Use of Oral Anti-Platelets in Post-Percutaneous Coronary Intervention Patients: Is there advantage in numbers?

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Background --- In-stent restenosis has been associated with the occurrence of death, myocardial infarction and revascularization after percutaneous coronary intervention. It has an incidence of 8% even in the drug-eluting stent era. The use of anti-platelets agents aspirin and clopidogrel has partially addressed this problem. The addition of cilostazol has been attributed in further decreasing the incidence of in-stent restenosis. Studies involving the use of cilostazol have largely involved the use of bare-metal stents. At the moment, there is only one study on cilostazol involving drug-eluting stents which focused mainly on diabetics.

Methods --- All patients above 19 years of age who had undergone elective percutaneous coronary intervention in the Philippine Heart Center and were given aspirin (300 mg once a day) and clopidogrel (75 mg once a day) with or without cilostazol (100 mg twice a day) were included in the study. Patients were followed up for of 4.5 months. Patients were monitored for the occurrence of primary outcomes which included death, myocardial infarction and revascularization. Secondary outcome included the occurrence of bleeding, either major or minor.

Results --- A total of 45 patients were included. In the dual anti-platelet group, the mean age was 63 years with predominance of males. In the triple anti-platelet group, the mean age was 59 years with predominance of males. Hypertension, diabetes mellitus, stroke and smoking were the most common risk factors without significant difference between the two groups (75% vs. 65%, p = 0.699, 50% 41%, p= 0.704, 12% vs. 5%, p= 0.452, 50% vs. 49%, p= 1.0 respectively). Statins were the most commonly prescribed medication (62% vs. 65%, p= 1.0). Drug-eluting stent was used in majority of patients (100% vs. 97%, p= 1.0). The addition of cilostazol to standard therapy of aspirin and clopidogrel did not show statistical significance in reducing death myocardial infarction and revascularization vs. that of aspirin and clopidogrel alone. There was a trend of increased incidence of minor bleeding in the triple anti-platelet group but was not statistically significant (0% vs. 5%, p= 0.568).

Conclusion --- The addition of cilostazol to standard therapy of aspirin and clopidogrel did not show statistically significant reduction in death, myocardial infarction and revascularization compared with aspirin and clopidogrel alone with a trend towards increased risk of minor bleeding complications. ***Phil Heart Center J 2012;16:22-25.***

Key Words: Percutaneous Coronary Intervention ■ Antiplatelet Therapy

In-stent restenosis remains one of the dreaded complications after percutaneous coronary intervention (PCI). In a study conducted by Scheller et al [1], in-stent restenosis after bare metal stent implantation has an incidence of 5-35%. In the era of drug-eluting stents, the incidence has been largely reduced to 8%.[2] However, despite the decrease in incidence, this continues to hamper the long-term success of PCI so that patients continue to experience major adverse cardiac events such as death, myocardial infarction and revascularization after percutaneous coronary intervention.

The use of anti-platelet agents is standard in patients who undergo percutaneous coronary intervention in an effort to reduce the incidence of restenosis after procedure. In the ACC/AHA guidelines of 2005 for percutaneous coronary intervention, the use of aspirin and clopidogrel is considered to be class I therapeutic management [3] post PCI. Aspirin is an irreversible inhibitor of cyclooxygenase to prevent the synthesis of

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thromboxane A2 which is a powerful vasoconstricting agent promoting platelet aggregation.[3]

Clopidogrel, on the other hand, is a type of thienopyridine derivative that causes irreversible platelet inhibition just like aspirin due to their effects on P2Y12 adenosine diphosphate receptor responsible for the activation of the GPIIb/IIIa. The combined effects of these two drugs have been documented in various clinical trials proving that they reduce the incidence of cardiovascular events (death, MI, revascularization) in patients after stenting.[4,5]

Cilostazol is a selective inhibitor of 3'5' -cyclic nucleotide phosphodiesterase III with both antiplatelet and vasodilating properties. It has been traditionally used as part of the pharmacologic management of claudication. However, recent studies [7,8,9,10] have already shown its potential benefit in post-PCI patients as an additional drug to aspirin and clopidogrel. A meta-analysis[11] was recently published reviewing the usefulness of cilostazol as an add-on therapy to aspirin and clopidogrel. In this meta-analysis, it showed a statistically significant reduction in angiographic restenosis (RR= 0.69) and repeat revascularization (RR= 0.69) with no significant increase in bleeding (RR= 0.71). Most of the studies however were small and used bare-metal stents. Only one (1) study made use of drug-eluting stents.[8] This study has shown benefit of using triple anti-platelets over that of dual-anti-platelets in reducing the incidence of death, MI and revascularization with no increased risk of bleeding.

