

## The Effect of Tirofiban and Clopidogrel Pretreatment on Outcome of Old Saphenous Vein Graft Stenting in Patients with Acute Coronary Syndromes

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OZKAN, M., SAG, C., YOKUSOGLU, M., UZUN, M., BAYSAN, O., ERINC, K. and ISIK, E. *The Effect of Tirofiban and Clopidogrel Pretreatment on Outcome of Old Saphenous Vein Graft Stenting in Patients with Acute Coronary Syndromes.* Tohoku J. Exp. Med., 2005, 206 (1), 7-13 — In spite of developments in interventional cardiology, the success rate of saphenous vein graft stenting is still low in patients with acute coronary syndromes. In this study, we aimed at finding out the effect of pretreatment with Tirofiban, a glycoprotein IIb/IIIa inhibitor, and clopidogrel, an adenosine diphosphate antagonist, on the outcome of saphenous vein graft stenting in patients with acute coronary syndrome. A total of 47 patients, who had lesions in saphenous vein grafts and acute coronary syndrome, could be randomized to treated group ( $n = 24$ ), who received Tirofiban and clopidogrel for 48 hours before the intervention, and untreated group ( $n = 23$ ), who did not receive Tirofiban and clopidogrel. In the untreated group, the intervention was performed just after the coronary angiography. All patients underwent stenting as the standard intervention. The groups were compared by Mann-Whitney's U-test or Chi-Square test. The level of statistical significance was set at 0.05. There were no significant differences regarding age, gender, and atherosclerotic risk factors between the two groups. In treated group, percutaneous coronary intervention was successful in all patients and no-reflow phenomenon occurred in only one patient. The rate of no-reflow or slow-flow phenomenon was significantly lower in treated group (one patient vs 9 patients,  $p = 0.004$ ). One patient in untreated group experienced ventricular fibrillation, which was converted to sinus rhythm after defibrillation. During short-term follow-up, there were no acute myocardial infarction, coronary bypass surgery or death in both groups. There was no major bleeding. Minor bleeding was more frequent in treated group, but it did not achieve statistical significance (3 vs 1;  $p = 0.322$ ). In conclusion, pretreatment with tirofiban and clopidogrel before percutaneous coronary intervention might result in better immediate outcomes in old saphenous vein grafts without any significant increase in bleeding complications. ——— saphenous vein graft; PTCA; glycoprotein IIb/IIIa inhibitor; clopidogrel

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The relief of symptoms after coronary artery bypass surgery (CABG) procedure is related to adequacy of revascularization and graft patency (Peduzzi and Hultgren 1979). However, recurrence of angina pectoris occurs at the rate of 3% to 20% per year after CABG and it is mostly related to the new atherosclerotic lesions in the grafted vessels and / or development of new stenosis in ungrafted arteries (Campeau et al. 1979). It has been reported that patency rate of grafted saphenous vein is 26% - 50% for 3 to 10 years after CABG and 94% for internal thoracic arteries (Lytle et al. 1983; Singh et al. 1983). Percutaneous interventions to grafted saphenous veins are also associated with poor immediate and long-term outcomes because of higher rates of insufficient dilatation, distal embolization and restenosis after percutaneous interventions as compared to native coronary vessels (Nguyen et al. 2003). Coronary stenting is an important development in the field of percutaneous coronary intervention (PCI) and has been used for the treatment of saphenous vein graft lesions with a procedural success rate of 92% (Savage et al. 1997; Eeckhout et al. 1999).

The platelet glycoprotein IIb/IIIa (GPIIb/IIIa) receptor antagonist, tirofiban, has been shown to reduce the incidence of thrombotic complications associated with high-risk percutaneous interventions as well as coronary events in patients with acute coronary syndromes (RESTORE -The Syndromes Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis - investigators 1997). Tirofiban also reduces ischemic events following elective percutaneous coronary interventions (EPISTENT - The Evaluation of Platelet IIb/IIIa Inhibitor for Stenting - investigators 1998). Clopidogrel is a thienopyridine and has been demonstrated to reduce stent thrombosis in patients with acute coronary syndromes. However, studies regarding pretreatment with a combination of tirofiban and clopidogrel before percutaneous coronary interventions in patients with acute coronary syndromes with culprit lesion in a grafted saphenous veins are lacking. Our aim was to seek the efficacy of primary success of the preprocedural glycoprotein IIb/IIIa inhibitor (tiro-

fiban) and clopidogrel administration in percutaneous coronary intervention in patients with acute coronary syndrome due to old saphenous vein graft disease.

