Safety and efficacy of thrombolysis with alteplase (50 mg) plus tirofiban versus alteplase (100 mg) alone in acute myocardial infarction: preliminary findings

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Key words:
Acute myocardial infarction; Platelet aggregation inhibitors; Reperfusion; Thrombolysis.

Background. **The goal of therapy in acute myocardial infarction (AMI) is the complete and timely restoration of coronary blood flow. Platelets have a pivotal role in the pathophysiology of AMI. The study was aimed at evaluating the safety and efficacy of the combination of 50 mg alteplase plus tirofiban vs 100 mg alteplase in AMI patients.**

Methods. **One hundred twenty patients (83 males, 37 females; mean age 54.3 ± 8 years) were hospitalized for suspected AMI within 6 hours of the onset of symptoms. All patients presented pain and persistent ST-segment elevation, were suitable candidates for thrombolysis (1st episode) and were randomized (double blind) into two groups. Group A (n = 60, 42 males, 18 females) received 50 mg alteplase (15 mg as bolus, followed by an infusion of 35 mg over 60 min) in combination with tirofiban (0.4 mcg/kg/min for 30 min followed by an infusion of 0.1 mcg/kg/min for 3 days). Group B (n = 60, 41 males, 19 females) received 100 mg of accelerated-dose alteplase alone. Reperfusion criteria were defined as follows: > 50% reduction in the ST-segment elevation; resolution of chest pain; double marker of creatine kinase (CK) and CK-MB activity 2 hours after the start of thrombolysis; reperfusion arrhythmias within the first 120 min of thrombolysis. The blood pressure, heart rate and ECG were continuously monitored. The mortality, re-AMI, recurrent angina, major and minor bleeding, and emergency bypass surgery or coronary angioplasty were checked.**

Results. **The groups were similar with regard to clinical data, risk factors, time elapsed from the onset of symptoms to thrombolytic therapy and AMI localization. Forty-seven patients (78.3%) from group A showed reperfusion (15-60 min) vs 25 patients (41.7%) from group B (43-105 min after the end of full-thrombolysis, p = 0.01). Group A patients showed an earlier CK peak and lower CK and CK-MB peaks than those in the control group (p = 0.0001, p = 0.011, p = 0.005, respectively). Nine patients (7.5%) died: 6 (10%) in group B and 3 (5%) in group A (p = NS). A non-fatal re-AMI occurred in 8 patients from group A and in 4 patients from group B (p = NS). Recurrent angina occurred in 27 patients (45%) from group A and in 11 (18.3%) from group B (p = 0.037). Twenty-three of these patients underwent urgent coronary angioplasty (17 from group A and 6 from group B) and 3 from group A and 1 from group B underwent urgent coronary artery bypass grafting (p = NS). The frequency of minor bleeding was higher in group A than in group B (56.7 vs 25%, p = 0.033). No major bleeding was observed in the study groups. At the predischarge echocardiogram, the ejection fraction was higher in group A than in group B (50 ± 9 vs 44 ± 7%, p = 0.001).**

Conclusions. **Our data suggest that the combination of glycoprotein IIb/IIIa inhibitors plus alteplase is feasible in AMI patients and that the increased risk of bleeding is an acceptable risk considering the advantage in terms of the reduction in the extent of an AMI. In addition, this combination can allow one to gain time when it is necessary to perform mechanical revascularization in patients admitted to a hospital without an interventional cardiology laboratory or in those who have to be referred to another hospital for urgent coronary artery bypass grafting.**

