COOPERATIVE STUDIES

High Dose Intravenous Streptokinase for Acute Myocardial Infarction: Preliminary Results of a Multicenter Trial

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To assess the efficacy of intravenous streptokinase in patients with acute myocardial infarction, 40 patients (30 men and 10 women, mean age 54 years) with acute myocardial infarction were given 1.5 million U of streptokinase intravenously in 1 hour, and coronary arteriography was performed repeatedly to assess reperfusion. Streptokinase treatment was begun 270 ± 86 (mean ± SD) minutes after the onset of chest pain. Of the 40 patients, 34 had total or near total coronary occlusion before streptokinase administration. In 14 (41%) of these 34 patients, some reperfusion occurred during the 90 minutes after the administration of streptokinase, but during the past several years, a number of studies have demonstrated that acute transmural myocardial infarction is frequently associated with coronary thrombosis (1) and that the prompt administration of a thrombolytic agent, such as streptokinase, may reestablish anterograde flow in the involved coronary artery (2–5). Some studies have suggested that timely reperfusion may improve left ventricular function (3) and survival (4) over the several months after the acute event. Intracoronary streptokinase induces thrombolysis in 70 to 80% of patients with acute myocardial infarction (2–5), but its widespread application in such patients is limited, because it requires the immediate availability of a cardiac catheterization laboratory and appropriate personnel. Intravenous streptokinase can be administered quickly and does not require sophisticated and expensive invasive facilities. Several studies have shown that it is generally safe and well tolerated, but results concerning therapeutic efficacy have been widely disparate. Rogers et al. (6) and Spann et al. (7,8) showed that intravenous streptokinase causes thrombolysis in less than 50% of patients, whereas Ganz et al. (9) reported lysis in 96% of patients.

In 1983, the National Heart, Lung, and Blood Institute initiated a collaborative clinical trial of intravenous thrombolytic therapy in patients with acute myocardial infarction. For this multicenter effort, 13 clinical centers, 5 core laboratories, a drug distribution center and a data coordinating center were organized to plan and perform the Thrombolysis...
in Myocardial Infarction (TIMI) Trial. The planning committee determined that the first phase (phase I) should compare the efficacy and safety of intravenous streptokinase and intravenous tissue-type plasminogen activator in a double-blind, randomized fashion. As a prelude to phase I, streptokinase was administered in open label fashion to 40 patients. This phase of our study is described in this report.

Methods

Patient population. At the 13 clinical centers, patients were enrolled in the study and given intravenous streptokinase if they met the following criteria: 1) younger than 76 years of age; 2) chest pain compatible with acute myocardial infarction greater than 30 minutes in duration; 3) electrocardiographic ST segment elevation of 0.1 mV or greater in 2 or more of the standard 12 leads; 4) an elapsed time from onset of chest pain to enrollment of less than 7 hours; and 5) coronary arteriographic evidence of 50% or greater luminal diameter narrowing of the artery supplying the area of infarction. Patients were excluded from enrollment if they had any of the following: 1) severe hypotension (systolic arterial pressure < 80 mm Hg) despite vasopressors; 2) uncontrolled hypertension (diastolic pressure > 120 mm Hg); 3) child-bearing potential; 4) a history of a bleeding disorder or an illness that placed the patient at high risk of a hemorrhagic complication with thrombolytic therapy, for example, previous gastrointestinal bleeding, an underlying malignancy, surgery in the preceding 2 weeks, a severe traumatic injury in the preceding 6 months or a cerebrovascular accident in the preceding 6 months; 5) the presence of known dilated cardiomyopathy, left bundle branch block or previous coronary artery bypass surgery; 6) previous participation in the TIMI Trial; and 7) inability to give informed consent.

Study design. After informed consent was obtained, each patient was taken immediately to the cardiac catheterization laboratory, and venous and arterial access were obtained. The coronary artery believed (from the electrocardiogram) not to be involved in the infarction was injected selectively, after which the "infarct-related artery" was visualized in a series of standard views. If the infarct-related artery had 50% or greater luminal diameter narrowing, intracoronary nitroglycerin (200 μg) was given, and arteriography was repeated. If the artery remained narrowed by 50% or greater, the patient received intravenous streptokinase, 1.5 million U during 1 hour. Cineangiography of the involved coronary artery was performed 10, 20, 30, 45, 60, 75 and 90 minutes after the initiation of streptokinase.

