Invasive strategy following fibrinolysis in ST-elevation acute myocardial infarction

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Key words:
Coronary angioplasty; Interventional procedures; Myocardial infarction.

Background. **A recognized drawback of ST-elevation acute myocardial infarction (STEMI) after fibrinolysis is persistent coronary occlusion or a less than TIMI 3 flow. The present study describes the results of systematic pre-discharge coronary angiography and revascularization, whenever indicated, following fibrinolytic therapy for STEMI.**

Methods. **Consecutive patients admitted with the diagnosis of STEMI between April 1, 2000 and April 30, 2002 were included in the study. Patients with contraindications to thrombolytic therapy and/or patients not eligible for angiography were excluded. All patients received "accelerated" treatment with alteplase and had a coronary angiography at least 24 hours later, in order to perform, if anatomically feasible, angioplasty with stenting. Angioplasty of non-infarct-related coronary arteries was allowed. The mortality, reinfarction and new revascularization rates were evaluated during index hospitalization and up to 30 days and 6 months.**

Results. **Eighty patients underwent cardiac catheterization at a median of 6.5 days following admission; in 86.3% of cases a patent infarct-related artery was found; in 71% of patients a coronary angioplasty was performed, with stenting in 88% of cases. Procedure-related complications were infrequent. No deaths occurred during hospitalization and at 30 days; at 6 months the mortality rate was 1.3%. In-hospital reinfarction occurred in 3.8% of patients, in 4% at 30 days and in 5.3% at 6 months. The rate of any new revascularization was 2.6% at 30 days and 11% at 6 months.**

Conclusions. **Although obtained in a small observational study, our data, unlike those from previous studies, suggest that an invasive strategy after fibrinolysis in STEMI is safe and associated with low mortality and morbidity rates in the short and medium terms.**

(Ital Heart J 2004; 5 (9): 688-692)

Received October 27, 2003; revision received May 27, 2004; accepted July 15, 2004.

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Background

Occlusive thrombosis of a coronary atherosclerotic plaque is the main pathogenetic mechanism leading to acute myocardial infarction[1,2]; when the occlusion is sudden and persistent in an epicardial coronary artery, the most common ECG pattern is ST-segment elevation. The treatment of choice has been shown to be mechanical recanalization by primary percutaneous transluminal coronary angioplasty (PTCA)[3,4].

The best outcomes of primary PTCA have been obtained in hospitals with advanced treatment facilities which the majority of hospitals do not have: centers that perform numerous procedures, supported by experienced personnel, with a 24-hour service, and a door-to-balloon time < 90 ± 30 min[5,6]. Even the favorable results reported in trials evaluating primary PTCA in patients transported from a local hospital without angioplasty facilities to an invasive treatment center[7,8] have been obtained from countries with a better than average connecting network between referring hospitals and tertiary care centers.

Fibrinolysis remains the mainstay of reperfusion treatment, because it is more widely available and less time-consuming than primary angioplasty[9]. Nevertheless, the incidence of persistent coronary occlusion after fibrinolysis is 19% and the incidence of a flow grade < 3, according to the Thrombolysis In Myocardial Infarction (TIMI) classification[10], is around 46%[11]. Furthermore, it is frequent to find critical stenosis in non-infarct-related coronary vessels.

Which is the best strategy to prevent major adverse cardiac events following fibrinolytic therapy is rather controversial. The current American College of Cardiology/American Heart Association (ACC/AHA) guidelines suggest that routine PTCA of the infarct-related artery should not be routinely performed following thrombolytic therapy[12].

These guidelines are largely derived from trials[13,14] conducted before the advent

of coronary stents and platelet glycoprotein IIb/IIIa receptor blockers. These two major advances in interventional cardiology have been found to reduce peri- and post-procedural adverse events in patients with unstable angina or non-ST-elevation acute myocardial infarction undergoing percutaneous interventions[15-22] or in patients with ST-elevation acute myocardial infarction (STEMI), together with primary angioplasty[23-25].