#### MATERIALS AND METHODS

This study was conducted between March 1999 and June 2004. We selected 47 consecutive patients who underwent saphenous vein graft stenting. Patients, who presented with acute coronary syndrome, were randomly divided into two groups. The treated group consisted of 24 patients (male/female: 19 / 5, mean age:  $62 \pm 7$  years), and untreated group consisted of 23 patients (male/female: 17 / 6, mean age:  $64 \pm 6$  years). The patients in treated group were assigned to receive aspirin, tirofiban and clopidogrel combination for two days before saphenous graft stenting, while the patients in untreated group underwent stent implementation immediately after initial coronary angiography. For both groups, all other medications were standard as suggested by ACC/AHA guidelines. The patients in treated group received Tirofiban (Aggrastat® 0.25 mg/ml sol; Merck Sharp Dohme, Whitehouse Station, NJ, USA)  $0.4 \mu\text{g/kg/min}$  for a period of 30 minutes followed by a maintenance infusion of  $0.1 \mu\text{g/kg/min}$  for 48 hours; aspirin 300 mg/day; clopidogrel (Plavix 75 mg tb.®, Bristol Myers Squibb, NY, USA) 300 mg loading dose followed by 75 mg/day maintenance dose; enoxaparin (Clexane,® Aventis Pharmaceuticals Co., Paris, France) 0.4 mg/day for two days. Tirofiban was continued for at least 8 hours after the procedure. The patients in untreated group received aspirin 300 mg before coronary angiography and, at the time of the procedure 10,000 IU heparin intravenously and 300 mg clopidogrel per os. In both groups, saphenous graft stenting was performed according to standard methods and procedural success was defined as final diameter stenosis  $< 30\%$  with a Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow at the end of the procedure, in the absence of death, myocardial infarction, no or slow flow phenomena or emergency CABG surgery. Major bleeding was defined as a reduction in hemoglobin  $> 5 \text{ g/100 ml}$  (or  $\geq 15\%$  in hematocrit), retroperitoneal bleeding, or any intracranial bleeding. Minor bleeding was defined as any bleeding complication other than major bleeding. Two experienced invasive cardiologists, who were unaware of patient's clinical data and randomization, evaluated the coronary angiograms.

The major risk factors were identified in each pa-

tient. The first follow-up examination was made  $35 \pm 5$  days after the intervention. Our hospital ethics committee approved the study protocol and all patients gave informed consent.

#### Statistical analysis

Continuous variables are expressed as mean  $\pm$  1 s.d. whereas the categorical variables are expressed as percentages. The continuous variables were compared by Mann-Whitney's U-test while categorical variables were compared by Chi-square test, or Fisher's Exact test, when needed.  $P$  value  $< 0.05$  was set significant.

### RESULTS

Baseline characteristics were similar (Table 1). Besides, mean time interval after CABG of patients in first group did not differ significantly as compared to those in other groups. Stent placement was achieved in all patients, however, in treated group no-flow phenomenon was detect-

ed in only one patient, and in untreated group no-flow was detected in 3 patients, and slow-flow in 6 patients ( $p = 0.04$ ). In addition, one patient in untreated group experienced ventricular fibrillation episode after stent implantation, which was successfully treated with electrical defibrillation. In both groups, there were no death or acute myocardial infarction during or after stent implantation. Besides, there was no major bleeding in each group. Minor bleeding has occurred in three patients in treated group and in one patient in untreated group ( $p = 0.322$ ) (Table 2).

