Prospective randomized trial of intravenous and intracoronary streptokinase in acute myocardial infarction

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ABSTRACT To evaluate the relative thrombolytic efficacy and complications of intracoronary vs high-dose, short-term intravenous streptokinase infusion in patients with acute myocardial infarction, we performed baseline coronary arteriography and then randomly allocated 51 patients with acute myocardial infarction to receive either intracoronary (n = 25) or intravenous (n = 26) streptokinase. Patients getting the drug by the intracoronary route received 240,000 IU of streptokinase into the infarct-related artery over 1 hr, whereas those getting the drug by the intravenous route received either 500,000 IU of streptokinase over 15 min (n = 10) or 1 million IU of streptokinase over 45 min (n = 16). Angiographically observed thrombolysis occurred in 76% (19/25) of the patients receiving intracoronary streptokinase, in 10% (1/10) of the patients receiving 500,000 IU of streptokinase intravenously, and in 44% (7/16) of the patients receiving 1 million IU of streptokinase intravenously. Among patients in whom thrombolysis was observed, mean elapsed time from onset of streptokinase infusion until lysis was 31 ± 18 min in patients receiving intracoronary streptokinase and 38 ± 20 min in those receiving intravenous streptokinase (p = NS). Among patients in whom intravenous streptokinase “failed,” intracoronary streptokinase in combination with intracoronary guidewire manipulation recanalized only 7% (1/15). Fibrinogen levels within 6 hr after streptokinase were significantly lower in the patients receiving intravenous streptokinase (39 ± 17 mg/dl) than the levels in those receiving intracoronary streptokinase (88 ± 70 mg/dl) (p < .05) but were similar 24 hr after streptokinase in the two groups. Bleeding requiring transfusion occurred in one patient in each group. Thus, in this prospective randomized trial of intracoronary vs intravenous streptokinase, hemorrhagic complications were few, although both regimens produced a systemic lytic state. Although the thrombolytic efficacy of intracoronary streptokinase was superior to that of high-dose, short-term intravenous streptokinase, the higher-dose intravenous regimen (1 million IU over 45 min) achieved thrombolysis in a significant minority (44%) of patients and might be useful therapy for patients not having access to emergency catheterization.

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RECENTLY, intracoronary streptokinase has achieved considerable popularity as a means for recanalizing acutely thrombosed coronary arteries in patients with evolving acute myocardial infarction.1–4 Unfortunately, emergency coronary arteriography and intracoronary streptokinase infusion require sophisticated equipment and a specially trained operator and are thus available to only a minority of patients sustaining acute myocardial infarction. Even when available the procedure is logistically difficult, costly, and potentially dangerous. Attention has recently been turned to the feasibility of high-dose, short-term intravenous streptokinase in lieu of intracoronary streptokinase to achieve thrombolysis in patients with acute myocardial infarction.5–8

Compared with intracoronary streptokinase, intravenous streptokinase has numerous theoretical advantages in the treatment of patients with acute myocardial infarction. When the need for coronary arteriography is eliminated, intravenous therapy might have a more widespread applicability, might be given sooner (thereby salvaging more myocardium), and would be
logistically simpler, more economical, and safer. Currently, little controlled data are available comparing the relative thrombolytic efficacy, as documented by serial coronary angiography, of high-dose, short-term intravenous streptokinase and intracoronary streptokinase therapy for patients with acute myocardial infarction.

Accordingly, this study was designed to evaluate prospectively the thrombolytic efficacy and potential complications of intravenous vs intracoronary streptokinase in a group of patients with acute myocardial infarction randomly allocated to receive these two forms of therapy after emergency coronary arteriography.

Methods

Patients. Patients who met all the following criteria were included in this study: (1) age 70 years or less, (2) clinical presentation suggestive of evolving acute myocardial infarction, (3) electrocardiogram showing ST segment elevation of $\geq 1.5$ mm in two or more leads or marked T waves changes alone in an otherwise classic clinical presentation, (4) no contraindication to thrombolytic therapy or anticoagulation, (5) emergency catheterization and thrombolytic therapy available within 12 hr of onset of pain (as an exception, patients with evolving acute infarction and recurrent severe pain 12 to 24 hr after infarction were eligible), and (6) consent given for emergency coronary and left ventriculography and reperfusion intervention.

