The Primary Care Physician And Thrombolytic Therapy For Acute Myocardial Infarction: Comparison Of Intravenous Streptokinase In Community Hospitals And The Tertiary Referral Center

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Abstract: **From September 1982 through December 1987, 1012 patients were treated with intravenous streptokinase within 6 hours of acute myocardial infarction. Most of them (816/1012, 81 percent) were treated in community hospitals by primary care physicians. The remaining 196 (19 percent) were treated in the referral center, usually by a cardiologist. Cardiac catheterization within 2 days showed an open infarct artery in 87 percent of the community hospital and 83 percent of the referral center patients (P = NS). Predischarge ejection fraction was similar for community hospital and referral center patients (49 percent ± 14 percent versus 51 percent ± 14 percent, respectively), and there was a similar rate of bleeding complications (10 percent versus 13 percent, respectively). We conclude that primary physicians can use intravenous streptokinase effectively and safely in the treatment of patients in community hospitals. (J Am Bd Fam Pract 1990; 3:1-6.)**

Intravenous thrombolytic therapy has become the standard care for acute myocardial infarction (AMI) because it improves survival,[1,2] saves left ventricular myocardium,[3,4] and reduces the likelihood of congestive heart failure.[5] Most studies of thrombolytic therapy have been performed in tertiary care facilities by cardiologists. Community hospital studies have been small,[6-9] and the safety of thrombolysis in the community hospital setting has not been established with certainty. We describe our 7-year experience comparing the efficacy and safety of intravenous streptokinase for AMI in community hospitals and a tertiary care center.

Methods

The treatment protocol has been described previously.[10] Informed consent was obtained using a format approved by the Springfield Committee for Research Involving Human Subjects. Briefly, patients with acute transmural myocardial infarction (AMI) and chest pain for less than 6 hours were treated with intravenous streptokinase. Risk of bleeding was minimized by excluding patients who had: (1) surgery or trauma within 6 weeks of AMI, (2) prior stroke, (3) active peptic ulcer disease, (4) sustained diastolic blood pressure in the emergency department greater than 100 mmHg, and (5) history of uncontrolled hypertension. Advanced age was not a contraindication to therapy, but "frail" elderly patients were not treated, while vigorous and active 80-year-olds were. Patients having had d.c. cardioversion for ventricular fibrillation or tachycardia were treated, but others who had prolonged cardiopulmonary resuscitation and external chest compression were excluded.

The electrocardiographic diagnosis of anterior AMI included at least 0.2 mv of S-T segment elevation in 2 or more precordial leads. The diagnosis of inferior AMI required both S-T segment elevation in inferior leads and reciprocal S-T segment depression in anterior or lateral

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leads. These criteria supported our intent to treat only patients with the largest infarctions.[11] Patients with subendocardial infarctions were excluded.[12,13]

Intravenous streptokinase was administered to patients in the emergency department as soon as the diagnosis of AMI was confirmed by the primary care physician. An initial dose of 500,000 IU was given intravenously for 5 minutes followed by 200,000 IU per hour for 4 hours. Then, heparin was given at about 1000 units per hour by continuous infusion, the dose adjusted to maintain partial thromboplastin times at 50–100 seconds. In patients who had an open infarct artery at catheterization, heparin was continued for at least 3 days or until the time of interventional revascularization, but it was discontinued when catheterization showed unsuccessful thrombolysis. All patients were given prophylactic lidocaine beginning with the initial streptokinase infusion, but they were not treated with aspirin during the acute phase of infarction.

Patients treated with intravenous streptokinase in community hospitals were transferred to our tertiary hospital, and angiography was performed within 48 hours of starting intravenous streptokinase. Most often, transfer occurred the day after thrombolytic therapy, at a time when clinical stability allowed transport by ambulance. Helicopter transport was used for those who were considered unstable. All patients were accompanied by a coronary care unit nurse during transfer.

Coronary revascularization, either by means of percutaneous transluminal coronary angioplasty or bypass surgery, was recommended for arteries showing ≥ 70 percent reduction in luminal diameter and supplying apparently viable myocardium. Most patients had a radionuclide left ventricular angiogram before hospital discharge.[10] For the purpose of this study, successful thrombolysis was defined as an open infarct artery at catheterization. Summary data are expressed as means ± standard deviations. Statistical significance was determined using the t-test for continuous variables and chi-square test for categorical variables.

