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U.K. Controlled Trial of Intrapleural Streptokinase for Pleural Infection

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ABSTRACT

BACKGROUND

Intrapleural fibrinolytic agents are used in the drainage of infected pleural-fluid collections. This use is based on small trials that did not have the statistical power to evaluate accurately important clinical outcomes, including safety. We conducted a trial to clarify the therapeutic role of intrapleural streptokinase.

METHODS

In this double-blind trial, 454 patients with pleural infection (defined by the presence of purulent pleural fluid or pleural fluid with a pH below 7.2 with signs of infection or by proven bacterial invasion of the pleural space) were randomly assigned to receive either intrapleural streptokinase (250,000 IU twice daily for three days) or placebo. Patients received antibiotics and underwent chest-tube drainage, surgery, and other treatment as part of routine care. The number of patients in the two groups who had died or needed surgical drainage at three months was compared (the primary end point); secondary end points were the rates of death and of surgery (analyzed separately), the radiographic outcome, and the length of the hospital stay.

RESULTS

The groups were well matched at baseline. Among the 427 patients who received streptokinase or placebo, there was no significant difference between the groups in the proportion of patients who died or needed surgery (with streptokinase: 64 of 206 patients [31 percent]; with placebo: 60 of 221 [27 percent]; relative risk, 1.14 [95 percent confidence interval, 0.85 to 1.54; P=0.43), a result that excluded a clinically significant benefit of streptokinase. There was no benefit to streptokinase in terms of mortality, rate of surgery, radiographic outcomes, or length of the hospital stay. Serious adverse events (chest pain, fever, or allergy) were more common with streptokinase (7 percent, vs. 3 percent with placebo; relative risk, 2.49 [95 percent confidence interval, 0.98 to 6.36]; P=0.08).

CONCLUSIONS

The intrapleural administration of streptokinase does not improve mortality, the rate of surgery, or the length of the hospital stay among patients with pleural infection.

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Pleural infection develops in about 65,000 patients each year in the United States and the United Kingdom.[1] Approximately 15 percent of patients die,[2] which is similar to the death rate among patients hospitalized with pneumonia,[3,4] and 15 to 40 percent require surgical drainage of the infected pleural space.[2,5] The median duration of inpatient care is 15 days, with 20 percent of patients remaining in the hospital for a month or longer.[2]

Apart from antibiotic therapy, treatment in patients with pleural infection consists mainly of drainage of the infected pleural fluid, and the intrapleural administration of fibrinolytic drugs is widely used in an attempt to reduce the need for surgery to achieve this drainage. Such therapy is intended to lyse the fibrinous septations within infected pleural-fluid collections and is supported by management guidelines.[6,7] Small trials[8-12] and case series[13] have suggested that these agents improve drainage of pleural fluid, as quantified radiographically, and may also reduce the need for surgery,[12] with few adverse effects. These studies have had low statistical power,[14] however, and have therefore been unable to assess accurately whether these benefits translate into a reduction in mortality or in the frequency with which patients require surgical drainage.

We report the results of the First Multicenter Intrapleural Sepsis Trial (MIST1), which was funded by the U.K. Medical Research Council and supported by the British Thoracic Society. The aim of this trial was to define the role of intrapleural streptokinase in the treatment of pleural infection. The primary end point was the proportion of patients who died or required surgical drainage for pleural infection when treated with intrapleural streptokinase or matching placebo, given as an adjunct to normal care. Secondary end points included mortality and the frequency of surgery, analyzed separately, the length of the hospital stay, the proportion of patients with improvement on chest radiography, and dynamic lung volumes.

METHODS

STUDY DESIGN

This study was a double-blind, randomized trial performed in 52 centers in the United Kingdom that together make up the MIST1 Group. This group includes 27 teaching hospitals and 25 local hospitals; 18 of the centers had on-site facilities for thoracic surgery.

INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria for the trial were the presence of pleural fluid that was macroscopically purulent, that was positive on culture for bacterial infection, that was positive for bacteria on Gram's staining, or that had a pH below 7.2 in a patient with clinical evidence of infection. Evidence of infection was assessed by the recruiting physician on the basis of clinical indicators such as fever, an elevated white-cell count, and an elevated serum level of C-reactive protein. Further details of the inclusion and exclusion criteria appear in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

CHEST-TUBE DRAINAGE AND ANTIBIOTIC THERAPY

All patients underwent chest-tube drainage and received intravenous antibiotics. Antibiotics were chosen by the managing clinician (usually the principal investigator at the medical center), in line with local microbiologic advice. Recommended regimens were listed in the protocol (see the Supplementary Appendix).

