

Intraleural fibrinolytic therapy: How low can we get?

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Pleural infection is a common medical problem with significant mortality and morbidity.¹ Despite advances in antibiotic therapy, the incidence of pleural infection is increasing in the Western world. The management of complicated pleural infections usually involves drainage of pleural effusion from the infected pleural cavity, typically with a pleural drain. When drainage fails, surgery is often required, but is contraindicated in patients who have significant medical comorbidities.

The Second Multicentre Intraleural Sepsis Trial (MIST2) by Rahman et al. showed that intraleural fibrinolytic therapy (IPFT) can improve drainage of pleural infection, resulting in the improvement of chest X-ray (CXR) opacification, shorter hospital length of stay and avoidance of surgery.² Patients in MIST2 were randomised into 4 groups, with the best clinical outcome seen in the group treated with the combination of alteplase and dornase (DNase). In this group, patients were administered 10 mg of alteplase and 5 mg of DNase to break down pleural septations and reduce fluid viscosity. Doses of alteplase and DNase were selected empirically by the investigators and did not undergo escalation studies. Fifty-two patients were randomised to the alteplase/DNase group, of which 48 completed the study. Despite the modest number of patients recruited, the results attracted strong interest and many respiratory units in the world adopted this treatment. Subsequently, Piccolo et al. performed a multicentre cohort study to validate the pragmatic, real-life application of IPFT for pleural infection.³ A total of 107 patients were included, and 92.3% of them did not require surgery. The study revealed survival rates of 97.8% and 91.2% at days 30 and 90, respectively. Significant changes in CXR opacity were also reported. Piccolo et al. concluded that IPFT with alteplase/DNase was an effective and safe option in the management of pleural infection.

Despite the MIST2 trial protocol being practised in units around the world, studies have been performed to improve the administration of IPFT. In this issue of the *Annals*, Yong et al.'s retrospective study of patients who received IPFT

for pleural infection in Tan Tock Seng Hospital is one such study.⁴ This study is among the first to look at treatment success with different starting doses of alteplase, while previous works were cohort studies investigating treatment with fixed de-escalated doses.^{5,6}

Studies investigating lower starting doses of alteplase were performed, as many physicians were concerned of the bleeding risks associated with alteplase. Prior to Yong et al.'s study, 2 cohort studies had been performed, looking at the effects of IPFT with lower starting doses of alteplase at 5 mg and 2.5 mg.^{5,6} The Alteplase Dose Assessment for Pleural Infection Therapy (ADAPT) study by Popowicz et al. was a multicentre study evaluating 61 patients who were prescribed a starting alteplase dose of 5 mg.⁵ Treatment was successful in 93.4%, with improved CXR opacity and avoiding the need for surgery. Popowicz et al. followed up with the ADAPT-2 study performed with 69 patients who were prescribed a starting alteplase dose of 2.5 mg.⁶ Treatment success was seen in 88.4% of patients. The ADAPT studies showed that with lower starting doses of alteplase, successful treatment was still achievable. The difference in the success rates may be due to patient's comorbidities in both studies, rather than the difference in starting alteplase dose. Two patients died in ADAPT; while 6 died in ADAPT-2, 4 of which had metastatic cancers. Apart from the ADAPT studies, a case report by Hart et al. described a patient who was successfully treated with a starting alteplase dose of 1 mg.⁷

Yong et al.'s work is unique, as patients receiving IPFT had different starting doses of alteplase.⁴ Out of 131 cases, only 9.5% received the starting alteplase dose of 10 mg. There were patients who received starting doses lower than that of ADAPT-2; 1.6%, 11.1% and 0.8% received starting doses of 0.5 mg, 1 mg and 1.25 mg, respectively. Majority of patients received starting doses similar to the ADAPT studies with 28.6% and 48.4% receiving starting doses of 2.5 mg and 5 mg, respectively. Yong et al. showed that the starting dose of alteplase did not suggest significant

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difference in the improvement of CXR, with a treatment success of 85.5%. However, the study also showed that those who received a starting dose less than 2.5 mg had significantly longer length of stay compared to those receiving 5 mg and 10 mg. Two statistically significant findings, which were not reported in any of the previous studies, were also noted. First, Yong et al. showed that a 1 unit increase in time of drain insertion to the first dose of IPFT decreases the odds of 3-month survival by 5%. Second, an increase in age by 1 year decreases the odds of 3-month survival by 6%. While these results are interesting, more studies should be performed to validate them.

