Original articles

Increased reperfusion by glycoprotein IIb/IIIa receptor antagonist administration in case of unsuccessful and failed thrombolysis in patients with acute myocardial infarction: a pilot study

Pietro Di Pasquale, Filippo M. Sarullo*, Sergio Cannizzaro, Maria G. Vitrano, Alfonso Giubilato, Sebastiano Scalzo, Francesco Giambanco**, Salvatore Paterna***

*Division of Cardiology "Paolo Borsellino", G.F. Ingrassia Hospital, *Division of Cardiology, Buccheri La Ferla Hospital, **Hemodynamic Service, Civic Hospital, ***Department of Internal Medicine, University of Palermo, Palermo, Italy*

Key words:
Acute myocardial infarction; Glycoprotein IIb/IIIa inhibitors; Thrombolysis.

Background. **The aim of this study was to evaluate the effectiveness of glycoprotein (GP) IIb/IIIa receptor inhibitors in acute myocardial infarction (AMI) patients in case of unsuccessful and failed thrombolysis.**

Methods. **Eighty-four patients hospitalized within 4 hours of symptom onset were randomized (single blind) into two groups. Regardless of the group, placebo or GP IIb/IIIa inhibitors were administered to patients who did not present with reperfusion signs (failed thrombolysis) 30 min after starting thrombolysis and 30-60 min after the end of full thrombolysis in patients with pain recurrence and ST-segment elevation (unsuccessful thrombolysis). Reperfusion was assessed by the creatine kinase peak occurring within 12 hours, by the observation of rapid ST-segment reduction (50-70% within 1 hour) in the 12-lead ECG continuous tracing, by the rapid regression of pain and by the development of early ventricular arrhythmias. Group 1 patients (n = 42) received, during failed thrombolysis or after 30-60 min of effective thrombolysis but with pain recurrence and ST-segment elevation (unsuccessful thrombolysis), treatment with i.v. GP IIb/IIIa inhibitors, heparin according to the TIMI 14 trial, and aspirin. Group 2 patients (n = 42) received a full dose of recombinant tissue-type plasminogen activator (rt-PA 100 mg) and placebo either during failed thrombolysis or, after 30 min of effective thrombolysis but with pain recurrence and ST-segment elevation, and standard heparin treatment and aspirin.**

Results. **In group 1, 39 patients showed rapid reperfusion (4 ± 3 min); 22 patients received rt-PA 65 mg and 20 patients received rt-PA 100 mg and subsequent GP IIb/IIIa inhibitor treatment. Coronary angiography, performed after 12-72 hours showed patency of the infarct-related artery in 39 patients whose clinical picture was suggestive of rapid reperfusion during administration of a bolus of GP IIb/IIIa inhibitors. In group 2, no patients showed reperfusion and they were submitted to rescue coronary angioplasty ($p < 0.05$). Side effects occurred in 3 cases in group 1 and in 2 cases in group 2. Patients receiving GP IIb/IIIa inhibitors showed a reduced incidence of stent treatment (p = NS) and a significant reduction in the occurrence of events (angina) within 30 days of treatment (p = NS).**

Conclusions. **Our data suggest that in patients with AMI and failed thrombolysis, treatment with GP IIb/IIIa receptor inhibitors is feasible. The increase in the risk of bleeding was acceptable. The most important result was that this combination is safe.**

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Address:

Dr. Pietro Di Pasquale

Divisione di Cardiologia "Paolo Borsellino" Ospedale G.F. Ingrassia Via Val Platani, 3 90144 Palermo E-mail: lehdi@tin.it