RANDOMIZATION

The randomization code was prepared and held centrally by the trial statistician. After written informed consent was obtained, patients were randomly assigned to treatment groups by means of a telephone call to the study center. Subjects received either 250,000 IU of streptokinase (Streptase, Aventis) or a matching placebo, both administered in 30 ml of normal saline delivered into the pleural space through the chest tube every 12 hours for six doses (for details, see the Supplementary Appendix).

PRIMARY END POINT

The primary outcome studied was the number of patients who died or required surgical drainage of the infected pleural fluid during the three months after randomization. Referral for surgical drainage was made by the recruiting physician on the basis of a substantial residual pleural-fluid collection and evidence of persistent infection (e.g., fever or a persistent, marked elevation in the blood white-cell count or serum C-reactive protein level). Insertion,

reinsertion, and repositioning of the chest tube were not classified as surgery when the end point was analyzed.

SECONDARY END POINTS

The secondary end points were the rate of death or surgical drainage 12 months after randomization; the rates of death and surgery, analyzed separately, at 3 and 12 months; the duration of the hospital stay; the severity of any residual abnormality on the chest radiograph 3 months after randomization; dynamic lung volumes 3 months after randomization; bleeding after surgery to drain empyema; and changes in the levels of antistreptokinase antibody from baseline to 3 months. Detailed definitions of these secondary end points are available in the Supplementary Appendix.

STATISTICAL ANALYSIS

A written analysis plan was prepared before the data were analyzed, and the analysis was performed in the Medical Research Council Clinical Trials Unit. It was decided before the data were analyzed that subjects who did not receive the assigned study drug because of death, surgery, or withdrawal of consent before the study drug arrived at their hospitals would be excluded from the primary analysis. The primary analysis was repeated with all subjects included. Outcomes were compared with use of relative risks (with Taylor series 95 percent confidence intervals), the Yates' corrected chi-square test, the unpaired t-test, the Mann–Whitney test, or analysis of variance, depending on whether the data were normally distributed (the data were analyzed with the use of Stata software, version 8[15]). The power calculations assumed an event rate of 30 percent with placebo and a reduction of this rate by 40 percent, to 18 percent, with intrapleural streptokinase; 450 patients were required for analysis, with an alpha value of 0.05, a power of 80 percent, and a 5 percent rate of noncompliance. Further details of the data analysis and power calculation are available in the Supplementary Appendix.

Aventis UK provided the streptokinase and placebo for the trial. The United Kingdom Medical Research Council provided funding for the trial. The British Thoracic Society promoted the trial. Neither the company nor these organizations had any influence on the design or execution of the trial or on decisions relating to publication.

RESULTS

PATIENTS

The demographic and clinical characteristics of the patients as recorded at baseline are shown in Table 1. Figure 1 shows the enrollment, assignment, and follow-up of the patients in the study. Three patients (1 percent) were lost to follow-up at three months — a lower rate than the 10 percent originally estimated. Recruitment was therefore halted when the number of patients for whom data could be analyzed reached the required size of 454. Twenty-four patients died, required surgery, or withdrew consent to the trial before receiving the study drug. Thus, the main analysis included 430 subjects (208 of whom received streptokinase, and 222 placebo). Follow-up for the primary outcome analysis was complete for 427 of these patients (99 percent). Fifty-four patients did not receive all six doses of the study drug. Most of these patients ceased to receive the assigned treatment because of an adverse event or because the chest tube became displaced at a time when residual pleural fluid was minimal, so that further chest drainage was not necessary.

Data on the duration of the hospital stay were available for all 430 subjects, and radiographic data were available for 373 patients (86.7 percent) at three months. Baseline data on dynamic lung volumes were available for only 70 patients (16 percent), since most patients were too ill for this assessment to be performed. It was thought that this small sample would not be representative, and these data were therefore not analyzed. Dynamic lung volumes were available for 249 patients (58 percent) at three months, and these results were analyzed.

The characteristics of the two study groups were similar, and the bacteriologic results were typical of pathogens isolated from patients with empyema in the United Kingdom (Table 1). These characteristics were also similar in the subgroups of patients for whom data on radiographic outcomes and lung function were available.

