Abciximab in rescue coronary angioplasty after full-dose tissue-type plasminogen activator

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Background. **Rescue angioplasty is a complex procedure because of frequent reocclusions secondary to a paradoxical pro-thrombotic effect brought about by thrombolytic therapy. Administration of abciximab may improve procedural results but its utilization in this setting is limited by the potential hemorrhagic risk. Very few data on this approach are currently available in the medical literature.**

Methods. **After failed full-dose tissue-type plasminogen activator (tPA), 30 patients (23 males, 7 females, mean age 64 ± 13 years) referred for rescue angioplasty received abciximab (0.25 mg/kg bolus + 0.125 mcg/kg/min × 12 hour infusion) (Abc+ group). The procedural results, hemorrhagic complications and in-hospital outcome observed in these patients were compared to those of 35 patients submitted to rescue angioplasty in the same time period (1997-1999) who did not receive abciximab (Abc- group).**

Results. **In the Abc+ group, 11 patients (37%) were in Killip class 3-4, 14 (47%) had multivessel disease, and 4 (13%) had previous bypass surgery. In all Abc+ patients, factors suggestive of procedural failure were present (i.e. saphenous vein graft occlusion, intraluminal thrombus, dissection, reocclusion, slow flow). The periprocedural heparin dose was 5000 IU in Abc+ and 100 IU/kg in Abc- patients (range 5000-10 000 IU). The procedure was successful in 29 Abc+ (97%) and in 34 Abc- patients (97%). A hemoglobin drop > 5 g occurred in 3 Abc+ (10%) and in 4 Abc- patients (11%) with a similar incidence of blood transfusion in the two groups. In all these cases, significant bleeding occurred at the vascular access site. There were 2 in-hospital deaths in Abc+ and 1 in Abc- patients.**

Conclusions. **Selected patients undergoing rescue angioplasty may be treated with abciximab without an undue increase in hemorrhagic complications. Larger studies are needed to confirm the feasibility of this approach and to assess its potential benefits.**

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Introduction

Large-scale clinical trials have demonstrated the beneficial effects of abciximab in percutaneous coronary interventions (PCI)[1]. In the subgroup of patients who are treated in the setting of acute coronary syndromes, abciximab reduces ischemic complications without an undue increase in bleeding[2]. Based on these results, abciximab has recently been evaluated in association with tissue-type plasminogen activator (tPA) in acute myocardial infarction, because of the potential synergistic effect on vessel patency and on prevention of re-thrombosis[3]. Angiographic data have confirmed that such combined therapy is associated with a substantially better improvement in coronary artery patency at 60 and 90 min compared to thrombolytic treatment alone[3]. However, the same study clearly observed a significant increase in the incidence of hemorrhagic events in patients treated with the association of full-dose tPA and abciximab[3].

The above-mentioned investigations were prompted by the understanding that conventional thrombolysis is associated with a significant failure rate[4]. At present, the most appropriate treatment for patients after failed thrombolysis remains controversial[5]. Centers provided with around-the-clock catheterization facilities may be oriented towards a high rate of rescue procedures. However, this approach has traditionally been associated with a lower success rate and a higher frequency of complications compared to pri-

mary procedures[6]. Although the utilization of coronary stents may contribute to increase the procedural success rate[7], high-risk patients undergoing rescue PCI still face a significant probability of failure[8]. The rationale for the administration of abciximab in rescue PCI is based on these concepts, but the potential for severe bleeding usually represents a major drawback to its use.

We describe our experience with administration of abciximab after full-dose tPA, emphasizing the issues of safety and tolerability.

Methods

Patient population. From January 1998 to March 2000, 30 patients (23 males, 7 females, mean age 64 ± 13 years, range 45-89 years) referred to our catheterization laboratory in the setting of acute myocardial infarction after failed thrombolysis were treated with abciximab. The indications to proceed to catheterization were either the persistence or the early recurrence of ST segment elevation after full-dose tPA. At entry, 14 patients had anterior, 13 inferior and 3 infero-lateral myocardial infarction. Previous bypass surgery had been performed in 4. Two patients had cardiogenic shock and 9 had evidence of left ventricular failure. This group of patients was identified as the Abc+ group. Data obtained in this series of patients were compared to those recorded in patients undergoing rescue PCI in the same time period but who did not receive abciximab. There were 35 such patients and they constituted the Abc- group.

