

Open Access

Celecoxib Does Not Attenuate the Antiplatelet Effects of Aspirin and Clopidogrel in Healthy Volunteers

Wonjae Lee, MD^{1,2}, Jung-Won Suh, MD^{1,3}, Han-Mo Yang, MD^{1,2}, Dong-A Kwon, MD^{1,2}, Hyun-Ju Cho, MSc^{1,2}, Hyun-Jae Kang, MD^{1,2}, Hyo-Soo Kim, MD^{1,2} and Byung-Hee Oh, MD^{1,2}

¹Department of Internal Medicine, Seoul National University College of Medicine, Seoul,

²Cardiovascular Center, Seoul National University Hospital, Seoul,

³Cardiovascular Center, Bundang Seoul National University Hospital, Seongnam, Korea

ABSTRACT

Background and Objectives: The prevalence of arthritis, which is often treated with celecoxib, is high in patients with coronary artery disease. Furthermore, celecoxib has been reported to reduce restenosis after coronary stenting by inhibiting expression of the proto-oncogene Akt. A concern is that celecoxib increases thrombogenicity by inhibiting the synthesis of prostacyclin in endothelial cells. However, it is not known whether the administration of celecoxib will attenuate the antiplatelet effects of aspirin and clopidogrel, which are used after stenting. We addressed this gap in our knowledge. **Subjects and Methods:** We recruited healthy volunteers (n=40) and randomized them into five subgroups (n=8 for each group: aspirin, celecoxib, aspirin+celecoxib, aspirin+clopidogrel, and aspirin+clopidogrel+celecoxib). Each subject received their medications for 6 days and blood samples were taken on day 0 and day 7. Celecoxib (200 mg twice a day), and/or aspirin (100 mg daily), and/or clopidogrel (75 mg daily) were administered. We compared platelet function among subgroups using light transmittance aggregometry and arachidonic acid metabolite assays. **Results:** Celecoxib treatment alone did not significantly affect platelet aggregation. The reduction in adenosine diphosphase (ADP)-induced platelet aggregation by aspirin+clopidogrel was not affected by addition of celecoxib ($31.3 \pm 6.9\%$ vs. $32.4 \pm 12.2\%$, $p=0.83$). Inhibition of collagen-induced platelet aggregation by aspirin+clopidogrel was not affected by addition of celecoxib ($47.6 \pm 13.4\%$ vs. $51.6 \pm 3.7\%$, $p=0.69$). Drug-induced changes in prostacyclin and thromboxane levels did not differ among treatment groups. **Conclusion:** Celecoxib treatment does not interfere with the antiplatelet effects of aspirin or clopidogrel, suggesting that celecoxib can be safely administered in combination with dual antiplatelet therapy in patients with coronary stenting without increased thrombogenicity. (**Korean Circ J 2010;40:321-327**)

KEY WORDS: Celecoxib; Platelet aggregation inhibitors; Thrombosis.

Introduction

Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, has been widely used to manage patients with osteoarthritis and rheumatoid arthritis. It causes less gastric irrita-

tion compared to nonselective COX inhibitors.¹⁾ High dose celecoxib reduced the number of colorectal polyps in patients with familial adenomatous polyposis.²⁾ Moreover, we recently reported that celecoxib reduced restenosis and target lesion revascularization after coronary stenting.³⁾

Recent clinical studies, however, have suggested that COX-2 inhibitors increase the incidence of cardiovascular events.⁴⁻⁶⁾ Rofecoxib was associated with adverse cardiovascular events in a colorectal adenoma chemoprevention trial, and it was withdrawn from the world market.⁴⁾ However, the results of clinical studies regarding celecoxib are controversial. Celecoxib was found to dose-dependently increase the composite end point of death from cardiovascular causes, myocardial infarction, stroke, or heart failure in the Adenoma Prevention with Celebrex (APC) trial.⁵⁾ Two other large studies, Prevention of

Received: November 18, 2009

Accepted: December 14, 2009

Correspondence: Hyo-Soo Kim, MD, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea

Tel: 82-2-2072-2226, Fax: 82-2-766-8904

E-mail: hyosoo@snu.ac.kr

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Spontaneous Adenomatous Polyps and Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT), did not show increased cardiovascular risk associated with celecoxib.⁷⁽⁸⁾