STUDY DRUGS

Independent assays of three study-drug vials expected to contain 250,000 IU of streptokinase confirmed that they contained the expected amounts (263,000 IU, 256,000 IU, and 298,000 IU); three placebo vials contained no active drug. In vitro assays confirmed high levels of fibrinolytic activity in

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Variable	Streptokinase (N=208)	Placebo (N=222)
Demographic and clinical characteristics		
Sex — no.		
Male	139	160
Female	69	62
Age — yr	60±18	61±18
Side with empyema — no. (%)		
Right	105 (60)	109 (55)
Left	71 (40)	88 (45)
Duration of symptoms before randomization — days		
Median	14	15
Interquartile range	8–28	8–28
Concurrent heparin or warfarin therapy at randomization — no. (%)	20 (10)	23 (10)
Portion of hemithorax opacified by pleural effusion on chest radiograph — %		
Median	40	35
Interquartile range	20–60	20–60
Chest-tube bore at randomization — French		
Median	12	12
Interquartile range	12–20	12–16
Coexisting illness — no. (%)†	135 (65)	159 (72)
Cardiac disease	49 (24)	67 (30)
Respiratory disease	30 (14)	52 (23)
Diabetes mellitus	22 (11)	22 (10)
Excess alcohol intake	22 (11)	19 (9)
Joint disease	17 (8)	23 (10)
Gastroesophageal disease	12 (6)	22 (10)
Neurologic disease	18 (9)	15 (7)
Kidney disease	13 (6)	7 (3)
Liver disease	8 (4)	10 (5)
Other	37 (18)	31 (14)
Thoracic-surgery facilities on site at the patient's hospital — no. (%)	109 (52)	112 (50)
Pleural-fluid characteristics		
Visibly purulent — no. (%)	170 (82)	185 (83)
Gram-positive for bacteria — no. (%)	43 (21)	45 (20)
Culture-positive for bacteria — no. (%)	34 (16)	30 (14)
pH in patients without frankly purulent fluid	6.8±0.4	6.8±0.5
Lactate dehydrogenase — IU/liter		
Median	7609	4439
Interquartile range	1862–23,010	1044–14,458

the study vials containing streptokinase and no fibrinolytic activity in the vials of placebo.

ADVERSE EVENTS

There was an excess rate of serious adverse events in the streptokinase group. Fourteen patients receiving streptokinase (7 percent) had such events, as compared with six (3 percent) in the placebo group (relative risk, 2.49 [95 percent confidence interval, 0.98 to 6.36]; P=0.08) (Table 2). No patients had more than one adverse event.

PRIMARY END POINT

There was no statistically or clinically significant difference between the groups in the proportion of patients who required surgical drainage or who

Table 1. (Continued.)

Variable	Streptokinase (N=208)	Placebo (N=222)
Microbiologic characteristics‡		
Positive blood culture — no. (%)	22 (13)	28 (16)
Positive pleural-fluid culture — no. (%)	121 (61)	111 (53)
Bacteria isolated from blood or pleural fluid — no. (%)§		
Streptococcus milleri group (*S. intermedius, S. constellatus, S. mitis*)	35 (12)	32 (11)
S. pneumoniae	14 (5)	22 (8)
Other streptococci	18 (6)	13 (5)
Enterobacteriaceae	18 (6)	22 (8)
Anaerobic bacteria	20 (7)	15 (5)
Staphylococcus aureus		
Antibiotic-sensitive	13 (5)	14 (5)
Methicillin-resistant	12 (4)	11 (4)
Enterococci	4 (1)	7 (2)
Other	7 (2)	10 (3)
Indexes of disease severity		
Systolic blood pressure — mm Hg		
Median	125	120
Interquartile range	110–137	110–136
Diastolic blood pressure — mm Hg		
Median	70	70
Interquartile range	60–80	60–76
Total white-cell count — $\times 10^9$/mm^3		
Median	14.1	13.8
Interquartile range	10.3–20.0	9.8–19.5
Blood urea nitrogen — mmol/liter¶		
Median	5.1	5.3
Interquartile range	3.6–8.5	4.0–7.9
Blood albumin — g/liter		
Median	27	28
Interquartile range	22–31	23–33
Cause of pleural infection		
Community-acquired infection — no. (%)		
Primary empyema	15 (7)	11 (5)
Secondary to pneumonia	166 (80)	173 (78)
Hospital-acquired infection — no. (%)		
Secondary to hospital-acquired pneumonia	12 (6)	18 (8)
Iatrogenic	5 (2)	5 (2)
Unknown	3 (1)	3 (1)

* Plus–minus values are means ±SD. Percentages are of patients for whom data were available.
† Patients may have had more than one coexisting illness.
‡ Patients whose cultures were negative are not included.
§ Patients may have had more than one type of bacteria isolated.
¶ To convert values to milligrams per deciliter, divide by 0.357.