Procedural data. Before starting the procedure, heparin infusion was stopped. After arterial puncture, a bolus of 5000 IU of heparin was administered through the arterial 7F sheath. Abciximab treatment was started according to the operator's judgment based on the presence of unfavorable angiographic or procedural characteristics (Table I). The operator felt that these findings constituted an increased risk for procedural failure. The protocol of administration of abciximab included a 0.25 mg/kg bolus followed by infusion of 0.125 mcg/kg/min for 12 hours. The PCI procedure differed in the Abc- group because after the initial bolus, additional heparin was administered at the end of the procedure in order to reach a total dose of 100 IU/kg. In these patients the median heparin dose was 7500 IU (range 5000-10 000 IU). Procedural success was defined as the achievement of TIMI 3 flow and of a residual stenosis < 20%[9], as previously reported. A TIMI 2 flow or a residual stenosis > 20% but < 50% were considered as suboptimal results.

Table I. Indications for abciximab use in the study population.

Saphenous vein graft disease	4
Dissection	9
Intracoronary thrombus	13
Reocclusion	4
Bifurcation with slow flow in collateral > 2 mm	3
Unsuitable for stenting	4
Slow flow post-stenting	3

Categories are not mutually exclusive.

Post-procedural management. After angioplasty, the activated clotting time was monitored and heparin infusion was started when it fell below 180 s. Unless major hemorrhagic complications occurred, heparin treatment was continued for at least 24 hours. The sheaths were withdrawn 24 hours after the procedure. In patients in whom a coronary stent was placed, oral treatment with 500 mg of ticlopidine was started upon arrival in the coronary care unit. Patients under intra-aortic counterpulsation were supported for at least 48 hours. Evidence of bleeding, either spontaneous or at the site of puncture, was recorded and the drop in hemoglobin concentration was monitored. According to previous studies, major bleeding was defined as any intracranial, retroperitoneal or intraocular hemorrhage or any overt bleeding associated with a drop in hemoglobin concentration > 5 g/dl[10]. The need for transfusion and/or vascular surgery was also recorded.

Hemorrhagic complications constituted the primary endpoint examined in the present study. Data on in-hospital mortality are also provided.

Statistical analysis. Data are presented as mean ± SD for continuous variables or as frequencies for categorical variables. Comparison between groups was performed using the non-parametric Mann-Whitney test for continuous variables and χ^2 statistics with Fisher's correction when appropriate for categorical variables. The minimum level of significance accepted was 0.05.

Results

The prevalence of angiographic/procedural risk factors for PCI failure was 100% in the Abc+ group and 57% (20/35) in the Abc- group ($p < 0.001$). Except for this finding, all other clinical and procedural characteristics did not significantly differ between the two groups (Table II). In Abc+ patients, abciximab infusion was started in the catheterization laboratory between 1 and 3 hours after termination of tPA infusion and in all patients was completed according to the dosage schedule. The procedure was successful in 29/30 patients. One failure occurred in an 86 year-old female who had a massive intracoronary thrombosis after successful stenting and left the catheterization laboratory with TIMI flow 0. In one other patient, TIMI flow 2 was ob-

Table II. Comparison of clinical characteristics in the two study groups.

	Abc+ (n=30)	Abc- (n=35)	p
Age (years)	64 ± 13	60 ± 15	0.259
Killip class 3-4	11 (37%)	14 (40%)	NS
Multivessel disease	14 (47%)	18 (51%)	NS
Previous bypass surgery	4 (13%)	–	0.087
Ejection fraction (%)	48 ± 12	46 ± 12	NS
Time from chest pain to recanalization (min)	330 ± 136	325 ± 148	NS
Peak CK-MB mass (ng/ml)	340 ± 324	410 ± 346	NS
Intra-aortic balloon counterpulsation	6 (20%)	12 (34%)	0.315
Infarct-related vessel			
Left anterior descending	11 (38%)	20 (58%)	NS
Right coronary artery	11 (38%)	12 (34%)	NS
Left circumflex	4 (12%)	3 (8%)	NS
Vein graft	4 (12%)	–	NS
Multivessel procedure	2 (7%)	–	NS
TIMI flow 0-1 at baseline	22 (73%)	23 (68%)	NS

tained. Procedural results and in-hospital events are summarized in table III. No hemorrhagic stroke occurred in the Abc+ group. Three female patients (aged 41, 77 and 79 years respectively) required blood transfusion because of a significant groin hematoma at the site of arterial puncture for intra-aortic balloon counterpulsation in 2 cases and because of venous puncture for temporary pacing (1 case). All 3 patients had an activated clotting time > 300 s after PCI. Two male patients (aged 76 and 89 years respectively) died of refractory cardiogenic shock in the hospital. Both had three-vessel disease and a left ventricular ejection fraction < 40%. The comparison of hemorrhagic complications in the two groups is illustrated in table IV.

Table III. Procedural results and in-hospital outcome in the two study groups.

