International Journal of Cardiovascular Interventions. 2005; 7: 41–45

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ORIGINAL ARTICLE

The impact of adjunctive eptifibatide therapy with percutaneous coronary intervention for acute myocardial infarction

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Abstract
The role of small molecules anti-glycoprotein (GP) IIb/IIIa pharmacotherapy during acute myocardial infarction (AMI) has not been established. The purpose of our study was to evaluate the clinical outcomes of patients sustaining AMI who underwent emergent percutaneous coronary intervention (PCI) and who were distinguished by the use of the anti-GP IIb/IIIa agent eptifibatide. We studied a consecutive group of 216 patients who underwent PCI for acute ST-elevation myocardial infarction and compared the outcomes of patients who received eptifibatide just prior and following the procedure (n=167) to those who were not on anti GP IIb/IIIa inhibitors (n=49). On average, patients treated using eptifibatide were younger and were more likely to be men, hypertensive, and smokers. The eptifibatide treated patients were less likely to have diabetes and renal failure and had worse angiographic characteristics. There were no significant differences between the groups in any of the clinical outcomes, including the composite endpoint (e.g. death, MI, repeat revascularization) and the rate of sub-acute stent thrombosis. Nonetheless, there was a non-significant trend towards lower 30 day mortality in the eptifibatide group (4.8% versus 12%, P=0.09). We concluded that in our comparative study of periprocedural administration of eptifibatide during emergent AMI angioplasty, there was a non-significant trend towards better short-term survival among eptifibatide treated patients although the composite endpoint did not differ between patients distinguished by the use of anti GP IIb/IIIa small molecule pharmacotherapy.

Key Words: *coronary angioplasty, glycoprotein IIb/IIIa inhibitors, myocardial infarction, stents*

Introduction

Administration of the glycoprotein (GP) IIb/IIIa inhibitor abciximab as adjunctive therapy to primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) has been shown to significantly reduce the composite endpoint of death, reinfarction and target vessel revascularization (TVR) (1–6). Furthermore, treatment with abciximab before and during catheter-based reperfusion for ST segment elevation AMI has been associated with improved thrombolysis in myocardial infarction (TIMI) grade 3 flow (7) and a reduction in infarct size (4). Despite the evidence of significant benefit for adjunctive use of abciximab with primary PCI for AMI, there are limited data about the efficacy of small molecule GP IIb/IIIa inhibitors in this setting (8–12). Early administration of tirofiban has been shown to improve initial TIMI grade flow in patients undergoing primary PCI for AMI (10–12). In a feasibility study of eptifibatide administration concomitant with primary stenting for AMI, high procedural rates of TIMI grade 3 flow were observed, but an increased rate of sub-acute thrombosis (9.1%) led to premature termination of the study (8). Given the paucity of data, our aim was to evaluate the 30-day clinical outcome of AMI patients undergoing primary PCI who receive adjunctive treatment with eptifibatide as compared with AMI patients undergoing PCI not treated with GP IIb/IIIa inhibitors.

Materials and Methods

We prospectively followed all patients who underwent primary PCI for ST elevation AMI, within 4 hours from chest pain, at the Rabin Medical Center between January 2000 and November 2003. Patients admitted with cardiogenic shock and those

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(Received 1 November 2004; accepted 1 February 2005)

ISSN 1462-8848 print/ISSN 1471-1796 online
DOI: 10.1080/14628840510011180

with contraindications to aspirin, heparin, GP IIb/IIIa inhibitors, or clopidogrel were excluded from the current analysis. Among the 266 patients followed, 167 received eptifibatide, 40 received tirofiban and 49 did not receive any GP IIb/IIIa inhibitors. Owing to cost considerations small molecule GP IIb/IIIa inhibitors are generally used in our institution. The current analysis included the patients who were treated with eptifibatide and the patients who did not receive any GP IIb/IIIa inhibitors. The decision to administer a GP IIb/IIIa inhibitor and the specific agent chosen were at the discretion of the operator. This study was, therefore, a non-randomized observational study.

In-hospital and 30 days clinical outcomes as well as angiographic data from the AMI intervention were obtained. AMI was defined as the presence for at least 30 minutes but less or equal than four hours of symptoms attributed to ischemia, and the presence of ST-segment elevation in at least two contiguous leads or left bundle-branch block. Baseline clinical characteristics, demographics, and in-hospital course were confirmed by independent hospital chart review. Clinical outcomes at 30 days were obtained by outpatient clinic follow up and serial telephone interviews. Cardiac events (death, recurrent AMI, repeat coronary angioplasty or bypass surgery) were confirmed by accompanying hospital documentation. The diagnosis of recurrent AMI during follow-up was based on recurrent chest pain accompanied by re-elevation of the cardiac enzyme levels to at least two times the upper limit of normal at least 48 hours from PCI. In addition, the appearance of new infarct-related electrocardiographic changes was required. The primary endpoint of the study was defined as death, recurrent AMI, or target vessel revascularization within 30 days of the PCI.