In both groups, diabetes mellitus was present in 20 patients. If the patients with diabetes mellitus were analyzed independently, only 1 patient (8.3%) in treated group, and 5 patients (62.5%) in untreated group had no-flow or slow flow phenomenon, and the difference was statistically significant ( $\chi^2 = 6.371$ ;  $p = 0.012$ ). In treated group, no-reflow phenomena occurred in only one pa-

TABLE 1. Baseline characteristics of the patients

	Treated group	Untreated group	$p$ value
Age	$62 \pm 7$	$64 \pm 6$	NS
Gender (male/female)	19 / 5	17 / 6	NS
Hyperlipidemia	10 (41.6%)	9 (39.1)	NS
DM	12 (50%)	8 (34%)	NS
Hypertension	9 (37.5%)	10 (43.4%)	NS
Smoking history	4 (16%)	5 (21.7%)	NS
Mean time interval after CABG	$8.54 \pm 3.09$	$9.78 \pm 3.11$	NS

CABG, coronary artery bypass graft; DM, diabetes mellitus.

TABLE 2. Patient data at the time of stent implantation

	Treated group	Untreated group	$p$ value
No reflow and slow flow phenomenon	1 ( 4.1%)	9 (39%)	$p = 0.004$ $\chi^2 = 8.389$
Ventricular fibrillation	-	1 ( 4%)	
Death	-	-	
Acute myocardial infarction	-	-	
Major bleeding	-	-	
Minor bleeding	3 (12.5 %)	1 (4.3%)	$p = 0.322$ $\chi^2 = 0.981$
Angina during follow-up	1 ( 4.1 %)	6 (48 %)	$p = 0.048$ $\chi^2 = 4.357$

tient and this patient was a 65 year-old male with hyperlipidemia, diabetes mellitus and hypertension.

### DISCUSSION

The present study showed that tirofiban and clopidogrel combination prior to the PCI procedure is beneficial in patients with acute coronary syndromes. The importance of antiplatelet treatment in patients with acute coronary syndrome is well established. Platelet activation plays a key role in the genesis of acute coronary syndromes (Badimon and Badimon 1996). Decreased platelet prostacyclin binding, increased thromboxane A2 biosynthesis, increased prostaglandin A2 and platelet receptor numbers have been reported in unstable angina (Modesti et al. 1995; Knight 1999). At the site of tissue injury, platelets adhere to exposed collagen in the endothelial wall and are activated by well-known mediators such as collagen, thromboxane-A2, serotonin, ADP, adrenalin and thrombin. Activated platelets release procoagulant and vasoconstrictor factors, which induce further platelet accumulation. Therefore, antiplatelet agents are expected to be useful in acute coronary syndromes. Although aspirin is an effective antiplatelet agent, coronary stenting is associated with a high incidence of stent thrombosis despite aspirin therapy. Ticlopidine or clopidogrel is structurally related thienopyridine derivatives and they exert their antiplatelet effects by inhibiting the adenosine diphosphate dependent pathway of platelet activation (Sharis et al. 1998). Trials have shown the superiority of the combination antiplatelet regimen of aspirin and thienopyridines over aspirin alone, or aspirin plus oral anticoagulation with warfarin in preventing stent thrombosis, not only in patients with optimal stent deployment but also in patients who are at high risk of stent thrombosis (Schomig et al. 1996; Schühlen et al. 1997; Bertrand et al. 1998; Leon et al. 1998; Urban et al. 1998). Regardless of the stimulus for their activation, the aggregation of platelets that leads to thrombus formation is finally regulated through their membrane binding sites for fibrinogen in the glycoprotein IIb/IIIa receptor complex. The

GIIb/IIIa antagonists block the binding of fibrinogen to these receptors, thus prevent the platelet aggregation induced by various platelet agonists.

Previously, GIIb/IIIa inhibitors have been used in ischemic syndrome management in Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) (Prism study investigators 1998), PRISM-PLUS (Prism-plus study investigators 1998), Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON) (Paragon study investigators 1998), Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) (The PURSUIT trial investigators 1998), PARAGON-B (Moliterno 2000), Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO) IV (Simoons et al. 2001) trials. These agents were also shown to reduce major cardiac events in patients undergoing coronary stent implantation (Ibbotson et al. 2003).