Study design. All patients gave a brief medical history, underwent a physical examination, and gave informed consent for the study before undergoing emergency cardiac catheterization, which included left ventriculography and coronary angiography (figure 1). Patients were premedicated with diphenhydramine hydrochloride 50 mg iv and methylprednisolone 1.0 g iv. A No. 7F or 8F side-arm valved sheath was inserted into the right or left femoral artery and was sutured in place. Heparin 5000 UI iv was administered. A pigtail ventriculography catheter was inserted, baseline left ventricular pressure was recorded, and biplane left ventriculography was performed in the 20 degree cranial–60 degree LAO/45 degree RAO projections.11 using 45 ml of diatrizoate sodium and diatrizoate meglumine (Renografin-76) that was power-injected over 3 sec.

Coronary angiography of the suspected noninfarct-related artery was then performed, followed by injections in the infarct-related artery. If a total occlusion or high-grade stenosis of the infarct-related artery was found, the patient was randomly assigned to receive either intracoronary or intravenous streptokinase therapy. Randomization was stratified according to the involved coronary artery — left anterior descending (LAD), left circumflex (LCX), and right coronary (RCA) — to ensure even distribution among these three groups.

Patients randomized to receive intracoronary streptokinase therapy first received 200 $\mu$g of nitroglycerin into the ostium of the infarct-related artery (left main coronary artery or proximal right coronary artery). To document the effects of nitroglycerin, another contrast injection in the infarct-related artery was made.

Streptokinase (Streptase-Hoechst) 240,000 IU in 240 ml of 0.9M NaCl was then administered at a rate of 4000 IU/min either by a constant infusion pump (IMED 922; IMED Corp., San Diego) or by 1 ml hand boluses at 15 sec intervals. To document the effects of therapy, contrast injections of the infarct-related artery were made at 15, 30, 45, and 60 min after intracoronary streptokinase was started. Ancillary reperfusion interventions such as subselective cannulation of the infarct-related coronary artery, with or without guidewire penetration of the thrombus, were permissible within the protocol, although as noted below they were rarely used.

Patients randomized to receive intravenous streptokinase therapy first received 400 $\mu$g of nitroglycerin sublingually, after which a repeat angiogram of the infarct-related artery was made. During the first part of the trial (phase I), patients randomized to receive intravenous therapy received 500,000 IU streptokinase in 50 ml 0.9M NaCl over 15 min in a peripheral intravenous line via a constant infusion pump. In the second portion of the trial (phase II), patients in the intravenous streptokinase group received 1 million IU of streptokinase in 90 ml of 0.9M NaCl in a peripheral intravenous line by constant infusion pump over 45 min. Serial angiograms of the occluded artery were made at 15 min intervals after therapy was started, and if no thrombolysis had been noted at 45 min after commencement of therapy, 120,000 IU of streptokinase was infused by the intracoronary route over 30 min as described above. Toward the end of the study, for reasons discussed below, we abandoned the policy of administering intracoronary streptokinase to patients in whom intravenous streptokinase therapy "failed" and simply observed these patients for an additional 30 min. Thus, all patients receiving intravenous streptokinase were observed by use of serial angiography at 15 min intervals for a total of 75 min.

For the purpose of this trial, thrombolytic therapy was designated as "successful" when, during the period of serial angiographic observation in the catheterization laboratory, any of the following events occurred and persisted: (1) a previously totally occluded vessel was observed to opacify by antegrade flow distal to the point of initial occlusion, filling left ventricular branches, (2) an initially subtotaly occluded vessel was ob-

**FIGURE 1.** Study design. During both phase I and phase II of the study, the intracoronary streptokinase dose and duration of infusion were unchanged. LV = left ventricular, SK = streptokinase, ASA = aspirin, angios = angiograms.
served to become less stenotic after thrombolytic therapy, or (3) a filling defect (probable thrombus) within an initially subtotally occluded vessel was observed to become smaller. Angiograms were read by a cardiac radiologist unaware of the randomized treatment assignment.

After thrombolytic therapy, the catheters were removed, but the femoral arterial sheath was left in place, and the patients were returned to the coronary care unit. Aspirin 325 mg daily and dipyridamole 50 mg every 8 hr were administered during the remainder of the hospitalization and for 6 months after discharge. Systemic heparinization during hospitalization was used at the discretion of the attending physician.

