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Effect of Atorvastatin and Clopidogrel Co-Administration After Coronary Stenting in Korean Patients With Stable Angina

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ABSTRACT

Background and Objectives: It was reported that atorvastatin co-administered with clopidogrel for 8 months did not affect the anti-platelet potency of clopidogrel in Korean patients with acute coronary syndrome, but not in patients with stable angina. We investigated whether co-administration of statins with clopidogrel affected the anti-platelet efficacy of clopidogrel in Korean patients with stable angina. **Subjects and Methods:** This was a randomized, open-label and two-period crossover design study conducted at two centers. Two hundreds thirty three patients with stable angina scheduled for coronary stenting were randomized into two groups. In Group A, 119 patients first received atorvastatin (10 mg) followed by fluvastatin (80 mg) for 12 weeks per treatment. In Group B, 114 patients received the same treatments in reverse order. **Results:** Baseline adenosine diphosphate (ADP, 10 μmol/L)-induced platelet aggregation was 54.4±9.1% in Group A and 53.8±9.0% in Group B (p=0.44), and significant differences were noted after each treatment period (p<0.001). Inhibition of platelet aggregation was similar between Group A and Group B at 24 hours following clopidogrel loading (29.2±11.0% vs. 30.4±12.7%; p=0.42). The two treatment least square means of 12-week ADP (10 mol/L)-induced platelet aggregation [29.50±0.79 {standard error (SE)}% on the atorvastatin treatment group vs. 28.16±0.70 (SE)% in the fluvastatin treatment group] in a 2×2 cross-over study were not significantly different (p=0.204). **Conclusion:** Statin and clopidogrel co-administration for 12 weeks is not associated with attenuated anti-platelet activity of clopidogrel in Korean patients with stable angina after coronary stenting, in support of the findings of similar studies conducted in Caucasian populations. **(Korean Circ J 2011;41:28-33)**

KEY WORDS: Clopidogrel; Cardiovascular diseases; Cytochrome P450 3A4 protein, human; Atorvastatin; Stents.

Introduction

Several large, randomized clinical trials and their meta-analyses have demonstrated the benefits of clopidogrel as an alternative to aspirin in patients at high risk for cardiovascular events.[1-5] Clopidogrel decreases the incidence of coronary artery stent thrombosis and has been approved for the reduction of myocardial infarction incidence, atherosclerotic cerebral infarction and vascular diseases.[6][7] Likewise, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) were found to reduce the risks of myocardial infarction, stroke and cardiovascular-related death in randomized trials and their meta-analyses.[8-10] Therefore, clopidogrel and statins are being frequently co-administered in patients with coronary artery stents.

Clopidogrel, an inactive thienopyridine prodrug *in vitro*, is activated *in vivo* by cytochrome P450 enzyme (CYP3A4) following oral administration.[11-13] This active metabolite binds selectively and irreversibly to the platelet purinergic $P2Y_{12}$ receptor, thereby inhibits adenosine diphosphate (ADP)-induced platelet aggregation. Some statins (e.g., atorvastatin, simvastatin, lovastatin) are predominantly metabolized by hepatic CYP3A4. Therefore, there has been controversies regarding possible drug interactions via this metabolic pathway after re-

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ports revealed that the anti-platelet activity of clopidogrel could be attenuated by lipophilic statins in patients undergoing coronary artery stenting.[14-16] However, the data from several clinical follow-up studies on major adverse events indicate that peri-procedural co-administration of statins with clopidogrel does not worsen the clinical progress of such patients.[17][18] Although severe drug-drug interactions between statins and clopidogrel have not been reported in recent *ex vivo* studies,[19-22] the follow-up durations of these studies (maximal duration=5 weeks) cannot be considered sufficient to reflect the long-term clinical outcomes of such combination therapy. Furthermore, concomitant prescription of statins with clopidogrel is common worldwide in patients who undergo percutaneous coronary intervention, but there have been few reports on the impact of co-administering statins and clopidogrel on the anti-platelet activity of clopidogrel in Asians. Recently, Hong et al.[23] demonstrated no significant differences in anti-platelet potency of clopidogrel when it was co-administered with 10 mg or 40 mg of atorvastatin for eight months in patients with acute coronary syndrome.[23]

The aim of this study was to evaluate consecutively whether the anti-platelet efficacy of clopidogrel would be similarly maintained over a 12-week period, when it was administered concomitantly with statins with different metabolic pathways in Korean patients with stable angina after coronary stenting.