Dual antiplatelet therapy with aspirin and clopidogrel is essential for at least one year in patients with coronary stenting, especially those with drug-eluting stents. It is the most important treatment for preventing a fatal complication, stent thrombosis.⁹⁽¹⁰⁾ Since the number of patients with ischemic heart disease is increasing, and many of them are elderly and have arthritis, there are more and more candidates for treatment with both celecoxib and antiplatelet agents.¹¹⁾ However, the safety profile of celecoxib with concomitant administration of aspirin and clopidogrel has not been evaluated. We conducted the current study to evaluate 1) whether celecoxib can be used safely with antiplatelet agents, and 2) whether celecoxib interferes with the antiplatelet activity of aspirin and clopidogrel.

Subjects and Methods

Subjects

Healthy volunteers including both men and women 20 to 30 years of age were recruited for this study. Subjects were proved to have no abnormalities on physical examination, 12-lead electrocardiogram, and routine laboratory tests. Subjects with a history of cardiovascular disease, or hemostatic disorder, and hypersensitivity to NSAIDs and clopidogrel, were excluded. Women with childbearing potential were tested for pregnancy, and women with a positive test result were excluded. Others were excluded if they were smokers, chronic drinkers or overweight (exceeding 20% of standard body weight). Subjects had to abstain from alcohol, beverages containing caffeine, and other drugs beginning one week before the study.

The study was approved by the review board of Seoul National University Hospital. Written and informed consent was obtained from all volunteers before enrollment in the study.

Study design

We designed a single-center, open label, parallel-group and randomized study. Young healthy volunteers (n=40) were randomized into 5 groups: celecoxib only (CCX), aspirin only (ASA), celecoxib+aspirin (CCX+ASA), aspirin+clopidogrel (CCX+CPD), and celecoxib+aspirin+clopidogrel group (CCX+ASA+CPD). Screening tests were performed 3 days before the initiation of the study. A celecoxib (Celebrex[®], Pfizer Korea, Seoul, Korea) dose of 200 mg twice a day was chosen since this is the usual dose in clinical practice for treating arthritis and pain. Aspirin (Rhonal[®], Kun-Wha Pharmaceuticals, Seoul, Korea) 100 mg daily, and/or clopidogrel (Plavix[®], Sanofi-Aventis, Seoul, Korea) 75 mg daily were used because they are the standard doses for treating patients with ischemic heart disease. Each subject received their assigned medications for

six consecutive days. Blood samples were collected at day 0 (pre) and day 7 (post) for assessment of platelet aggregation. Urine samples were collected at the same time to evaluate prostacyclin and thromboxane levels.

Whole blood samples were drawn into four standard sodium citrate containing tubes. Samples were centrifuged at 1,200 rpm for 2 minutes and 30 seconds. Platelet aggregation was induced by adenosine 5'-diphosphate (adenosine diphosphate, ADP) or collagen. It was measured using a Chronolog Lumi-Aggregometer (model 560-Ca, Chrono-log Corp., Haver-town, PA, USA). The extent of platelet aggregation in samples was expressed by the maximum increase in light transmittance compared to baseline values.

Urine 6-keto PGF_{1 α} , a stable metabolite of prostaglandin I₂ (PGI₂), was measured as described in previous studies.¹²⁾⁽¹³⁾ Urine samples were centrifuged to remove any precipitates. Correlate-EIA[™] Immunoassay kits (Assay Designs, Inc., Ann Arbor, MI, USA) were used to measure urine levels of 6-keto PGF_{1 α} . Values obtained using the kit were adjusted by VAGUE, the urine creatinine level of each subject. Urine samples were also used to measure urinary 11-dehydro-TXB₂, which is a major metabolite of TXB₂. Correlate-EIA[™] Immunoassay kits (Assay Designs, Inc., Ann Arbor, MI, USA) designed for urinary 11-dehydro-TXB₂ were used.

