The Use of Abciximab in Coronary Angioplasty _ An Asian Centre's Experience

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ABSTRACT

Background: Abciximab, a monoclonal antibody to platelet glycoprotein IIb/IIIa receptor, has been shown to be effective in reducing ischemic complications after coronary angioplasty in recent trials. However, little is known about its efficacy and safety when used in Asian patients.

Methodology: Based on our abciximab registry, we performed a retrospective analysis of 115 Asian patients who received the antiplatelet agent while undergoing percutaneous coronary intervention in our centre. They constituted 18.4% of the total number of patients undergoing percutaneous revascularisation during the corresponding period. The majority of the patients were males (84%). The mean age of the cohort was 54 and the mean weight was 70 kg. The ethnic composition of the study population was: Chinese 54%, Indians 21%, Malays 19% and Others 6%. All patients received aspirin 100 mg and weight-adjusted heparin before the procedure. Abciximab may be administered on a preplanned basis prior to the procedure or be given as a 'bailout' strategy.

Results: There was a high clinical success rate of 95.8% and low incidence of ischemic complications when abciximab was given during coronary angioplasty. There were 0% Q myocardial infarction, 3.3% non-Q myocardial infarction and 0.8% death in our series. Bleeding complications were uncommon at 7.6%, predominantly involving the groin and gingiva. Thrombocytopenia occurred in 5.8% of patients. Abciximab was noted to increase the procedural activated clotting time (ACT) by 38 seconds when given concomitantly with heparin. The mean maximal procedural ACT achieved was 323 w 51 seconds.

Conclusions: Abciximab may be used safely and efficaciously in Asian patients undergoing coronary angioplasty. The drug confers protection against ischemic complications during the procedure whether it is administered electively or as a 'bailout'. There is however, a need to redefine the heparin regime for our patients, given the high ACT obtained when abciximab is administered.

Keywords: abciximab, coronary angioplasty

INTRODUCTION

Although percutaneous coronary intervention (PTCA) has been effective in reducing coronary ischemia and providing excellent symptom relief[1,2], it is still beset with acute and medium-term complications of abrupt closure and restenosis respectively. Abrupt closure occurs in 4% to 9% of cases and results in considerable morbidity and mortality[3-5] while restenosis continues to plague coronary angioplasty at a rate of 30% to 50%[1]. Recently, it has been shown that a new class of potent antiplatelet agents, the platelet glycoprotein (GP) IIb/IIIa receptor antagonists, may be effective in the prevention of thrombus formation in the setting of coronary intervention. This may potentially reduce the short- and medium-term complications and improve clinical outcomes following percutaneous revascularisation[6,7].

The monoclonal antibody to GP IIb/IIIa receptor, abciximab (c7E3 Fab, ReoProt) has been the most extensively evaluated agent of this class of drugs and its efficacy has been proven in many clinical trials[8,9]. It acts by inhibiting fibrinogen's ability to bind onto GP IIb/IIIa receptors, "the final common pathway" of platelet aggregation and thus abolishing thrombosis mediated by platelet/ fibrinogen interaction. In the landmark EPIC trial (Evaluation of c7E3 Fab in the Prevention of Ischemic Complications), abciximab resulted in a marked 35% reduction in acute ischemic syndromes at 30 days. Its use was however accompanied by a doubling of the incidence of major bleeding complications. In the follow-up EPILOG study (Evaluation of PTCA to Improve Long-Term Outcomes by c7E3 Glycoprotein IIb/IIIa Receptor Blockade), the use of abciximab and low-dose weight-adjusted heparin showed a significant 56% reduction in the composite clinical endpoints without any associated increase in haemorrhagic complications[9]. With these encouraging results as background, we present our single centre experience with the use of this agent among Asian patients undergoing coronary angioplasty.