Subjects and Methods

Patients

This was a randomized, open-label, two-sequence, two-period crossover design study conducted at two centers. The hospital institutional review board reviewed and approved the study protocol. The study was conducted in accordance with the principles set forth in the Guideline for Good Clinical Practice and the Declaration of Helsinki and its amendments.[24]

Patients newly diagnosed with stable angina scheduled for coronary stenting, and who had never received treatment for hypercholesterolemia {low density lipoprotein-cholesterol (LDL-C) ≥100 mg/dL} were recruited. One month prior to study entry, no patients received statin therapy. Eligible patients were informed of the nature of the study and gave written informed consent.

Exclusion criteria

Patients with acute coronary syndrome, active bleeding, bleeding diathesis, malignancies, oral anticoagulation therapy using a coumadin derivative, recent treatment (<14 days prior) using a glycoprotein IIb/IIIa antagonist or a platelet count $<100\times10^9$/L were excluded. In addition, patients taking known CYP3A4 inducers or inhibitors were excluded, unless they were taking one of the drugs included in Table 1.

Screening, randomization and treatment

Enrolled patients were randomized with sequentially numbered, opaque sealed envelops containing sheets containing details of the assigned treatment. Of 260 enrolled patients, 233 were randomly assigned to one of two treatment sequences using permuted block randomization in blocks of six. Group A was comprised of 119 patients who received atorvastatin first just after coronary stenting, followed by fluvastatin (Lescol XL®; Norvatis Pharma AG). In Group B, 114 patients first received fluvastatin just after coronary stenting followed by

Table 1. Demographic and clinical characteristics of the intention-to-treat population

Characteristic	Group A (n=119)	Group B (n=114)	p*	Total (n=233)
Age (year)	57.9±11.3	60.1±10.8	0.741	59.2±11.6
Female gender	42 (35.3)	39 (34.2)	0.801	81 (34.8)
BMI (kg/m^2)	23.7±2.6	22.9±3.1	0.798	22.7±5.6
Risk factors				
Current smoking	14 (11.6)	12 (10.5)	0.821	26 (11.2)
Hypertension	75 (63.0)	72 (63.2)	0.885	147 (63.1)
Diabetes mellitus	39 (32.8)	35 (30.7)	0.761	74 (31.8)
Medication				
CCB	65 (54.6)	66 (57.8)	0.843	131 (56.2)
β-blocker	74 (62.2)	76 (66.7)	0.635	150 (64.4)
ACE inhibitor	59 (49.6)	56 (49.1)	0.623	115 (49.4)
ARB	48 (40.3)	43 (37.7)	0.493	91 (39.1)
Nitrates	31 (26.1)	29 (25.4)	0.794	60 (25.8)
Diuretics	17 (14.3)	13 (11.4)	0.834	30 (12.9)

The data are expressed as the mean±SD or number (percentage). *Comparison between Group A and Group B. BMI: body mass index, CCB: calcium-channel blocker, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker

atorvastatin. All drugs were administered once daily in the morning at a dose of 10 mg for atorvastatin and 80 mg for fluvastatin for each 12 week per treatment period. A 4-week washout interval separated the treatment periods, during which pravastatin, which is not metabolized mainly via the CYP pathway in the liver, was given once daily. The comparative efficacy of the available statins on lipids and lipoproteins showed that the potency of 10-mg atorvastatin is similar to that of 80-mg fluvastatin.[25] All patients received 100-mg aspirin and a 300-mg loading dose of clopidogrel before coronary stenting, and daily doses of 75-mg clopidogrel and 100-mg aspirin after coronary stenting during the study. Compliance with the treatments was monitored through patient diaries and periodic telephonic follow-ups between assessments. Patients were instructed to follow the National Cholesterol Education Programme Step I (or stricter) diet.

