Reduction of Major Adverse Cardiac Events With Intracoronary Compared With Intravenous Bolus Application of Abciximab in Patients With Acute Myocardial Infarction or Unstable Angina Undergoing Coronary Angioplasty

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Background—In patients with acute myocardial infarction or unstable angina undergoing coronary angioplasty, abciximab reduces major adverse cardiac events (MACE). Clinical trials have studied intravenous administration only. Intracoronary bolus application of abciximab causes very high local drug concentrations and may be more effective. We studied whether intracoronary bolus administration of abciximab is associated with a reduced MACE rate compared with the standard intravenous bolus application.

Methods and Results—We stratified 403 consecutive patients with acute myocardial infarction or unstable angina undergoing coronary angioplasty according to the type of application of abciximab. A 20-mg bolus of abciximab was given intravenously in 109 patients and intracoronarily in 294 patients. There were no differences between the groups with regard to diabetes mellitus, cardiogenic shock, successful intervention, or preprocedural and postprocedural TIMI flow. At 30 days, the incidence of MACE (death, myocardial infarction, urgent revascularization) was significantly lower in the patients with intracoronary compared with intravenous administration of abciximab (10.2% versus 20.2%; P<0.008), which was independent from stenting in multivariate analysis. The effect was most pronounced in patients with preprocedural TIMI 0/1 flow (MACE: intracoronary 11.8% versus intravenous 27.5%, P<0.002; n=273).

Conclusions—In patients with acute myocardial infarction or unstable angina undergoing emergency coronary angioplasty, intracoronary bolus application of abciximab is associated with a reduction of MACE compared with the standard intravenous bolus application of abciximab. Prospective, randomized trials are warranted to further assess intracoronary application of abciximab. (Circulation. 2003;107:1840-1843.)

Key Words: angioplasty • stents • glycoproteins • myocardial infarction

In patients with acute coronary syndromes undergoing coronary angioplasty, abciximab reduces the occurrence of major adverse cardiac events (MACE). All clinical trials studied solely the intravenous administration of abciximab. There is only limited information on the efficacy of local, intracoronary administration of abciximab. In patients with acute coronary syndrome, intracoronary administration of abciximab with very high local concentrations of the antibody may be favorable in dissolution of thrombi and microemboli with subsequent better and faster recovery of myocardial microcirculation and reduction of MACE.

We analyzed whether an intracoronary bolus application of abciximab is associated with a reduced incidence of MACE compared with the standard intravenous route in patients with acute myocardial infarction or unstable angina undergoing emergency coronary angioplasty.

Methods

Study Population

We examined a series of 403 consecutive patients with unstable angina or acute myocardial infarction undergoing emergency coronary intervention between March 1996 and December 2001, retrospectively stratified according to the method of application of abciximab. A 20-mg bolus of abciximab was given intravenously in 109 patients and intracoronarily in 294 patients, followed by 12 hours of intravenous infusion of 10 mg in both groups. The groups were included contemporaneously. Four experienced operators performed the interventions. Patients were pretreated with at least 500 mg acetylsalicylic acid and received heparin adjusted to the activated clotting time (>280 seconds). Stenting was performed at the oper-
ator’s discretion in case of dissection or residual luminal stenosis >50% after balloon dilation. Procedural success was defined as a reduction of luminal diameter stenosis below 50% residual lumen narrowing. TIMI flow was evaluated before and after intervention. Patients with stents received ticlopidine (500 mg/d) or clopidogrel (75 mg/d) for at least 4 weeks in addition to continued acetylsalicylic acid (100 mg/d).

MACE were defined as acute myocardial infarction, need for urgent revascularization, or death. Patients were followed up for 30 days after intervention. The local ethics committee approved the study, and all patients gave written, informed consent for the procedure.

Quantitative Coronary Angioplasty
Coronary angiography of the target lesion before and after angioplasty was performed in the same projections. Angiographic measurements were done with the Pie Medical software 2.1 (Pie Medical Imaging). For quantitative coronary measurements, the same 2 orthogonal views were analyzed. Acute gain was calculated as the difference in luminal diameter after and before the procedure.

Statistical Analysis
Continuous variables were presented as mean ± SD; categorical variables were presented as percentages. U test or t test was performed for group comparison with continuous, nonparametric, or parametric variables. Categorical variables were compared by χ² analysis. To account for differences between the groups, multivariate regression and factorial multivariate analysis of covariance. Statistical significance was defined as P<0.05.

Results
Study Population
Clinical variables are presented in Table 1. There were no differences in cardiovascular risk profile, cardiac history, or clinical presentation with acute myocardial infarction or unstable angina, cardiogenic shock, and preceding resuscitation. Additionally, the target vessel, lesion morphology, and TIMI flow before and after the intervention did not differ (Table 2). By chance, the rate of stenting was higher in patients with intracoronary administration of abciximab (73%) compared with patients with intravenous use (59%). However, subgroup analysis for the individual study years revealed no significant differences. Quantitative coronary angiography data showed a larger reference diameter (RD), higher minimal lumen diameter (MLD) after angioplasty, and a higher acute gain in the group with intracoronary bolus administration compared with the group with intravenous administration of abciximab (Table 2). Adjunctive therapy received by each treatment group did not differ.
Follow-up data were available from all 403 patients. The MACE rate was significantly lower in patients with intracoronary abciximab bolus (10.2%, n=30 of 294 patients) compared with patients with intravenous administration (20.2%, n=22 of 109 patients; P<0.0008). The lower frequency of MACE after intracoronary abciximab was independent from the operator and the treatment year. It was also evident in the subgroups of patients with stenting (intracoronary 10.7%, n=23 of 214; intravenous 20.3%, n=13 of 64; P<0.05), balloon angioplasty alone (intracoronary 8.8%, n=7 of 80; intravenous 20.0%, n=9 of 45; P=0.07), or patients without cardiogenic shock (intracoronary 2.8%, n=7 of 252; intravenous 13.5%, n=12 of 89; P<0.0003). Even after adjusting for the higher rate of stenting in the intracoronary group, the lower MACE rate after intracoronary compared with intravenous bolus administration persisted. MACE did not differ between patients with stenting or balloon angioplasty (13.0% versus 12.8%). The postprocedural RD and acute gain did not significantly differ between patients with and without MACE (RD 3.02±0.53 mm versus 3.11±0.64 mm, P=0.16; acute gain 2.19±0.96 mm versus 2.37±0.83 mm, P=0.34).