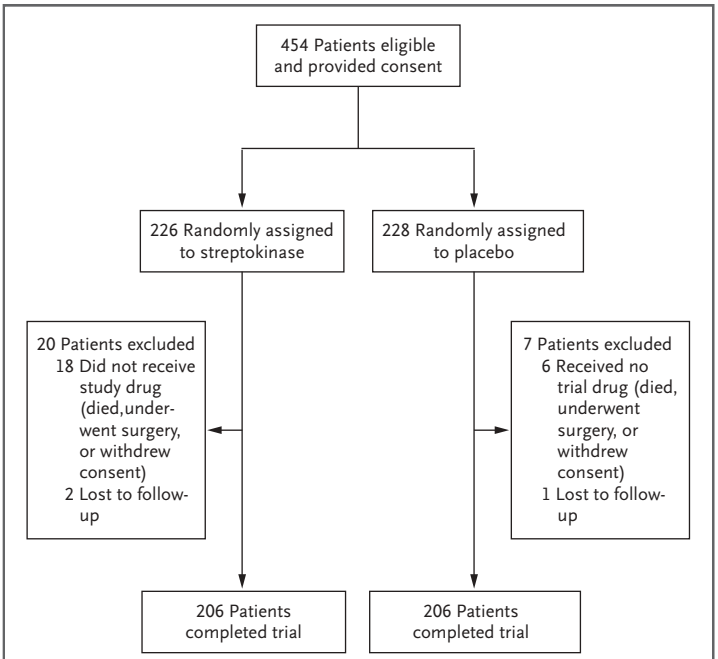

Figure 1. Enrollment, Randomization, and Follow-up in the Trial.

Table 2. Adverse Events Possibly Attributable to Study Treatment, According to Severity and Type.

Variable	Streptokinase (N=208)	Placebo (N=222)	Relative Risk (95% CI)*	P Value
	no. (%)			
Severity				
Serious	14 (7)	6 (3)	2.49 (0.98–6.36)	0.08
Other	8 (4)	8 (4)	1.07 (0.41–2.81)	0.91
Total	22 (11)	14 (6)	1.68 (0.88–3.19)	0.15
Type				
Hemorrhage (local pleural or systemic)	7 (3)	6 (3)		
Chest pain	4 (2)	1 (<1)		
Fever, rash, and allergy	5 (2)	1 (<1)		
Other	6 (3)	6 (3)		

* CI denotes confidence interval.

died in the three months after randomization. In the streptokinase group, 64 of 206 patients (31 percent) had one of these outcomes, as did 60 of 221 patients (27 percent) in the placebo group (relative risk, 1.14 [95 percent confidence interval, 0.85 to 1.54]; P=0.43) (Fig. 2).

SECONDARY END POINTS

Death and Surgical Drainage Combined

At 12 months after randomization, there remained no difference in the proportion of patients who required surgical drainage or died. In the streptokinase group, 79 of 198 patients (40 percent) had one of these outcomes, as did 73 of 216 patients (34 percent) in the placebo group (relative risk, 1.18 [95 percent confidence interval, 0.92 to 1.52]; P=0.24) (Fig. 2).

Death and Surgical Drainage Analyzed Separately

When death and the need for surgical drainage were analyzed separately, there were no differences between the groups at 3 or 12 months. At three months, 32 of 206 patients (16 percent) in the streptokinase group and 30 of 221 (14 percent) in the placebo group had died (relative risk, 1.14 [95 percent confidence interval, 0.72 to 1.81]; P=0.66). Also at three months, 32 of 206 patients (16 percent) in the streptokinase group and 32 of 221 (14 percent) in the placebo group had required surgery (relative risk, 1.07 [95 percent confidence interval, 0.68 to 1.69]; P=0.87). At 12 months, 45 of 198 patients in the streptokinase group (23 percent) and 44 of 216 in the placebo group (20 percent) had died (relative risk, 1.12 [95 percent confidence interval, 0.77 to 1.61]; P=0.64), and 36 of 198 in the streptokinase group (18 percent) and 34 of 216 in the placebo group (16 percent) had needed surgery (relative risk, 1.16 [95 percent confidence interval, 0.75 to 1.77]; P=0.60). Seven patients (two in the streptokinase group and five in the placebo group) died after surgery.