Introduction

Thrombolytic treatment has proved to be effective in significantly reducing mortality (30 to 6.3%) among patients thrombolysed within 6 hours of the symptom onset[1]. Acute myocardial infarctions (AMI) involving a large area of the myocardium are associated with a high mortality (20-25%)[2] and these patients appear to receive a greater benefit by an aggressive approach (primary or rescue coronary angioplasty-PTCA) when thrombolysis is unsuccessful[3-5]. Such patients previously had to be referred to rescue PTCA, and were hence exposed to all the potential risks of this technique[3-5]. These risks are greater when patients (unstable patients and those with a prolonged interval from the time of symptom onset to reperfusion) are admitted to hospitals which are not equipped with an interventional laboratory thus necessitating

their transfer to other hospitals. Unfortunately, in one quarter of patients occlusive thrombi are not lysed, reocclusion occurs in 10% of patients, and incomplete reperfusion in 30%[6,7]. As interventional laboratories are not available in all hospitals, and often, when they are available, they are not open 24 hours a day, other attempts to achieve reperfusion were employed (rescue thrombolysis). This resulted in an increased incidence of major bleeding[8]. The recent TIMI 14 trial showed that at 90 min the combination of reduced-dose thrombolysis and abciximab determined TIMI grade 3 flow in 77% of patients and that patency was achieved in 94% of patients receiving the combination[9]. The aim of this study was to evaluate the safety, tolerability and effectiveness of glycoprotein (GP) IIb/IIIa receptor inhibitors in AMI patients with unsuccessful and failed thrombolysis. In our study, thrombolysis was terminated 30 min after starting treatment because, in the last 10 years, we had observed that reperfusion occurs within the first 30 min.

Methods

Study population. From January to August 2000, 225 consecutive patients with suspected AMI were admitted to hospital.

Eligibility criteria included a first episode of AMI, inclusion of the patient in Killip class I-II, an acceptable echocardiographic window and hospital admission and thrombolysis within 4 hours of symptom onset (pain). On the ECG there had to be an ST-segment elevation involving more than one lead and > 1 mm in the peripheral leads and/or 2 mm in the precordial leads. Concomitant alterations of the segmental kinetics as visualized on the echocardiogram performed at entry also had to be present.

Serum creatine kinase (CK, CK-MB isoenzyme) levels before thrombolysis had to be within normal limits. All patients admitted into the study had to have either unsuccessful reperfusion during thrombolysis (first 30 min) or recurrence of pain and ST-segment elevation after efficacious thrombolysis (after 30-60 min). There was no age limit. Informed consent was obtained from all patients.

Exclusion criteria included unsuitability for thrombolysis, left bundle branch block, a history of cardiomyopathy or heart failure, and successful reperfusion.

There had to be evidence of typical behavior of the ST segment with a rapid reduction (50-70% within 1 hour) as observed during 12-lead ECG continuous monitoring, rapid regression of pain, an enzymatic (CK) peak within 12 hours of thrombolysis, and early ventricular arrhythmias within 2 hours of the start of thrombolysis. The CK peak within 12 hours and rapid ST-segment reduction (50-70% within 1 hour) in the 12-lead ECG continuous monitoring were considered mandatory and had to be associated with one of the other reperfusion criteria.

AMI was classified according to the localization of the alteration in segmental contractility as diagnosed during echocardiography performed at entry and according to the localization of the alterations of the ST segment in the standard 12-lead ECG + V3R-V4R leads registered at admission before thrombolysis. All the patients were submitted to our standard treatment protocol including nitrates, heparin, aspirin and, where possible, three 5 mg doses of intravenous metoprolol. The thrombolytic drug used was the accelerated recombinant tissue-type plasminogen activator (rt-PA).