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Introduction

The initial cascade of events responsible for acute myocardial infarction (AMI, ST-segment elevation) has been well elucidated. The vast majority of cases are precipitated by spontaneous plaque rupture resulting in platelet adhesion, activation and aggregation, and finally thrombosis[1,2]. The initial thrombus produces a hemostatic plug that limits blood flow to varying degrees. Most cases of acute infarction are the result of complete thrombotic occlusion of the coronary artery[3]. The two therapeutic approaches for the initial treatment of AMI, direct coronary angioplasty (PTCA) and

thrombolytic therapy, share the same goal: rapid and sustained reperfusion in order to improve the long-term clinical outcome. While both approaches have greatly reduced mortality, each has limitations that might be counteracted through the aggressive management of the thrombus. In case of direct PTCA, dealing with a coronary thrombus during the intervention can prove problematic; procedural complications of thrombosis including distal embolization, the no-reflow phenomenon, thrombus propagation, and rethrombosis are poorly amenable to mechanical technologies[4]. Long-term issues include vessel restenosis or reocclusion. These can be silent, result in signs or symptoms of ischemia, or cause a second AMI[5]. Thrombolysis is associated with a somewhat different but parallel set of issues related to thrombus management. Despite advances in thrombolytic strategies, normal coronary perfusion (TIMI flow 3) will be restored in only 57% of patients[6-8]. Unfortunately, of these 50-60% with initially successful thrombolysis, approximately one half will experience recurrent ischemia or reocclusion in the ensuing hours and days[9-11]. Thus, despite progress in fibrinolytic strategies and high acute patency rates, optimal (prompt, complete, and sustained) myocardial reperfusion occurs in only about one fourth of all treated patients[10]. A greater appreciation of the role of platelets in the pathophysiology of thrombosis has suggested that potent inhibition of platelet aggregation might improve the outcome following AMI. Aspirin, which prevents platelet aggregation by inhibiting the formation of thromboxane A_2, is known to enhance the efficacy of thrombolytic therapy[12] and is a critical adjunct to coronary intervention. However, aspirin has only a limited antiplatelet effect, inhibiting only one of the myriad of pathways leading to platelet activation[13,14]. Recent investigations have hypothesized that the use of platelet glycoprotein (GP) IIb/IIIa receptor inhibitors combined with thrombolytic agents would lead to more effective platelet inhibition and to improved angiographic and clinical efficacy. Emerging experimental and clinical data, including those of the Thrombolysis in Myocardial Infarction (TIMI) 14 trial[15], suggest that combining GP IIb/IIIa receptor inhibition with reduced-dose thrombolytic therapy improves the early infarct-related artery patency without increasing the bleeding risk. To evaluate the safety and efficacy of the combination of reduced-dose thrombolytic therapy (alteplase, Actilyse, Boehringer Ingelheim, Florence, Italy) and full-dose GP IIb/IIIa inhibitors (tirofiban, Aggrastat, Merck Sharp & Dohme, Rome, Italy) and to compare such a therapeutic regimen, in terms of its effects on the incidence of death, reinfarction, recurrent ischemia, major or minor bleeding, urgent PTCA and coronary artery bypass grafting (CABG), with full thrombolytic therapy (alteplase) alone in patients who are suitable candidates for thrombolysis, a randomized double-blind study in patients with an AMI was carried out.

Methods

Population and eligibility criteria. From November 1999 to October 2000, 337 consecutive patients with a suspected AMI were admitted to our hospital. To be eligible to enter the trial, patients had to present with a first episode of AMI, be < 70 years of age, be classified in Killip classes I-II, have an acceptable echocardiographic window, and to be admitted to the hospital and thrombolysed within 6 hours of the onset of symptoms (pain). On the electrocardiogram (ECG) there had to be an ST-segment elevation involving more than 3 leads, > 1 mm in the peripheral leads and/or 2 mm in the precordial leads, with concomitant alterations in wall motion as evaluated during echocardiography performed at entry[16]. The basal creatine kinase levels (CK, CK-MB before thrombolysis) had to be within the normal range. The ethical committee of the Buccheri La Ferla-Fatebenefratelli Hospital approved the study protocol. Informed consent was obtained from all patients.

Exclusion criteria. Patients who were not suitable candidates for thrombolysis or who presented with left bundle branch block on the admission ECG and those who had a history of cardiomyopathy or heart failure were excluded from the study. Patients receiving beta-blockers were also excluded from the study. Patients who showed no enzymatic alterations after thrombolysis were classified as having unstable angina and were excluded from the study.

