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It is reasonable to recommended intrapleural alteplase for loculated pleural effusions

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ABSTRACT A critical appraisal and clinical application of Thommi G, Shehan J, Robison K, Christensen M, Backemeyer L, McLeay M. A double blind randomized cross over trial comparing rate of decortication and efficacy of intrapleural instillation of alteplase vs placebo in patients with empyemas and complicated parapneumonic effusions. *Respir Med*. 2012;17(2):716-723. doi: 10.1016/j.rmed.2012.02.005

Keywords: alteplase, pleural effusion, empyema

Clinical Context

A 46-year-old male with stage 4 adenocarcinoma of the lung and malignant effusion, managed with intrapleural catheter, was admitted for treatment of catheter-related infection of his effusion. Due to concerns about the cuff of the catheter acting as a reservoir for infectious agents, as well as patient complaints of pain at the catheter site, the catheter was removed. IV antibiotics were administered and the patient was advised to have a pigtail catheter placed to drain the infected intrapleural fluid. However, the patient feared pain regarding the pigtail catheter insertion and desired to be discharged home on IV antibiotics. By the time the patient agreed to catheter placement on day seven of admission, the fluid had developed many loculations and little fluid could be drained. Due to the patient's stable clinical picture and his strong desire to return to his family, it was decided that the pigtail catheter be removed and to discharge him home on IV nafcillin with instructions to monitor temperatures and return if fever recurred. The patient was so intent upon discharge that further interventions were not given much consideration. However, his case raises the question of whether administration of thrombolytics through the catheter could have broken down the loculations and allowed for resolution of the complicated pleural effusion prior to discharge.

Clinical Question

Does administration of intrapleural thrombolytics lead to better resolution of a loculated effusion compared to simple drainage with standard medical therapy?

Research Article

Thommi G, Shehan J, Robison K, Christensen M, Backemeyer L, McLeay M. A double blind randomized cross over trial comparing rate of decortication and efficacy of intrapleural instillation of alteplase vs placebo in patients with empyemas and complicated parapneumonic effusions. *Respir Med*. 2012;17(2):716-723. doi: <u>10.1016/j.rmed.2012.02.005</u>.

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Literature Review

The relevant literature was found via PubMed and UpToDate searches with the search terms "loculated pleural effusion" and "intrapleural thrombolytics." These studies are split between one large trial (N = 454) that concludes that thrombolytics should not be used in the treatment of pleural effusion¹ and several smaller studies ($N \le 100$) in favor of the use of thrombolytics in the treatment of pleural effusion²⁻¹⁰. There are also three meta-analyses of the randomized, placebo-controlled trials written on this topic, all of which conclude that intrapleural thrombolytics likely reduce the need for surgical intervention in some patients, but that the data are heterogenous¹¹⁻¹³.

The large study whose conclusions advise against the use of thrombolytics is a double-blind trial in which 454 patients with pleural infection were randomly sorted to receive either intrapleural streptokinase or placebo. The primary end point, the number of patients who died or ended up needing surgical drainage after three months, was found to be comparable between the two groups, with a relative risk of 1.14 (95% CI 0.85 to 1.54; p = 0.43). However, the inclusion criteria for the study—any patient with evidence of infected pleural effusion—did not sufficiently narrow down the subject pool to those who were ideal candidates for thrombolytic therapy. The main rationale for the use of thrombolysis in this context is to break down septations or loculations that prevent free flow of fluid through the catheter. By including patients in the study regardless of evidence of blockage or loculation, the authors may have diluted the trial with patients who were not legitimate candidates for the therapy under study, rendering the trial incapable of detecting the true effect of thrombolytics in patients who could benefit from them. At the request of peer reviewers, as noted by the authors, a post-hoc analysis of patients both with and without baseline radiographic evidence of loculation was performed, which likewise concluded that there was no difference between the treatment and placebo arms¹⁴. However, the trial was clearly not designed for this analysis, and it resulted in the researchers using a poor imaging modality to assess for loculation. Instead of more suitable modalities, such as thoracic ultrasound or computed tomographic (CT) scanning, investigators were forced to rely on baseline frontal radiographs, which are unsuited to characterizing the features of pleural effusions¹⁵. Additionally, there were only 84 patients with loculations in both groups combined, suggesting that the subgroup was underpowered to find a difference if one existed. This detracts from the validity of the subgrouping and, by extension, the value of the post-hoc analysis.

Of the nine studies that support the use of thrombolytic therapy, five had no control arm; two were retrospective reviews of cases of intrapleural alteplase treatment²⁻³; two were single-arm prospective studies of similar cases⁴⁻⁵; one was a randomized trial comparing the efficacies of intrapleural streptokinase and intrapleural urokinase, without a control group⁶; two were single-center, randomized, placebo-controlled trials, using inclusion criteria that were too broad for this situation (patients were grouped together if they had either empyema or a complicated parapneumonic effusion, and only a subset of these patients had loculations)²⁻⁸; and the remaining two papers were both double-blind, randomized studies that included patients who had been diagnosed with multiloculated pleural effusions based on ultrasound and/or CT evidence⁹⁻¹⁰. Both of these last studies also required participants to have failed simple tube drainage, which may indicate a blockage of free flow. The larger of the two, $N = 100^9$ (versus $N = 31^{10}$), was selected for appraisal. This paper had only two patients with malignant parapneumonic pleural effusions, which underrepresents our patient. However, due to the lack of large randomized, controlled trials of intrapleural thrombolytics for patients with loculated malignant effusions, it was reasonable to approach our patient's loculated effusion similarly to loculated effusions caused by infectious processes.