The individual components of MACE in patients with intracoronary versus intravenous administration were as follows: urgent revascularization, 0.3% versus 4.6% (P<0.002); recurrent myocardial infarction, 0.3% versus 2.8% (P<0.04); and death, 9.5% versus 15.6% (P<0.09). Mortality rate was largely related to cardiogenic shock and was 51.6% in the 62 patients with and only 3.8% in patients without cardiogenic shock. In patients without cardiogenic shock, mortality was significantly lower with the intracoronary bolus of abciximab (2.0%; n=5 of 252) compared with intravenous administration (9.0%; n=8 of 89). From multiple regression analysis including the application form of abciximab, stenting, and the postprocedural MLD and RD, only the application form of abciximab had a significant impact on the occurrence of death (P<0.003).

There was a significant interaction between the preprocedural TIMI flow, the application of abciximab, and MACE. In patients with preprocedural TIMI 0/1 flow, MACE occurred significantly less often after intracoronary abciximab (11.8%, n=24 of 204), compared with the intravenous use (27.5%, n=19 of 69; P<0.002). In contrast, MACE did not differ between the treatment forms in patients with preprocedural TIMI 2/3 flow (intracoronary 6.7%, n=6 of 90; intravenous 7.7%, n=3 of 39).

Discussion

Our study of patients undergoing emergency angioplasty for treatment of acute myocardial infarction or unstable angina revealed a 50% reduction of MACE in patients receiving an intracoronary bolus of abciximab relative to patients with the standard intravenous bolus of abciximab, both followed by a 12-hour intravenous infusion. This was mainly related to patients with preprocedural TIMI 0/1 flow and independent from stenting or balloon angioplasty.

Reports of intracoronary use of abciximab in humans are limited to a small number of patients with angiographically visible thrombus in coronary arteries and nonoccluded saphenous vein grafts, revealing a rapid reduction of thrombotic mass. Given the results of GUSTO-IV ACS (Global Use of Strategies To Open occluded coronary arteries IV in Acute Coronary Syndromes) showing a lack of benefit of intravenous abciximab when used as medical therapy for unstable angina or non-ST-elevation myocardial infarction and the data showing that glycoprotein IIb/IIIa inhibitors are most beneficial in patients undergoing percutaneous coronary intervention, it is quite logical to consider an intracoronary administration regimen. The present study is the first comparing the intravenous and intracoronary bolus application of abciximab.

High, local doses of abciximab from intracoronary administration may facilitate the diffusion of the antibody to platelets inside flow-limiting thrombi, resulting in an improved dissolution of thrombi and microemboli at the culprit lesion and in the distal microcirculation. This is supported by our finding that the lower MACE rate after intracoronary bolus application was mainly due to patients with preproce-
dural TIMI 0/1 flow. Depending on the relation between inflow and washout from residual perfusion and the size of the ischemic area, the concentration of abciximab at the culprit lesion after intracoronary injection compared with intravenous bolus administration might vary between 280:1 (minimal washout) and 1:1 (normal flow). Even in a TIMI 3 situation, intracoronary bolus application will result in short, very high local concentrations, facilitating diffusion of the drug into fresh thrombi. After intravenous bolus application of 20 mg abciximab, platelet aggregation is reduced to <20% within 10 minutes. Other potential mechanisms are antiinflammatory effects from cross-reactivity of abciximab with the leukocyte $\alpha_{5}\beta_{2}$ integrin. Although the non–glycoprotein IIb/IIIa properties of abciximab do not seem to translate into long-term clinical benefit with intravenous application, this could be different with high local concentrations from intracoronary bolus administration.

**Study Limitations**

The study is retrospective and nonrandomized. Furthermore, patients with intracoronary abciximab received stents more often compared with patients with intravenous application. However, from multivariate analysis, the impact of intracoronary application of abciximab on MACE was independent from stenting. Furthermore, in a recent randomized comparison of patients with acute myocardial infarction undergoing percutaneous transluminal coronary angioplasty (PTCA) alone, PTCA plus abciximab, stenting alone, or stenting with abciximab, there was no difference in the combined end point (death, stroke, reinfarction, target vessel revascularization) at 30 days between the groups with PTCA plus abciximab and stenting plus abciximab (4.8% versus 4.4%).

**Conclusions**

In patients with acute myocardial infarction or unstable angina undergoing emergency coronary angioplasty, intracoronary bolus application of abciximab is associated with a reduction of MACE compared with the standard intravenous bolus application of abciximab. Prospective, randomized trials are warranted to further assess this positive effect.

**References**

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_Circulation_. 2003;107:1840-1843; originally published online April 7, 2003; doi: 10.1161/01.CIR.0000066852.98038.D1

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/14/1840

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