclusions on how this performs compared to usual doses.
- For the patients who died, most had care withdrawn in the context of advanced illness. It is unclear whether this represents treatment failure of the tPA.
- tPA and DNase were administered differently at the two study sites (administered concurrently at GSTT; administered separately at SCGH).
- These two sites had already completed another study on reduced dose of tPA (5mg in ADAPT). This may affect the applicability to hospitals without such protocols.

Funding

Medical Research Future Fund

Suggested Reading

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5. Aleman C, Porcel JM, Alegre J, Ruiz E, Bielsa S, Andreu J, et al. Intrapleural fibrinolysis with urokinase versus alteplase in complicated parapneumonic pleural effusions and empyemas: a prospective randomized study. Lung. 2015;193(6):993-1000.
6. Lau EPM, Eshragi M, Dootson K, Yeoh C, Ywe Phu W, Gary Lee YC, et al. An international survey on the use of intrapleural tPA/DNase therapy for pleural infection. ERJ Open Res. 2022;8:00590-2021.

Article citation

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