Results

From September 1982 through December 1987, 1012 patients who met entry criteria were treated with intravenous streptokinase. Most (816/1012, 81 percent) were treated in rural hospitals ranging in size from 30 to 367 beds (median, 117 beds) by primary care physicians (family physicians, emergency physicians, or internists). The remaining 196 (19 percent) were treated in the referral center, usually by a cardiologist.

Table 1. Clinical Characteristics.

	Community Hospital	Referral Center
	n = 816* (percent)	n = 196* (percent)
Age (years)	56 ± 11	57 ± 11
Men	656 (80)	151 (77)
First AMI	685 (84)	166 (85)
Anterior AMI	340 (42)	70 (36)
Inferior AMI	465 (57)	122 (62)
Killip II (rales)	237 (29.0)	70 (35.7)
Killip III (pulmonary edema)	18 (2.2)	3 (1.5)
Killip IV (cardiogenic shock)	35 (4.3)	9 (4.6)
CP to SK (minutes)	173 ± 96	161 ± 76
ER to SK (minutes)	86 ± 48	77 ± 47

CP = Onset of chest pain.
SK = Intravenous streptokinase.
ER = Arrival in emergency room.
*There was no statistically significant difference between community hospital and referral center patients for any of these characteristics.

Clinical characteristics of the community hospital and referral center patients were similar (Table 1). Most were men and most were having their first AMI. The location of infarction in both groups was similar, with a majority having inferior AMI. The frequency of heart failure on admission, defined as rales (Killip Class II), pulmonary edema (Class III), or cardiogenic shock (Class IV), was similar in community hospitals and the referral center (Table 1). Time from onset of chest pain to treatment also was similar (173 ± 96 minutes versus 161 ± 76 minutes, P = NS). The referral center was somewhat more prompt in initiating therapy after arrival in the hospital, but even there, it took an average of 77 minutes (Table 1).

The effectiveness of treatment was similar in both locations (Table 2). More than 80 percent of patients in both community hospitals and the referral center had an open infarct artery at the time of catheterization (Table 2). Death during

Table 2. Clinical Outcome.

	Community Hospital	Referral Center
	n = 816* (percent)	n = 196* (percent)
Reperfusion	710 (87)	162 (83)
Anterior AMI	289/340 (85)	59/70 (84)
Inferior AMI	410/465 (88)	99/122 (81)
Post/Lat AMI	11/11 (100)	4/4 (100)
Peak CPK (IU/L)	2605 ± 2813	2400 ± 1691
Elevated CPK	793/811 (98)‡	192/195 (98)‡
Death	39 (5)	12 (6)
PTCA	181 (22)	36 (18)
CABG	346 (42)	96 (49)
PTCA + CABG	25 (3)	6 (3)
Discharge EF†	(49 ± 14)	(51 ± 14)
Days in hospital	11 ± 5	12 ± 7

CPK = Creatine phosphokinase.
PTCA = Percutaneous transluminal coronary angioplasty.
CABG = Coronary artery bypass grafting.
*There was no statistically significant difference between community hospital and referral center patients for any of these clinical outcomes.
†Predischarge left ventricular ejection fraction was measured using radionuclide angiogram in 62 percent patients (503/816) for community hospitals and 67 percent (131/196) treated in the referral center.
‡Data not available for 6 patients.

hospitalization occurred in 5 percent of community hospital patients and 6 percent of patients at the referral center. A critical issue is whether primary care physicians in community hospitals properly selected patients for treatment with streptokinase. Were all patients treated actually having AMI? This appears to be the case because the frequency of creatine kinase elevation and peak creatine kinase measurements were similar in both settings (Table 2).

All patients in the study had cardiac catheterization. Those with critical (≥ 70 percent reduction in luminal diameter) or unstable-appearing lesions in the infarct artery or with multivessel disease usually needed a revascularization procedure, and the likelihood of revascularization was similar for community hospital (64 percent) and referral center patients (67 percent, Table 2). Predischarge left ventricular ejection fractions measured with a radionuclide angiogram and duration of hospitalization were similar for the two groups (Table 2).