At the end of the streptokinase infusion, intravenous heparin therapy was begun at 1,000 U/h. After the 90 minute cineangiogram, the patient was transferred to the coronary care unit with venous and arterial sheaths in place. Heparin treatment was continued for 8 to 10 days, during which time an attempt was made to maintain the activated partial thromboplastin time at 2 to 2½ times normal. The vascular sheaths were removed 24 to 48 hours after streptokinase administration. After 8 to 10 days of heparin therapy, aspirin and dipyridamole were administered and heparin was discontinued. If possible, a repeat cardiac catheterization, including selective coronary arteriography, was performed at this time.

Measurements. A Coagulation Core Laboratory was established at the Thrombosis Research Center, Temple University, Philadelphia, Pennsylvania, to assess the changes in plasma levels of fibrinogen, plasminogen and fibrinogen degradation products. Blood samples were collected before and 1 to 3 and 24 hours after the initiation of streptokinase. In addition, samples were obtained at the time of hospital discharge (8 to 10 days later). Because of the presence of heparin in the blood samples, fibrinogen concentrations were measured by the method of Martin et al. (10) in citrated plasma prepared from blood collected in the presence of 250 U/ml of aprotinin (Trasylol, FBA Pharmaceuticals). Plasma plasminogen activity was measured in citrated plasma by the method of Friberger and Knos (11) using a chromogenic substrate, S-2251 (Kabi Diagnostics). The results are expressed as percent of activity in relation to that in pooled normal plasma taken as 100%. The levels of fibrinogen degradation products were measured in serum harvested from blood (2 ml) collected in tubes containing thrombin (20 NIH U), soybean trypsin inhibitor (3,670 NF U) and protamine sulfate (50 μg, Eli Lilly Company). The Thrombo-Wellcotest method was employed using latex particles coated with antibodies against fibrinogen fragments D and E (Wellcome Diagnostics).

Analysis of data. The cineangiograms obtained during both catheterizations were analyzed by the Radiographic Core Laboratory at the University of Washington, Seattle, Washington. In assessing the adequacy of perfusion in the infarct-related artery, the following grading system was used: grade 0 = no anterograde movement of contrast material beyond the point of occlusion ("no perfusion"); grade 1 = penetration of the obstruction with contrast material but failure to opacify the distal coronary artery bed ("minimal perfusion"); grade 2 = passage of contrast material past the obstruction, with anterograde movement and clearance of contrast material slower than that seen in a nondiseased artery ("partial perfusion"); and grade 3 = prompt appearance and disappearance of contrast material in the portion of the artery distal to the obstruction ("complete perfusion"). On the basis of this grading system, coronary occlusion was considered to be present when perfusion was graded as 0 or 1, and reperfusion was believed to have occurred if perfusion improved to grades 2 or 3.

Clinical evidence of reocclusion after streptokinase administration was believed to be present if at least two of the following occurred: 1) reappearance or distinct worsening of ischemic pain similar in nature to the pain of in-
fraction; 2) 0.1 mV or greater ST segment elevation or reelevation in the electrocardiographic leads in which it was present on the qualifying electrocardiogram; and 3) a greater than 50% increase in serum creatine kinase in two consecutive samples, each containing the MB isoenzyme.

In assessing the plasminogen, fibrinogen and fibrinogen degradation product concentrations before streptokinase infusion and 1 to 3 and 24 hours and 8 to 10 days after streptokinase initiation, a paired $t$ test was used. All data are reported as mean $\pm$ SD. For all analyses, a probability (p) value of less than 0.05 was considered significant (12,13).

Results

Patient features. Forty patients (30 men and 10 women, aged 54 $\pm$ 11 years; range 38 to 75) with acute myocardial infarction received intravenous streptokinase. Initial 12 lead electrocardiography revealed ST segment elevation in the anterior leads in 18 patients, the inferior leads in 18 and both the anterior and the inferior leads in 4. By cineangiography, the right coronary artery was the involved vessel in 21, whereas the left anterior descending coronary artery was involved in 19. Of the 40 patients, 19 had single vessel coronary artery disease, 13 had double vessel disease and 8 had triple vessel disease. The elapsed time from the onset of chest pain to the institution of thrombolytic therapy averaged 270 $\pm$ 86 minutes (range 137 to 482); it was less than 240 minutes in 16 patients.