Reperfusion criteria. These included evidence of rapid (50%) reduction (within 2 hours) of ST-segment elevation, rapid regression of pain, an enzymatic peak (CK) occurring within 12 hours of thrombolysis, a CK, CK-MB level greater than twice normal values and occurring 2 hours after starting thrombolysis, early ventricular arrhythmias diagnosed within 2 hours of the start of thrombolysis, and bradycardia with hypotension. After starting thrombolysis, the 50% reduction in the ST-segment elevation on the surface ECG was considered mandatory and had to be associated with one of the other reperfusion criteria[17-22].

Acute myocardial infarction classification and treatment. AMIs were classified as anterior, inferior and lateral according to the localization of the alterations in segmental contractility as revealed by the echocardiogram performed at entry and according to the alterations of the ST-segment in the standard 12-lead + V3R-V4R ECG taken at entry before thrombolysis. All patients received our standard treatment: nitrates 20-100 U/min, aspirin 160 mg/dl, and where possible three doses of intravenous metoprolol. The thrombolytic drug used was the recombinant tissue-type plasminogen activator.

Study protocol. Patients suitable for thrombolysis were randomized (double blind) into two groups. Random-

ization was carried out using sequentially numbered boxes. The control group (group B) received 100 mg of alteplase according to a front-loaded regimen (15 mg bolus, initial infusion of 0.75 mg/kg up to a total of 50 mg over 30 min, followed by infusion of 0.50 mg/kg up to a total of 35 mg over 60 min) and standard dose heparin consisting of a bolus of 70 U/kg (maximum 5000 U) and subsequent infusion of heparin (maximum 1200 U/hour) for 72 hours. The experimental group (group A) received alteplase (15 mg bolus, followed by infusion of 0.50 mg/kg up to a total of 35 mg over 60 min) and tirofiban 0.4 mcg/kg/min for 30 min followed by an infusion of 0.1 mcg/kg/min for 3 days. Tirofiban-treated patients received low-dose heparin with a bolus of 60 U/kg (maximum 4000 U) and infusion of 7 U/kg/min (maximum 800 U/hour). For both groups, infusion was adjusted according to a nomogram to a target activated partial thromboplastin time of 50 to 70 s. The blood pressure, heart rate and ECG were monitored continuously (Hewlett Packard System, Andover, CA, USA), recorded on tape (first 6 hours), and then analyzed to check for any rhythm disturbance, and focusing on the time of pain cessation and of regression of the ST-segment alteration. Episodes of ventricular tachycardia and ventricular fibrillation were recorded. Blood CK levels were measured every 2 hours during the first 24 hours and then every 6 hours until normalization in order to determine the enzymatic peak (12 hours). Before discharge, the surviving patients underwent 24-hour Holter monitoring in order to identify and evaluate any late ventricular arrhythmias, taking into account only those in a Lown's class > 2. These patients were also submitted to a symptom-limited exercise test. All the patients admitted into the study underwent hemodynamic evaluation 6-9 days after admission. PTCA or CABG was performed according to angiographic findings and left ventricular function. ECG and hemodynamic data were assessed and revised by two independent observers so as to reduce bias in the assessment of reperfusion following administration of the GP IIb/IIIa/placebo infusion. The two treatments were prepared before randomization, stored in hospital and used according to the sequence of randomization. The physician who treated the patients was unaware of the treatment administered. Patients enrolled in the study were regularly followed up as outpatients after discharge. Echocardiography was carried out according to a standard procedure at entry (just after randomization) and before discharge. The analysis of wall motion was obtained by subdividing the left ventricular chamber into 16 segments according to the American Society of Echocardiography recommendations[23] and the ejection fraction was determined by the area-length method. The mean of three measurements was used. The interobserver and intraobserver coefficients of variation were 4 and 3% respectively. The systolic thickening and motion of the left ventricular walls were classified as normal, hyperkinetic, hypokinetic, and akinetic. As usual, the wall motion score index was calculated by adding the numeric value assigned to each segment and dividing by the number of visualized segments. The physicians who performed an echocardiogram as part of the hemodynamic study were unaware of the patients' clinical and analytic data.