Statistics

Platelet aggregation results are presented as means and standard deviations. Changes from baseline values were calculated to detect the average differences in the platelet aggregation for each treatment group. The Wilcoxon rank sum test was used to analyze for between group differences. Results for urinary 6-keto PGF_{1 α} were calculated to show changes from baseline values. The Mann-Whitney test was performed to show whether any differences in prostacyclin between groups was statistically significant. Statistical Package for the Social Sciences (SPSS) software (Version 12.0 for Windows, SPSS Inc, Chicago, IL, USA) was used for statistical analysis. A $p < 0.05$ was considered to indicate statistical significance.

Results

Forty healthy subjects who met the inclusion criteria were screened and randomized. The baseline characteristics of subjects are described in Table 1. The ages of volunteers ranged from 21 to 35 years. Mean ages among the treatment groups were similar while the distribution of gender varied. All subjects completed the study, and there were no notable adverse events during the study.

Platelet aggregation

Fig. 1A shows ADP-induced platelet aggregation measured before and after each treatment. The CCX group showed no

Table 1. Baseline characteristics

	CCX	ASA	ASA+CCX	ASA+CPD	ASA+CPD+CCX
Number of subjects	8	8	8	8	8
Age (year)	25.3±2.6	23.3±2.6	26.0±2.7	23.6±2.8	24.5±2.6
Male/Female	3/5	7/1	3/5	7/1	3/5
Hb (g/dL)	13.8±1.4	15.6±1.1	14.0±1.7	15.8±1.0	14.5±1.0
Platelet count (×103/mm ³)	262.5±28.0	236.3±47.6	235.4±43.4	258.8±45.9	223.5±33.1

Values of age, hemoglobin, and platelet count are mean±standard deviation. CCX: celecoxib, ASA: aspirin, CPD: clopidogrel, Hb: hemoglobin

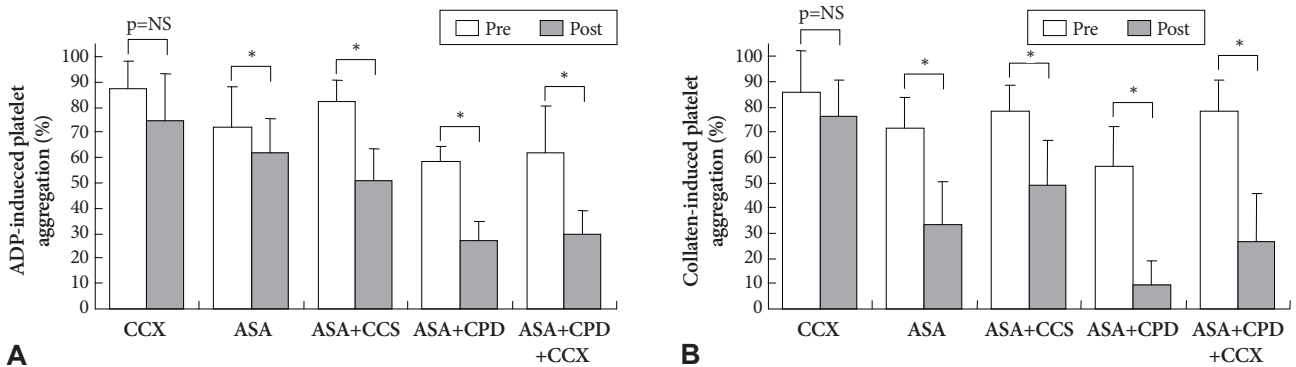


Fig. 1. Platelet aggregation (%) induced by (A) ADP, and (B) collagen. Platelet aggregation was measured on day 0 (Pre), and day 7 (Post). Values are means±standard deviation. *p<0.05. ADP: adenosine 5'-diphosphate, CCX: celecoxib, ASA: aspirin, CPD: clopidogrel, Pre: pre-treatment, Post: post-treatment.

