Ticlopidine Treatment Before Percutaneous Coronary Intervention in Patients With Stable Angina Pectoris

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ABSTRACT

Purpose: Platelet inhibition reduces periprocedural cardiac events in patients referred to percutaneous coronary intervention (PCI). In patients with stable angina pectoris, there is no reliable evidence that pretreatment with ticlopidine (Ticlid) plus aspirin decreases adverse cardiac events compared with pretreatment with aspirin alone. This study sought to determine whether treatment with combination of aspirin plus ticlopidine prior to PCI is associated with lower incidence of adverse cardiovascular events in short-term follow-up than pretreatment with aspirin alone.

Methods: In a prospective, non-randomized comparison, a total of 241 consecutive patients (163 males; 63 ± 11 years) referred to PCI for stable angina pectoris received 100 mg/d of aspirin alone (group A, 158 patients) or 100 mg/d of aspirin plus 750 mg/d of ticlopidine for at least 3 days (group B, 83 patients) before PCI. The primary end point was the incidence of troponin (T) level greater than 1.5 ng/mL 24 hours after PCI; the secondary end point was the incidence of death, myocardial infarction, ischemia-driven target vessel revascularization, symptomatic stent thrombosis, stroke, and major bleeding in the 3 months after PCI.

Results: Both groups were comparable with regard to baseline clinical, angiographic, and procedural characteristics. There was no statistically significant difference in the primary end point (10.1% versus 9.6% versus). Over a follow-up period of 11 ± 5 weeks, in group A the incidence of myocardial infarction was 3.2%, repeat PCI 10.9%, and cardiac surgery 4.5%. The corresponding event rates in group B were myocardial infarction 0%, repeat PCI 12.8%, and cardiac surgery 2.6%. There were no reports of symptomatic stent thrombosis, stroke, major bleeding, or death during follow-up. There was no statistically significant difference in the secondary end point (18.6% versus 15.4%).

Conclusions: In the patients referred for elective PCI for stable angina pectoris, pretreatment with aspirin plus ticlopidine compared with pretreatment with aspirin alone decreases neither the incidence of procedural myocardial infarction nor the incidence of adverse cardiovascular events during short-term follow-up.

INTRODUCTION

Optimal pretreatment in elective percutaneous intervention (PCI) is mainly based on the administration of aspirin before PCI. After intervention and stent placement, the combination of aspirin with ticlopidine (Ticlid) or clopidogrel (Plavix) is used to reduce the incidence of subacute stent thrombosis.[1-4] Therefore, some patients referred to coronary angiography for stable angina pectoris are pretreated with combination antithrombotic therapy (aspirin + ticlopidine or aspirin + clopidogrel) to achieve maximum platelet inhibition during PCI performed at the same time as coronary angiography.[1, 2, 5-9] However, some premedicated patients are found to have surgical disease on angiography, and irreversible platelet inhibition becomes a concern for subsequent surgical revascularization.[10] Moreover, there is no reliable evidence that pretreatment with combination therapy in patients with stable angina pectoris decreases adverse cardiac events compared with pretreatment with aspirin alone.

In this study, we sought to compare the clinical effect of pretreatment with ticlopidine plus aspirin and aspirin alone.

METHODS

Patients

Patients with stable angina pectoris or a pathological exercise test (bicycle ergometry, dobutamine stress echocardiography or single-photon emission computed tomography) referred for PCI were enrolled in this study. They had no major diseases other than angina pectoris. Patients suffering from acute coronary syndromes in the last 3 weeks were excluded.

All data analyzed in this study were obtained prospectively. Demographic, procedural, and outcome data regarding study population were entered into an electronic study database. From this database, 241 consecutive patients (163 males; 63 ± 11 years) selected for elective PCI for stenotic coronary lesion were enrolled in this study. These patients were divided into 2 groups based on antithrombotic pretreatment prescribed by the referring cardiologist. Written informed consent was obtained from each patient.

Antithrombotic Therapy

The antithrombotic protocol called for administration of 100 mg/d of aspirin for several days before PCI, continued indefinitely. In group A, ticlopidine treatment was started at least 3 days before the procedure (ticlopidine 750mg/d) and after coronary stent implantation was maintained for 1 month (ticlopidine 500 mg/d). In group B, ticlopidine treatment was started 1 hour after coronary stent implantation (ticlopidine 1000 mg/d on the day of the procedure) and maintained for 1 month at a decreased dosage (ticlopidine 500 mg/d). Routine blood count analyses were performed 2 weeks after PCI.