Statistical analysis. Results are expressed as mean ± SD. Data were analyzed by the two-tailed Student's t-test to identify differences between the groups. Nominal data were analyzed by the χ^2 test or Fisher's test. A p value of < 0.05 was considered statistically significant.

Results

One hundred twenty patients met the entry criteria and continued the study in accordance with the study protocol. The patients who had a proven reperfused AMI at late coronarography had an infarct-related artery (IRA) patency corresponding to the classification of reperfusion based on non-invasive diagnosis; unreperfused patients showed an occluded IRA. The groups were similar with regard to age, sex, diabetes, smoking habits, hypertension, and adjuvant therapy (beta-blockers). Table I shows the clinical data of all patients admitted into the study with proven unreperfused and reperfused AMI. No significant difference was observed between the two groups regarding the time elapsed from symptom onset to thrombolysis and regarding the localization of the AMI. Table II shows the results of the study. The group of patients receiving alteplase plus tirofiban showed a higher incidence of reperfusion (15-60 min) after the start of thrombolysis (78.3 vs 41.7%, $p < 0.001$) and an earlier CK peak and lower CK and CK-MB peaks in comparison with patients receiving fibrinolytic therapy only ($p = 0.0001$, $p = 0.011$, $p = 0.005$, respectively). Table III shows the intrahospital data. Mortality was higher among patients receiving alteplase alone than among those treated with alteplase plus tirofiban but the difference was not significant. Three patients died in group A (2 of irreversible heart failure and 1 of a fatal re-AMI); 6 patients died in group B (4 of irreversible heart failure and 2 of a fatal re-AMI). The difference in the frequency of non-fatal re-AMI 4 ± 3 days after admission was not statistically significant. Four patients from group B received a further administration of recombinant tissue-type plasminogen activator (50 mg) before emergency PTCA was performed (TIMI 1 flow). The frequency of recurrent angina was higher in group A than in group B ($p = 0.037$). Twenty-three of these patients underwent urgent PTCA (17 from group A and 6 from group B) (TIMI 2 flow). Patients in group A showed a higher ejection fraction and a lower wall motion score index compared to those in group B ($p = 0.001$, $p = 0.001$, respectively). Table III also shows the incidence of bleeding among the patients admitted into the study. Minor bleeding was more common among patients in group A than among those in group B ($p = 0.033$) and occurred

Table I. Clinical data of randomized patients.

	Group A (n=60)	Group B (n=60)	Total (n=120)	p
Sex (M/F)	42/18	41/19	83/37	NS
Age (years)	55 ± 7	54 ± 9	54.3 ± 8	NS
Onset of symptoms (min)	105 ± 54	110 ± 50	108 ± 52	NS
Anterior AMI	22	23	45	NS
Inferior + lateral AMI	29	29	58	NS
Anterior + inferior AMI	9	8	17	NS
Beta-blockers	18	20	38	NS
Hypertension	34	36	70	NS
Diabetes	21	20	41	NS
Hypercholesterolemia	30	28	58	NS
Smokers	40	37	77	NS
Ejection fraction at admission (%)	41 ± 8	39 ± 7		NS
WMSI at admission	2.01 ± 0.19	2.07 ± 0.18		NS

AMI = acute myocardial infarction; WMSI = wall motion score index.

Table II. Effects of thrombolysis.

	Group A (n=60)	Group B (n=60)	Total (n=120)	p
Reperfused	47 (78.3%)	25 (41.7%)	72 (60%)	0.01
Unreperfused	13 (21.7%)	35 (58.3%)	48 (40%)	0.011
CK peak max (IU/l)	1560 ± 782	1980 ± 981		0.011
CK peak time (min)	486 ± 142	684 ± 246		0.0001
CK-MB peak (ng/ml)	190 ± 172	286 ± 196		0.005

CK = creatine kinase.

Table III. Results during the hospitalization period.