Laboratory tests

Blood samples for platelet activity were drawn 1 hour before (baseline) and 24 hours after the loading dose of clopidogrel, as well as after each treatment period at weeks 12 and 24. A blood sample was taken from the forearm vein and collected in a 3.8% sodium citrate tube. Platelet aggregation was assessed within 2 hours of blood sampling. *Ex vivo* platelet aggregation was measured using a two-channel whole blood aggregometre (Chrono-log Corp., Havertown, PA, USA). Platelet-rich plasma was obtained as a supernatant after centrifugation of the citrated blood at 1,000 rpm for 10 minutes. The final platelet count was adjusted to 2×10^8/mL with autologous plasma. Platelet-poor plasma was obtained by a second centrifugation of the blood at 3,500 rpm for 10 minutes. The maximal light transmission curve was assessed for 5 minutes after adding 10 μmol/L ADP as a marker for platelet aggregation. The platelet-poor plasma was used as the baseline reference.

All patients were required to fast for 12 hours before blood sampling for serum lipid parameter concentrations. Serum LDL-C, total cholesterol (TC), triglyceride (TG) and high density lipoprotein cholesterol (HDL-C) concentrations were determined at baseline, weeks 12 and 24. The LDL-C concentrations were calculated by using the Friedewald formula.[30] TC and TG concentrations were measured by calorimetric enzyme assay using a Hitachi 747-200 automatic analyzer. HDL-C was measured after precipitation by a calorimetric enzyme assay. Our laboratory has been certified by the Korean Association of Quality Assurance for Clinical Laboratories, Seoul, Korea.

Statistical analysis

The analysis was performed according to the intention-to-treatment (ITT) principle, defined as patients who received ≥1 dose of a study drug and had data available from ≥1 follow-up assessment in each of the study period. Comparisons of lipid concentrations were based on all randomized patients who had taken at least one dose of atorvastatin or fluvastatin. Continuous demographic parameters and study data were expressed as the mean±SD, and comparisons between the groups were analyzed by independent t-tests. Power analysis was performed with G Power Version 3.0.[26] All the tests were two-tailed. For analysis of the Student's t-test, the effective total sample size to give a power level of 0.95 (α=0.05, estimated effect size=0.5) was 210. Categorical variables in the baseline characteristics were analyzed using the chi-square test. We used the paired t-test to analyze the results within each group. We considered the results of the two-sided tests significant if the p was less than 0.05. All statistical analyzes were performed using SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Statistical analyzes for the comparison of least squares means with standard error (SE) for 12-week ADP (10 mol/L)-induced platelet aggregation (atorvastatin group vs. fluvastatin group) in a 2×2 crossover design were estimated from the model that included treatment, period, and carryover effect using NCSS software for Windows (NCSS, Kaysville, Utah, USA; NCSS version 2007) according to the methodology described by Chow and Liu.[31][32]

Results

Fig. 1 summarizes the study patient flow. Of the 233 enrolled patients, 119 patients were randomized to Group A and 114 patients to Group B. A total of 22 patients were withdrawn from the study, 12 from Group A and 10 from Group B due to consent withdrawal, non-compliance and other factors. The demographic and clinical characteristics of 223 enrolled patients included in the ITT population are summarized in Table 1.