Blood Analysis

Blood samples for laboratory measurements, blood count and troponin I (TnI), were taken the morning of the intervention. Blood samples for TnI measurements were taken 24 hours after PCI. TnI was assayed in the plasma using immunometric assay (IMMULITE Turbo Troponin I, Diagnostic Products Corporation, Los Angeles, CA).

Coronary Angiographic Findings and PCI

Only patients with de-novo stenotic lesions were treated in this study. Stenoses were visually assessed independently by 2 examiners. Quantitative analysis was used only in borderline cases or when the assessment of both examiners was controversial.

Stenosis that reduced the lumen diameter by 50% or more was considered significant. The coronary artery tree was divided into 3 compartments (left anterior descending artery, left circumflex artery, and right coronary artery) to diagnose from one to three coronary artery diseases.

PCI procedures were performed by standard technique using monorail balloon catheter systems and premounted stents. Femoral approach with 5-7 F guiding catheters were used for all patients. Number of treated lesions, inflations, and inflation pressures were determined by the operators. Stent delivery was routinely followed by high-pressure balloon inflations (>16 atm). In selected cases, direct coronary stenting was used.[11] Atherectomy devices were not used in this study. Angiographic success was defined as residual diameter stenosis < 20% by visual estimation and the ultimate achievement of thrombolysis in myocardial i n farction (TIMI) flow grade 3.

Heparin (100 IU/kg) was administered intravenously at the beginning of the procedure, to keep the clotting time > 250 seconds. The activated clotting time was measured 10 minutes after heparin injection. All patients were treated with intracoronary injections of 1 mg of isosorbide dinitrate during PCI. Neither glycoprotein IIb/IIIa inhibitors nor drug eluting stents were used in this study.

Complete clinical examination with ECG was performed on the postprocedural day. Therapy with statins was started in all patients after PCI.[12]

Follow-up

All patients were contacted via telephone or mail using a standardized questionnaire 3 months after the procedure. All adverse events were confirmed by reviewing the medical records.

End Points

The primary end point of this study was the incidence of myocardial infarction (MI) based on postinterventional release of TnI. The secondary end point was the 3-month composite incidence of death (all-cause), MI, target vessel revascularization, stroke, major bleeding, and coronary stent thrombosis.

The cutoff level for diagnosis of acute MI suggested by both the manufacturer and the biochemical laboratory of our institution was TnI > 1.5 ng/mL. This level was considered for the primary analysis. A secondary analysis was performed using 1 ng/mL as the cutoff level for positive TnI. Stroke was defined as any new neurological deficit lasting > 24 hours. MI was defined as symptoms of ischemia with new electrocardiographic changes and a rise in creatine kinase-MB (CK-MB) and/or troponin. Major bleeding was defined as bleeding with a hemoglobin loss > 5g/dL or necessity of red blood cell transfusion. Stent thrombosis was defined as a new onset of ischemic symptoms in the postprocedural period with a stent occlusion in repeated coronary angiography.

Statistical Analysis

Microsoft Excel was used for the study database. Data are presented as mean ± SD. Unpaired Student's *t* test, and chi-square test were used as appropriate. A value of $P \leq 0.05$ was considered statistically significant.

RESULTS

Two hundred and forty-one consecutive patients with stable angina pectoris underwent PCI. Both groups were similar in baseline characteristics like sex, cardiovascular risk factors, and history of MI; there were statistically significant differences ($P < 0.05$) in total plasma cholesterol level and lipid-lowering medication at admission. There were no significant differences in angiographic and procedural data between both groups of patients. Clinical and procedural characteristics are shown in Tables 1 and 2.

Primary End Point

The incidence of MI based on postinterventional release of TnI > 1.5 ng/mL was 10.1% in group A versus 9.6% in group B.