Transfer from the community hospital to the referral center was accomplished within 12 hours in 124 of 816 patients (15 percent). Another 409 patients (50 percent) were transferred 12 to 36 hours after the onset of AMI, and the remainder were transferred more than 36 hours afterwards. No patient died during transfer, and the average transfer distance was 71 ± 41 miles (range, 27–180; median, 64).

Complications

Bleeding is the major complication of thrombolytic therapy, and it was observed in 108 of the 1012 patients (10.7 percent). Risk of bleeding was similar for community hospital and referral center patients (Table 3). Groin hematoma from cardiac catheterization was common, and 38 patients required either longer hospitalization or another intervention. Only 1 patient required surgical drainage of the hematoma, and 7 needed transfusion. Gastrointestinal bleeding was the other most common cause of bleeding, and 13 patients required transfusion (Table 3). Hematuria was seen rarely (Table 3). Only 3 of the 1012 (0.3 percent) patients had intracranial bleeding as a result of treatment, and one of them died. This was the only patient in this series who died as a result of bleeding.

Complications other than bleeding, especially allergic reactions and arrhythmias, were studied

Table 3. Bleeding Complications.

Bleeding Site	Community Hospital	Referral Center
	n = 816* (percent)	n = 196* (percent)
Catheterization	22 (2.7)	16 (8.2)
Transfusion	2 (0.3)	5 (2.6)
GI	30 (3.7)	7 (3.6)
Transfusion	12 (1.5)	1 (0.5)
GU	12 (1.5)	0
Transfusion	0	0
Intracranial	2 (0.3)	1 (0.5)
Transfusion	0	0
Other	16 (2.0)	2 (1.0)
Transfusion	3 (0.4)	1 (0.5)
Total	82 (10.1)	26 (13.3)
Transfusion	17 (2.1)	7 (3.6)

GI = gastrointestinal.
GU = genitourinary.
*There was no statistically significant difference between community hospital and referral center patients for any of these clinical outcomes.
†Other includes venipuncture (15), ankle hematoma (1), scleral hemorrhage (1), retroperitoneal bleed (1).

carefully in the first 334 patients (initial 3 years). Allergic reactions to streptokinase were uncommon; no patient had anaphylactic shock or hives. Hypotension was observed occasionally during the initial, bolus infusion of streptokinase. When this occurred, the bolus infusion was stopped; 200 mL normal saline was given intravenously; and streptokinase was then infused at 200,000 units/hour. Using this approach, only 2 of the 334 patients (0.6 percent) were unable to receive the full 1.2-million-unit dose of streptokinase. Ventricular arrhythmias are common early after AMI, and ventricular ectopy may worsen during reperfusion. Nonsustained ventricular tachycardia occurred in 25 percent (82 of 334) of our patients after starting streptokinase infusion, and 3 percent (9 of 334) required d.c. cardioversion for either ventricular tachycardia or fibrillation. By contrast, heart block, commonly observed in patients with inferior myocardial infarction, was not a reperfusion arrhythmia. Instead, patients with inferior infarction and heart block had dramatic improvement with reperfusion.

Discussion

Duration of ischemia is directly related to the extent of myocardial injury in patients with AMI. The best predictor of myocardial salvage with reperfusion therapy is time from onset of symptoms to treatment.[14-16] Our earlier experience with intracoronary streptokinase confirmed that cross-country transfer of patients drastically delays therapy.[10] Because delay means more injury, a strategy requiring that all patients be transferred to another hospital for initial therapy of AMI (such as intracoronary thrombolysis, acute percutaneous transluminal coronary angioplasty, or acute coronary artery bypass surgery) is misguided. Patients who are candidates for thrombolytic therapy should be treated as soon as the diagnosis of AMI is made. Thrombolytic therapy for AMI thus belongs in the community hospital, in the emergency department, and in the hands of the primary care physician.

Yet there has been reluctance among primary care physicians to use thrombolytic drugs, possibly because of the risks of therapy. A recent survey indicated that family physicians who regularly treat AMI are one-third as likely to use thrombolytic therapy as cardiologists.[17] Our large study shows that primary care physicians in community hospitals can treat patients as effectively as cardiologists in the referral center and with no increase in complication rates.