Serial measurements were made of plasma fibrinogen levels at 6 hr intervals and of creatine kinase isoenzyme levels (CK-MB) at 3 hr intervals for the initial 48 hr after admission. Bleeding complications, including the formation of hematomas at the catheterization site and need for transfusions, were carefully documented. The femoral arterial sheath was removed when plasma fibrinogen levels rose to 100 mg/dl or greater, which usually occurred on the second day of hospitalization. Systemic heparinization, when used, was interrupted for approximately 3 hr before and 3 hr after the arterial sheath was removed to ensure adequate hemostasis.

**Measurement techniques.** Fibrinogen levels were assayed by the modified thrombin time method of Ellis and Stransky. CK-MB isoenzyme levels were assayed with the diethylaminoethyl Sephadex minicolumn chromatographic technique. Global ejection fraction was derived from the biplane left ventricular angiograms as previously described. A comparison of global and regional ejection fractions between baseline and follow-up ventriculograms was made and will be the subject of a separate report. Coronary arterial lesions are reported as percent diameter stenosis estimated visually.

**Statistical methods.** Data are reported as mean ± SD. The nonpaired t test was used to assess the significance of difference among continuous variables. The chi-square test with Yates' continuity correction was used to assess the significance of difference among dichotomous variables.

**Results**

**Patients.** Fifty-one patients satisfied the study criteria and were randomized between intravenous (26 patients) and intracoronary (25 patients) streptokinase therapy. Baseline clinical and angiographic characteristics of the two groups of patients were similar (table 1). The overall population had a mean age of 53 years and was made up predominantly of men. Seven of the 51 patients had experienced a prior documented myocardial infarction and one patient had previously undergone coronary revascularization surgery. Six patients had required cardioversion for ventricular fibrillation between the time of onset of infarct symptoms and beginning emergency catheterization.

<table>
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<th>Parameter</th>
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<th>IC streptokinase group (n = 25)</th>
<th>p value</th>
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<td>4 (15%)</td>
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*Between onset of MI symptoms and beginning cardiac catheterization.

IV = intravenous, IC = intracoronary, MI = myocardial infarction, CABGS = coronary artery bypass graft surgery, LV = left ventricular, CAD = coronary artery disease.

The overall population had a mean age of 53 years and was made up predominantly of men. Seven of the 51 patients had experienced a prior documented myocardial infarction and one patient had previously undergone coronary revascularization surgery. Six patients had required cardioversion for ventricular fibrillation between the time of onset of infarct symptoms and beginning emergency catheterization.

Hemodynamic parameters, including left ventricular pressure and left ventricular global ejection fraction, were similar between the two patient groups. Approximately half of the patients (25/51) had single-vessel coronary artery disease. The infarct-related artery was totally occluded immediately before administration of streptokinase in 88% (45/51) of the patients. The infarct-related artery was usually either the left anterior descending or right coronary artery. Interval between onset of myocardial infarction symptoms and randomization to therapy averaged 6.8 ± 3.0 hr in the intravenous streptokinase group and 6.5 ± 2.2 hr in the intracoronary streptokinase group (p = NS).

**Success of therapy**

**Intracoronary streptokinase treatment.** Of the 25 patients randomly allocated to receive intracoronary streptokinase treatment, all patients had a totally occluded infarct-related artery that did not change with contrast injections. Two of the 25 patients (8%) had minimal patency restored immediately after intracoronary nitroglycerin infusion.

Intracoronary streptokinase was judged to be successful, as described above, in 76% (19/25) of the patients receiving intracoronary streptokinase, in 64% (9/14) during phase I of the study, and in 91% (10/11) during phase II of the study (figure 2). Successful thrombolysis was observed in 77% (10/13) of patients with LAD lesions, 67% (2/3) of patients with LCX lesions, and 85% (3/3) with RCA lesions.
lesions, and 78% (7/9) of patients with RCA lesions (p = NS).

In two of the 25 patients receiving intracoronary streptokinase, subselective catheterization of the infarct-related artery (the LAD) was accomplished with a No. 3F intracoronary catheter and was successful in restoring patency in one of these two patients. In one patient receiving intracoronary streptokinase, thrombolysis of an LAD lesion was not achieved after 240,000 IU of streptokinase was delivered into the ostium of the left main coronary artery. Because it was believed that the streptokinase might have been selectively administered into the LCX in this patient, the catheter position was changed and an additional 240,000 IU of streptokinase was administered over 30 min, and successful lysis was noted at the end of this infusion (90 min).