	Group A (n=60)	Group B (n=60)	Total (n=120)	p
Mortality	3 (5%)	6 (10%)	9 (7.5%)	NS
Non-fatal re-AMI	8 (13.3%)	4 (6.6%)	12 (10%)	NS
Recurrent angina	27 (45%)	11 (18.3%)	38 (31.6%)	0.037
Major bleeding	0	0	0	NS
Minor bleeding	34 (56.7%)	15 (25%)	49 (40.8%)	0.033
Urgent PTCA	17 (28.3%)	6 (10%)	23 (19.2%)	0.060
Urgent CABG	3 (5%)	1 (1.7%)	4 (3.3%)	NS
Thrombocytopenia	2 (3.3%)	1 (1.6%)	3 (2.5%)	NS
Ejection fraction (%)	50 ± 9	44 ± 7		0.001
WMSI	1.75 ± 0.20	1.89 ± 0.19		0.001

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty. Other abbreviations as in table I.

at the site of vascular punctures. In no case did major bleeding occur. No difference was observed in the frequency of urgent CABG (three-vessel disease) between the two groups. None of these patients presented with important bleeding during surgery and postoperatively. Only 2 patients in group A needed blood transfusion because of gross hematuria (one blood transfusion in each patient). Thrombocytopenia occurred in 2 patients of group A and in 1 patient of group B (p = NS). Table IV shows the angiographic data and the IRA patency of those patients from both groups who underwent coronary angiography. One hundred and ten patients underwent coronary angiography (56 from group A and 54 from group B); 9 patients died before coronary angiography was performed and 1 patient refused treatment (group A). Patients in group A showed a significantly higher incidence of IRA patency than those in group B ($p < 0.01$). In patients without any non-invasive sign of reperfusion (TIMI 0-1 flow) the IRA was found to be non-patent. Eighty-four patients (43 from group A and 41

Table IV. Angiographic data.

	Group A (n=56)	Group B (n=54)	Total (n=110)	p
Patency (TIMI 2-3 flow)	47 (83.9%)	28 (51.8%)	75 (68.2%)	< 0.01
No patency (TIMI 0-1 flow)	9 (16.1%)	26 (48.2%)	35 (31.8%)	< 0.016
One-vessel disease	36 (64.3%)	26 (48.1%)	62 (56.4%)	NS
Two-vessel disease	13 (23.2%)	15 (27.8%)	28 (25.4%)	NS
Three-vessel disease	7 (12.5%)	9 (16.7%)	16 (14.6%)	NS
No critical stenosis	2 (3.6%)	2 (3.7%)	4 (3.6%)	NS
Infarct-related artery				
Anterior descending artery	26	25	51 (46.4%)	
Right coronary artery	22	20	42 (38.2%)	
Circumflex coronary artery	10	17	17 (15.4%)	

from group B) underwent echocardiographic examination prior to discharge. The patients who necessitated urgent CABG/PTCA were not submitted to echocardiography, since they were sent to other hospitals for treatment. No patient discharged from hospital presented with events during the first 30 days. It was not possible to determine the length of hospitalization since 27 patients were sent to other hospitals for CABG/PTCA (from 4 to 10 days).