The objective of this study are: determine the incidence of morbidity and mortality of patients who underwent elective PCI and were given dual and triple oral anti-platelet agents at 4.5 months after the procedure; to determine the incidence of death, MI and revascularization of post-PCI patients who were given aspirin and clopidogrel at 4.5 months after the procedure; to determine the incidence of death, MI and revascularization of post-PCI patients who were given aspirin, clopidogrel and cilostazol at 4.5 months after the procedure; to compare the incidence of death, MI and revascularization of post-PCI patients who were given aspirin and clopidogrel with or without cilostazol at 4.5 months after the procedure and to determine the adverse effects of dual and triple anti-platelet treatment among post-PCI patients.

METHODOLOGY

This was a prospective cohort study involving all patients age 19 years and above who underwent elective percutaneous coronary intervention at the Philippine Heart Center and were given anti-platelets aspirin + clopidogrel with or without cilostazol after PCI were included in the study. Patients were grouped into Group A for those on dual anti-platelet therapy (aspirin and clopidogrel) and Group B for those on triple anti-platelet therapy (aspirin and clopidogrel plus cilostazol). Based on the studies reviewed, the following doses and their respective durations are used: aspirin 300 mg once a day for 6 months then 80 mg once a day thereafter, clopidogrel 75 mg once a day, cilostazol 100 mg 1 tablet twice a day for 6 months. Enrollment of patients started from August 1-September 30, 2008. Excluded were patients who are allergic to any of the test drug (aspirin, clopidogrel or cilostazol) were excluded from the study.

Data Gathering

Baseline characteristics were obtained from all patients which included age, gender, risk factors, number of vessels involved, type of stents used and present medications of patients and were tested for statistical significance.

Primary outcomes such as occurrence of death, myocardial infarction and revascularization were noted in each group at 4.5 months from the time of the procedure. Myocardial infarction is defined as the occurrence of cardiac enzyme elevation associated with anyone of the following: angina, anginal equivalent, EKG changes consistent with ischemia (ST elevation or depression, T wave inversion, pathological Q waves, wall motion abnormalities on echocardiography).

Secondary outcome included occurrence of bleeding either major or minor. Major bleeding is defined as fatal bleeding, symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial or intramuscular with compartment syndrome and/or bleeding causing a drop in hemoglobin level of 20 g/L or more or leading to transfusion of two or more units of whole bleed or red cells.[12] Minor bleeding is any bleeding not included in the above definition.

Table 1. Baseline characteristics of PCI patients according to number of antiplatelet therapy

Characteristics	Dual antiplatelet (n= 8)	Triple antiplatelet (n=37)	p-value
Age, mean	63	59	0.32
Gender (% males)	4 (40%)	30 (88%)	0.05
Risk Factors			
HPN	6 (75%)	24 (65%)	0.699
DM	4 (50%)	15 (41%)	0.704
Stroke	1 (12%)	2 (5%)	0.452
Smoking	4 (50%)	18 (49%)	1.000
Risk Factors			
HPN	7 (88%)	20 (54%)	
DM	0 (0%)	11 (30%)	0.136
Stroke	1 (12%)	6 (16%	
Smoking			
Stents used			
Bare Metal	1 (12%)	2 (5.4%)	0.452
Drug-eluting	8 (100%)	36 (97%)	1.000
Medications			
ACEI	2 (25%)	6 (16%)	0.618
ARB	4 (50%)	12 (32%)	0.427
CCB	2 (25%)	9 (24%)	1.000
BB	3 (38%)	15 (41%)	1.000
Statins	5 (62%)	24 (65%)	1.000
Diuretic	1 (12%)	2 (5.4%)	0.452
Nitrates	2 (25%)	8 (22%)	1.000

Data was analyzed using the Mann-Whitney U test to determine association.

RESULTS

A total of forty-five (45) patients were included in the study. Eight (8) were placed on dual anti- platelet therapy (Group A) and thirty-seven (37) were placed on triple anti-platelet therapy (Group B).