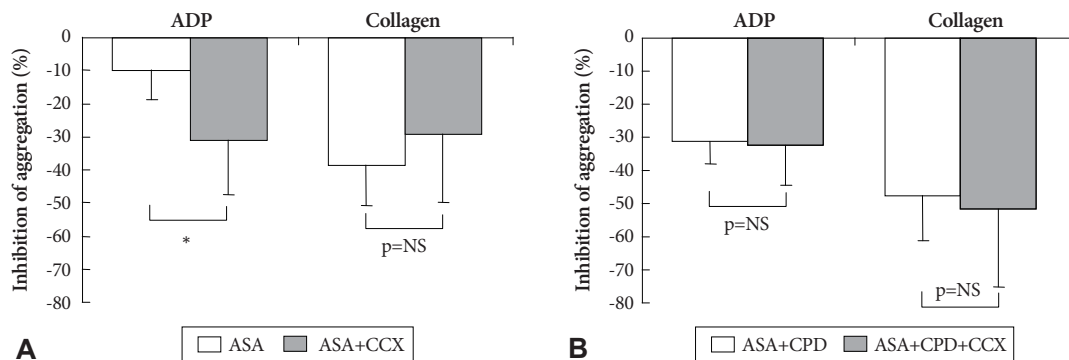


Fig. 2. Reductions in platelet aggregation (Pretreatment inhibition %-Post-treatment inhibition %) by antiplatelet agents with or without addition of celecoxib. A: comparison between aspirin (ASA) and aspirin+celecoxib (ASA+CCX). B: comparison between aspirin+clopidogrel group (ASA+CPD) and aspirin+clopidogrel+celecoxib (ASA+CPD+CCX). Values are means±standard deviation. *p<0.05. ADP: adenosine 5'-diphosphate.

significant change in platelet aggregation after treatment (pretreatment 86.9±11.0% vs. post-treatment 74.6±18.5%, p=0.29). ASA and ASA+CPD groups showed significantly reduced ADP-induced platelet aggregation compared to baseline (p<0.05), and this reduction was not affected by addition of celecoxib.

Changes in collagen-induced platelet aggregation are shown in Fig. 1B. Celecoxib treatment alone did not affect collagen-induced platelet aggregation (pretreatment 85.9±15.0% vs. post-treatment 76.5±14.4%, p=0.12). ASA or ASA+CPD group showed reduced collagen-induced platelet aggregation compared to baseline (p<0.05), which was not affected by celecoxib.

The reduction in ADP-induced platelet aggregation by ASA

(Δ aggregation, Pretreatment inhibition %-Post-treatment inhibition %) was not retarded by addition of CCX; rather, it was potentiated (9.8±9.2% vs. 30.9±16.8%, p=0.021) (Fig. 2A). The reduction in collagen-induced platelet aggregation by aspirin was not significantly retarded by addition of celecoxib (ASA group 38.6±12.1% vs. ASA+CCX group 29.1±20.9%, p=0.29) (Fig. 2A).

We also compared the 'Δ aggregation' between ASA+CPD and ASA+CPD+CCX groups. The reduction in ADP-induced platelet aggregation by ASA+CPD was not significantly affected by addition of celecoxib (ASA+CPD group 31.3±6.9% vs. ASA+CPD+CCX group 32.4±12.2%, p=0.83) (Fig. 2B). Inhibition of collagen-induced platelet aggregation by aspirin and clopidogrel was also not affected by addition of celecoxib