MATERIALS AND METHOD

Patient population

Our centre is the first in Asia to employ abciximab in patients undergoing coronary angioplasty. Between October 1996 and June 1998, a total of 648 cases of percutaneous coronary interventional procedures were performed. Among them, 115 (18.4%) patients received abciximab while undergoing coronary angioplasty on 119 occasions. There were 4 patients who received abciximab a second time. Demographic data for these patients are shown in Table I. The mean age of the population is 54 w 11 years old and the mean weight is 70 w 11 kg. Male patients predominate at 84%. There was also a higher representation of Indians (21%) in this cohort compared to the national population percentage.

The lesions involved and procedural characteristics are shown in Table II. Most procedures were performed in native coronary arteries, in main, the left anterior descending artery (57%). The majority of the target lesions were judged to be of high risk and were graded as B or C by the American College of Cardiology/American Heart Association classification[10]. Coronary stenting was performed in 83% of cases in our centre. This combined use of abciximab and coronary stenting was carried out even before the release of the EPISTENT findings (Presented at the 47th American College

of Cardiology Meeting, 1998), reflecting an early belief among our operators that there is a complementary role between the two treatment strategies. More than half of the patients underwent multilesional angioplasty (58%), indicating that they were generally of a higher risk subset.

Indications for the use of abciximab

On the basis of the findings of the three large-scale trials[8,9,11], it is suggested that the use of abciximab is appropriate across the board in all patients undergoing PTCA, irrespective of their clinical risk strata.

In our centre, the indications for the use of abciximab (Table II) included EPIC inclusion criteria of: (1) acute ischemic syndromes of evolving myocardial infarction within 12 hours after the onset of symptoms, early postinfarction angina or rest angina with associated electrocardiographic changes, and (2) clinical or angiographic characteristics indicating high risk, according to the criteria of the American Heart Association and the American College of Cardiology[10]. In these cases, abciximab was often administered prophylactically before the commencement of the procedure. Abciximab was also used in our centre for indications beyond the EPIC trial. These included: (1) suboptimal results from balloon angioplasty or stent implantation; (2) debulking procedures such as rotational atherectomy or (3) any situation in which the operators considered the patient at high risk of developing ischaemic complications. In general, when abciximab was given for indications beyond the EPIC trial, it was administered intraoperatively or after the interventional procedure.

Patients were generally excluded from the use of this drug if they were 80 years or older, were known to have a bleeding diathesis, had undergone major surgery within the preceding six weeks, or had history of stroke.

Treatment protocol

All the patients were treated with aspirin and heparin. Aspirin was administered orally in a dose of 100 mg at least 2 hours before the procedure, unless otherwise contraindicated. Heparin was given intra-arterially via the guiding catheter in an initial bolus dose of 70 units per kilogram if the use of abciximab was planned for before the interventional procedure. However, should abciximab not be considered, heparin is given at the usual dose of 100 units per kilogram. Routinely, ticlopidine at a bolus dose of 500 mg was also given 12 hours before an elective procedure in preparation for possible coronary stenting. Activated clotting time (ACT) was kept above 300 seconds for patients who were not intended to receive abciximab prior to the procedure.

Abciximab, when given, was administered intravenously in a bolus dose of 0.25 mg per kilogram of body weight, followed by an infusion of 0.125 mg/kg/min (not exceeding 10 ug/min) for 12 hours. Elective use of abciximab was commenced 10 minutes before the procedure and the bolus dose given over 5 minutes. Repeat blood sample was taken 10 minutes after the commencement of abciximab to determine the increment and maximal value of the ACT.

Vascular sheath was removed within 6 hours of the completion of the procedure or when the ACT was less than 175 seconds. Sheaths were removed even while abciximab was being continually infused. Effective hemostasis was achieved with mechanical and manual compression.