Critical Appraisal

The study being examined is a double blind randomized trial with two treatment arms. In the first arm of the trial, randomlyassigned patients underwent three days of daily treatment with either intrapleural alteplase or placebo. Adequate response to treatment was evaluated by improvement on chest CT, though the major outcome variable was a reduction in surgical intervention. Subjects were determined to have failed treatment if pleural fluid had not decreased by 50% by the fourth day. Patients who did not respond were offered the opportunity to cross over into the second arm of the study, in which they would receive three days of the other treatment. Again, response was assessed by CT scan, using the same criterion of 50% resolution. Treatment was deemed successful if the effusions resolved and did not recur within six weeks (as determined by chest radiograph), thus eliminating the need for surgical intervention. Patients were included in the study if they had either empyema (either pH < 7 OR pleural culture positive OR frank pus noted) or a complicated parapneumonic effusion (both exudate AND CT scan and ultrasound showed multiple loculations with a pneumonic process) and had failed to resolve their effusions with chest tube drainage and standard medical therapy. Patients with empyema and complicated parapneumonic effusion (CPE) underwent the same study but were analyzed in separate groupings. This allowed for isolated consideration of patients with loculations, as opposed to the larger study from the literature review. Patients were excluded if they were at increased risk for various bleeding complications, were below the age of 18, or were pregnant.

Overall, adding across the two arms, 58/61 treatments (26 cross over) with alteplase were successful, versus 4/34 treatments (one cross over) with placebo (p < 0.001). Considering only the patients with loculated pleural effusions, 42/45 treatments (22 cross over) with alteplase were successful, versus 4/29 treatments (one cross over) with placebo (p < 0.001).

Strengths of this study include the fact that, since this was a cross over study, some patients were able to serve as their own controls, thus reducing the opportunity for confounding. Also, the double-blinded nature of the study ensured that bias was not introduced into the study by the prior knowledge of the patients, physicians, or investigators. This includes the primary investigator, who read all chest radiographs and CT scans blindly. Weaknesses include the fact that this cross over study lacks uniformity within sequence by design; if patients clear their effusions in the first arm of the trial, they cannot cross over to receive the other treatment. This detracts from the ability of patients to serve as their own controls. There is also the inherent cross over study issue of the "wash-out period"—patients who failed initial treatment were crossed over the day after completion of the first arm, which may have allowed the placebo and alteplase treatments to affect each other. Although there is little concern for residual placebo affecting a subsequent alteplase treatment, it was possible for patients crossing from alteplase treatment to placebo treatment to have falsely elevated responses to the placebo as a result of insufficient clearance of the drug. The absolute size effect of efficacy for alteplase compared to placebo indicates the active treatment provided benefit. Finally, any study is limited by the population studied—in this case, participants tended to be older adults (age mean 64 ± 15), as well as predominately male (male to female ratio 37:21). This makes it more difficult to generalize the findings of this study to other demographics.

This double blind randomized trial meets criteria for level 1b evidence according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence.

Based on the response ratios above, the number needed to treat (NNT) in the case of loculated effusions is 1.26, meaning that more than half of treated patients will see better outcomes on alteplase treatment versus a placebo control. For a calculation of a number needed to harm, it is best to look at the major adverse event associated with thrombolytic therapy, which is hemorrhage. In the treatment arm, two patients experienced bleeding during alteplase treatment, one of whom was removed from the trial, presumably to avoid further complications (both patients required transfusions; neither patient died). Therefore, among the total number of patients treated, this gives a rate of bleeding of 2/62. The number needed to harm (NNH) for bleeding = 31.

Clinical Application

When conveying this information to patients with loculated pleural effusions, it is important to note that this trial only applies to patients whose effusions were infectious in nature. In the patient described above, his pleural effusion was malignant in origin, so the conclusions of the paper must be extrapolated with caution. Patients should be told that, according to this study, the treatment is highly effective at resolving effusions, with a small risk of significant bleeding that may require transfusion. However, this is one study in a somewhat contested area of medicine, and patients should know that the collected evidence is not of the highest caliber. In addition, patients should be informed that the major alternative to this management is surgical debridement of the loculated effusion. Depending on how amenable patients are to surgery versus a more experimental but less invasive treatment, they may choose one option or the other.

In the case of the patient in the Clinical Context, several factors contributed to pursuing antibiotic treatment versus more aggressive drainage interventions, chief among them being the patient's wishes in the face of a short life-expectancy. This patient had spent much of the previous two months admitted to the hospital due to complications from his stage 4 adenocarcinoma. Allowing him to return home to his family on antibiotics was a quality of life decision as opposed to a purely medical one. However, this decision was not without its cost—an

increased risk of sepsis, possible expansion of the effusion, cumbersome temperature monitoring, and extended home IV antibiotic treatments were all negative consequences. If circumstances had been slightly different, it might have been of benefit to this patient to stay a few more days in the hospital and receive alteplase treatment before discharge.

In order to learn more and further help future patients, it will be necessary to conduct more randomized controlled trials, specifically for malignant effusions. Such trials may require collaboration across multiple treatment centers in order to recruit enough patients. In doing this, it may be possible to establish intrapleural alteplase as a way to resolve loculated malignant effusions more effectively and rapidly, thus ensuring greater patient safety and decreased length of stay.

Take-home points

- 1.) Intrapleural alteplase infusion is probably an effective and relatively safe treatment for loculated pleural effusions
- 2.) Large studies are most applicable if their inclusion criteria capture a clinically significant patient population
- 3.) Every decision should weigh the evidence with the patient's wishes and quality of life

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