REVIEW ARTICLE

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Antiplatelet Agents in High-Risk Patients with Coronary Artery Disease

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ABSTRACT

The role of platelets is well known in the atherogenesis, acute coronary syndrome and development of complications of percutaneous coronary intervention. Until recently, aspirin was the only antiplatelet agent available for the primary and secondary prevention of coronary heart disease. Over the past several years, there has been a substantial expansion in our antiplatelet armamentarium, as well as in our understanding of the clinical importance of antiplatelet therapy in patients with coronary artery disease. The benefits and limitations of the currently available antiplatelet agents, including aspirin, thienopyridines (ticlopidine and clopidogrel) and the platelet glycoprotein IIb/IIIa blockers, in the secondary prevention of coronary heart disease, and high-risk clinical situations, such as unstable angina, acute myocardial infarction and percutaneous coronary intervention, have been reported. Antiplatelet agents should be used, in proper combination, in all relevant cases, as they have been shown to improve the prognosis of various forms of high-risk patients with coronary artery disease. **(Korean Circulation J 2004;34(1):23-27)**

KEY WORDS: Platelet aggregation inhibitors; Coronary disease; Angioplasty, transluminal, percutaneous coronary; Glycoprotein IIb/IIIa blockers.

The role of platelets in cardiovascular events is well known. It is expected that the effective inhibition of platelets will improve the prognosis of atherosclerotic cardiovascular diseases. Various antiplatelet drugs are being developed, and tested under various conditions. Antiplatelet agents can be classified according to the mechanism of their action; Class I: Aspirin, NSAID's and sulfinpyrazone, which inhibit prostaglandin H synthase, Class II: Dipyridamole, which inhibits the destruction of cyclic AMP by phosphodiesterase, and consequently suppresses the activity of the platelets, Class III: Ticlopidine and clopidogrel, which inhibit the ADP from combining with the platelet receptor, P2Y12, and Class IV: Drugs that block the glycoprotein (GP) IIb/IIIa receptors of the platelets. Cilostazol, which was developed in Japan, can be classified as Class II, but research on its use in cardiovascular diseases is limited. Aspirin, ticlopidine, clopidogrel and GP IIb/IIIa receptors will be reviewed.

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Secondary Prevention in Chronic Ischemia

The use of aspirin in the secondary prevention of cardiovascular diseases was analyzed extensively in the Antiplatelet Trialist's meta-analysis, which analyzed 145 studies.[1] This analysis included 100,000 patients, 70% of which were high-risk patients, such as myocardial infarction, angina pectoris, history of revascularization and stroke. The use of aspirin reduced 35% of the non-fatal myocardial infarctions and 18% of the deaths caused by vascular disease in these patients.

According to the recent, more extensive meta-analysis of Antithrombotic trialist's collaboration (287 studies, 212,000 patients), aspirin was found to be effective in every form of high-risk diseases. With regard to the dosage of aspirin, 75-150 mg is effective for long-term use, but in an acute stage, more than 150 mg is necessary as

the starting dose. The analysis concluded that the use of other antiplatelet drugs, in addition to aspirin, may bring additional benefits, but more research is needed.[2)]

The use of ticlopidine in the secondary prevention has not been as widely studied as aspirin, but a few studies have proved its effectiveness. According to the Canadian American Ticlopidine Study, which included 1,072 patients with histories of transient ischemic attacks or strokes, the use of ticlopidine, for a mean of 24 months, decreased strokes, myocardial infarctions or vascular deaths by 30.2%.[3)] Ticlopidine Aspirin Stroke study, which included similar patient groups, revealed that ticlopidine was a little more effective than aspirin in the prevention of deaths and non-fatal strokes.[4)]

In the CAPRIE study, which studied 19,185 patients with atherosclerotic vascular disease, who were treated with either 75 mg of clopidogrel or 325 mg of aspirin, and observed for 1−3 years, the clopidogrel was more effective than aspirin in the prevention of the recurrence of myocardial infarctions, ischemic strokes or vascular deaths.[5)]

Unstable Angina

Aspirin

The effectiveness of aspirin has been proved in 4 studies, including the VA cooperative study. Among 2,579 patients with unstable angina, the death rate was reduced by 50% in the group given 75−1200 mg of aspirin, compared to the placebo group.[6-9)]

Ticlopidine/Clopidogrel

Only one randomized trial has examined the use of ticlopidine in patients with unstable angina. This study enrolled 652 patients, within 48 hours of admission, who were randomly assigned to receive: 1) conventional therapy, consisting of calcium-channel antagonists, beta-blockers, nitrates, or some combination of these three agents, or 2) conventional therapy plus ticlopidine, 250 mg twice daily. The conventional therapy did not include aspirin, as when the trial was designed, aspirin was not routinely used to treat patients with unstable angina. At the 6 month follow-up, the ticlopidine group had a significant 46% reduction in the primary combined end point of vascular death and nonfatal myocardial infarction (7.3% compared with 13.6%; p=0.009). Of note; no difference in the number of events was seen over the first 10 days, which was consistent with the delayed onset of the antiplatelet effect of ticlopidine.[10)]

The effect of clopidogrel in unstable angina was proved in the CURE study.[11)] This study included 12,562 patients with unstable angina and a non-Q wave myocardial infarction, and compared groups who had both aspirin and clopidogrel or aspirin only. In the former group, the cardiovascular deaths, strokes and myocardial infarctions were decreased by 20%. The bleeding was more frequent in the former group, but fatal bleeding or a brain hemorrhage was no more frequent.