Cineangiographic and clinical results. Before streptokinase administration, 6 patients showed angiographic evidence of partial occlusion (perfusion grades 2 or 3), whereas in the other 34 the infarct-related vessel was totally or nearly totally occluded (perfusion grades 0 or 1). During the 90 minutes after the initiation of intravenous streptokinase, reperfusion (an improvement to perfusion grades 2 or 3) occurred in 14 (41%) of these 34 patients (Fig. 1). Furthermore, 90 minutes after streptokinase was begun, 3 of the 14 once again showed total occlusion. Five patients demonstrated only partial reperfusion (grade 2) and the other six continued to have total reperfusion (grade 3). Of the five patients with partial reperfusion 90 minutes after the institution of streptokinase, four had no clinical evidence of reocclusion during the subsequent 24 hours, and one had prolonged chest pain 3 hours after the termination of streptokinase therapy (at a time when the activated partial thromboplastin time was 102 seconds [control value 35]). Of the six patients with complete reperfusion 90 minutes after the institution of streptokinase, none had clinical evidence of reocclusion during the next 24 hours.

Thus, of the 34 patients whose infarct-related artery was occluded before streptokinase therapy, only 10 (29%) demonstrated successful reperfusion 90 minutes after the institution of streptokinase and no clinical evidence of reocclusion during the next 24 hours (Fig. 1).

Of the 16 patients who received streptokinase earlier than 4 hours after the onset of chest pain, 15 had perfusion grade 0 or 1 of the infarct-related artery before drug administration. In 5 (33%) of these 15, partial or complete reperfusion (grade 2 or 3) was noted at 90 minutes. Of the 24 subjects who received streptokinase more than 4 hours after the onset of pain, 19 had perfusion grade 0 or 1 of the infarct-related artery before the institution of therapy. In 6 (32%) of these 19, partial or complete reperfusion (grade 2 or 3) was observed at 90 minutes (P = NS in comparison with the patients who received streptokinase < 4 hours after the onset of pain).

Repeat catheterization was performed 8 to 10 days after streptokinase administration in 22 patients. Eighteen did not have repeat catheterization because of patient refusal (n = 8), referring physician refusal (n = 2), death (n =
2) or the necessity for coronary artery bypass surgery or angioplasty during the several days after streptokinase therapy (n = 6). Repeat catheterization was performed in 6 of the 11 patients with complete or partial reperfusion at 90 minutes; persistent patency was demonstrated in 5 and totally occluded vessel in 1 patient. Repeat catheterization was accomplished in 13 of the 23 patients who had grade 0 or 1 perfusion at 90 minutes. Although six still had grade 0 or 1, the other seven had grade 2 or 3. In these seven, anterograde flow was reestablished at some time between the 90 minute cineangiogram and the repeat study.

As noted, streptokinase induced reperfusion during the 90 minutes of observation in 14 patients. In three of these patients, however, the infarct-related artery was occluded once again 90 minutes after streptokinase treatment was begun. A repeat catheterization 8 to 10 days after streptokinase administration was performed in only one of these three subjects; in this individual, the infarct-related artery was totally reperfused (grade 3).

Coagulation results. Mean values for plasminogen, fibrinogen and fibrinogen degradation products are displayed in Table 1. With the administration of streptokinase, plasminogen and fibrinogen levels decreased and fibrinogen degradation products increased. These findings are consistent with the induction of a systemic lytic state by streptokinase. At the time of hospital discharge 8 to 10 days later, plasminogen and fibrinogen degradation product concentrations were similar to baseline study, whereas fibrinogen levels were significantly higher than baseline study.

Morbidity and mortality during streptokinase therapy. Of the 40 patients receiving intravenous streptokinase, 3 (8%) died during the month after the institution of therapy; in all 3, death was attributed to severe underlying coronary artery disease and its sequelae. Almost all morbidity was due to bleeding and, in most patients, did not interfere with the ability of the investigators to adhere to the protocol. The appearance of a hematoma at the site of venous and arterial punctures was noted in 26 patients. Six subjects had a sufficient decrease in hematocrit to require transfusion. Gastrointestinal bleeding occurred in two patients, but surgical intervention was not required. Although hemorrhagic events were frequent, none were fatal.

Discussion
In patients with acute transmural myocardial infarction, intracoronary streptokinase has been shown to induce thrombolysis rapidly in 70 to 80% (2–5). However, its application to large numbers of patients is limited, because a cardiac catheterization laboratory and supporting technical personnel are required. Intravenous streptokinase can be given quickly without the need for a catheterization laboratory. Several investigators (6–8,14–16) administered high dose (500,000 to 1,500,000 U over 15 to 90 minutes) intravenous streptokinase and performed acute coronary angiography to assess its efficacy in causing reperfusion. In general, thrombolysis was achieved in about half the patients, ranging from 44 (6) to 63% (14). In other studies in which the occurrence of thrombolysis was judged by indirect criteria (without acute angiography), intravenous streptokinase was reported to induce thrombolysis in 96% (9).