Table 1. Baseline Clinical Characteristics

	Group A (n = 83)	Group B (n = 158)	*P* value
Age (yrs)	62.5 ± 11	62.8 ± 10.3	NS
Gender (% male)	65	72	NS
Angina pectoris class (CCS)	1.9 ± 1.3	1.8 ± 1.2	NS
History of myocardial infarction (%)	57	61	NS
Smokers (%)	35	34	NS
Hypertension (%)	65	65	NS
Hypercholesterolemia > 5 mmol/L (%)	49	42	NS
Total plasma cholesterol (mmol/L)	5.1 ± 1.2	4.7 ± 1.2	$p < 0.05$
LDL-cholesterol (mmol/L)	3.3 ± 0.9	3.2 ± 1.3	NS
HDL-cholesterol (mmol/L)	1.2 ± 0.4	1.2 ± 0.5	NS
Hypertriglyceridemia > 2 mmol/L (%)	39	35	NS
Plasma triglyceride (mmol/L)	2.1 ± 1.7	1.9 ± 2.3	NS
Diabetes mellitus (%)	32	36	NS
Lipid lowering medication on admission (%)	50	64	$P < 0.05$

The difference did not achieve statistical significance. Similarly, in the secondary analysis based on postinterventional release of TnI > 1 ng/mL, the difference did not achieve statistical significance (15.5 versus 13.3%).

Secondary End Point

Out of 241 patients treated by direct coronary stenting, short-term follow up (11.5 ± 5 weeks in both groups) was available in 234 patients (97%). Among 156 patients (99%) followed-up in group A, 29 patients (18.6%) experienced secondary end point (3-month composite incidence of death, MI, target vessel revascularization, stroke, major bleeding, and coronary stent thrombosis).

Among 78 patients (94%) followed-up in group B, the secondary end point occurred in 12 patients (15.4%). There was no statistical difference in the secondary end point occurrence in both groups. Clinical analysis of the short-term follow up is summarized in Table 3. During the follow up, we did not observe any cases of severe ticlopidine-induced neutropenia or thrombocytopenia.

DISCUSSION

Antithrombotic Effect

Platelet aggregation during PCI is strongly inhibited by thienopyridine derivatives. This effect is markedly time dependent. The phased development of antithrombotic effects in patients pretreated with thienopyridine derivatives has been confirmed in several studies.[9, 13] However, it remains to be established whether the theoretical superiority of prolonged antithrombotic therapy also translates into an overall clinical benefit in patients with elective PCI for stable angina pectoris. Several studies sought to determine the clinical impact of pretreatment with combination antithrombotic therapy in patients undergoing elective PCI for angina pectoris. Steinhubl et al[8] showed that longer duration of ticlopidine pretreatment was strongly associated with a lower incidence of procedure related non-Q-wave MI. However, the population of this study was heterogeneous and included patients with both stable and unstable angina. Recently, Atmaca et al[5] found that antiplatelet treatment with ticlopidine prior to the coronary stenting is associated with decreased inci-

Table 2. Angiographic and Interventional Data

	Group A (n = 158)	Group B (n = 83)	*P* value
Stenosis located in LAD, LCx, RCA, CABG (%)	34/35/31/1	42/32/35/1	NS
One/two/three vessel disease (%)	46/30/23	41/30/28	NS
A/B1/B2/C lesions (%)	22/20/19/40	18/20/29/33	N
Stenosis of treated lesions (%)	76 ± 9	76 ± 10	NS
Intracoronary thrombosis (%)	10	8	NS
Treated lesions	1.3 ± 0.5	1.2 ± 0.5	NS
Stents per one procedure	1.1 ± 0.5	1 ± 0.4	NS
Patients treated with stent (%)	77	78	N
Angiographic success (%)	97	96	NS
Acute main or side branch occlusion (%)	4	3	NS
Inflation time (s)	37± 30	35 ± 25	NS
Reintervention up to 24 hours (%)	1	1	NS
Troponin I > 1.5 ng/mL (%)	10.1	9.6	NS
Troponin I > 1 ng/mL (%)	15.8	13.3	NS

dence of procedure-related minor myocardial injury. Unfortunately, that study was small, retrospective, and nonrandomized, and patients were followed up only during the short hospital stay.

In our study, we prospectively selected patients with stable angina pectoris, who represent the majority of patients undergoing PCI in our institution. Our data illustrate that early risk of procedure-related minor myocardial injury is low in this group of patients and it is likely to be dependent on the operator's skills and technique. Despite previous studies, our data demonstrate that in a lower-risk study population, the rate of periprocedural adverse events is low and not dependent on combined antithrombotic pretreatment. On the other hand, we must emphasize that the end point differences in both groups are apparent, and statistical insignificance is determined by a small number of patients. Thus, results of this study suggest the mild trend in favor of combined pretreatment strategy.