Platelet GP IIb/IIIa receptor blockers

According to studies, such as PRISM-PLUS, PURSUIT, PARAGON and PRISM, when tirofiban, eptifibatide and lamifiban were used, in addition to aspirin and heparin, 15−32 deaths or myocardial infarctions were prevented per 1000 treated patients.[12-15)] The CAPTURE trial revealed that abciximab was effective when used before percutaneous intervention.[16)] However, the GUSTO IV-ACS study showed that abciximab was not effective in patients with unstable angina or a non-Q wave myocardial infarction.[17)] The subjects of the GUSTOIV-ACS were low risk patients, and this might have caused the difference.

Acute Myocardial Infarction

In the ISIS-2 study, including 17,187 patients with myocardial infarctions, aspirin reduced the death rate of the 5th week, regardless of the use of streptokinase.[18)] Especially, the death rate of the group that used both aspirin and streptokinase was decreased 42% compared to the control group. In the follow-up study, the effect was persistent for 10 years. Aspirin's effectiveness has

been proved in many other studies, and the addition of the drug did not increase the risk of an acute hemorrhage.

There has been no mega-trial where ticlopidine or clopidogrel was used in an acute myocardial infarction, but the possibility of their effectiveness has been suggested from studies with small numbers of the patients. The effect of clopidogrel in acute myocardial infarction would be confirmed by the results of the CCS-2 study, which divided 30,000−40,000 patients into two groups, one with aspirin, and the other with both aspirin and clopidogrel.

In pilot studies, platelet GP IIb/IIIa receptor blockers were found to be more effective when used with thrombolytic agents. However, according to the Gusto-V trial, which included more patients, in order to prove the effectiveness, combined the use of abciximab and a half-dose of reteplase, failed to reduce the death rate compared to the reteplase group, with a higher bleeding rate.[19] However, the relapses of the myocardial infarctions were significantly reduced, which opened up the possibility for much more research on the role of the combination therapy in the case of intervention, after thrombolytic therapy, in myocardial infarctions. There are a few ongoing studies.

Usage in Coronary Intervention

Aspirin should be used in all patients who undergo coronary intervention, as it reduces the frequency of a Q-wave myocardial infarction and thrombus formation at target vessel. The use of aspirin, with ticlopidine, after coronary stenting, reduces thrombus formation and cardiac events. Among the studies using clopidogrel in coronary intervention, the recently released CLASSICS, PCI-CURE and CREDO trials are representative examples.[20-22] A loading dose followed by the long-term administration of clopidogrel was beneficial in reducing major cardiovascular events compared to a placebo, and showed a similar effect to ticlopidine, but with less frequent side effects.

The effect of abciximab in coronary intervention has been proved in the EPIC (high risk PTCA), EPILOG (elective PTCA) and EPISTENT (elective stenting) trials.[23-25] Especially, in the EPISTENT trial, the 2,399 patients undergoing coronary intervention were divided into 3 groups; patients who had stenting only, those who had stenting and abciximab, and those who had balloon angioplasty and abciximab. The deaths and myocardial infarctions in the 3 groups, at 30 days, were 7.8, 3.0 and 4.7%, respectively, with the second group showing the lowest percentage. Target vessel revascularizations at 6th months were 10.6, 8.7 and 15.4%, respectively, with the second group again having the lowest percentage. The death rate in the first year for the first group was 2.4%, but in the second group this was 1.0%, which was significantly lower.

In the RESTORE and IMPACT II studies, which used tirofiban or eptifibatide, the frequencies of cardiac events at 30 days to 6 months were low in the tirofiban and eptifibatide groups, but the difference was not statistically significant, limiting the use of these drugs in coronary intervention.[26][27]

Intravenous GP IIb/IIIa receptor blockers do not seem to have the same effects with the present dosage and protocol. However, more studies are needed, for the result may vary depending on different protocols. The TARGET trial compared abciximab and tirofiban in patients with angina pectoris who had stenting.[28] The myocardial infarctions at the 30th day were significantly high in the tirofiban group, but the primary endpoint of death/myocardial infarction/revascularization at the 6th month and first year showed no differences. However, This study was designed to observe the combined primary endpoint at the 30th day. In this trial, clopidogrel pretreatment reduced the deaths and myocardial infarctions, irrespective of the type of GP IIb/IIIa blocker used, without excess 30-day bleeding events.[29] In a retrospective study of patients with acute myocardial infarctions, or unstable angina, undergoing coronary angioplasty, an intracoronary bolus application of abciximab was associated with a reduction of major adverse cardiac events, compared with the standard intravenous bolus applica-

tion of abciximab, which warrants prospective, randomized trials.[30]

It would be much more convenient if oral GP IIb/IIIa receptor blockers were developed that could have the same effect as the intravenous form, including its potential long term use. However, the GP IIb/IIIa receptor blocker of orally use, which was developed with high expectation, gave disappointing results compared to the result of the intravenous abciximab study.

In summary, antiplatelet agents have been shown to improve the prognosis of various high-risk patients with coronary artery disease. They should be used, in proper combination in all relevant cases, for longer survival and better quality of life.

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