RESULTS

Clinical outcomes

A high procedural success rate (98.3%) was achieved in all our patients undergoing coronary intervention. Angiographic success rate, defined as less than 50% diameter stenosis post-procedure, for all the lesions attempted was 98.8% (178/180 lesions). Clinical success, defined as angiographic success without complicating events of myocardial infarction (MI), death or emergency revascularisation, was 95.8% (114/119 patients). Myocardial infarction was defined by one of two criteria: new, clinically significant Q waves in two or more contiguous electrocardiographic leads, or elevation in creatine kinase or its MB isoenzyme to at least three times the upper limit of normal. There was no documented Q MI but there was a 3.3 % incidence of non Q MI, as defined above. One patient died on the third day of hospitalisation after undergoing primary angioplasty for anterior MI complicated by cardiogenic shock. Another patient underwent emergency percutaneous revascularisation when she developed new infarction involving the left anterior descending (LAD) artery territory, hours after undergoing successful coronary stenting of her right coronary artery. She was later found to have a large left atrial thrombus which might have embolised to the LAD artery.

Complications

The most frequently recognised adverse effect with the use of abciximab was bleeding, as shown in the EPIC trial. Major bleeding, defined as intracranial hemorrhage, a > 5 gm/dL decrease in hemoglobin (Hb), or a > 15% decrease in hematocrit, did not occur in any of our patients. This may be attributed to our concomitant use of low-dose weight-adjusted heparin, early sheath removal and effective groin compression.

Minor bleeding, defined as spontaneous and observed hematuria, hematemesis, gingival or groin bleeding, or any documented blood loss of < 5 gm/dL fall in hemoglobin; remained low at 7.6%. The most common complications were that of groin hematoma and gingival bleeds.

Another recognised complication with the use of abciximab is thrombocytopenia. The specific causative mechanisms are unknown although immune-mediated clearance of platelets has been postulated. When thrombocytopenia develops after the administration of abciximab, it occurs rapidly within hours. As a routine procedure in our centre, all patients who receive abciximab, would have platelet counts checked at 6 and 12 hours later. The incidence of acute thrombocytopenia was low in our cohort, with acute and severe thrombocytopenia occurring in 2.6% and 3.2% of patients respectively. Profound thrombocytopenia (defined as platelet count > 20,000/mm^3) occurred in 2 patients with one reaching a nadir of 9,000/mm^3. None of the patient had intracranial haemorrhage.

There was also no documented incidence of hypersensitivity reaction or significant immune response to the antiplatelet agent.

DISCUSSION

Elective versus 'rescue' abciximab

Although results from EPIC, CAPTURE and EPILOG trials indicated that pretreatment with abciximab was warranted in all patients undergoing

precutaneous coronary revascularisation, but economic considerations have driven physicians to use it only when complications arise intraoperatively. This 'bail-out' practice was applied in 61/119 (51%) patients in our registry. Consistent with the findings from other reports[12,13], our experience showed that 'bail-out' or 'rescue' use of abciximab was effective in reducing ischemic complications or the need for emergency reintervention. There was no significant increase in bleeding and vascular complications in these patients despite having already received high dose heparin.

Activated clotting time

In the EPIC trial, there was a doubling of the incidence of major bleeding complications among patients who received abciximab. It was believed that the concurrent administration of high doses of heparin might have potentiated the haemorrhagic toxicity of the antiplatelet agent. The subsequent use of lower doses of heparin, as well as early removal of the vascular sheath in the EPILOG trial eliminated this bleeding risk. As it is well known that there is a linear relationship between the bleeding risk and the level of the activated clotting time (ACT), we first studied the level of the ACT achieved with the use of low-dose weight-adjusted heparin as recommended in the EPILOG trial in our Asian patients.

The mean increment in ACT was 38 seconds, which was similar to the mean of 35 seconds observed in the EPIC trial[14], although the heparin dose was not weight-adjusted in the latter. The maximal ACT attained in our patients following administration of abciximab, both prophylactically and as a "bail out", was more than 300 seconds (Table VI). This suggested that the EPILOG regime of low-dose heparin might still be too high for Asian patients, which are of smaller body build. As such, a new regime was started in our centre with low-dose weight-adjusted heparin of 50 units per kilogram given at the beginning (Table VII). This brought about a significant reduction in the intraprocedural maximal ACT following administration of abciximab (Table VIII). Whether this new regime would translate into clinical benefits of reduced bleeding but retained efficacy of abciximab use, remains to be validated.