In the first 10 patients receiving intracoronary therapy, streptokinase was delivered by the hand bolus technique with a success rate of 50% (5/10), whereas in the remaining 15 patients a constant infusion pump was used to deliver the streptokinase with a success rate of 93% (14/15) (p < .05). Intracoronary guidewire manipulation was used in three of the 25 patients receiving intracoronary therapy but did not prove useful in reestablishing patency in any patient.

**Intravenous streptokinase therapy.** Of the 26 patients randomly allocated to receive intravenous streptokinase therapy, the infarct-related artery was subtotally occluded on the initial angiogram in two patients and, after contrast, changed from totally to subtotally occluded in an additional two patients. No change in vessel caliber was noted after sublingual nitroglycerin administration.

During phase I of the study (500,000 IU of streptokinase administered intravenously over 15 min), successful thrombolysis was observed in only one of 10 patients (10%). During phase II of the study (1 million IU of intravenous streptokinase administered over 45 min), successful thrombolysis was noted in 44% (7/16). Overall, the success rate with intravenous streptokinase was 31% (8/26). Successful thrombolysis was observed in 18% (2/11) of patients with LAD lesions, 50% (1/2) of patients with LCX lesions, 33% (4/12) of patients with RCA lesions, and in the one patient who had a partially occluded saphenous vein graft to the LAD (p = NS). For the overall study, as well as for both phases I and II, the frequency of thrombolysis with intravenous therapy was significantly less than that for the intracoronary therapy (figure 2).

Of the 18 patients in whom intravenous streptokinase therapy failed, 16 patients underwent other interventions after 45 min of observation, and two patients underwent no further interventions but were observed for an additional 30 min (figure 1). Of the 16 patients undergoing further interventions, one patient subsequently received successful emergency percutaneous transluminal coronary angioplasty. One patient had a successful disruption of his thrombus with intracoronary guidewire manipulation followed by intracoronary streptokinase. Recanalization was not achieved in the remaining 14 patients, each of whom received intracoronary streptokinase (120,000 IU over 30 min) and eight of whom had undergone attempted dissolution of their thrombus by guidewire. Thus, of the 15 patients receiving intracoronary streptokinase and guidewire manipulation as secondary interventions after failure of intravenous streptokinase as the primary intervention, successful thrombolysis occurred in only 7% (1/15), in striking contrast to the 76% (19/25) success rate observed with intracoronary streptokinase when used as primary intervention (p < .0005). Because of this observation, we subsequently abandoned the use of intracoronary streptokinase as a secondary intervention for patients in whom intravenous streptokinase therapy failed.

**Interval from onset of infarction until therapy.** The interval between the onset of myocardial infarction symptoms and beginning therapy averaged 6.3 ± 2.1 hr (range 3.7 to 12.0) among the 27 patients in whom therapy succeeded (6.4 ± 2.2 hr in the 19 patients receiving intracoronary streptokinase and 6.3 ± 2.0 hr in the eight patients receiving intravenous streptokinase)
(figure 3). The interval between onset of infarction and onset of therapy averaged 7.1 ± 2.9 hr (range 3.8 to 19.3) among the 24 patients in whom therapy failed in the study (6.9 ± 2.4 hr in the six patients receiving intracoronary streptokinase and 7.2 ± 3.4 hr in the 18 patients receiving intravenous streptokinase). Thus, patients having successful thrombolysis had a shorter interval between onset of symptoms and treatment than patients in whom therapy failed (6.3 ± 2.1 vs 7.1 ± 2.9 hr), but the difference was not statistically significant.

Interval until lysis. The elapsed time between streptokinase therapy and detection of successful thrombolysis during the catheterization laboratory observation averaged 31 ± 18 min among the 19 patients in whom intracoronary streptokinase was successful and 38 ± 20 min among the eight patients in whom intravenous streptokinase was successful (p = NS) (figure 4). Although there was considerable overlap among the elapsed time until lysis in both groups, it was unusual to detect lysis in the intravenous group before 30 min after onset of therapy, whereas lysis was frequently observed in the intracoronary group as early as 15 min after streptokinase was started.

Systemic anticoagulation. Of the 51 study patients, systemic heparinization was used after thrombolytic therapy in 24 (47%); 12 patients were in the intracoronary group and 12 patients were in the intravenous group. Mean duration of systemic heparinization was 7.2 ± 4.7 days (range 1 to 14) in the group overall, 6.7 ± 4.8 days in the intracoronary group, and 7.8 ± 4.8 days in the intravenous group (p = NS).