Coronary angioplasty and intracoronary stent implantation were performed using standard percutaneous techniques via the femoral artery. All patients were treated with unfractionated heparin intravenously during the procedure (70 units/kg bolus) and adjusted to achieve an activated clotting time of 225–300 seconds. Eptifibatide was administered in the catheterization laboratory just prior to initial balloon inflation, at an intravenous bolus dose of 180 μg/kg (single bolus) and maintenance infusion of 2 μg/kg/min for 18–24 hours. Following the procedure, all patients received aspirin at a dose of 100–325 mg once daily and clopidogrel at a loading dose of 300 mg followed by 75 mg daily for one month.

Angiographic films were reviewed at our angiographic core laboratory using the MDView^{TM} Quantitative Angiographic System (Medcon^{TM} Telemedicine Technology, Tel-Aviv, Israel). An experienced cardiologist who was unaware of the group allocation and clinical outcome performed the analysis. Standard morphologic criteria were used for the identification of lesion location, lumen diameters, and length. Reference and minimal lumen diameter was determined before and after stent implantation using an automated edge-detection algorithm. Based on these measurements, percent diameter stenosis was determined before and after interventions, as were TIMI flow grades (0 to 3). The criteria used for the diagnosis of coronary thrombus were based on the presence of either radio-contrast haziness, lumen-filling defects, irregular edges accompanied by coronary stenosis ($>50\%$) and sub-optimal distal flow with or without coronary occlusion.

Continuous variables are presented as mean $\pm$ standard deviation. Chi-square tests and Fischer exact tests were used for analysis of categorical variables when appropriate, and the Student *t*-testing was used for analysis of continuous variables. Statistical analysis was performed using STATISTICA software, and $P=\leqslant 0.05$ was considered significant for all analysis.

Results

Among the 216 patients followed, 167 were treated with eptifibatide and 49 did not receive GP IIb/IIIa inhibitors. As shown in Table I, the patients in the eptifibatide group had a lower mean age (59 ± 13 versus 66 ± 13 years, $P=0.001$), were more likely to be men (85 versus 69%, $P=0.01$), hypertensive (62 versus 43%, $P=0.02$), current smokers (55 versus 37%, $P=0.02$) and admitted with an anterior AMI (53 versus 37%, $P=0.04$) and less likely to have diabetes (19 versus 37%, $P=0.01$) and renal failure (4.8 versus 16%, $P=0.01$). Both groups received similar medications prior to the PCI (Table II). As demonstrated in Table III, patients in the eptifibatide group tended more often to have two to three vessel coronary artery disease (62 versus 47%, $P=0.06$), and thrombus containing lesions (87 versus 76%, $P=0.06$). In addition, the average culprit vessel stenosis before the PCI was more severe in the eptifibatide group (mean of $95\pm12\%$ versus $90\pm16\%$, $P=0.01$). Table IV outlines the in-hospital and 30 days clinical outcomes. There were no significant differences between the groups in any of the clinical outcomes, including the rate of subacute stent thrombosis and the composite endpoint. Nonetheless, there was a trend towards lower 30 day mortality in the eptifibatide group (4.8 versus 12%, $P=0.09$). Major and minor bleeding rates also did not differ significantly between the two groups.

Conclusions

This is the first comparative study to evaluate the effect of adjunctive administration of the small molecule GP IIb/IIIa inhibitor eptifibatide during

Table I. Demographic and clinical characteristics.

	Eptifibatide (n=167)	No GP IIb/IIIa inhibitor (n=49)	P value
Age (years)	59±13	66±13	0.001
Men	142 (85%)	34 (69%)	0.01
Diabetes mellitus	32 (19%)	18 (37%)	0.01
Hyperlipidemia*	75 (45%)	24 (49%)	0.6
Systemic hypertension	104 (62%)	21 (43%)	0.02
Current smoking	92 (55%)	18 (37%)	0.02
Prior CABG	2 (1.2%)	3 (6.1%)	0.1
Prior percutaneous coronary intervention	25 (15%)	10 (20%)	0.4
Renal failure (creatinine≥1.5 mg/dl)	8 (4.8%)	8 (16%)	0.01
Prior stroke	11 (6.6%)	4 (8.2%)	0.7
Peripheral vascular disease	7 (4.2%)	1 (2%)	0.4
Anterior myocardial infarction	89 (53%)	18 (37%)	0.04
Systolic blood pressure (mm Hg)	136±23	131±28	0.2
Diastolic blood pressure (mm Hg)	77±13	74±12	0.1
Door to needle time (hours)	1.7±1.8	2.2±3.0	0.2

* Hyperlipidemia, diagnosis previously made by physician or receiving lipid-lowering therapy.

Table II. Medical treatment prior to the percutaneous coronary intervention.