In the dual anti-antiplatelet group, the mean age was 63 years and 40% of which are males. In the triple anti-platelet group, the mean age was 59 years, majority of which are males (88%). The most common risk factors noted were hypertension, diabetes mellitus, stroke and smoking with no statistical difference between the two groups (75% vs 65%, p = 0.699, 50% 41%, p= 0.704, 12% vs 5%, p= 0.452, 50% vs 49%, p= 1.0 respectively). There were seven (7) patients in the triple anti-platelet group who had previous history of revascularization (5 PCI and 2 CABG surgeries) and only one (1) patient in the dual anti-platelet group had PCI. Majority of the patients had single vessel disease. In the dual anti-platelet group, 88% had one-vessel disease and 12% had triple vessel disease. In the triple anti-platelet group, 54% had single vessel disease, 30% had two-vessel disease and 16% had triple vessel disease. Drug-eluting stents were used in 100% of patients in the dual anti-platelet therapy and 97% in the triple anti-platelet therapy with no statistical difference between the two (p-value= 1.0). Two patients had additional bare metal stents used. One patient used only bare-metal stent and was placed on triple anti-platelet therapy.

Table 2. Outcomes of PCI patients according to number of antiplatelet therapy

	Dual antiplatelet (n= 8)	Triple antiplatelet (n=37)	p-value
Death	0	0	1.000
MI	0	0	1.000
Revascularization	0	0	1.000
Bleeding			
Major	0	0	
Minor	0	5	0.568

For the medications used, in the dual anti-platelet group, majority (62%) of the patients were placed on statins, followed by angiotensin receptor blockers (50%), beta-blockers (38%), ACE- inhibitors, nitrates and calcium channel blockers (25%) and diuretics (12%). In the triple anti-platelet group, statins were also the most commonly prescribed medication (65%), followed by beta-blockers (41%), angiotensin receptor antagonist (32%), calcium channel blockers, nitrates (22%), and diuretics (5.4%). No statistical differences between the two groups were noted.

No death, myocardial infarction nor revascularization occurred in both groups. Minor bleeding complications in the form of petechiae were noted in 13% of the patients in the triple anti-platelet group. No major bleeding occurred in both groups. Other complications such as headache (4) were noted in patients taking triple anti-platelets and one (1) in the dual anti-platelet group. One (1) patient in the triple anti-platelet group experienced gastritis. No discontinuation of antiplatelets was done despite the occurrence

DISCUSSION

The meta-analysis on the use of cilostazol as an add-on therapy to a combination of aspirin and clopidogrel involved studies employing the use of bare-metal stents with the exception of one study (DECLARE-Long study) which involved the use of drug-eluting stents.[11] In this meta-analysis, it showed that the addition of cilostazol to standard therapy appears to be effective and safe in re-ducing the risk of restenosis and repeat revascularization. The above results however employed the use of drug-eluting stents in majority of patients (100% in the dual anti-platelet group and 97% in the triple anti-platelet group with a p-value of 1.000). Contrary to the results of the meta-analysis, the use of triple anti-platelet therapy had no significant advantage over that of dual-antiplatelet therapy in terms of reducing death, myocardial infarction and revascularization after percutaneous coronary intervention after a follow-up period of 4.5 months. Although not statistically significant (*p*-value= 0.568), there was however a trend towards increased incidence of minor bleeding complications in patients taking triple anti-platelets (0% vs. 5%). The presence of diabetes (50% vs. 41%, *p*-value = 0.704) and increasing number of vessels (*p*-value = 0.136) involved in intervention, both of which may increase probability of restenosis, did not influence the outcomes in both groups. It is interesting to note however that despite the presence coronary artery disease, the use of class 1 medications for secondary prevention remains suboptimal with the statins being the most com monly prescribed with no significant statistical difference between the two groups. Other medications included ACE-inhibitors, angiotensin receptor antagonists, calcium channel blockers, beta-blockers, diuretics and nitrates.

The present study has several limitations. First, despite its being prospective, this study was an observational one which therefore relies on consultants' prescribing methods and management strategies limiting the control of the investigators on patient's medications. Secondly, the population was small and follow-up was only for 4.5 months, which may have been inadequate to monitor for outcomes. A randomized study involving a larger population and a longer study period is therefore recommended to better assess outcomes.

CONCLUSION

The addition of cilostazol to standard therapy of aspirin and clopidogrel did not show statistically significant reduction in death, myocardial infarction and revascularization compared with aspirin and clopidogrel alone. There was however a trend towards increased risk of minor bleeding complications but not in major bleeding complications in the triple anti-platelet group. A larger population and a longer study period are needed to better assess outcomes.

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