Only limited information exists on a strategy of systematic coronary angiography and, possibly, revascularization prior to hospital discharge in patients treated with fibrinolytic therapy on admission. In the present article, we present the results of a single-center, observational study including patients with these characteristics.

Methods

This study has been conducted on a population of consecutive patients referred to our hospital between April 1, 2000 and April 30, 2002 with a diagnosis of acute myocardial infarction.

Patients presenting with typical chest pain lasting < 12 hours and associated with ECG signs of persistent ST-segment elevation of at least 1 mm in ≥ 2 standard leads, or 2 mm in ≥ 2 precordial leads, or new or presumed new left bundle branch block, were eligible for enrollment.

Exclusion criteria were the usual contraindications to fibrinolytic therapy: symptoms lasting > 12 hours; uncontrolled hypertension; history of hemorrhagic stroke; active or recent bleeding; ischemic cerebrovascular accident within 1 year; suspected aortic dissection. Furthermore, patients not eligible for angiography were also excluded.

Fibrinolytic treatment was administered using tissue plasminogen activator, in accordance with the "accelerated" protocol[26], together with intravenous unfractionated heparin, aspirin and beta-blockers when not contraindicated.

Angiography was carried out no sooner than 24 hours following admission, with an approach left to the discretion of the attending physician. The aim of the invasive procedure was to perform angioplasty with stenting of the infarct-related artery, if anatomically feasible. In case of multivessel disease, angioplasty of non-infarct-related arteries could be performed.

Procedure-related reinfarction was diagnosed on the basis of a post-angioplasty increase in creatine kinase and MB levels > 3 times the upper limit of normal, or > 3 times the last abnormal value. For all patients, blood samples were analyzed immediately after the procedure and 12 hours later. Major bleeding was defined as an intracranial hemorrhage or bleeding requiring blood transfusion or resuscitation.

The endpoints were: 1) death during hospitalization and at 30 days and 6 months; 2) non-fatal reinfarction during hospitalization and at 30 days and 6 months; 3) necessity of new revascularization (PTCA or bypass surgery) at 30 days and at 6 months.

In-hospital reinfarction was diagnosed on the basis of an increase in creatine kinase and MB serum levels > 2-fold the upper limit of normal, or > 2-fold the last abnormal value. Reinfarction at 30 days and at 6 months was diagnosed only in the presence of a documented increase in creatine kinase and MB serum levels associated with typical chest pain or ECG changes.

All patient data were collected during regular follow-up visits or, whenever the patients did not or were unable to attend, by telephone interview.

Results

Between April 2000 and April 2002, 160 patients with STEMI have been treated in our Center; 80 patients met the inclusion criteria and were enrolled in the study: their characteristics are shown on table I. Seventy patients were excluded because of contraindications to fibrinolytic therapy (39 of them due to a delayed arrival, 21 because the ECG criteria were not satisfied, and 10 because of other contraindications); 10 patients were excluded because they had not been submitted to angiographic evaluation (3 of them died earlier than 48 hours following admission, 3 had an intracranial hemorrhage, and 4 had significant comorbidities).

The median length of hospital stay was 9 days (25-75%, 7-12 days). Additional treatment during the first 24 hours following admission included: aspirin (98% of patients), unfractionated heparin (95%), low-molec-

Table I. Baseline characteristics of the patients.

No. patients	80
Age (years)	62 ± 11
Males	70 (88%)
Current smokers	43 (54%)
Hypertension	36 (45%)
Hyperlipidemia	29 (36%)
Diabetes	17 (21%)
Killip class	
1-2	79 (99%)
3-4	1 (1.2%)
Infarct localization	
Anterior	31 (39%)
Inferior	21 (26%)
Other	23 (29%)
Non-Q	5 (6%)
Ejection fraction (%)	53 ± 9
Hospital length of stay (days)	
Mean	10 ± 6
Median	9 (7-12)*
Time from symptom onset to admission (hours)	
Mean	2.3 ± 1.5
Median	2 (1.2-3)*

* values are medians and 25th-75th percentile range.

ular-weight heparin (3.8%), platelet glycoprotein IIb/IIIa receptor blockers (13%), beta-blockers (70%), nitrates (73%), and ACE-inhibitors (35%).