Study protocol. As described above, patients suitable for thrombolysis received thrombolytic treatment as well as aspirin and heparin. The patients receiving thrombolytic treatment and not showing any signs of reperfusion during thrombolysis (first 65 mg of rt-PA, bolus of 15 mg and then 50 mg over 30 min) and those showing, after the end of full and effective thrombolysis (100 mg), pain recurrence and ST-segment elevation (within 30-60 min) were randomized in a single blind fashion to one of two groups. Single blind randomization was carried out using sequentially numbered boxes and was decided at the time of admission. Randomization was performed 30 min after having started thrombolysis for patients not showing reperfusion signs (failed thrombolysis), and 30-60 min after the end of full thrombolysis for patients with pain recurrence and ST-segment elevation (i.e. 120-150 min from starting thrombolysis). Group 1 (n = 42) who did not show, during the first 65 mg of rt-PA, any sign of reperfusion stopped thrombolytic treatment and received standard i.v. treatment with GP IIb/IIIa receptor inhibitors (either abciximab 0.25 mg/kg bolus plus 125 μg/kg/min infusion for 12 hours, or tirofiban 0.4 μg/kg/min for 30 min plus 0.1 μg/kg/min for 72 hours or eptifibitade 180 μg/kg bolus plus 2.0 μg/kg/min infusion for 72 hours). This therapeutic regimen (abciximab, tirofiban, eptifibatide) was also administered to those group 1 patients who, within 30-60 min of full thrombolysis (100 mg), presented with pain recurrence and ST-segment elevation (Fig. 1). All the patients received heparin therapy according to the recommendations of the TIMI 14 trial and 160 mg of aspirin. In patients of group 2 (n = 42) thrombolysis was continued if still being administered and they were also treated with placebo (saline solution either as bolus and subsequent infusion until rescue PTCA) plus a standard dosage of heparin and 160 mg of aspirin. Therefore, in this group all patients received a full dose of rt-PA (100 mg). Those patients in group 1 who showed reperfusion after GP IIb/IIIa treatment (resolution of pain, ST-segment resolution in the 12-lead ECG continuous monitoring, etc.) performed coronary angiography after 12-72 hours and, when necessary, were submitted to PTCA/coronary artery bypass graft (CABG). Patients who did not present with

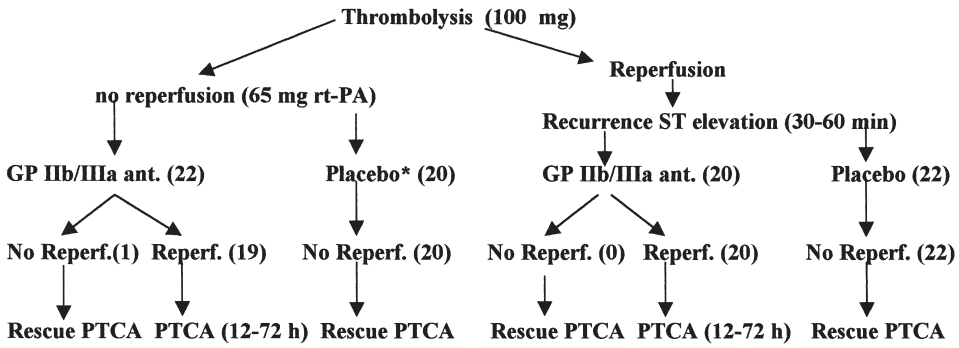

Figure 1. *Study protocol. GP = glycoprotein; PTCA = coronary angioplasty; rt-PA = recombinant tissue-type plasminogen activator. * = in the placebo groups a full dose (100 mg) of rt-PA was administered.*

any signs of reperfusion were immediately referred to rescue PTCA/CABG. Once thrombolysis had been started, the blood pressure, heart rate, and ECG were monitored continuously. Blood CK levels were measured every 3 hours during the first 24 hours and then every 6 hours until normalization. The enzymatic peak (12 hours) was also determined. Major and minor bleeding was defined according to the criteria of the TIMI II trial[10]. All the patients underwent hemodynamic evaluation. The decision to perform PTCA/CABG was based on angiographic findings and left ventricular function. ECG and hemodynamic data were assessed and revised by two independent observers in order to reduce bias in the assessment of reperfusion following administration of the GP IIb/IIIa/placebo infusion. Patients enrolled in the study were regularly followed up as outpatients. Patients were submitted to echocardiographic evaluation before discharge and 1 month following treatment when, as part of the PTCA protocol, they were also submitted to exercise testing.

Statistical analysis. Results are expressed as mean ± SD. Data were analyzed using the two-tailed Student's t-test to identify differences between the groups and ANOVA for repeated measures. The Bonferroni correction was used for intragroup data. Nominal data were analyzed by the χ^2 test. P values of < 0.05 were considered statistically significant.