CONCLUSION

Our findings indicate that abciximab can be safely and efficaciously used among Asian patients undergoing both high and low-risk coronary angioplasty. The strategy of intraprocedural bail out use of abciximab appeared to be similarly effective with no consequent increase in bleeding complications in our preliminary experience. There appeared to be a need to redefine the heparin regimes appropriate to our Asian population and also to the interventional settings in which abciximab may potentially be used on a bail out basis.

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Table I - Baseline clinical characteristics

Age (years)	54 w 11	
Male sex (%)	84%	
Weight (kg)	70 w 11	
Ethnic groups		
Chinese	62/115	(54%)
Indians	24/115	(21%)
Malays	22/115	(19%)
Others	7/115	(6%)
Risk factors		
Diabetes	36/115	(30%)
Hypertension	58/115	(49%)
Smoking	60/115	(50%)
Hypercholesterolemia	90/115	(76%)
Previous infarction	51/115	(43%)
Previous interventional procedures		
Coronary angioplasty	12/115	(10%)
Coronary bypass surgery	3/115	(3%)

Table II - Lesion and procedural characteristics

Number of diseased vessels (% of group)		
Single vessel	63/119	(53%)
Double vessel	46/119	(39%)
Triple vessel	10/119	(8%)
Location		
Left anterior descending artery		57%
Left circumflex artery		15%
Right coronary artery		23%
Bypass graft		3%
Left main		2%
Types of interventional procedures		
Coronary stenting		83%
Conventional balloon angioplasty		11%
Rotablation		3%
Rotastenting		3%
No. of vessel treated		
Single vessel PTCA	102/119	(86%)
Multivessel PTCA	17/119	(14%)
Multilesional PTCA	69/119	(58%)

Table III - Indications for the use of abciximab

EPIC trial indications	
Acute ischemic syndromes	23%
High risk coronary anatomy	47%
Beyond EPIC trial indications	
Suboptimal balloon/stent results	23%
Others (eg. debulking procedures)	7%

Table IV - Clinical outcomes

Q MI	0 patient	(0%)
Non Q MI	4 patients	(3.3%)
Death	1 patient	(0.8%)
Repeat emergency procedures	1 patient	(0.8%)

Table V - Complications with the use of abciximab

Major bleeding	0/119 (0%)
Minor bleeding	9/119 (7.6%)
Thrombocytopenia	
Mild (< 100,000/mm^3)	3/119 (2.6%)
Severe (< 50,000/mm3)	4/119 (3.2%)
Blood transfusion	2/119 (1.6%)
Platelet transfusion	4/119 (3.3%)

Table VI - Effect of weight-adjusted heparin and abciximab on activated clotting time

	Pre-abciximab (secs)	Post-abciximab (secs)	Difference (secs)
Elective	287 w 48	318 w 52	31 w 23
Rescue	283 w 47	327 w 50	44 w 25
Overall	285 w 47	323 w 51	38 w 25

Table VII - Comparison of EPILOG and NUH weight-adjusted heparin regimes

	EPILOG	NUH
ACT < 50 seconds	Heparin at 70U/kg	Heparin at 50U/kg
ACT 150 - 199 seconds	Heparin at 50U/kg	Heparin at 25U/kg
ACT > 200 seconds	No heparin	No heparin
Maximum initial heparin dose	7000 U	5000 U
Target final ACT	225 to 300 seconds	200 to 250 seconds

Table VIII - Comparison of the final maximal ACTs with the EPILOG and NUH regimes

	Final maximal ACT (seconds)
EPILOG regime (n = 39)	302 w 55 seconds
NUH regime (n = 19)	258 w 45 seconds
	(p = 0.004)