FIGURE 3. Success of streptokinase therapy related to time and mode of infusion. There was a trend toward a shorter interval between onset of acute myocardial infarction (AMI) symptoms and onset of therapy in patients in whom thrombolytic therapy was a success in both intravenous (IV) and intracoronary (IC) streptokinase groups.

FIGURE 4. Elapsed time between onset of streptokinase therapy and lysis. Mean elapsed time until lysis was 31 ± 15 min in the 19 patients in the intracoronary (IC) group and 38 ± 20 min (p = NS) in the eight patients in the intravenous (IV) streptokinase group in whom thrombolysis occurred. Thrombolysis before 30 min was unusual among the patients receiving intravenous streptokinase.

Hospital course

Ancillary reperfusion intervention. Of the 51 patients, emergency percutaneous transluminal coronary angioplasty was attempted in three (one in the intracoronary group and two in the intravenous group), and emergency coronary revascularization surgery was attempted in three patients (one in the intracoronary group and two in the intravenous group). One of the patients who underwent emergency coronary revascularization surgery could not be weaned from cardiopulmonary bypass and died. Otherwise, there were no hospital deaths among these 51 patients. Additionally, elective percutaneous transluminal coronary angioplasty was performed before hospital discharge in eight patients (four in each group), and elective coronary revascularization surgery was performed before hospital discharge in eight patients (three in the intracoronary group and five in the intravenous group).

Cardiac enzyme analysis. Serial CK-MB enzyme determinations were available on 38 of the patients who had total occlusion of their infarct-related artery immediately before beginning streptokinase and who had not undergone emergency coronary artery revascularization surgery within 24 hr of streptokinase administration. Of these 38 patients, there were 19 in whom streptokinase had been successful in restoring patency of the infarct-related artery and 19 in whom it had failed (figure 5). Time interval from onset of symp-
During the interval between baseline and follow-up angiography, systemic heparinization was administered *continuously* in 12 patients (seven in the intravenous group and five in the intracoronary group) for a mean of 11.4 ± 1.3 days, was administered *transiently* in 12 patients (five in the intravenous group and seven in the intracoronary group) for a mean of 3.1 ± 2.5 days, and was *not administered* in 12 patients (six in each group). Among patients having a patent infarct-related vessel after streptokinase on the baseline study, the vessel was demonstrated to be patent on the follow-up study in 100% (10/10) of those receiving continuous heparinization, in 78% (7/9) of those receiving transient heparinization, and in 71% (5/7) of those not systemically heparinized (*p* = NS). Among patients having occluded vessels after streptokinase on the baseline study, two received continuous heparinization, three transient heparinization, and five no heparinization; at follow-up angiography, all patients still had occlusion of the infarct-related coronary artery.

One patient in the intravenous group had a 90% stenotic RCA at baseline, and a very large thrombus was visualized within the artery. This patient received 500,000 IU of streptokinase intravenously over 15 min followed by 120,000 IU of intracoronary streptokinase over 30 min. Throughout the entire period of observation in the catheterization laboratory, no resolution of the thrombus was noted, and the vessel remained 90% stenotic. At follow-up angiography 12 days later, however, no thrombus or residual stenosis was noted, and...
the patient’s left ventricular ejection fraction had increased from 46% to 66%. Although therapy in this patient was classified as unsuccessful according to the previously defined criteria, clearly both his vessel patency and ventricular function had improved over time. None of the other patients with subtotally occluded arteries experienced such dramatic spontaneous improvement.

Complications. Hemorrhagic complications with thrombolytic therapy were infrequent in this study (table 2). Hematoma formation, usually at the femoral arterial puncture site, was common in patients in both intravenous and intracoronary streptokinase groups but it was rarely of any clinical consequence.

Bleeding requiring transfusion occurred in only two patients, both while receiving heparin, one requiring 2 units transfusion for blood loss into a large hematoma and a second requiring 3 units transfusion for a suspected retroperitoneal bleed. Hematocrit fell significantly in both patient groups (figure 7).

Evidence of a systemic lytic state was noted in patients in both intravenous and intracoronary groups, but the falls in plasma fibrinogen levels were most profound in the intravenous group, as expected, since they received more streptokinase (figure 8). Two days after streptokinase, fibrinogen levels had spontaneously risen into the normal range in both patient groups.