In patients with acute coronary syndromes the superiority of an early invasive strategy over a conservative approach in the setting of GIIb/IIIa blockade with tirofiban has been demonstrated in Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) trial (Cannon et al. 2001). The PCI of saphenous vein grafts carries a 10%-20% risk of adverse clinical event. Since distal embolizations, no-reflow phenomena and periprocedural myocardial infarction occur more frequently during PCI of vein grafts, pretreatment with intensive antithrombotic regimen seems prudent. Although initial experience with GPIIb/IIIa antagonists in PCI of vein grafts was encouraging, a meta-analysis revealed that adjunctive GPIIb/IIIa antagonist therapy including abciximab or eptifibatid have failed to improve the outcome of percutaneous bypass graft interventions. Besides, it was also associated with higher incidence of major bleedings (6.8% vs 1.4% in placebo) and minor bleedings (14.9% vs 8.1% in placebo) (Roffi et al. 2002). In our study, the PCI was performed after two days of tirofiban administration; however in the aforementioned meta-analysis, abciximab

or eptifibatide were used during the PCI procedure. Therefore, the overwhelming amount and composition of embolized material might render these agents ineffective, because GPIIb/IIIa antagonists, like aspirin and heparin, do not have thrombolytic activity and in addition they do not prevent platelet adhesion. The procedural complications are predominantly attributable to distal embolization of friable material and thrombus. Accordingly, the distal protective devices were shown to be effective in achieving better results (Baim et al. 2002). Because the presence of thrombus is an important cause of unfavorable results, its disappearance may be useful. For this reason, pretreatment with a thrombolytic agent (urokinase) was used in ROBUST trial. However, it did not improve the acute results, with an initial patency of 69% and a mortality of 6.5% (Hartmann et al. 1996). Our results are in contrast with the results of these studies. A possible explanation may be that our study was designed to prevent the thrombus formation, not to lyse it. Therefore, prevention of thrombus formation may have resulted in more favorable results. Accordingly, the ATLAS trial (Acolysis during Treatment of Lesions Affecting Saphenous Vein Bypass Grafts), which compared the coronary ultrasound thrombolysis with abciximab followed by percutaneous coronary intervention in lesions with angiographic or clinical evidence of thrombus, was prematurely stopped because abciximab arm was apparently superior (Neitzel et al. 1986). In our study, we did not evaluate the lesions with regard to the presence of thrombus, however all the enrolled patients were presented with acute coronary syndrome and thereby, it is very likely that culprit lesions were accompanied by overlying thrombus.

In our study, overall success rate was 37/47 (79%). This rate was lower than some other studies (Hong et al. 2001). This may be the result of patient selection. Our cases were recruited from those patients with acute coronary syndromes. The thrombus formation is more frequent in such patients. In consistent with this finding, success rate was 96% in treated group, which the thrombus formation is less likely.

Another finding of the present study was that the benefit from pretreatment seems more evident in patients with diabetes mellitus. The evidence from angiographic and pathological studies that promotes vein graft atherosclerosis is inconsistent: some investigators have implicated diabetes as a risk factor and others have not (Campeau et al. 1984). However, all these studies are retrospective and give no information about the nature of the lesion. For this reason, it is difficult to establish a link between the high benefit and the lesion characteristics in diabetic patients. However, it is well known that microvascular damage is present in most of the diabetic patients, possibly due to increased oxidative stress mechanisms (Duman et al. 2003). The no-reflow phenomena are generally explained by the presence of microvascular dysfunction as well as distal microembolization. The combination of higher thrombosis rate and microvascular dysfunction might explain the higher benefit of pretreatment with GPIIb/IIIa antagonists and clopidogrel in both patients with or without diabetes mellitus.

### CONCLUSION

Our study revealed that tirofiban and clopidogrel, when administered before PCI to degenerated saphenous vein grafts, are beneficial in primary and short-term success of the procedure and this combination may improve the outcomes. This beneficial effect seems to be more prominent in patients with diabetes mellitus. Thus, we recommend the administration of GPIIb/IIIa antagonists and clopidogrel combination prior to PCI for degenerated saphenous vein graft lesions, especially in patients with diabetes mellitus. The randomized large-scale trials will provide more information about such a combination therapy.

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