Clin. Cardiol. 24, 197–201 (2001)

Rescue Use of Abciximab Improves Regional Left Ventricular Function after Early Incomplete Reperfusion in Acute Myocardial Infarction

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Summary

Background: Abciximab was shown to have important beneficial effects beyond the maintenance of epicardial coronary artery patency. However, it remains uncertain whether abciximab may lead to a better functional outcome in patients with acute myocardial infarction (AMI) and with incomplete reperfusion after primary angioplasty (PA).

Hypothesis: The study aimed to evaluate whether rescue use of abciximab may lead to a better functional outcome in such patients.

Methods: The study included 25 patients with first AMI who met the following criteria: (1) total occlusion of the infarct-related artery, (2) PA within 12 h of symptom onset, (3) postprocedural diameter stenosis < 30%, and final Thrombolysis in Myocardial Infarction (TIMI) flow grade 2. Echocardiographic examination was performed before and on Days 7 and 30 after PA. The study population was divided into two groups: Group 1 (usual care, n = 13) and Group 2 (rescue use of abciximab, n = 12). Baseline characteristics were similar between the two groups.

Results: Peak level of creatine kinase was higher in Group 1 than in Group 2 (5,800 ± 2,700 vs. 3,800 ± 2,000 U/l, $p < 0.05$). At 1 month follow-up, infarct zone wall motion score index (2.71 ± 0.26 vs. 2.05 ± 0.63, $p < 0.01$) and left ventricular (LV) volume indices were smaller in Group 2 than in Group 1, whereas LV ejection fraction was higher in Group 2 than in Group 1 (52.1 ± 7.8 vs. 42.1 ± 6.4, $p < 0.01$). At 1-month, abciximab was the only independent predictor of wall motion recovery index by multiple regression analysis.

Conclusions: Rescue use of abciximab may reduce the infarct size in patients with AMI and TIMI grade 2 flow after PA, which may improve the recovery of regional LV function.

Key words: abciximab, myocardial infarction, wall motion recovery

Introduction

Reperfusion therapy has become the mainstay in the treatment of acute myocardial infarction (AMI) over the last decade.[1–4] However, successful coronary recanalization may not always be associated with successful myocardial reperfusion.[5] Several clinical trials have demonstrated that patients with Thrombolysis in Myocardial Infarction (TIMI) grade 2 flow have clinical outcomes closer to those of patients with TIMI grade 0 or 1 than to patients with TIMI grade 3.[6–10] Therefore, the primary goal of reperfusion therapy is to achieve rapid, complete, and sustained restoration of infarct artery blood flow.

The adequacy of myocardial reperfusion depends not only on infarct-related artery patency but also on microvascular integrity.[11–14] In experimental studies, platelet aggregation and vasoconstrictors released by platelets play an important role in microvascular damage in AMI, suggesting that antiplatelet therapy may contribute to microvascular preservation in AMI.[15, 16] Recent studies support that abciximab has important beneficial effects beyond the maintenance of epicardial coronary artery patency.[17, 18] However, it remains uncertain whether abciximab may lead to a better functional outcome in patients with AMI and TIMI grade 2 flow after primary angioplasty (PA). We hypothesized that rescue use of abciximab

This study was supported by grant from the Asan Institute for Life Science (#97-060).

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Received: February 15, 2000
Accepted with revision: May 23, 2000

may improve the recovery of regional left ventricular (LV) function after early incomplete reperfusion in AMI. To test this hypothesis, we serially measured LV function in patients with AMI treated with PA, and assessed the impact of abciximab on LV recovery in these patients.

Methods

Study Patients

The study population comprised 26 consecutive patients with first AMI, admitted to our hospital between June 1997 and May 1999, who met the following criteria: (1) typical chest pain lasting > 30 min, (2) ST-segment elevation of > 0.1 mV in ≥ 2 continuous leads, (3) total occlusion of the infarct-related artery, (4) a coronary artery lesion suitable for PA, (5) PA within 12 h of symptom onset, and (6) postprocedural diameter stenosis < 30% and final TIMI grade 2 flow (corrected TIMI frame count > 40). Exclusion criteria included the presence of previous bypass surgery, atrial fibrillation, valvular heart disease, ischemic events during the follow-up, or inadequate quality of echocardiographic image. One of the 26 patients was excluded from the study because of inadequate quality of echocardiographic image; thus, 25 patients were enrolled in the study. All patients were to receive standard medical care, including aspirin, at the time of enrollment.