The incidence of post-infarction angina was 11% and the incidence of major ventricular arrhythmias was 7.5%.

All patients underwent coronary angiography at a median of 6.5 days following admission (25-75%, 4-9.3 days). The infarct-related artery was patent in 86.3% of cases.

Angiography showed single-vessel disease in 49% of cases, two-vessel disease in 35%, three-vessel disease in 7.5%, and non-stenotic vessels in 8.5%. The left anterior descending coronary artery was involved in 55% of patients, the left circumflex coronary artery in 29%, and the right coronary artery in 50%.

Angioplasty was performed in 71% of patients, 88% of whom underwent stent implantation. A surgical revascularization procedure was indicated in 5% of the patients. In the remaining 24% no revascularization procedure was proposed because of the absence of critical stenoses (8%) or because of a non-favorable coronary anatomy (16%). Platelet glycoprotein IIb/IIIa receptor blockers were administered during angioplasty in 23% of cases. Rescue angioplasty was performed in 3 cases (3.8%).

Procedure-related reinfarction occurred only in 2.5% of cases and a femoral pseudoaneurysm in 1.3%. No major bleeding occurred.

No deaths occurred during hospitalization and the non-fatal reinfarction rate, including periprocedural reinfarction, was 3.8% (Table II).

Thirty-day follow-up data were available for 95% of patients (for 64% of cases obtained during clinical assessment and for 36% by telephone interview). No patient died; the non-fatal reinfarction rate was 4% whereas the rate of new revascularization procedures was 2.6% (Table II).

Six-month follow-up data were available for 94% of the study population (for 65% of cases obtained during clinical assessment and for 35% by telephone interview): 1 patient died (1.3% of cases), a non-fatal reinfarction occurred in 5.3% of patients, and 11% underwent new revascularization (Table II).

Table II. Short- and medium-term outcomes.

In-hospital (n=80)	
Death	0
Non-fatal reinfarction	3 (3.8%)
At 30 days (n=76)	
Death	0
Non-fatal reinfarction	3 (4%)
Any new revascularization	2 (2.6%)
At 6 months (n=75)	
Death	1 (1.3%)
Non-fatal reinfarction	4 (5.3%)
Any new revascularization	8 (11%)

The in-hospital mortality for all patients with STEMI treated in the same period in our Center (including patients ineligible for thrombolytic therapy or angiographic study) was 5.6% and the in-hospital reinfarction rate was 3.1%.

Discussion

The best strategy following fibrinolytic therapy in the setting of STEMI is a rather debated issue[27]. The most followed strategy is still the conservative one whereby patients are referred to cardiac catheterization only if they have spontaneous or provoked recurrent ischemia. With the invasive approach, routine coronary arteriography is performed in all patients after thrombolysis, and is followed by "adjunctive" angioplasty of the infarct-related artery whenever there is a critical residual stenosis or a total, persistent occlusion. The latter conditions are associated with a worse prognosis: a TIMI 0-1 flow grade after fibrinolysis has been associated with a higher mortality at both short- and long-term follow-up[11,28]. In case of residual stenosis, the aim of angioplasty is to optimize the results obtained by fibrinolysis and hence prevent occlusion and reinfarction. In case of persistent occlusion**,** the theory supporting the invasive strategy is based on the "open artery hypothesis"[29,30]; according to this, there is a time-independent benefit associated with late recanalization of an occluded infarct-related artery. In an analysis of the Survival and Ventricular Enlargement (SAVE) study population, Lamas et al.[31] found a higher incidence of congestive heart failure and death in patients with an occluded infarct-related artery, compared to patients with a patent artery. However, this is a retrospective, non-randomized study and for this reason, the results cannot be considered conclusive. Furthermore, the results of the Open Artery Trial (OAT), specifically designed to test the "open artery hypothesis", are not yet available[32,33].