	Eptifibatide (n=167)	No GP IIb/IIIa inhibitor (n=49)	P value
Aspirin	160 (96%)	44 (90%)	0.1
Beta blockers	42 (25%)	14 (29%)	0.7
Angiotensin converting enzyme inhibitors	53 (32%)	14 (29%)	0.8
Statins	50 (30%)	15 (31%)	0.9

Table III. Angiographic characteristics and procedural factors.

	Eptifibatide (n=167)	No GP IIb/IIIa inhibitor (n=49)	P value
Culprit coronary vessel			0.13
Left anterior descending	89 (53%)	18 (37%)	
Left circumflex	18 (11%)	7 (14%)	
Right coronary artery	55 (33%)	20 (41%)	
Diagonal branch	4 (2.4%)	3 (6.1%)	
Vein graft	1 (0.6%)	1 (2%)	
Two-3 vessel coronary disease	104 (62%)	23 (47%)	0.06
Thrombus containing lesion	145 (87%)	37 (76%)	0.06
Pre TIMI 0/1 flow	117 (70%)	30 (61%)	0.2
Post TIMI 3 flow	162 (97%)	47 (96%)	0.7
Pre % stenosis	95±12	90±16	0.01
Post % stenosis	4±11	8±18	0.05
Lesion length (mm)	17.2±6.4	17.7±7.4	0.6
Pre min. lumen diameter (mm)	0.72±0.76	0.45±0.66	0.8
Post min. lumen diameter (mm)	3.0±0.7	2.8±0.8	0.2
Stent deployed	160 (96%)	48 (98%)	0.7
Heaprin coated stent	87 (52%)	24 (49%)	0.7
Stent diameter (mm)	3.1±0.4	3.05±0.5	0.2
Procedural success	162 (97%)	46 (94%)	0.3

primary PCI for ST segment elevation AMI. There were no significant differences in in-hospital or 30 days clinical outcomes or bleeding complications between patients treated with eptifibatide and patients not treated with any GP IIb/IIIa inhibitor.

The lack of clinical benefit in our study from adjunctive eptifibatide treatment during and following primary PCI for AMI appears to be in contrast to the demonstrated benefit with the GP IIb/IIIa inhibitor abciximab (1–6). This disparity may have a number of possible reasons. The dose of eptifibatide

Table IV. In-hospital and 30-day clinical outcome.

	Eptifibatide (n=167)	No GP IIb/IIIa inhibitor (n=49)	P value
In-hospital			
Death	6 (3.6%)	3 (6.1%)	0.4
Recurrent myocardial infarction	6 (3.6%)	0%	0.3
Stent thrombosis	3 (1.8%)	0%	0.8
Major bleeding complications*	4 (2.4%)	1 (2%)	0.8
Minor bleeding complications	5 (3%)	2 (4.1%)	0.8
Thrombocytopenia <20000	0%	0%	1
30 Days			
Death	8 (4.8%)	6 (12%)	0.09
Stent thrombosis	6 (3.6%)	0%	0.3
Recurrent myocardial infarction	11 (6.6%)	1 (2%)	0.3
Composite endpoint—death/MI/TVR	15 (9%)	8 (16%)	0.2

*Requiring red blood cells transfusions.

used in this study was a single bolus of 180 μg/kg followed by a 2 μg/kg/min infusion for 18–24 hours. This dosing regimen is lower than the double bolus dose used in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy trial (ESPRIT) (13) and is shorter than the 72–96 hour maintenance period Wong reported (9). In addition, eptifibatide was administered relatively late—at the catheterization laboratory just prior to initial balloon inflation—in contrast to the early administration of abciximab in the Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up (ADMIRAL) trial (3). A recent meta-analysis has shown that early administration of abciximab or tirofiban in AMI patients undergoing primary PCI improves coronary patency with favorable trends for clinical outcomes, as compared to late administration (14). Another possible explanation is the differences in clinical and angiographic characteristics between the two groups compared in our study. Patients in the eptifibatide group were more likely to be men, hypertensive, smokers and have an anterior AMI, and less likely to have diabetes and renal failure. In addition, they tended more often to have two to three vessel coronary artery disease, thrombus containing lesions, and lesions with a higher degree of stenosis. The more severe baseline angiographic characteristics may have adversely affected outcomes in the eptifibatide group, reducing potential clinical advantages of the drug. Moreover, the fact that this is an observational non-randomized study with a relatively small control group further limits the power of this study. Finally, there may be inherent differences in the clinical effects of abciximab and the small molecule GP IIb/IIIa inhibitors, as suggested by other clinical trials (15).

However, our study did demonstrate that administration of eptifibatide during and following AMI interventions appears to be safe. In contrast to the study reported by Kaul et al (8), there was no increased risk of sub-acute thrombosis. In addition, major and minor bleeding rates in the two study groups were similar. Therefore, given the apparent safety, the lower incremental cost of eptifibatide as compared to abciximab (16) and the clinical benefit demonstrated previously with abciximab (1–6), larger and randomized clinical trials are required to assess whether eptifibatide administration may be beneficial in the setting of primary PCI for AMI.

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