Duration of the Hospital Stay

There was no difference in the duration of the hospital stay between the two groups (streptokinase group: median stay, 13 days; range, 1 to 271; placebo group: median, 12 days; range, 2 to 152; P=0.16 by the Mann–Whitney test) (Fig. 2).

Outcomes on Chest Radiography

The side on which the pleural infection occurred and the size of the pleural-fluid collection were similar in the two study groups at baseline (Table 1). There was no difference between the groups in the degree of pleural thickening at three months (Table 3). Also at three months, there was a small

but significant difference in favor of placebo in the height of the thorax on the side with empyema. There was no difference between the groups in the degree of reduction in the size of the pleural opacity at three months (Table 3).

Among all patients there was a small but significant difference between baseline and three months in the mean (±SD) vertical height of the thorax on the side not affected by disease, suggesting a small change in radiographic projection or patient inspiratory effort (at baseline: right, 22.8±3.4 cm; left, 20.8±3.4; at three months: right, 24.1±2.9 cm; left, 22.2±3.5; difference: right, 1.3 cm [95 percent confidence interval, 0.6 to 1.9]; P<0.001; left, 1.4 cm [95 percent confidence interval, 0.6 to 2.3]; P<0.001).

Dynamic Lung Volumes

The dynamic lung volumes were similar in the two groups at three months. The mean forced expiratory volume in one second was 2.22±0.78 liters in the streptokinase group and 2.18±0.90 liters in the placebo group (difference, −0.04 liter [95 percent confidence interval for the difference, −0.25 to 0.17]; P=0.69). The mean forced vital capacity was 3.04±0.93 liters in the streptokinase group and 2.99±1.11 in the placebo group (difference, −0.05 liter [95 percent confidence interval for the difference, −0.31 to 0.21]; P=0.70).

Bleeding after Drainage Surgery

Nine patients (5 in the streptokinase group and 4 in the placebo group) underwent video-assisted thoracoscopic drainage, 39 (17 in the streptokinase group and 22 in the placebo group) underwent thoracotomy with pleural decortication, and 9 (5 in the streptokinase group and 4 in the placebo group) underwent another form of open surgical drainage. The surgeon noted excessive perioperative bleeding in three patients (one in the streptokinase group and two in the placebo group). There was no difference in the patients' blood-transfusion requirements (data not shown).

Antistreptokinase Antibodies

The antistreptokinase-antibody level was markedly increased in the patients receiving streptokinase. Among 111 patients in the streptokinase group, the level was 2402±2818 arbitrary units at baseline and 10,707±4470 at three months (difference, 7953±4861 arbitrary units). Among 127 patients in the placebo group, the corresponding values were 2357±3031 arbitrary units at baseline and 2619±3298 arbitrary units at three months (difference, 357±2862 arbitrary units). The difference between the groups was 7956 arbitrary units (95 percent confidence interval, 6592 to 8600; P<0.001).