Life-threatening bleeding was uncommon in our study; only 2.4 percent of patients bled seriously enough to require transfusion, 3 had intracranial bleeding (0.3 percent), and only 1 patient (0.1 percent) died from a bleeding complication. The risk of bleeding is reduced by excluding patients with active peptic ulcer disease, uncontrolled hypertension, history of stroke or transient ischemic attack, and recent trauma or surgery (see Methods). We have seen large hematomas at arterial puncture sites, so routine arterial blood gas measurements should be avoided. While such precautions lower the risk, bleeding still is a risk of therapy that patients and their families must understand before treatment. But when the risk of bleeding is being considered by the physician and family, they must also understand that the mortality risk from transmural myocardial infarction can exceed 10 percent. The reduction in mortality and heart failure demonstrated by randomized trials[1-4] and the low mortality observed in community hospitals in the present study justify thrombolysis despite the 10 percent risk of bleeding. Thrombolytic therapy for AMI should represent the "standard of care" for community hospitals.

We have limited thrombolytic therapy to patients with AMI and S-T segment elevation ("transmural infarction") for three reasons. First, these patients usually have transmural injury, develop Q waves, have the largest infarction, and therefore have the highest mortality risk with AMI. It appears reasonable to limit higher risk therapies to that higher risk group.[12,13] Second, patients with S-T segment depression or T-wave inversion either have no subsequent elevation of creatine kinase or have smaller infarction; we have found that they generally have patent though tightly stenosed coronary arteries. Their ischemia often can be controlled with a combination of vasodilators and anticoagulants and with a lower risk of bleeding when compared with thrombolytic drugs.[18,19] Third, limitation of thrombolysis to those with ischemic S-T segment elevation reduces the chance of treating patients with noncardiac chest pain such as peptic esophagitis or gastritis, dissecting aneurysm, and even pericarditis.

An important finding in our study is that community hospital physicians appropriately selected patients for thrombolysis. Patients from community hospitals and the referral center had a similar frequency of elevated creatine kinase measurements. But this would be misleading if patients treated with streptokinase in community hospitals were not transferred. During the first 2 years of this study, we monitored community hospitals for this possibility and found that just 3 of 195 (1.5 percent) patients treated with streptokinase were not transferred.[20] The converse issue is whether thrombolytic therapy was inappropriately withheld from patients with acute transmural infarction in the community hospitals. We did not survey all patients evaluated in the emergency departments of these 23 hospitals (including the referral center), and thus cannot quantitate failure to treat. This issue is complicated by the fact that not all physicians practicing in each of these 23 hospitals participated in this experimental study.

We continued to use the dose of intravenous streptokinase chosen in 1982 throughout the study. The Food and Drug Administration approved intravenous streptokinase for AMI in November 1987, and the recommended dose was 1.5-million units intravenously during a 60-minute period. This total dose is not substantially different from that used in our study, and we are now using the FDA approved dose. Another important recent development with streptokinase therapy is the demonstration that 2 aspirin administered with intravenous streptokinase substantially improves survival.[21] It is noteworthy that in the aspirin study, patients chewed 2 aspirin tablets rather than swallowed them in order to achieve a more rapid blood level; we have incorporated this into our protocol.

Follow-up has been described for the initial 192 patients in this study; only 4 percent, (7/180) of the survivors of hospitalization died during the next 2 years.[20] This excellent survival rate for patients with acute, transmural AMI may be attributed to a treatment strategy including both thrombolytic therapy and early revascularization. For this reason, and because coronary reocclusion and unstable angina are commonly seen after thrombolytic therapy, we continue to recommend transfer of patients for cardiac catheterization after initial stabilization.

The next major advance in reperfusion therapy for AMI must be achievement of even earlier application of thrombolytic therapy. Our patients treated both in community hospitals and the referral center had a delay of 80 minutes from time of arrival in the emergency department to the initial streptokinase infusion. That is too long, and the goal of every program must be to shorten its response time. This and improved patient awareness of early symptoms of AMI would shorten average time to treatment, and thus further reduce morbidity and mortality with AMI.

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