The baseline values of ADP-induced platelet aggregation were similar between the groups: 54.4±9.1% for Group A and 53.8±9.0% for Group B {95% confidence interval (CI) of differences=-2.13, 3.02; p=0.44}. These values showed significant differences when compared with the results after each treatment period (p<0.001). As shown in Fig. 2, platelet aggregation was similarly inhibited in Groups A and B: 29.2±11.0% vs. 30.4±12.7% (95% CI of differences=-5.12, 1.81; p=0.42) 24 hours following clopidogrel loading (day 1), 30.8±11.8% vs. 28.1±10.3% (95% CI of differences=-1.16, 5.49; p=0.08) after Period 1 (week 12), and 27.0±11.6% vs. 28.2±10.9% (95% CI of differences=-2.98, 3.22; p=0.45) after Period 2 (week 24). Co-administration of clopidogrel with atorvastatin or fluvastatin inhibited platelet activity to the same extent as with clopidogrel alone within each group: Day 1 vs. week 12 (p=0.31), day 1 vs. week 24 (p=0.61) and week 12 vs. week 24 (p=0.12) in Group A. Day 1 vs. week 12 (p=0.23), day 1 vs. week 24 (p=0.19) and week 12 vs. week 24 (p=0.82) in Group B.

The two treatment least square means of the 12-week ADP

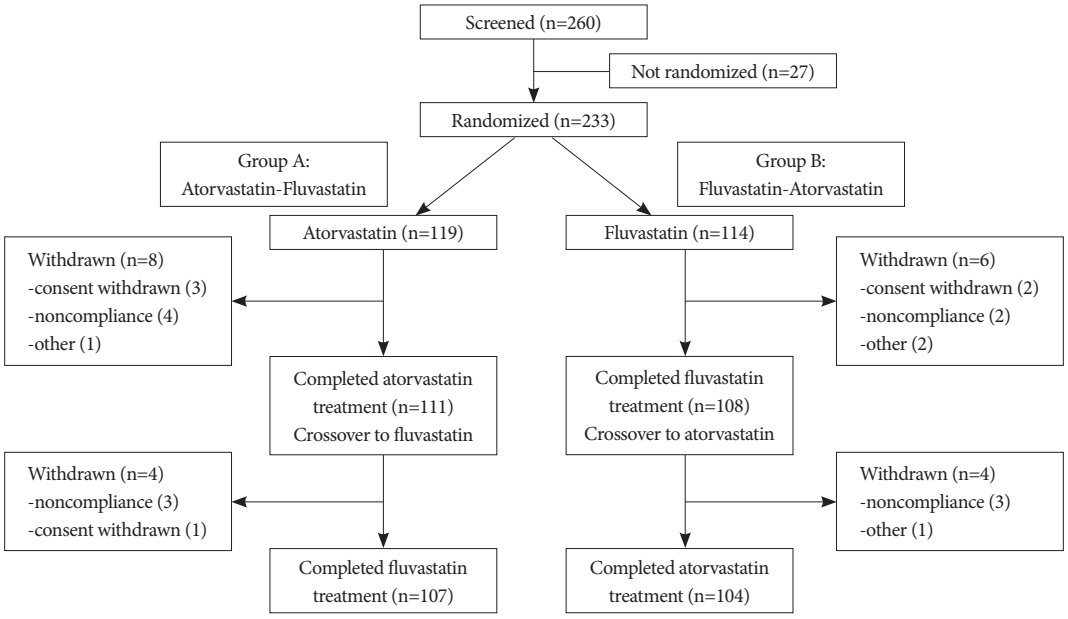

Fig. 1. The study protocol.