Results

Eighty-four consecutive patients (62 males, 22 females) were included into the study and met the entry criteria. The patients' age ranged from 40 to 80 years. These patients were randomized into two groups (single blind). The two groups were similar with regard to clinical data and risk factors (Table I). All the patients receiving GP IIb/IIIa inhibitors, whether 65 mg or 100 mg of rt-PA, presented with the rapid onset of signs of reperfusion and subsequent coronary angiography (12-72 hours) showed patency of the infarct-related artery (TIMI 3 flow) corresponding to the classification of reperfusion based on the non-invasive diagnosis (Tables II and III). This group included 42 patients: 22 patients received 65 mg of rt-PA and 20 received 100 mg of rt-PA followed by GP IIb/IIIa receptor inhibitor treatment. Hemodynamic evaluation, performed after 12-72 hours showed patency of the infarct-related artery in 39 patients. Thirty-nine patients showed rapid

Table I. Clinical data of the enrolled patients.

	Group 1 (n=42)	Group 2 (n=42)
Sex (M/F)	30/12	32/10
Age (years)	58.5 ± 12	59.2 ± 13
Hypertension	22	20
Diabetes	10	13
Hypercholesterolemia	26	27
Smokers	16	18
Inferior AMI	17	16
Anterior AMI	13	14
Lateral AMI	2	2

AMI = acute myocardial infarction.

Table II. Clinical findings.

	Group 1 (n=42)	Group 2 (n=42)
CK peak (IU/l)	1985 ± 954	2015 ± 1055
CABG/PTCA*	12/28	11/31
Ventricular tachycardia**	32	9
Lown class > 2*	3	6
Beta-blockers*	25	27
rt-PA dose (65 mg)	22	–
Abciximab	10	–
Tirofiban	8	–
Eptifibatide	2	–
rt-PA dose (100 mg)	20	42
Abciximab	10	–
Tirofiban	7	–
Eptifibatide	3	–

CABG = coronary artery bypass graft; CK = creatine kinase; PTCA = coronary angioplasty; rt-PA = recombinant tissue-type plasminogen activator. * p = NS; ** = $p < 0.05$.

Table III. Angiographic results and side effects.

	Group 1 (n=42)	Group 2 (n=42)
Patency*	39	–
No patency*	1	42
Side effects		
Major bleeding	3	2
Minor bleeding	8	10
Platelet reduction	2	–
Mortality	2	3
Coronarography		
3 vessels	6	7
2 vessels	11	13
1 vessel	23	22
Restenosis**	6	12
Stent**	12	18

* = $p < 0.05$; ** p = NS.