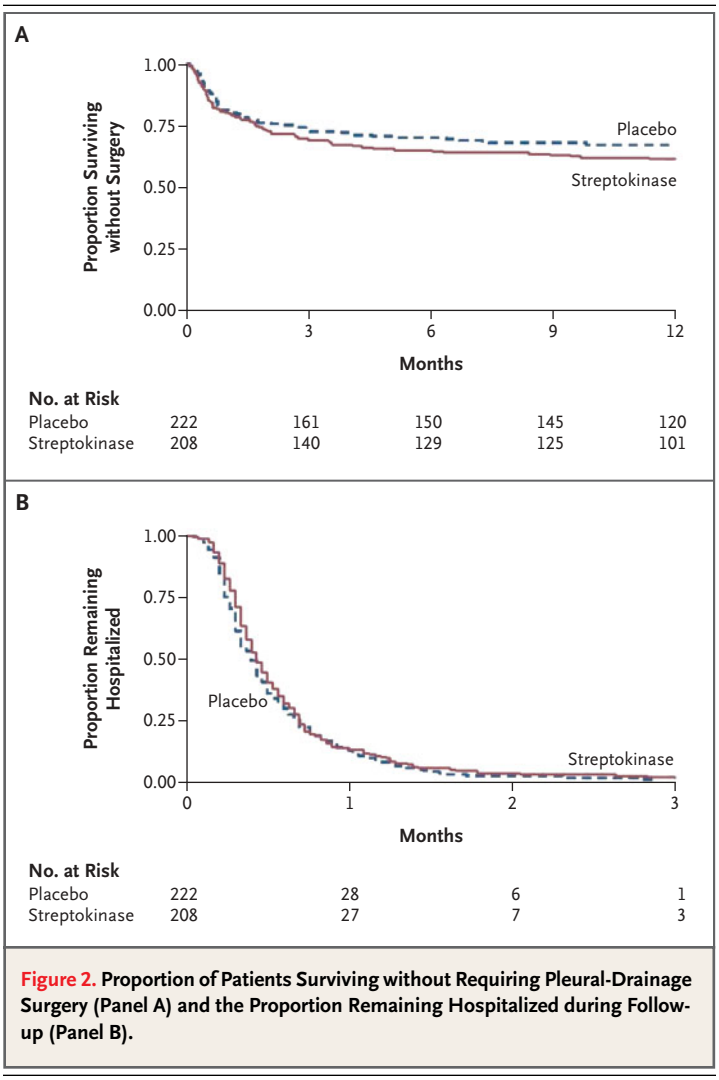

Figure 2. Proportion of Patients Surviving without Requiring Pleural-Drainage Surgery (Panel A) and the Proportion Remaining Hospitalized during Follow-up (Panel B).

Subgroup Analyses

There was no evidence of a reduction in the need for surgical drainage or in mortality after the administration of streptokinase in any of the subgroups we analyzed, including those with and those without frankly purulent pleural fluid at baseline and those with and those without definite septation or loculation (details are available in the Supplementary Appendix).

Table 3. Outcomes on Chest Radiography at Three Months.*

Outcome	Streptokinase	Placebo	Difference between Groups (95% CI)	P Value
Residual pleural thickening at lateral chest wall — mm†	12±14	15±19	3 (−1 to 7)	0.20
Vertical height of thorax on affected side — mm†	209±30	221±33	12 (4 to 19)	0.003
Improvement in the area of pleural-fluid opacity in patients not requiring surgery — no. (%)‡				0.30§
No. of patients	102	133		
0–25%	7 (7)	12 (9)		
26–75%	6 (6)	12 (9)		
76–90%	12 (12)	24 (18)		
>90%	77 (75)	85 (64)		

* Methods of measurement are described in detail in the Supplementary Appendix. Plus–minus values are means ±SD.
† A total of 184 patients in the streptokinase group and 202 in the placebo group were analyzed.
‡ A total of 102 patients in the streptokinase group and 133 in the placebo group were analyzed. Percentages are of the total number of patients who did not require surgery and who could be assessed.
§ Chi-square equals 3.69, with 3 degrees of freedom.

DISCUSSION

This controlled trial in patients with pleural infection demonstrates that intrapleural streptokinase does not reduce mortality, the need for drainage surgery, or the duration of the hospital stay and does not improve outcomes as measured radiographically or by tests of lung function. The results of our analysis exclude with 95 percent confidence the possibility of an improvement of 15 percent or more in the relative risk of death or the need for surgery as a result of the administration of streptokinase. This finding is unexpected, since it has been assumed on the basis of small trials that intrapleural fibrinolytic agents such as streptokinase are beneficial in patients with pleural infection, and since the administration of streptokinase is included in the management guidelines of major respiratory societies.[6,7]

The consensus in favor of the use of streptokinase arose because intrapleural fibrinolytic agents produced short-term improvements in radiographic outcomes and were apparently effective as rescue therapy after failed chest-tube drainage.[8-11,13] Previous trials have not had adequate statistical power to assess whether these improvements in intermediate surrogate outcomes were associated with improvements in the major outcomes of clinical interest — mortality and the need for surgery. The results of the current trial show that they are not.