Discussion

Platelet aggregation plays a pivotal role in the development of acute coronary artery thrombosis and recurrent ischemia after successful thrombolysis. Better understanding of the pathogenesis of acute coronary syndromes, deriving also from pathologic studies of patients dying of AMI following fibrinolysis which revealed the presence of platelet-rich and fibrin-poor thrombi at the site of plaque rupture, has significantly influenced the choice of the therapeutic strategy for acute coronary syndromes. As mentioned, most patients receiving fibrinolysis have inadequate or only transient coronary flow restoration. This is partly due to the increased platelet and thrombin activity following fibrinolysis. In response to stimulation by thrombin, platelets express GP IIb/IIIa receptors on their surface, promoting cross-linking by ligands such as fibrinogen. Thus, they provide a greater surface area for the formation of the prothrombinase complex and for additional thrombin generation[24]. Other consequences of platelet activation that promote thrombus formation include the release of plasminogen activator inhibitor-1 and of vasoconstrictor substances[24]. Thus, the platelet-rich thrombus is not only more resistant to thrombolysis, but may also promote reocclusion due to additional platelet activation after initially successful thrombolysis. Therefore, the transition from conventional fibrinolytic therapy to one that is more platelet-centric is evolving, because a powerful antiplatelet agent used in combination with a thrombolytic agent not only offers the potential for enhancing thrombolysis and reducing the risk of reocclusion but also permits this to be accomplished with reduced doses of thrombolytic agents and heparin. Recently the combination of GP IIb/IIIa with thrombolytic agents resulted in an increased reperfusion in patients with AMI[15]. In addition, myocardial perfusion, as assessed by ST-segment resolution, was also significantly improved by the combination[21]. The incidence of major hemorrhage was similar among the tissue-type plasminogen activator plus abciximab and control groups (-6% in each). The in-hospital mortality was similar in all groups, ranging from 3 to 5%. One of the main concerns regarding combination therapy with a potent fibrinolytic agent and a potent antiplatelet agent is bleeding, in particular intracranial hemorrhage[25]. The review of three randomized trials shows that GP IIb/IIIa inhibitors produce no increase in the incidence of intracranial hemorrhage[26]. Our most important result was the observed safety of this combination (2 side effects only). In fact, no patient had fatal intracranial bleeding and only 2 patients necessitated blood infusion. There is a strong rationale for combining the GP IIb/IIIa receptor inhibitors with thrombolytic agents[15,27]. Our data show that this combination was able to produce earlier hemodynamic stabilization in patients with an AMI. This implies reduced myocardial damage, as evidenced by the faster CK peak and by the lower CK and CK-MB peaks in the tirofiban group. In addition, the combination determined a significantly higher ejection fraction in comparison with that observed following alteplase therapy alone. Besides, even the mortality was reduced though the difference was not significant (5 vs 10%, p = NS). Nevertheless the combination was not able to produce stable myocardial perfusion: 58.3% of patients receiving GP IIb/IIIa inhibitors showed recurrent angina (8 non-fatal re-AMI and 27 myocardial angina), after the end of the tirofiban infusion period. Since our hospital does not have a catheterization laboratory, we were not able to perform angiographic control immediately before and after GP IIb/IIIa inhibitor administration and coronary angiography was subsequently performed in other hospitals. We found it difficult to explain the higher incidence of non-fatal re-AMI and recurrent angina. We hypothesized that many factors

could compromise the GP IIb/IIIa efficacy: 1) individual variability: since platelet thrombus formation depends on the absolute number of GP IIb/IIIa receptors available for aggregation, individual variations in splenic size, platelet count[28] and number of receptors per platelet may influence the dose response. Variations in intrinsic platelet competence and receptors observed with age[29], gender[30] and diabetes[31] may also affect the dose response; 2) inter and intraindividual variations in the dose-response can also contribute to the occurrence of suboptimal effects. Failure of the maintenance infusion to sustain platelet inhibition > 80% has also been observed with each intravenous agent and the intrapatient divergence appears to increase with the duration of infusion[32,33]; 3) of perhaps greater concern is the possibility that these agents promote thrombotic events (partial agonist activity). Some authors showed antagonist-induced receptor activation with both antibody-fragment and small-molecule GP IIb/IIIa inhibition, and, during periods or after drug discontinuation, the platelets may be left more activated than before therapy[34]. In addition, it is possible that patients had to be referred to interventional strategies earlier, within 72 hours and/or soon after the discontinuation of GP IIb/IIIa infusion. In our study, the patients underwent hemodynamic study 6-9 days after admission. Perhaps, this delay was responsible for the higher incidence of re-AMI in patients receiving the combination. Our data suggest that the use of GP IIb/IIIa receptor inhibitors together with thrombolytic agents in AMI patients is feasible and that an increase in bleeding is an acceptable risk considering the reduced AMI area. The major limitation of this study was the small number of patients and the delay between the suspension of treatment and interventional strategies. This is mainly a study of feasibility and tolerability. Further and larger studies are requested to verify these very preliminary findings.

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