Discussion

This prospective randomized study comparing the effects of intravenous and intracoronary streptokinase in patients with acute myocardial infarction undergoing emergency coronary arteriography demonstrates unequivocally that intracoronary streptokinase has a thrombolytic efficacy superior to that of intravenous streptokinase. However, high-dose, short-term intravenous streptokinase may lyse coronary arterial thrombi in a large minority (44%) of patients in whom it is administered in high doses, and, because of its increased availability, intravenous streptokinase may have a definite role in the treatment of patients who do not have immediate access to cardiac catheterization. Additionally, this trial shows the relative ineffectiveness of intracoronary streptokinase when used as a secondary intervention in patients in whom intravenous streptokinase therapy failed. The complication rates of both intracoronary and intravenous streptokinase are acceptably low.

**Thrombolytic effectiveness.** The frequency of thrombolysis with intracoronary streptokinase observed in

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**FIGURE 7.** Change in hematocrit after streptokinase therapy. During the first 4 days after infarction, hematocrit fell significantly in patients receiving intravenous (IV) streptokinase (SK) and in those receiving intracoronary (IC) streptokinase. BSL = baseline.

**FIGURE 8.** Change in plasma fibrinogen levels after streptokinase therapy. Plasma fibrinogen levels fell dramatically with the administration of both intracoronary (IC) and intravenous (IV) streptokinase (SK) and demonstrated a systemic lytic state with both routes of streptokinase administration. Although a more profound lytic state was noted in the patients receiving intravenous streptokinase, by 2 days after therapy fibrinogen levels had returned to the normal range in both groups. BSL = baseline.
our study correlates closely with the reported experience of others, but the frequency of thrombolysis with intravenous therapy is somewhat lower. No previous trial has compared the two modes of therapy by using a prospective randomized design with coronary arteriographic control. Since the original description of intracoronary thrombolytic therapy by Rentrop et al., numerous clinical reports have confirmed the effectiveness of streptokinase as an intracoronary thrombolytic agent, and thrombolytic success rates are generally quoted to range from 65% to 85%. Although the efficacy of intravenous streptokinase therapy in the treatment of acute myocardial infarction has been widely tested, in many previously reported trials streptokinase has been administered without use of coronary arteriography to document whether the thrombolytic therapy was successful in restoring patency to a thrombosed coronary artery. Only recently has serial coronary arteriography been used to assess the effects of high-dose, short-term intravenous streptokinase therapy, and in these studies the reported thrombolytic efficacy of intravenous streptokinase has ranged from 46% to 67%.

The present study documents an overall thrombolytic effectiveness of 76% (19/26) with intracoronary streptokinase (figure 2), which is equivalent to that of other reported series. Moreover, the success rate rose from 64% (9/14) to 91% (10/11) during the two sequential phases of the study, possibly reflecting a learning curve phenomenon. It is possible that the change in the intracoronary streptokinase infusion method from hand bolus to constant infusion pump accounts for the higher thrombolytic effectiveness of intracoronary streptokinase during the latter part of the study. The thrombolytic effectiveness with the 500,000 IU intravenous streptokinase was 10% (1/10), lower than that reported by others. However, the thrombolytic effectiveness of the 1 million unit intravenous streptokinase regimen was 44% (7/16), similar to the 46% effectiveness reported by Spann et al. using similar dosages, but lower than the 67% success rate reported by Neuhaus et al., who infused 1.55 ± 0.49 million IU of streptokinase intravenously over 61 ± 16 min.

Although the thrombolytic effectiveness of the intravenous streptokinase would appear to be significantly less than that of intracoronary streptokinase, it should be remembered that the intravenous regimen is potentially applicable to many more patients than is the intracoronary regimen. The overall usefulness of any therapeutic regimen for myocardial infarction is a function of not only the effectiveness of the therapy but also the proportion of the infarct population on whom it can be used. Although intracoronary streptokinase may have a thrombolytic effectiveness approaching 90%, it is not likely that more than 10% of patients experiencing acute myocardial infarction in this country will have immediate access to coronary arterial catheterization facilities, and thus the overall usefulness of this form of therapy for the general population of patients experiencing acute myocardial infarction is reduced to only 9% (90% × 10%). On the other hand, although the thrombolytic effectiveness of intravenous streptokinase may approach only 50%, it is potentially applicable to perhaps 90% of patients with acute myocardial infarction, yielding an overall usefulness of approximately 45% (90% × 50%), five times that of the intracoronary streptokinase regimen.