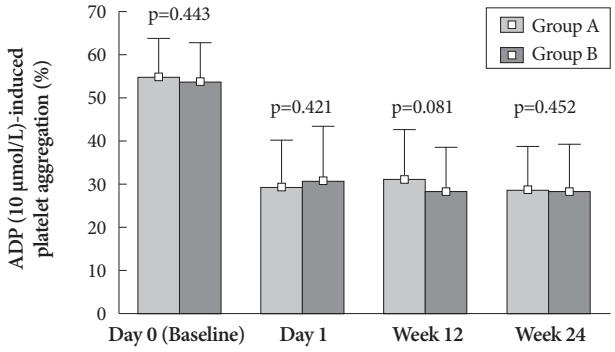

Fig. 2. Inter-individual time dependency of adenosine diphosphate (ADP, 10 μmol/L)-induced platelet aggregation from the baseline (day 0), through 300-mg clopidogrel loading (day 1), to clopidogrel co-administration with atorvastatin or fluvastatin (weeks 12 and 24) in the intention-to-treat population. The bars and whiskers represent the mean and standard deviation, respectively.

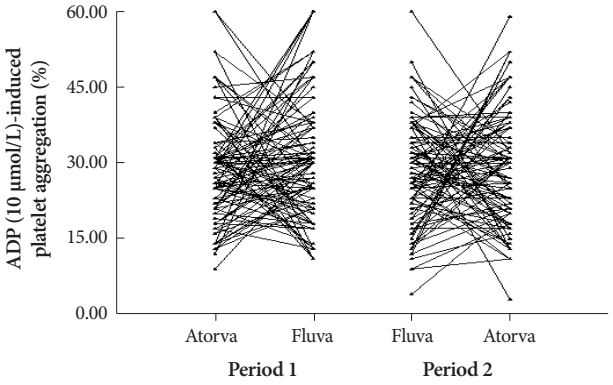

Fig. 3. Least squares mean ADP (10 μmol/L)-induced platelet aggregation (%) at week 12. T-test for proving similarity of atorvastatin vs. fluvastatin effect on clopodogrel {29.50±0.79% (SE) vs. 28.16± 0.70% (SE), p=0.204}. Assumption of equal period effect and carry-over effect were attained (p=0.343 and p=0.124 for each effect). Atorva: atorvastatin treatment, Fluva: fluvastatin treatment, ADP: adenosine di-phosphate, SE: standard error.

(10 mol/L)- induced platelet aggregation {29.50±0.79 (SE)% on the atorvastatin treatment group vs. 28.16±0.70 (SE)% in the fluvastatin treatment group} in a 2×2 cross-over study were not significantly different (p=0.204) (Fig. 3).

The baseline values of lipid parameters were not significantly different between the groups, and changes from the baseline values were consistent in both groups (Table 2). Liver enzyme levels were not elevated ≥3 times the upper limit of the normal, nor were the creatinine kinase levels elevated ≥10 times the upper limit of the normal. Further, no rhabdomyolysis was reported.

Discussion

In this study, co-administration of clopidogrel with atorvastatin or fluvastatin inhibited platelet activity to the same extent as with clopidogrel alone within each group.

The results of this study, which had a longer follow-up period than previous *ex vivo* studies, suggest that co-administration of a CYP3A4-metabolized statin such as atorvastatin (metabolized by CYP3A4) or non-CYP3A4-metabolized statin such as fluvastatin (metabolized by CYP2C9) with clopidogrel does not significantly affect the anti-platelet efficacy of clopidogrel in Korean patients with symptomatic coronary artery disease treated by coronary stenting. Overall, the treatments were well tolerated and no adverse effects were observed. To our knowledge, this is the longest randomized study investigating the impact of statins on *ex vivo* anti-platelet effect of clopidogrel.

A number of concerns were raised regarding the possibility of specific deleterious interactions between clopidogrel and statins when studies provided controversial results that short-

Table 2. % Change in the lipid concentrations from the baseline values after treatment with both statins