Angioplasty Procedure

Left and right coronary angiography was performed in all patients, and thereafter PA was performed according to the study protocol at our institution. Two types of stents were used in this study: NIR stent (Boston Scientific Corporation, Boston, Mass., USA) and CrossFlex stent (Cordis, Johnson & Johnson Corp., Miami, Fla., USA). After predilation, the stents were deployed at single high pressure (≥ 12 atm) and, if necessary, adjunct high-pressure balloon dilation was performed to achieve angiographic optimization. During the procedure, we gave an intravenous bolus dose of 10,000 units heparin, and all patients received intravenous heparin for 3 days with an infusion rate of activated partial thromboplastin time at 1.5 to 2.0 times of normal. Abciximab was used in a chronologically consecutive manner, which eliminated the potential for operator selection bias. Therefore, we used abciximab in the last 12 patients immediately after PA, which was given as a bolus of 0.25 mg/kg body weight, followed by a 12-h infusion at a rate of 10 μg/min. All patients received an initial single dose of 500 mg ticlopidine immediately after the procedure which was continued at 250 mg twice a day for a period of 4 weeks.

Echocardiography, Electrocardiography, and Cardiac Enzymes

All patients underwent complete echocardiographic examination with HP 2500 (Hewlett Packard Co., Andover, Mass., USA) before, and on Days 7 and 30 after PA. Images were recorded on videotape by an S-VHS cassette recorder for analysis. Cardiac enzyme (creatine kinase, creatine kinase-MB) was serially measured at 4-h intervals up to 24 h and later at 8-h intervals up to 72 h after intervention, and the maximum level was used as an enzymatic marker of infarct size. A 12-lead electrocardiogram (ECG) was obtained at the time of presentation, and subsequent ECGs immediately after and 24 h after PA. The sum of ST-segment elevation (Σ ST-segment elevation) was measured manually 20 ms after the end of the QRS complex from leads I, aVL, and V_1 through V_6 for left anterior descending coronary artery occlusion, and leads II, III, aVF, V_5, V_6, and reciprocal ST-segment depressions in V_1 and V_2 for right coronary artery after occlusions as described previously.[19] Persistent ST-segment elevation was defined as ≥ 50% of the initial value at 24-h follow-up.

Definition and Analysis

Two experienced angiographers blinded to the study purpose analyzed the infarct-related artery using an on-line quantitative coronary angiography system (Ancor V2.0, Siemens Medical Systems, Erlangen, Germany). Percent diameter stenosis, minimal lumen diameter (MLD), and reference diameter were measured before predilation, after stent placement. Contrast flow through the epicardial vessel was graded using the standard TIMI trial flow scale of 0 to 3.[20]

Echocardiograms were analyzed by two investigators blinded to clinical and angiographic data, and discrepancies were resolved by consensus. Echocardiographic images were transferred to the hard disk of a TomTec Imaging System (TomTec Imaging System, Unterschleissheim, Germany) to obtain quantitative data. Left ventricular end-systolic and end-diastolic volumes were calculated by computer software according to a modified Simpson's rule. Three measurements of the technically best cardiac cycles, avoiding postectopic beats, were taken from each examination and the average volumes were obtained. The volume indices were obtained by dividing the volume by the body surface area at each time point. The LV ejection fraction was calculated as stroke volume/end-diastolic volume. Regional wall motion was assessed according to a 16-segment model. For each segment, wall motion was scored as 1 (normal), 2 (hypokinetic), 3 (akinetic), or 4 (dyskinetic). In evaluating regional wall motion abnormality, attention was paid to the systolic thickening in the central portion of each segment. In each patient, both global and infarct-zone wall motion score indices were derived. Wall motion recovery index was defined as improved wall motion at follow-up compared with the baseline study, and was obtained by dividing the number of improved wall motion segments (a reduction in segmental score of at least one grade) at follow-up by the number of abnormal wall motion segments within the infarct zone at baseline.

Inter- and intraobserver reproducibility was checked by selecting 10 random study echocardiograms. The agreement was good for measurements of wall motion score index (interobserver variability: $r = 0.93$, $p < 0.01$; intraobserver vari-

ability: $r = 0.95$, $p < 0.01$). Inter- and intraobserver variability values in the evaluation of end-systolic and end-diastolic volumes were < 5%.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD) for continuous variables, and frequencies for the categorical variables. Continuous variables were compared by unpaired Student's *t*-test, categorical variables by chi-square test. The comparisons between the two patient groups over time were made with a 2-way repeated-measures analysis of variance (ANOVA). Linear regression analysis was performed on all variables to identify determinants of wall motion recovery index, and variables found to be $p < 0.1$ by univariate analysis were entered into a stepwise multiple linear regression analysis. A p value < 0.05 was considered statistically significant.