Moreover, intravenous streptokinase can be administered sooner after onset of symptoms, thus potentially salvaging more myocardium. The intravenous regimen is logistically simpler and avoids the psychological trauma, the documented risk, and the expense of emergency cardiac catheterization. All of these advantages make intravenous streptokinase a highly attractive regimen, even though its current effectiveness is documented at only 44% in this study. Greater thrombolytic effectiveness was seen with the higher-dose regimen in our study, and further improvement in success rates may be noted when the intravenous dosage regimen is increased even further.

Elapsed time between beginning streptokinase and thrombolysis. It has been previously observed that high-dose, short-term intravenous streptokinase therapy often lyses coronary arterial thrombi somewhat slower than direct intracoronary streptokinase infusion, although no previous study has compared these two regimens in a controlled fashion. The present study demonstrates that after onset of intravenous streptokinase infusion, lysis rarely occurs before 30 min, whereas lysis quite frequently occurs with intracoronary streptokinase within 15 min of onset of therapy (figure 4). However, the mean elapsed time until lysis between intravenous and intracoronary groups was not significantly different in our series.

Likelihood of “late” thrombolysis. Since intravenous streptokinase tends to produce lysis at a slower rate than the intracoronary regimen, the possibility arises that some patients treated with intravenous streptokinase might have undergone “late” thrombolysis and might have actually been misclassified as having had unsuccessful therapy, whereas in reality therapy was successful. Two lines of reasoning suggest that this was not the case.
First, serial CK-MB isoenzymes (figure 5) showed that elapsed time from onset of symptoms until CK-MB\textsubscript{max} was significantly longer (22 ± 7 hr) in those patients in whom thrombolysis did not occur during the catheterization laboratory observation than in those in whom thrombolysis did occur (15 ± 5 hr; p < .001).\textsuperscript{3,5} However, within the subgroups of patients in which streptokinase therapy produced successful thrombolysis as well as within the subgroups in which it failed, there was no significant difference between the mean interval from onset of symptoms until CK-MB\textsubscript{max} among the intravenous and intracoronary randomized subsets. If a significant number of patients classified as failing intravenous streptokinase had undergone thrombolysis immediately after the angiographic observation period, a shorter interval between onset of symptoms and CK-MB\textsubscript{max} might have been expected in that subgroup. This phenomenon was not observed (figure 5). However, the precision of the enzymatic "wash-out peak" analysis is blunted somewhat because many patients in both the intracoronary and intravenous groups received therapy more than 6 hr after onset of symptoms, making a "reperfusion peak" more difficult to discern. Nevertheless, in this randomized study it is relevant that the data for CK-MB levels were identical for patients receiving intravenous and intracoronary therapy within the groups in which thrombolysis was a success or failure (figure 5).

Second, if a significant number of patients in the intravenous streptokinase group had experienced late thrombolysis, either related to the streptokinase therapy or to spontaneous thrombolysis, one might have expected to find infarct-related arteries open at the time of follow-up catheterization 2 weeks after infarction that had not been open after the initial therapy on the day of admission. However, among the 36 patients who did undergo repeat coronary arteriography at a mean of 2 weeks after infarction, no patient was observed to have had recanalization of an occluded infarct-related artery in the interval between the two studies (figure 6). Patent arteries in four patients (one in the intravenous group and three in the intracoronary group) had reoccluded, however, after the initial study. Several of the other patients showed dramatic reduction in the extent of their subtotal coronary arterial stenoses, possibly related to further resolution of thrombus or healing of the atherosclerotic lesion.

In our study, the follow-up patency rate of infarct-related arteries in patients treated with intravenous streptokinase is lower than that reported by Schroder et al.\textsuperscript{5} and is likely related to the shorter duration between symptoms and onset of therapy, the higher dosage of intravenous streptokinase used, and the uniform continuous systemic anticoagulation used in their study. In our study, patients with patent vessels at the end of the baseline intervention more often had patent vessels at follow-up when they were continuously systemically anticoagulated, but this trend did not reach statistical significance.