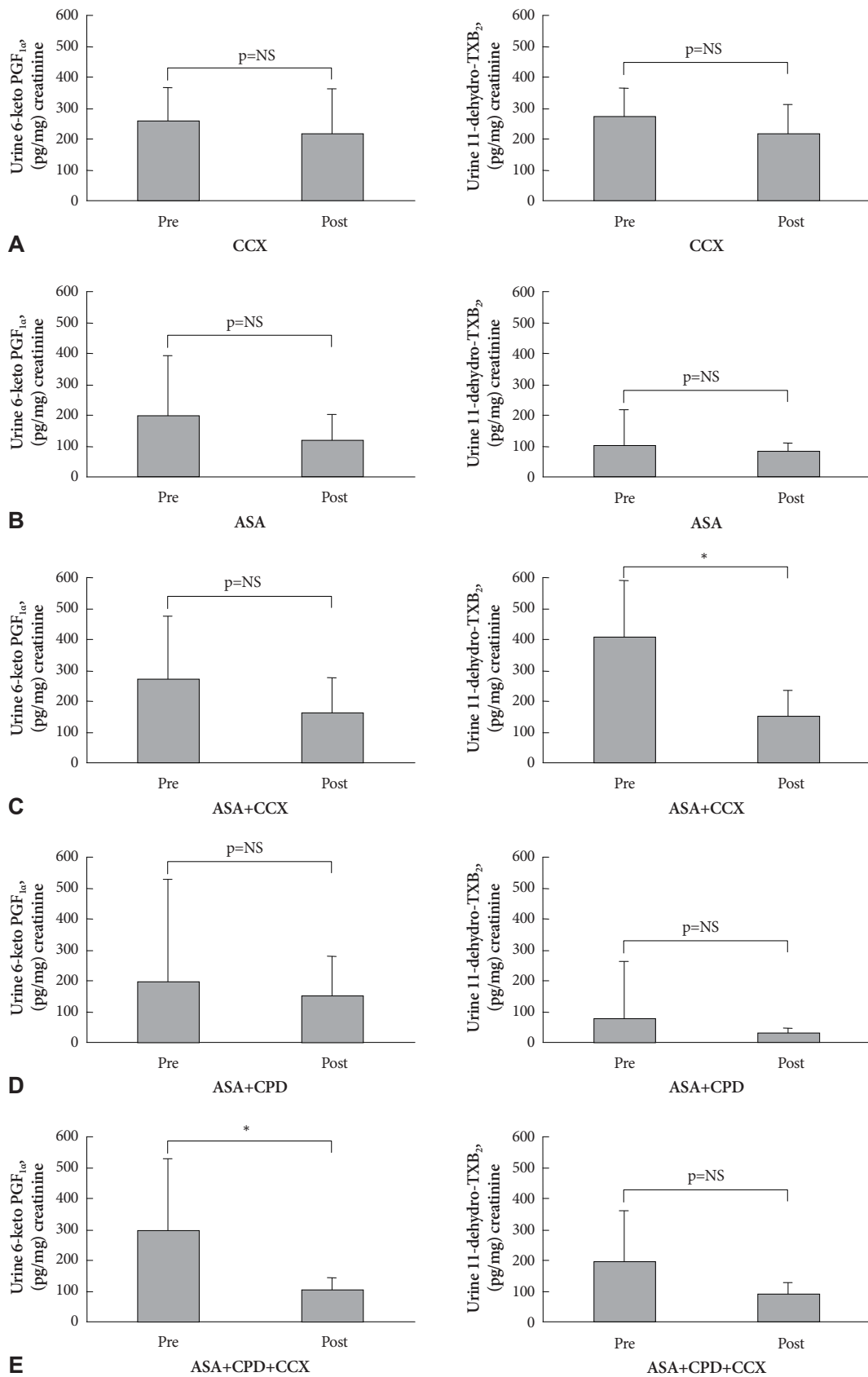


Fig. 3. Effects of celecoxib, aspirin, and clopidogrel on the production of prostacyclin and thromboxane B₂. Urinary excretion of 6-keto PGF_{1α} (pg/mg creatinine) and 11-dehydro TXB₂ (pg/mg creatinine) were measured before and after each treatment. A: celecoxib (CCX), B: aspirin (ASA), C: aspirin+celecoxib (ASA+CCX), D: aspirin+clopidogrel (ASA+CPD), E: aspirin+clopidogrel+celecoxib (ASA+CCX+CPD). Values are means±standard deviation. *p<0.05. Pre: pre-treatment, Post: post-treatment.

(47.6±13.4% vs. 51.6±23.7%, p=0.69) (Fig. 2B).

Prostacyclin production

Pretreatment mean urine 6-keto PGF_{1α} values adjusted by urine creatinine were not different among groups (Fig. 3). All groups tended to have decreased adjusted urine 6-keto PGF_{1α} levels after administration of study medications compared to pretreatment values. These trends were not statistically significant except for the ASA+CPD+CCX group (Fig. 3E) (Pretreatment 296.8±231.4 pg/mg creatinine vs. post-treatment 102.0±43.1 pg/mg creatinine, p=0.025). When we compared the changes in urine 6-keto PGF_{1α} levels (pretreatment value-post-treatment value) (Fig. 4), there were no significant differences between ASA and ASA+CCX groups (75.8 ±199.7 pg/mg creatinine vs. 108.8±295.5 pg/mg creatinine, p=1.0) or between ASA+CPD and ASA+CPD+CCX groups (49.5±406.6 pg/mg creatinine vs. 194.8±219.9 pg/mg creatinine, p=0.20) (Fig. 4A).