TABLE I Baseline characteristics

	Group 1 (n = 13)	Group 2 (n = 12)
Age (years)	61.1 ± 11.4	57.0 ± 10.7
Male / female	11/2	10/2
Killip classification		
I (%)	6 (46.2)	6 (50.0)
II (%)	6 (46.2)	6 (50.0)
III (%)	1 (7.6)	
Risk factors		
Diabetes mellitus (%)	2 (15.4)	3 (25.0)
Cholesterol (>200 mg/dl) (%)	3 (23.1)	3 (25.0)
Hypertension (%)	6 (46.2)	4 (33.3)
Smoking (%)	7 (53.8)	5 (41.7)
Time to reperfusion (h)	4.8 ± 3.0	5.1 ± 3.5
Peak CK, U/l	5,800 ± 2,700	3,800 ± 2,000 [a]
Peak time of CK (h)	8.5 ± 2.8	7.5 ± 2.7
IZ WMSI before angioplasty	2.87 ± 0.13	2.78 ± 0.25
E peak (cm/s)	60.0 ± 28.0	70.0 ± 15.0
A peak (cm/s)	74.0 ± 20.0	70.0 ± 25.0
Deceleration time (ms)	157.5 ± 50.3	149.0 ± 46.1
End-systolic volume index (ml/m^2)	26.6 ± 5.8	26.0 ± 3.7
End-diastolic volume index (ml/m^2)	48.5 ± 8.5	46.9 ± 7.9
Left ventricular ejection fraction (%)	44.8 ± 8.1	44.2 ± 4.4
Multivessel disease (≥ 2) (%)	6 (46.2)	5 (41.7)
Σ ST-segment elevation (mV)		
Before angioplasty	2.5 ± 1.2	2.3 ± 1.1
Immediately after angioplasty	1.6 ± 1.3	1.6 ± 0.7
24 h after angioplasty	1.4 ± 0.8	0.7 ± 0.6 [a]

[a] $p < 0.05$.

Abbreviations: CK = creatine kinase, IZ WMSCI = infarct zone wall motion score index.

Results

Baseline Characteristics

The study population was divided into two groups: Group 1 (usual care, n = 13) and Group 2 (use of abciximab, n = 12). As shown in Tables I and II, there were no significant differences between groups for age, gender, risk factors, time to reperfusion, echocardiographic variables, and angiographic characteristics. No serious hemorrhagic complications were observed during hospitalization, but one patient in Group 2 required transfusion because of severe local hematoma.

Abciximab and Infarct Size

Patients in Group 1 had higher peak levels of creatine kinase than those in Group 2 (5,800 ± 2,700 vs. 3,800 ± 2,000 U/l, respectively, $p < 0.05$). The time from first balloon inflation to peak creatine level did not differ between the two groups (Table I). All patients showed persistent ST-segment elevation (≥ 50% of the initial value) immediately after PA. However, persistent ST-segment elevation (≥ 50% of the initial value) at 24-h follow-up was more common in Group 1 than in Group 2 (69.2 vs. 16.7 %, respectively, $p < 0.05$) (Table I).

Temporal Changes in Regional and Global Left Ventricular Function

Figure 1 shows temporal changes in regional contractile function (wall motion score index and wall motion recovery index) within the infarct zone. In Group 2, infarct zone wall

TABLE II Angiographic characteristics

	Group 1 (n = 13)	Group 2 (n = 12)
Infarct-related artery		
Left anterior descending coronary artery (%)	10 (76.9)	8 (66.7)
Right coronary artery (%)	3 (23.1)	4 (33.3)
Angioplasty		
Balloon angioplasty (%)	3 (23.0)	3 (25.0)
Stent placement (%)	10 (76.9)	9 (75.0)
CrossFlex stent (%)	3 (23.1)	3 (25.0)
NIR stent (%)	7 (53.8)	6 (50.0)
Reference artery size (mm)	3.3 ± 0.3	3.4 ± 0.8
Minimal lumen diameter (mm)		
Baseline	0	0
Final	2.9 ± 0.3	3.0 ± 0.6
Diameter stenosis (%)		
Baseline	100	100
Final	12.0 ± 9.6	11.8 ± 11.2
Balloon to artery ratio	1.1 ± 0.2	1.1 ± 0.1
Maximum inflation pressure (atm)	13.2 ± 3.4	14.0 ± 3.5

No differences between the two groups.