Although the ADAPT studies and Yong et al.'s work revealed that lower starting doses of alteplase resulted in the successful treatment of pleural infections, there are patients in these studies who were administered with escalated doses of alteplase for their IPFT.^{4,5,6} The decision to escalate alteplase was performed at the discretion of the attending physician in accordance with the treatment response from CXR. In ADAPT, 11.5% of 61 patients received dose escalation while in ADAPT-2, 24.6% of 69 patients did. In Yong et al.'s study, 28.2% of 131 cases received dose escalation. Whether dose escalation in these patients affected the overall treatment success cannot be concluded. Among the 3 studies, only ADAPT reported evaluating treatment success after excluding those who received dose escalation, with a treatment success rate of 89%.⁵

With regard to bleeding risks, pleural bleed from IPFT in various studies ranged from 1.8 to 6.7%.^{2-6,8-10} Patients in these studies were noted to have either an underlying comorbidity that increased bleeding risk or had prior anticoagulant therapy. A retrospective multicentre study by Akulian et al. reported pleural bleeding in 4.1% of 1833 patients, with those on anticoagulation and increasing RAPID scores having a statistically significant higher incident.⁸ The study also reported that there was no difference in bleeding between those who received alteplase at 5 mg and 10 mg. In Yong et al.'s study, the 6.1% of pleural bleed was comparable to previous works. Although it did not report if the dose of alteplase was an independent risk factor for pleural bleeding, patients who received lower starting doses in this study tended to have more comorbidities, especially anaemia, chronic kidney disease and end-stage renal failure. This suggests that a targeted dose regime for alteplase with regard to the patient's comorbidities, rather than the starting dose

of alteplase, determines risk of pleural bleed. Further studies would be necessary to validate this observation.

Other than the starting doses of alteplase, another interesting area of investigation not addressed by Yong et al. was the method of administration of IPFT—concurrent versus sequential administration of alteplase and DNase.^{9,10} In Yong et al.'s study, alteplase in MIST2 was first administered via the pleural drain and the drain was clamped for 40–60 minutes before DNase administration. While the study by Piccolo et al. adopted a similar protocol to MIST2, it was documented that 28% of the patients received concurrent administration of alteplase and DNase, i.e. DNase was administered immediately after alteplase without clamping the tube.³ Subsequently, Majid et al. looked at the effects of the concurrent instillation of alteplase and DNase.⁹ The study revealed that those who received concurrent instillation did not require the full 6 doses and treatment was successful in 90.4% of the patients. A retrospective cohort study by Goh et al. comparing sequential and concurrent administration of alteplase and DNase showed similar success rates for sequential and concurrent administration, with no significant difference in the reduction of CXR opacity and pleural bleeding.¹⁰

Finally, Yong et al. raised some interesting points on future research directions. Prior studies did not consider comparing the differences in CXR clearance with starting doses of alteplase and if this could be used as one of the predictors for treatment success. Yong et al. also suggested other factors that may affect survival that warrants further research, such as the timing of administration of the first dose of IPFT and patient demographics such as age.

IPFT undoubtedly plays an important role in the treatment of pleural infections. IPFT recommendation has been included in guidelines, such as the British Thoracic Society Guideline.¹ However, the optimal IPFT regime remains to be determined. While we wait for further studies on these treatment parameters, we will have to rely on current evidence for the starting dose of alteplase.

Declaration

All authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

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