In view of the negative results, we confirmed that the trial drugs were active and that patients correctly received the assigned study treatment. The independent analysis of the vials of streptokinase and placebo demonstrated the expected levels of active drug, and the fibrinolytic efficacy of the streptokinase used in this trial was confirmed in vitro. The increase in antistreptokinase-antibody titers after the administration of streptokinase confirms that the trial groups correctly received the assigned treatments. It is unlikely that the negative results are due to an inadequate regimen of treatment with streptokinase. The six-dose regimen, in which a total of 1.5 million units of streptokinase is administered, represents more doses and a larger total dose of the drug than the regimens used in earlier studies examining intermediate surrogate end points, which had positive results.[8,10,13] Finally, the overall combined rate of death or the need for surgery was similar to that in previous studies,[2,5,16,17] suggesting that our study population was representative.

The subgroup analyses show that the negative results are not explained by the characteristics of the study sample. In particular, there is no evidence that efficacy was influenced by the presence of overtly purulent pleural fluid, the duration of the illness before randomization, the initial chest-tube size, or the presence or absence of pleural-fluid septation or loculation on the baseline chest radiograph.

An a priori decision was made to exclude from our analysis the 24 subjects who received no study drug because they died, required urgent surgery, or withdrew their consent before the delivery of the study drugs to their hospitals. Inclusion of these

patients did not change the primary result of the trial (74 of 224 patients in the streptokinase group [33 percent] and 63 of 227 in the placebo group [28 percent] required surgical drainage or died) (relative risk, 1.19 [95 percent confidence interval, 0.90 to 1.58]; P=0.26).

There was a substantial systemic antistreptokinase-antibody response in the group receiving streptokinase. Such a response might inhibit the efficiency of streptokinase given later for a myocardial infarction or venous thromboembolism. Therefore, patients who have received intrapleural streptokinase and later require systemic fibrinolysis should receive a different fibrinolytic agent.

The results of this trial make it possible to define the role of intrapleural fibrinolytic agents in pleural infection. Generally, the use of these drugs should be avoided, since they produce no advantage in long-term outcomes and have some adverse effects. However, studies conducted before this trial have established that fibrinolytic agents do lead to macroscopically effective in vivo lysis of intrapleural fibrin adhesions[18] and reduce the volume of infected pleural-fluid collections.[8,13] Our study was not designed to readdress this question. It was designed to assess whether streptokinase decreased mortality or the need for surgery. Thus, there may still be a role for fibrinolytic agents in treating the small subgroup of patients who have an exceptionally large, chest-tube–resistant collection of pleural fluid that causes substantial dyspnea, hypoxemia, or hypercapnia by the mechanical impairment of lung function.

It is interesting to consider why streptokinase did not improve long-term outcomes in this trial. The answer is probably that streptokinase alone did not produce sufficient clearance of pleural fluid — possibly because infected pleural fluid is viscous, lumpy, and resistant to tube drainage.[19,20] Streptokinase does not improve these characteristics[19,20]; it simply breaches the barriers between pockets of pus. Therefore, despite the partial unification of the pleural collection, the fluid may still fail to drain adequately, because it cannot pass down the chest tube. This fact might explain the particular efficacy of pleural-fluid drainage with the aid of fibrinolytic agents in patients with loculated malignant pleural effusion,[21] in whom the pleural fluid is thin and only the fibrin septations inhibit the removal of fluid. If this is true, then reducing the viscosity of pus may improve outcomes in pleural infection; DNase is a candidate for this role, since it reduces viscosity by fragmenting the free uncoiled DNA found in pus.[19,20] This is the rationale for its use in airway clearance in cystic fibrosis. In pleural infection, data from both in vitro studies[19,20] and case reports on clinical use[22] suggest that DNase may also be helpful in draining empyema. Appropriate trials are needed to explore this possibility.

An alternative, and challenging, explanation for the results of this trial might be that reducing the volume of infected pleural fluid is less important than is widely believed in patients receiving modern antibiotics. This possibility would call into question the preeminent role assigned to the drainage of thoracic pus for 2500 years[23] and thus should be considered only a speculative hypothesis requiring further research.

In summary, in this trial, intrapleural streptokinase had a modest adverse-event profile in patients with pleural infection but was ineffective in reducing mortality, the need for surgical drainage, or the length of the hospital stay. We conclude that the use of intrapleural streptokinase should generally be avoided in pleural infection.

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APPENDIX

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