FIG. 1 Time course of infarct zone wall motion score index (WMSI) (A) and wall motion recovery index (B). Infarct zone wall motion recovery was more rapid and complete in Group 2 than in Group 1. Data are mean ± standard deviation. —●— = Group 1, —■— = Group 2.

motion score index significantly decreased from baseline to 1-month follow-up (2.78 ± 0.25 vs. 2.05 ± 0.63, respectively, $p < 0.05$). In contrast, it remained unchanged in Group 1 (2.87 ± 0.13 vs. 2.71 ± 0.26, respectively, p = NS). Baseline regional and global LV function was similar between the two groups (Table I). At 1-month follow-up, LV ejection fraction was higher in Group 2 than in Group 1 (52.1 ± 7.8 vs. 42.1 ± 6.4, respectively, $p < 0.01$). Left ventricular end-systolic volume index (33.5 ± 7.1 vs. 41.0 ± 11.5 ml/m^2, respectively, $p < 0.01$) and LV end-diastolic volume index (71.2 ± 15.2 vs. 79.5 ± 16.6 ml/m^2, respectively, p = NS) were smaller in Group 2 than in Group 1.

Determinants of Wall Motion Recovery Index at 1 Month

Infarct zone wall motion recovery index at 1 month was significantly associated with use of abciximab ($p < 0.01$) and the absence of persistent ST-segment elevation at 24 h follow-up ($p < 0.05$). However, abciximab was the only independent predictor of wall motion recovery index by multiple regression analysis. Time to reperfusion or angiographic collaterals or the presence of preinfarction angina (antecedent angina ≤ 24 h before the onset of AMI) was not significantly related to wall motion recovery index at 1 month.

Discussion

The major findings of this study are that (1) rescue use of abciximab may improve the recovery of regional LV function in patients with AMI with TIMI grade 2 flow after PA compared with conventional heparin treatment, and (2) it seems to reduce the infarct size in these patients. These findings support that platelet activation may contribute to inadequate myocardial reperfusion, which can be pharmacologically modified by glycoprotein IIbIIIa receptor blockade.

Complete Reperfusion and Microvascular Damage

Early and complete restoration (TIMI grade 3 flow) of infarct-related artery is a critical determinant of clinical outcomes after reperfusion therapy in AMI. However, complete restoration of epicardial coronary artery flow is not always associated with adequate myocardial reperfusion, which is a prerequisite for myocardial viability. Even in patients with TIMI grade 3 flow, myocardial contrast echocardiography sometimes reveals no reflow to the infarct myocardium. Previous studies have demonstrated that no or low reflow is related to little improvement of regional and global LV function at follow-up, implicating more extensive necrosis and greater functional impairment in AMI. Initial no reflow is more common in patients with TIMI grade 2 flow than in those with TIMI grade 3 flow.[11] Therefore, new therapeutic approaches may be needed to enhance the quality of reperfusion therapy in these patients.

Effects of Abciximab on Myocardial Salvage

Reperfusion is a dynamic phenomenon, characterized by serial changes in flow in the postischemic microcirculation.[21] Early impairment of tissue perfusion may be partially reversible in the first hours or days after reperfusion therapy.[22,23] Although no reflow is generally associated with no or poor functional recovery, recent study suggests that improvement in microvascular perfusion may occur after initial no reflow, which is associated with preservation of contractile reserve and gradual functional recovery.[14] Therefore, patients with TIMI grade 2 flow may achieve the recovery of microcirculatory and regional LV function after reperfusion therapy.

Distal embolization of platelet aggregates, vasoconstrictor released by platelets, and inflammatory responses may compromise the recovery of microcirculatory function in the infarct area.[15,16,24] Abciximab may be useful in preventing embolization of platelet aggregates into the microcirculation as well as platelet adhesion to the injured endothelium,[25] enhancing the recovery of microvascular perfusion and contractile function in the area at risk.[17] This study reveals that rescue use of abciximab may improve the recovery of regional LV function in patients with AMI with TIMI grade 2 flow. Persistent ST-segment elevation ≥ 50% of the initial value at 24-h follow-up, indirectly reflecting sustained inadequate myocardial reperfusion,[19] was more common in the conventional treatment group than in the abciximab group. These results indicate that postischemic microvascular dysfunction may be partially reversible even in patients with TIMI grade 2 flow.

Study Limitations

Several potential limitations need to be addressed. First, 30-days follow-up angiogram was not obtained in this study, and

therefore the possibility of silent reocclusion could not be excluded. Second, our findings are derived from a selected population with AMI who was treated with PA. Therefore, our results may not be generally applicable to all patients receiving reperfusion therapy. Finally, this is a nonrandomized study and therefore it has inherent limitations. However, abciximab was used in a chronologically consecutive manner, which eliminates the potential for operator selection bias. Despite these limitations, this study reveals that rescue use of abciximab may be beneficial for recovery of regional LV function in patients with AMI with TIMI grade 2 flow.

Acknowledgment

The authors are indebted to Dong Soon Shin, R.N., and Young-Hee Kim, R.N., for their important contribution to data collection, and to Soon Deok Jang, CVT, for assistance in preparing coronary angiograms.

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