CRITICAL CARE

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New strategies to manage complicated pleural effusions

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Expanded abstract

Citation

Rahman NM, Maskell NA, West A, Teoh R, Arnold A, Mackinlay C, Peckham D, Davies CW, Ali N, Kinnear W, Bentley A, Kahan BC, Wrightson JM, Davies HE, Hooper CE, Lee YC, Hedley EL, Crosthwaite N, Choo L, Helm EJ, Gleeson FV, Nunn AJ, Davies RJ: *N Engl J Me*d 2011, **365:**518-26. PMID: 21830966, available on www.pubmed.gov

Background

More than 30% of patients with pleural infection either die or require surgery. Drainage of infected fluid is the key to successful treatment, but intrapleural fibrinolytic therapy did not improve outcomes in an earlier, large, randomized trial therapy (Multicenter Intrapleural Sepsis Trial [MIST1]).

Methods

Objective: To evaluate the efficacy and safety of intrapleural DNase alone, alteplase alone, or the combination of both, to improve pleural drainage.

Design: Multicenter, double-blind, double-dummy, 2x2 factorial randomized trial.

Setting: Eleven centers in the United Kingdom (UK).

Subjects: Adult patients (mean age 59 years, 72% men), who had clinical evidence of infection, and pleural fluid that had macroscopic purulence, a positive culture or Gram stain for bacteria, or a pH < 7.2.

Intervention: Patients were assigned to 1 of the 4 study interventions for 3 days: double placebo, intrapleural tissue plasminogen activator (t-PA) and DNase, t-PA and placebo, or DNase and placebo.

Outcomes: The primary outcome was the change in pleural opacity, measured as the percentage of the hemithorax occupied by effusion, on chest radiography on day 7 as compared with day 1. Secondary outcomes included referral for surgery, duration of hospital stay, and adverse events.

Results

The mean (±SD) change in pleural opacity was greater in the t-PA–DNase group than in the placebo group (−29.5 ± 23.3% vs. −17.2 ± 19.6%; difference, −7.9%; 95% confidence interval [CI], −13.4 to −2.4; P = 0.005). The change observed with t-PA alone and with DNase alone (−17.2 ± 24.3 and −14.7 ± 16.4%, respectively) was not significantly different from that observed with placebo. The frequency of surgical referral at 3 months was lower in the t-PA–DNase group than in the placebo group (2 of 48 patients [4%] vs. 8 of 51 patients [16%]; odds ratio for surgical referral, 0.17; 95% CI, 0.03 to 0.87; P = 0.03) but was greater in the DNase group (18 of 46 patients [39%]) than in the placebo group (odds ratio, 3.56; 95% CI, 1.30 to 9.75; P = 0.01). Combined t-PA–DNase therapy was associated with a reduction in the hospital stay, as compared with placebo (difference, −6.7 days; 95% CI, −12.0 to −1.9; P = 0.006). Hospital stay with either agent alone was not significantly different from that with placebo. The frequency of adverse events did not differ significantly among the groups.

Conclusions

Intrapleural t-PA–DNase therapy improved fluid drainage in patients with pleural infection and reduced the frequency of surgical referral and the duration of hospital stay. Treatment with DNase alone or t-PA alone was ineffective.

Commentary

More than 65,000 cases of pleural infection occur in the United States and United Kingdom each year [1], and the incidence is increasing in both children and adults [2]. Both community and hospital acquired bacterial pneumonia are complicated by pleural infections [3]. Despite the advances in therapeutic strategies, pleural infections are associated with high mortality rates of 10-20% [4].

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There are several classifications of pleural effusions based on evolution (exudative, fibrinoproliferative with evidence of loculation, and formation of fibrous peel) and fluid characteristics (clear, viscous, or pus). Drainage alone is usually adequate for an uncomplicated effusion. However, drainage is often insufficient for patients with pleural infection who have a complicated effusion with increased viscosity and loculation [5]. The standard management of pleural infections consists of antibiotics and draining the infected pleural fluid [6]. However, more than 30% of patients fail standard therapy and require surgical referral. These patients incur a longer duration of hospital stay of 12-15 days and increased utilization of healthcare resources [4].

Observational data suggest that using fibrinolytic drugs in the intrapleural space can decrease the failure rate, reduce surgical referral, and improve chest tube drainage by cleaving intrapleural fibrinous septations [7,8]. This theory was tested by many randomized controlled trials using different fibrinolytics, but failed to improve clinically meaningful end points [9]. Most notably, the 454 patients in the Multicenter Intrapleural Sepsis Trial (MIST1) showed no benefit from intrapleural streptokinase. However, the absence of benefit was felt possibly due to the presence of free extracellular deoxyribonucleic acid (DNA) and other bacterial components in the pleural space, which increase fluid viscosity and hinder fibrinolysis [8]. Adding DNase to cleave the free DNA may reduce fluid viscosity and permit pleural clearance by fibrinolytic drugs [10].

To test this hypothesis, the second multicenter trial (MIST2) by Rahman and colleagues was conducted at 11 centers in the UK. In this randomized trial, the authors used a different intrapleural fibrinolytic agent (t-PA rather than streptokinase) and added DNase for cleavage of free DNA. The authors conducted a standard factorial study analysis and found a significant interaction between t-PA and DNase with regard to the primary outcome. They therefore compared each of the three intervention groups to placebo.

The t-PA-DNase combination was significantly superior to placebo and each drug alone in improving the changes in opacity on chest x-ray on day 7 vs. day 1 (primary end point), decreasing the number of surgical referrals at 3 and 12 months (4% vs. 14%), and decreasing the days of hospitalizations by 6.7 days. However, monotherapy with either t-PA or DNase showed no benefit when compared to placebo, and DNase alone resulted in an increase in surgical referrals and hospitalization days compared to placebo.

Strengths of this trial include: a well-defined study protocol, multicenter, randomized, double-blind, double-dummy design, and complete follow-up. There are a few limitations. First, although only 3 serious adverse events with pulmonary bleeding (intrapleural hemorrhage, hemoptysis) occurred, all three were in the t-PA-DNase group (n = 52). Future use of this drug combination should carefully monitor for pulmonary bleeding. Second, the primary end point was the absolute change in chest x-ray opacity. However, the trial was powered to detect a slightly different endpoint, the proportion of patients who had a 50% relative reduction in opacity. Nevertheless, the overall results were striking, with only one patient in the t-PA-DNase arm not achieving any opacification reduction, compared to several patients in the other arms. Additionally, there was reduction in the number of surgical referrals, a patient-centered endpoint.

Recommendation

Rahman and colleagues should be commended for demonstrating that dual intrapleural therapy with t-PA and DNase in patients with pleural infection improved changes in opacity on chest x-ray and reduced need for surgical intervention and hospital stay. Although larger trials are needed to replicate these results, dual intrapleural therapy may be a useful option, especially for patients who are high-risk for surgery.

Competing interests

The authors declare that they have no competing interests.

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