Another advantage provided by the invasive strategy is to give a complete evaluation of the coronary arteries and to identify, and eventually treat, stenosis in coronary branches other than the infarct-related one.

Despite all these observations, previous trials[13,14] directly comparing the conservative, ischemia-driven strategy with the invasive strategy have not revealed any increased benefit of the latter approach. On the basis of these data, the ACC/AHA guidelines[12] classify the routine invasive strategy as class III (not indicated).

Actually, in the SWIFT (Should We Intervene Following Thrombolysis?) trial[14], the in-hospital mortality was 2.7% in the conservative strategy group and 3.3% in the invasive strategy group. At 1-year follow-up the mortality rates were 5 and 5.8% respectively. In the TIMI IIB trial[13], the 42-day mortality was 4.7% in the conservative strategy group and 5.2% in the invasive strategy group.

It has to be said that these studies belong to the very early stages of interventional cardiology. In the invasive arm of the TIMI IIB trial, angioplasty was performed in only 53% of patients, and similarly in the same arm of the SWIFT trial only 43% of patients received angioplasty. Furthermore, the two major therapeutic advances in interventional cardiology (coronary stents and platelet glycoprotein IIb/IIIa receptor blockers) that have been proved to reduce peri- and post-procedural adverse events[15-25], were not yet available.

In our study, angioplasty was performed in 71% of patients and stents were implanted in 88% of these patients. Platelet glycoprotein IIb/IIIa receptor blockers were administered in 13% of cases during the acute phase and in 23% of cases during the interventional procedure. Our study was not a randomized, controlled trial. However, we have found much lower in-hospital mortality rates at 30 days and 6 months of follow-up compared to the invasive arms of the above-mentioned trials despite the possible differences in patient characteristics.

Invasive procedure-related complications were rare: no major bleeding occurred and the periprocedural reinfarction rate was only 2.5%.

The median in-hospital length of stay was 9 days, lower than the 11 days of the invasive arm of the SWIFT trial.

The results of our study are more similar to those of the recent GRACIA trial[34]. This study included 500 patients, randomized to undergo either stenting within 24 hours of thrombolysis or an ischemia-guided approach after thrombolysis. PTCA with stenting was performed in 80% of patients in the invasive strategy group; in this group, 2% of patients died within 30 days of follow-up; the combined endpoints of reinfarction and new revascularization procedures occurred in 2.8% of patients in the invasive strategy group. The length of hospitalization was 7 days.

The main limitations of our study are the small number of patients studied and the observational, nonrandomized design, without a control group. As a consequence, our results cannot be regarded as conclusive, but merely suggest the need of larger scale randomized, multicenter trials to establish the validity of a systematic invasive strategy after fibrinolysis.

The short-term mortality and reinfarction rates may be considered too low as compared with those of trials on fibrinolysis[35] or those of the more recent observational studies on STEMI, such as the BLITZ study[36]. However, our patient population is not comparable with that of the above-mentioned studies. In contrast to the BLITZ study, we have excluded patients who were not eligible for fibrinolysis, and in contrast with the fibrinolysis trials, we have excluded patients (such as patients dead before 48 hours from admission) in whom coronary angiography was contraindicated. In so doing, we selected a population without a high-risk profile, as did the SWIFT and TIMI IIB investigators. However, our mortality and morbidity rates were still lower than those observed in these two trials, probably because of the advances in interventional cardiology.

In summary, our data suggest that an invasive strategy after thrombolysis in patients with STEMI is safe and is associated with low mortality and morbidity rates at short- and medium-term follow-up. This strategy could be particularly appealing to hospitals without a 24-hour service for primary angioplasty.

Acknowledgments

The authors would like to thank Mrs. Maria Angela Ciotta for her kind help.

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