Thromboxane production

In all five groups, treatment with anti-platelet agents with or without celecoxib showed a tendency towards decreased levels of urinary 11-dehydro-TXB₂ (Fig. 3). In the ASA+CCX group there was a statistically significant decrease in the level of urine 11-dehydro-TXB₂ after treatment (Fig. 3C) (Pretreatment 409.5±181.6 pg/mg creatinine vs. post-treatment 152.6±82.1 pg/mg creatinine, p=0.012).

The reduction in urine 11-dehydro-TXB₂ was more profound after ASA+CCX than after ASA treatment alone (Fig. 4B) (256.96±213.1 pg/mg creatinine vs. 17.2±114.1 pg/mg creatinine, p=0.005). Reductions in urinary 11-dehydro-TXB₂ were not significantly different between ASA+CPD and ASA+CPD+CCX groups.

Discussion

We demonstrated that celecoxib does not affect the ability of aspirin and clopidogrel to inhibit platelet aggregation induced by ADP or by collagen in healthy individuals. Our study

shows that the effect of celecoxib on prostacyclin production is not significant when added to a regimen of aspirin and clopidogrel. Moreover, celecoxib tended to decrease the level of thromboxane production further when given in combination with aspirin and clopidogrel. No adverse events during the study was observed.

Effect of celecoxib on prostacyclin and thromboxane metabolism

There has been a concern that COX-2 inhibitors might increase thrombogenicity and are associated with adverse cardiovascular events. The rationale was that COX-2 inhibitors suppress the synthesis of prostacyclin in endothelial cells while they cannot inhibit thromboxane A₂ formation due to unopposed expression of COX-1 in platelets.¹⁴ It was demonstrated that urinary excretion of 2, 3 dinor-6 keto PGF_{1α} and 6-keto PGF_{1α}, which represents prostacyclin biosynthesis, was reduced by celecoxib at 4-6 hours after dosing, and partially recovered after 12-24 hours.¹³ The effect of aspirin and clopidogrel on prostacyclin production was assessed *in vitro* in a previous study,¹⁵ where aspirin reduced endothelial production of 6-keto PGF_{1α} significantly in a concentration-dependent way, whereas clopidogrel did not. However, celecoxib did not interfere with normal mechanisms of platelet aggregation and hemostasis and did not alter serum thromboxane B₂ level in healthy adults.¹⁶

In our study, prostacyclin production tended to decrease in all five groups after treatment. Although it was not statistically significant, prostacyclin production seemed to decrease more in the ASA+CCX group than in the ASA group, and more in the ASA+CPD+CCX than in the ASA+CPD group. But these changes in prostacyclin production were paralleled by changes in thromboxane. Our results shows that urinary 11-dehydro-TXB₂ levels were also decreased significantly more in the ASA+CCX group than in the ASA only group, and tended to decrease more in the ASA+CPD+CCX group compared to the ASA+CPD group. Together, these results suggest that celecoxib as a COX-2 inhibitor has a neutral effect on platelet aggregation since it has mild inhibitory effects not only