reperfusion during administration of the bolus of GP IIb/IIIa inhibitors (4 ± 3 min) and they also presented with rapid regression of pain and of the ST-segment elevation (50-70%). One patient presented with signs of reperfusion 30 min after having started GP IIb/IIIa treatment. Vessel patency was hemodynamically confirmed after 72 hours. Only one patient did not show any signs of reperfusion and he was immediately referred to rescue PTCA (occluded descending coronary artery) (Tables II and III). In this group, we decided to perform coronary angiography 12-72 hours after treatment so as to perform this technique in the best possible conditions of stabilization and to avoid the risks associated with early mechanical procedures. Group 2 included 42 patients. All patients received 100 mg of rt-PA and placebo during failed thrombolysis or, in case of pain and recurrence of ST-segment elevation, 30-60 min after effective thrombolysis (unsuccessful thrombolysis). None of these 42 patients presented with any signs of reperfusion during and after placebo administration and they were rapidly submitted to rescue PTCA (Tables II and III). Heparin (low dose) treatment was given according to the recommendations of the TIMI 14 trial in the GP IIb/IIIA group[9] and in full doses in the placebo group. Significant side effects were observed in 3 patients included in group 1: one case of mild pericardial bleeding, one case of severe hematuria which remitted once heparin was withdrawn, and one case of hematemesis. Minor bleeding occurred in 8 patients. In no case was blood transfusion required. Two group 1 patients presented with thrombocytopenia (< 100 000) 6 hours following the initiation of treatment with abciximab. Two patients who were thrombolysed too late (> 6 hours) following symptom onset and presenting with an extensive anterior AMI, showed rapid reperfusion but, as confirmed by echocardiography and pericardiocentesis, they died of cardiac rupture 24 hours later. Ten patients in the placebo group presented with minor bleeding (access sites), 1 patient with severe hematuria and 1 patient with retroperitoneal bleeding after rescue PTCA. Two patients with three-vessel disease died during emergency surgery. Follow-up of these patients is ongoing. Table I shows the clinical data obtained for each group. In group 1, 6 patients had three-vessel, 11 patients two-vessel and 23 patients one-vessel disease. Two patients died before coronary angiography. In group 2, 7 patients had three-vessel, 13 patients two-vessel and 22 one-vessel disease. The incidence of PTCA or CABG was similar in both groups. One month following treatment 12 patients (submitted to rescue PTCA) from the placebo group presented with recurrence of pain and of ECG alterations either at rest or during exercise testing. Repeat coronary angiography confirmed restenosis of the PTCA-treated vessel. Six patients included in group 1 presented with recurrence of pain and of ECG changes during exercise testing. Again, coronary angiography confirmed restenosis of the PTCA-treated vessel (p = NS). The end-systolic volume and ejection fraction were better in group 1 than in group 2, but the differences were not statistically significant (data not shown). Besides statins and the usual post-AMI treatment (beta-blockers, nitrates, ACE-inhibitors, etc.), all patients received aspirin and ticlopidine twice daily. Twelve patients in group 1 vs 18 in group 2 were submitted to stent implant (p = NS). Long-term follow-up and recruitment of a larger population are ongoing.

Discussion

Among patients who are submitted to thrombolysis, the limited success in the restoration of coronary blood flow and in decreasing the incidence of reocclusion has been attributed to platelet activation[11,12]. Following plaque rupture, a different set of factors is critical in the pathogenesis of thrombus formation: the degree of plaque rupture, the degree of stenosis and the physical and chemical properties of the surface exposed. Badimon et al.[13] have shown that platelet deposition and subsequent thrombus formation occurred within 5-10 min of plaque rupture. The thrombus obstructing the infarct-related artery in ST-segment elevation AMI consists of numerous components including platelets, thrombin and fibrin mesh. The dynamic interplay between factors promoting thrombosis vs those promoting thrombolysis is shifted in favor of the former. Although thrombolytic agents target the fibrin mesh component of the thrombus, their use is associated with both an increased thrombin activity as well as with platelet activation[14-16]. In response to stimulation by thrombin, platelets express GP IIb/IIIa receptors, thus promoting cross-linking by ligands such as fibrinogen and providing a greater area for the formation of the prothrombinase complex and additional thrombin formation[17]. This leads to further additional