	Abc+ (n=30)	Abc- (n=35)	p
Procedural results			
Angiographic success (including TIMI 2 post)	29 (97%)	34 (97%)	NS
Suboptimal result (TIMI 2 post)	1 (3%)	4 (11%)	NS
Procedural failure	1 (3%)	1 (3%)	NS
Stenting	25 (83%)	34 (97%)	0.137
In-hospital events			
Death	2 (7%)	1 (3%)	NS
Target vessel revascularization	1 (3%)	2 (6%)	NS
Reinfarction	–	1 (3%)	NS

Table IV. Hemorrhagic complications in the two study groups.

	Abc+ (n=30)	Abc- (n=35)	p
Mean drop in Hb (g/dl)	2.7 ± 1.5	2.6 ± 1.9	NS
Bleeding with Hb drop > 5 g/dl	3 (10%)	4 (11%)	NS
Blood transfusion	3 (10%)	4 (11%)	NS
Puncture site bleeding	8 (27%)	9 (26%)	NS
Intracranial bleeding	–	1 (3%)	NS
Hematuria	3 (10%)	1 (3%)	NS
Surgery for vascular complications	–	2 (6%)	NS
ACT > 300 s post-procedure	9 (30%)	7 (20%)	NS

ACT = activated clotting time; Hb = hemoglobin.

Discussion

Failed rescue PCI is associated with a poor outcome. In the TIMI 4 trial database the in-hospital event rate in these patients was as high as 83%[6]. Thus, once the decision to proceed to rescue PCI has been made, all efforts are necessary in order to achieve an adequate procedural result. Patients with angiographic/procedural features such as those described in our series are at increased risk of failure[11]. In this setting, abciximab is one of the most effective options available to the interventional cardiologist. The main issue raised by the utilization of abciximab in this situation is whether the expected benefits are outweighed by hemorrhagic complications. In our experience this was not evident. Two main factors may account for this: 1) tPA and abciximab were administered sequentially, with a > 1 hour interval. Previous studies showed that the plasma half-life of tPA in humans is about 45 min[12]. This time sequence significantly differs from the combined tPA-abciximab administration proposed in TIMI 14 study[3]; 2) the heparin dose was reduced in Abc+ patients.

One large clinical series on abciximab treatment in rescue PCI derives from the analysis of the GUSTO-III database[13]. In this study, 392 rescue PCI were performed among > 15 000 patients comprising the total study population. This corresponds to a 2.6% rate of referral for PCI after thrombolysis. Since the GUSTO-III is a multicenter study, the rate of referral for rescue PCI may vary considerably among different centers and many may have actually performed fewer procedures than we did. Eighty-three patients were treated with abciximab after thrombolysis (tPA or rateplase) while 309 patients received conventional treatment. Thus, abciximab was administered to one fourth of the total rescue PCI population.

In our series, we report a total of 65 rescue procedures performed in a 27-month period. In the same interval, 480 thrombolytic treatments were administered for acute myocardial infarction at our institution. Thus, the rate of referral for rescue PCI in our population was > 10%, with a frequency of abciximab treatment close to 50%. Also, the time interval for rescue PCI in the GUSTO-III study was as long as 24 hours with a median of 4 hours, while all patients in our series were treated within 3 hours of termination of tPA treatment.

Procedural results and complication rates in the two studies appear similar, with a 16% transfusion rate in the GUSTO-III and a 10% transfusion rate in our series. However, there is a trend towards a higher frequency of severe bleeding in the GUSTO-III trial (3.6 vs 1%, p = 0.08), possibly due to the larger population examined and/or the higher median dose of heparin employed in that series of patients compared to ours (7500 vs 5000 IU). We observed that female patients on intra-aortic balloon counterpulsation are the subgroup at the highest risk for hemorrhagic complications. For this reason, prophylactic intra-aortic balloon pumping should be considered with caution in abciximab-treated females.

Very prolonged activated clotting times were commonly found after the procedure in both Abc+ and Abc- groups. A further reduction in the heparin dosage would probably contribute to limit the incidence of severe bleeding, but the efficacy of lower doses in this setting requires confirmation. Also, as previously observed[14], earlier sheath removal may contribute to decrease local bleeding.

The aim of our study was to report on the feasibility of abciximab treatment after tPA. The number of patients studied is too limited to provide adequate insight into the potential prognostic impact of this treatment. The previously cited GUSTO-III database reports a trend towards a beneficial effect in terms of the 6-month mortality observed in a population of 392 patients[13]. The main conclusion of our study is that abciximab can be administered in selected cases of rescue PCI in which the risk of procedural failure is high. In this preliminary series, the hemorrhagic risk, both in terms of frequency and severity, appears to be acceptable. Further data concerning both the safety and efficacy of such treatment are required before this approach can be recommended for a broader population undergoing rescue PCI.

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