TnI Examination

The low incidence of positive TnI patients might be the result of a high cut-off point in measuring troponin levels. Therefore, we performed the secondary postprocedural troponin analysis with the cut-off point 1 ng/mL. Interestingly, the low incidence of TnI-positive patients was in secondary analysis as well. Probably, the short inflation times during PCI could play a positive role in troponin release.[14] Additionally, TnI was measured just 24 hours after PCI and the later TnI release could be missed. The importance of the later troponin measurements were confirmed in the recent TOPSTAR trial, which demonstrated the advantages of troponin measurement up to 48 hours after PCI.[6] A possible pathophysiologic mechanism could be a continuous, ongoing, stent-derived microembolization leading to repetitive release of microemboli with obstruction of microvessels.

Clinical Implications

The addition of ticlopidine for more than 72 hours to aspirin markedly reduces the activation of coagulation and platelets.[1] Historically, since ticlopidine has delayed onset of activity, antiplatelet therapy was initiated before coronary angiography whenever there was a possibility of conse-

Table 3. Adverse Coronary Events During Follow-up (secondary end point)

	Group A (n = 156)	Group B (n = 78)	*P* value
Death	0	0	NS
PCI (%)	10.9	12.8	NS
CABG (%)	4.5	2.6	NS
Myocardial infarction (%)	3.2	0	NS
Total (%)	18.6	15.4	NS

quent ad hoc stent implantation. This practice has continued in most centers even though a clopidogrel has in some countries replaced ticlopidine.[10] In this study, however, the use of combination antithrombotic therapy prior to PCI for stable angina pectoris was not associated with a significantly lower occurrence of cardiovascular adverse events. These findings raise concern regarding the routine administration of combined antithrombotic therapy before anticipated but undecided PCI. The concept of antithrombotic pretreatment even prior to routine coronary angiography for stable angina pectoris is based solely on the assumption of strong antiplatelet effect resulting in decrease of minor myocardial injury associated with PCI. However, the superiority of this approach has not yet been objectively documented. Further studies will be needed to better define the role of antithrombotic treatment before elective PCI for stable angina pectoris. Currently, in the low-risk patient population, we do not have to start routinely with combined antithrombotic therapy several days prior to elective coronary angiography for stable angina pectoris. It is probably safe to begin with administration of ticlopidine or clopidogrel immediately after coronary artery stenting.

Limitations

Since patients were not randomized to ticlopidine exposure, unrecognized confounding factors may exist. We enrolled consecutive patients with stable angina pectoris in this study. The decision regarding the antithrombotic pretreatment was made by the referring cardiologist. Hence, only approximately one third of the patient population (83 patients) enrolled in this study was treated by ticlopidine at least 72 hours prior to PCI. To achieve more robust statistical data from this study we would need more patients, mainly in the group with combined antithrombotic pretreatment.

Subclinical stent thrombosis may have occurred in some patients and been totally undetected. It is also possible that stent thrombosis may have occurred in patients that died during the follow-up. On the other hand, the routine use of high-pressure stent deployment and combined antithrombotic therapy after the procedure led to a marked decrease of clinically relevant stent thrombosis rate in our institution.

These data were collected by relying on patient interviews and a standardized questionnaire. This methodology is common to most prospective clinical studies and it is believed that this study design is able to reflect the incidence of adverse coronary events during follow up.

This study included only patients who had received a 4-week ticlopidine regimen after coronary stent implantation. Therefore, our conclusions must be limited to these patients and should not be extrapolated to patients receiving clopidogrel. It is of note that the use of ticlopidine has been replaced by clopidogrel in many countries.

Finally, 7 patients (3%) were lost to fol-

low-up; however, it is highly probable that even if some of these patients had suffered from some of adverse events, the findings of this study would not change significantly.

CONCLUSION

The results of this nonrandomized study suggest that in patients referred to elective PCI for stable angina pectoris, pretreatment with aspirin plus ticlopidine compared to pretreatment with aspirin alone decreases neither the incidence of procedural MI nor the incidence of adverse cardiovascular events during the short-term follow-up. Larger and randomized studies are warranted to determine the optimal antithrombotic pretreatment in this population representing the majority of patients undergoing PCI.

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