Parameter	Time point	Group A (n=119)	Group B (n=114)	p*
	Baseline (mg/dL)	149.7±33.5	154.4±29.3	0.261
LDL-C	Period 1 (%)	49.4±14.2	44.7±11.3	0.134
	Period 2 (%)	46.4±12.5	46.0±12.8	0.851
	Baseline (mg/dL)	217.5±38.1	222.1±39.2	0.373
TC	Period 1 (%)	36.1±11.6	34.9±14.2	0.762
	Period 2 (%)	33.9±10.5	34.5±11.9	0.822
	Baseline (mg/dL)	235.6±95.3	227.6±90.9	0.546
TG	Period 1 (%)	23.2±27.2	17.0±26.3	0.272
	Period 2 (%)	19.0±24.2	11.7±25.4	0.583
	Baseline (mg/dL)	37.1±10.4	37.6±9.8	0.971
HDL-C	Period 1 (%)	-4.3±19.4	-4.7±22.6	0.893
	Period 2 (%)	-4.1±23.4	-5.2±19.1	0.512

The data are expressed as the mean±SD. *Comparison between Group A and Group B. LDL-C: low density lipoprotein-cholesterol, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein-cholesterol

term therapy with clopidogrel in conjunction with atorvastatin could attenuate the anti-platelet efficacy of clopidogrel, suggesting that the co-administration of CYP3A4-metabolized statins with clopidogrel may competitively inhibit metabolic activation of clopidogrel in the liver.[14-16] However, Serebruany et al.[20] showed that atorvastatin did not affect platelet biomarkers after clopidogrel administration, compared with other statins or no statin, within 24 hours in patients undergoing coronary stenting. Mitsios et al.[19] showed that the therapeutic efficacy of clopidogrel in patients with acute coronary syndrome was not significantly affected by concomitant administration of atorvastatin for 5 weeks, and clopidogrel did not affect the therapeutic efficacy of atorvastatin. Mukherjee et al.[21] reported that there was no significant difference in the clinical benefit between a CYP3A4-metabolized statin and a non-CYP3A4-metabolized statin when used in conjunction with clopidogrel. The present study has contributed to the growing body of evidence that drug-drug interaction between clopidogrel and statins has no clinical relevance in patients with cardiovascular disease treated with clopidogrel and a standard statin-dosing regimen.

This study has several limitations. First, its open-label, unblinded design limits its generalizability beyond the study groups. However, randomized assignment of patients and the crossover design of this study could mitigate bias. The crossover design was considered feasible if a sufficiently long washout period could be included between the treatments. Second, we investigated only a single platelet function marker. Neubauer et al.[16] demonstrated that the impact of statins on clopidogrel's inhibitory effect on platelet function was much less impressive when maximal concentrations of ADP (100 mol/L) are used. They speculated that very high concentrations of ADP stimulated platelets via additional, unspecific receptor sites. Furthermore, low concentrations of ADP (1 mol/L) exerted only minor platelet stimulation, but significant results were seen when a moderate concentration of ADP (10 mol/L) was used for platelet stimulation.[16] Therefore, we chose this concentration of ADP (10 mol/L) as our stimulation dose for platelet aggregometry. Finally, no *in vivo* investigations had been performed, and the study included only the usual basal dosage of atorvastatin. However, data from a post hoc analysis of the Clopidogrel for Reduction of Events during Observation trial showed no adverse effect on the 28-day or 1-year composite clinical end points with clopidogrel and statin co-administration.[17] Similarly, the prospective Maximal Individual Therapy of Acute myocardial infarction PLUS registry demonstrated that there was no significant difference between atorvastatin therapy and other statin therapies in the clinical outcomes of patients receiving clopidogrel over a follow-up period of 14 months.[18] Further studies on clopidogrel-dependent platelet inhibition with dosing increments of statins may be needed. Polymorphisms of CYP2C19 could have affected clopidogrel resistance in this study.[27][28] However, the incidence of clopidogrel non-responders is known to be less than 10%.[29]

In conclusion, the anti-platelet activity of clopidogrel was maintained when co-administered with a statin for 12 weeks in Korean patients with coronary stents. The results support the long-term clinical benefit of a CYP3A4-metabolized and non-CYP3A4-metabolized statins administered concomitantly with clopidogrel.

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