In the present study, intravenous streptokinase, 1.5 million U given over 1 hour, induced acute reperfusion in only 41% of patients, and persistent reperfusion without clinical evidence of reocclusion was present in only 29% (Fig. 1). In our experience, therefore, high dose intravenous streptokinase successfully induces thrombolysis and sustains vessel patency in only a few patients.

Possible reasons for the low reperfusion rate in this study. In all studies that demonstrated angiographically that intravenous streptokinase achieves thrombolysis in more than 50% of patients, the drug was administered an average of less than 4 hours from the onset of chest pain. Neuhaus et al. (14) gave intravenous streptokinase an average of 3.2 hours after chest pain and achieved thrombolysis in 24 (63%) of 38 patients; Schroder et al. (15) administered the drug an average of 3.8 hours after the onset of chest pain, and thrombolysis occurred in 11 (52%) of 21 patients; Alderman et al. (16) gave streptokinase an average of 203 minutes after the appearance of chest pain, achieving lysis in 8 (62%) of 13 patients. In contrast, Rogers et al. (6) gave high dose intravenous streptokinase an average of 6 to 7 hours after the onset of chest pain, and lysis occurred in only 7 (44%) of 16 patients. A similar reperfusion rate (21 [49%] of 43) was noted by Spann et al. (8) when streptokinase was given

Table 1. Coagulation Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Streptokinase</th>
<th>1 to 3 Hours After Streptokinase</th>
<th>24 Hours After Streptokinase</th>
<th>At Hospital Discharge</th>
</tr>
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<tbody>
<tr>
<td>Plasminogen (%)(n = 29)†</td>
<td>97 ± 22</td>
<td>15 ± 8*</td>
<td>37 ± 12*</td>
<td>107 ± 35</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)(n = 30)</td>
<td>342 ± 98</td>
<td>161 ± 85*</td>
<td>239 ± 92*</td>
<td>638 ± 280*</td>
</tr>
<tr>
<td>Fibrinogen degradation products (μg/ml)(n = 30)</td>
<td>21 ± 80</td>
<td>283 ± 168*</td>
<td>70 ± 41*</td>
<td>7 ± 4</td>
</tr>
</tbody>
</table>

All data are mean ± standard deviation. *p < 0.01 in comparison with baseline study (before streptokinase administration); †plasminogen results are expressed as percent of activity of pooled normal plasma taken as 100%.
within 6 hours of chest pain. In our study, intravenous streptokinase was given an average of 270 ± 86 minutes after the onset of pain and within 4 hours in only 16 patients. Similar to the studies just mentioned (6,8,14–16), the administration of streptokinase was delayed in each patient until coronary arteriography was accomplished so that reperfusion could be evaluated directly. The acute reperfusion rate among patients with coronary occlusion was 41%, a result similar to that of Rogers et al. (6) and Spann et al. (8), whose average elapsed time from chest pain to institution of streptokinase was similar to ours. Thus, as noted by others (14,15), the likelihood that intravenous streptokinase will induce thrombolysis appears to be related to the elapsed time from the chest pain, which may be presumed to be the time of thrombus formation.

In our study, coronary arteriography was performed repeatedly for 90 minutes after the administration of intravenous streptokinase. During this period of arteriographic observation, reperfusion occurred in 14 (41%) of 34 patients but was not noted in the other 20 (59%). In some of these 20 patients, it is conceivable that thrombolysis with resultant reperfusion occurred after the 90 minute arteriogram.

Successful maintenance of reperfusion after streptokinase therapy. In the present study, acute reperfusion occurred in 14 (41%) of 34 patients but was sustained in only 10 (29%) (Fig. 1). Spann et al. (8) noted a similar finding: of 43 patients given intravenous streptokinase, early reperfusion occurred in 21 (49%) but was sustained in only 15 (35%). As suggested by Harrison et al. (17), the patients in whom reperfusion occurred but was not sustained may have had residual high grade coronary artery stenosis with an extremely small cross-sectional area, rendering them at high risk of rethrombosis during the hours to days after thrombolytic therapy.

Conclusions. Our data, obtained in a consecutive cohort of patients with acute myocardial infarction from a number of centers throughout the country, demonstrate that high dose intravenous streptokinase achieves thrombolysis in only about 40% of patients and leads to persistent vessel patency in only about 30%. If intravenous thrombolytic therapy is to have a substantial impact on the morbidity and mortality of acute myocardial infarction, an agent that achieves thrombolysis in a higher percentage of patients must be identified, tested and proved effective and safe.

Appendix

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References