**Intracoronary streptokinase as a secondary intervention.** One possible application of thrombolytic therapy in acute myocardial infarction might be to administer intravenous streptokinase to patients with suspected infarction in emergency transport vehicles\textsuperscript{5,18} or in emergency rooms en route to the cardiac catheterization laboratory, and then to administer streptokinase by the intracoronary route to those patients in whom intravenous streptokinase failed. The overall effectiveness of intracoronary streptokinase as a primary intervention in our study was 76% compared with an effectiveness of 6% as a secondary intervention (p < .0005). This was an unexpected observation in our study and is not readily explained.

One possible explanation might be relative plasminogen depletion after the initial intravenous dose. Streptokinase is an indirect plasminogen activator, first binding to plasminogen and then the bound complex activates unbound plasminogen to form plasmin. The large bolus doses of intravenous streptokinase administered in our study may have formed a complex with most of the available plasminogen and left only a small amount of free plasminogen available for activation to plasmin, explaining why further intracoronary streptokinase infusion was ineffective.\textsuperscript{19}

**Complications.** One concern with intravenous high-dose streptokinase regimens has been that hemorrhagic complications might be much higher than that experienced with the lower-dose regimens of intracoronary streptokinase. Indeed, in one large randomized prospective trial of intravenous streptokinase vs placebo, the hemorrhagic complications, including cerebrovascular accidents, were significantly greater in patients receiving streptokinase than in controls.\textsuperscript{30}

The low rate of hemorrhagic complications with intravenous streptokinase in our study (table 2) is consistent with the reports of others who have used high-dose, short-term intravenous streptokinase in the treatment of patients with acute myocardial infarction.\textsuperscript{5-7} The shorter duration of streptokinase administration in these recent studies may account for the lower frequency of hemorrhagic complications than had been reported with earlier studies in which longer durations of infusion were used.

In the present study, we documented with serial
fibrinogen levels that a systemic lytic state was produced by both the intracoronary and intravenous streptokinase regimens (figure 8). Marked systemic fibrinolysis after similar doses of intracoronary streptokinase has been previously reported.21-22 We found the systemic fibrinolytic state to be somewhat more profound in patients receiving intravenous streptokinase, but within 24 hr after onset of therapy, the statistical distinction between the patients receiving intravenous and intracoronary streptokinase was lost. We did note a fall in hematocrit in both patient groups (figure 7). Although this phenomenon was probably partially explained by frequent blood sampling and by hematoma formation in some patients, a fall in hematocrit of similar magnitude has been previously reported in patients with acute myocardial infarction not receiving thrombolytic therapy.23

Limitations of study design. The current study had a prospective randomized design, and its primary endpoint was the angiographic documentation of thrombolysis promptly after therapy. Since clinical judgment dictated that all patients were not managed absolutely identically after the baseline catheterization, interpretations of late results from these patients are subject to limitations. For example, ancillary reperfusion interventions such as emergency percutaneous transluminal coronary angioplasty and emergency coronary revascularization surgery were performed in some patients, and these interventions might have influenced the interpretation of subsequent measurements, such as the left ventricular function or the patency of the infarct-related artery at the time of repeat angiography.

Another limitation of the study is the lack of inclusion of a significant number of patients admitted within the first few hours after onset of symptoms of acute infarction. Our data (figure 3) and those of other investigators5, 24-28 suggest that thrombolytic therapy may be most successful in lysing clots when administered early, and it is conceivable that the success rate of either form of therapy, or both, might have been greater had the patients been administered the therapy sooner after onset of symptoms. For example, in patients treated with high-dose, short-term intravenous streptokinase within 3 hr of symptoms, Neuhaus et al.26 reported a thrombolytic success rate of 73% and Schroder et al.5 reported a success rate of 100%, with the latter investigators using guidewire recanalization and intracoronary streptokinase in selected patients. Our patient population, however, is not an unrealistic one and falls well within the range of inclusion of most similar studies on thrombolysis in acute myocardial infarction.

A major strength as well as a major limitation of our study design was the requirement that patients receiving intravenous streptokinase must first receive baseline coronary arteriograms. This requirement undoubtedly handicapped those receiving intravenous streptokinase by adding 1 to 2 hr to the interval between onset of symptoms and beginning therapy. However, other than by angiography, there is no absolutely precise way to document coronary arterial reperfusion.

Finally, although the objective of this study was to assess the thrombolytic efficacy of streptokinase administered by two routes, coronary artery recanalization does not necessarily ensure benefits for the patient because left ventricular function may not reliably improve in all patients after successful thrombolysis.27

References


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