activation of platelets and to the release of plasminogen activator inhibitor-1 and of vasoconstrictor substances[17]. Recent angioscopic studies have shown that a substantial portion of occlusive thrombi (previously thought to consist only of fibrin-rich "red" clot) consists of platelets (the so-called "white" clot)[18]. Binding of the GP IIb/IIIa receptor with fibrinogen or with the von Willebrand factor represents the final common pathway of clot formation. Blockade of these receptors results in profound suppression of platelet aggregation[19]. Recently, the combination of GP IIb/IIIa receptor inhibitors and thrombolysis was found to increase the incidence of reperfusion in patients with AMI[19-21]. In the TIMI 14 trial, the combination of reduced doses of rt-PA plus abciximab resulted in a substantially increased rate of TIMI grade 3 flow (77% at 90 min as compared with 62% for rt-PA alone)[9]. Overall, using the combination of abciximab plus rt-PA, at 90 min patency was achieved in 94% of patients as compared with 78% for rt-PA alone. An even greater difference in the patency rate was observed at 60 min (91% of patients with the combination vs 70% for rt-PA). As assessed by ST-segment resolution, even myocardial perfusion was significantly improved by the combination[22]. The incidence of significant hemorrhage was similar among the rt-PA plus abciximab and control groups (-6% in each). The in-hospital mortality was similar in all groups, and ranged from 3 to 5%. Similarly, in the recent GUSTO V trial the difference in mortality was not significant but the incidence of PTCA within 6 hours of treatment was significantly reduced among patients receiving the combination[23]. In addition, similar to what reported in previous randomized trials[24], the incidence of side effects (bleeding complications) was similar in both groups[23]. Our data suggest that, in patients with AMI, it is possible to use GP IIb/IIIa receptor inhibitors in case of unsuccessful and failed thrombolysis. The increase in the risk of bleeding was acceptable[10]. In fact, no patient developed fatal cerebral hemorrhage or required plasma infusion. The combination of therapy used in these patients allowed us to overcome the thrombolytic resistance[25]. The most important result was that this combination was safe (three side effects only). We hypothesized, to explain our results, that in patients with recurrence of ST-segment elevation and pain the GP IIb/IIIa receptor inhibitors were able to avoid and/or reverse the platelet activation stimulated by thrombin generation at the site of vascular injury[13,14]. In addition, we hypothesized that in patients who had received unsuccessful thrombolytic treatment (30 min) thrombolysis determined incomplete lysis of the clot (only fibrin) thus facilitating the effect of GP IIb/IIIa receptor antagonists on platelet-rich thrombi. This is the first time that the combination of GP IIb/IIIa receptor inhibitors plus thrombolysis was used in the setting of unsuccessful and failed thrombolysis. The high incidence of reperfusion in patients receiving GP IIb/IIIa receptor inhibitors (39 patients) was noteworthy. Therefore, rescue GP IIb/IIIa receptor inhibitor therapy could be a viable strategy in hospitals without invasive facilities. Before starting this study, 10 patients receiving 65 mg of rt-PA plus GP IIb/IIIa receptor inhibitors were submitted to angiography 60-90 min following the initiation of treatment. Coronary angiography confirmed the patency (TIMI grade 3 flow) of the infarct-related artery in all those patients in whom ECG (12-lead continuous monitoring) was suggestive of reperfusion. In addition, to justify our hypothesis we have administered GP IIb/IIIa receptor inhibitors to 10 patients who presented with ST-segment elevation within 10 min of symptom onset (patients hospitalized in the coronary care unit for chest pain but without significant ECG alterations)[26]. All these patients immediately received GP IIb/IIIa receptor inhibitors without thrombolysis and they presented with signs of reperfusion which was subsequently confirmed at coronary angiography performed between 1-12 hours following treatment. ECG (12 leads) revealed rapid normalization of the ST segment. These patients received this treatment because we hypothesized that the clot consisted mainly of platelets and that fibrin deposition was still ongoing and not sufficiently copious to necessitate thrombolytic treatment. These very preliminary data suggest that in patients with AMI it is possible to use GP IIb/IIIa receptor inhibitors in case of unsuccessful or failed thrombolysis. This treatment protocol could be useful not only in patients admitted to hospitals without an interventional laboratory but also to avoid the risks associated with rescue PTCA. In fact, this protocol allowed us to perform PTCA in stable patients and in non-emergency conditions thus avoiding the important problems determined by rescue PTCA. We hypothesized that combined treatment could help us to overcome the thrombolytic resistance. In fact, we observed an increased incidence of reperfusion in this high-risk group of patients (unsuccessful and failed thrombolysis).

Study limitations. The most important limit of the study was that the number of patients was rather small. In fact, 40% of patients were not suitable for thrombolysis, while in about 25-30% of patients reperfusion did not occur neither during nor after thrombolysis. We decided to stop thrombolysis and to resort to GP IIb/IIIa receptor inhibitors after 65 mg of rt-PA because in the last 10 years we had observed that thrombolysis determines effective reperfusion only during the first 30-60 min of treatment. Another important limit was the single blind randomization. However, in view of the high risk of the patients enrolled and because of ethical problems we were unable to perform a double-blind treatment. These are very preliminary data and further studies including larger populations are required.

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