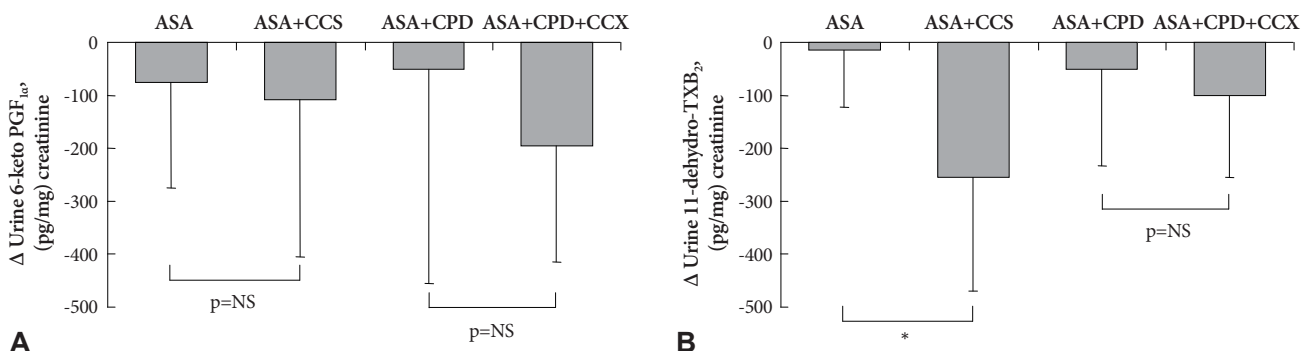


Fig. 4. Effects of celecoxib on the production of prostacyclin and thromboxane B₂ in combination with antiplatelet agents. The height of bars represents changes (post-treatment-pre-treatment) of (A) urinary 6-keto PGF_{1α} levels (pg/mg creatinine) and (B) 11-dehydro TXB₂ levels (pg/mg creatinine). Values are means±standard deviation. *p<0.05. CCX: celecoxib, ASA: aspirin, CPD: clopidogrel.

on prostacyclin production but also on thromboxane production, thus not changing the balance of prostacyclin and thromboxane.

No effect of celecoxib on aspirin's anti-platelet action

In this study, aspirin inhibited ADP-induced platelet aggregation and collagen-induced platelet aggregation by 13% and 55% respectively. This result is consistent with a previous study that reported values of 14% and 50%.¹⁷⁾ We confirmed that celecoxib did not affect the platelet aggregation response to collagen in healthy volunteers receiving aspirin as Wilner et al.¹⁸⁾ previously reported. Also in patients who were taking aspirin and had both osteoarthritis and ischemic heart disease, celecoxib, unlike ibuprofen, did not influence aspirin's action to irreversibly inactivate platelet COX-1.¹⁹⁾

Potential beneficial effects of celecoxib on the vasculature

In addition, celecoxib is known to have COX-independent biological effects. We previously reported that celecoxib in animal studies inhibits neointimal hyperplasia after balloon injury by blocking Akt signaling.²⁰⁾ Celecoxib also decreases inflammatory responses and neointimal hyperplasia, possibly through inhibition of MCP-1 expression.²¹⁾ It also suppressed aortic endothelial cell tissue factor expression, leading to prevention of thrombus formation in the vasculature, which was observed for celecoxib but not for other COX-2 inhibitors.²²⁾

No thrombotic risk of celecoxib under dual anti-platelet agents

In the current study, we evaluated the effect of dual antiplatelet therapy (aspirin and clopidogrel) on platelet aggregation and whether celecoxib affects the antiplatelet aggregation activity of aspirin and clopidogrel. Clopidogrel has a potent anti-thrombotic action by blocking P2Y₁₂, a platelet ADP receptor, and also inhibits platelet aggregation induced by collagen.¹⁵⁾²³⁾

In our study, we demonstrated a significant additional inhibitory effect of clopidogrel on both ADP- and collagen-induced platelet aggregation when added to aspirin. More importantly, we observed that the enhanced antiplatelet effect of dual antiplatelet therapy compared to aspirin alone is not altered by concomitant celecoxib use. This result is consistent with our previous prospective randomized clinical trial,³⁾ where additional of celecoxib treatment for 6 months after coronary stenting significantly reduced late loss of the stented segment and the target lesion revascularization rate without any increase in adverse thrombotic events. It is noteworthy that all patients in this trial were taking both aspirin and clopidogrel for more than six months after stenting.

NSAIDs class adverse effects

Despite these results indicating that celecoxib does not attenuate the antiplatelet action of aspirin and clopidogrel, and that celecoxib might even have a favorable effect on the cardiovascular system, several clinical studies have questioned the safety of celecoxib treatment for the cardiovascular system. The Cross Trial Safety Analysis which assessed cardiovascular risk based on >16,000 patient-years of follow-up from six randomized placebocontrolled trials including APC,²⁴⁾ PRE-SAP, and ADAPT concluded that celecoxib increases the number of adverse cardiovascular events. But such risk may not be celecoxib-specific. Rather, it may be that the increased risk is associated with the entire class of NSAIDs. The mechanism of class risk of NSAIDs may be multi-factorial, i.e., induction of blood pressure elevation and platelet aggregability, etc. Actually, celecoxib's cardiovascular risk has been reported to be relatively low compared with other NSAIDs.²⁵⁻²⁷⁾ Addition of celecoxib to patients who take dual anti-platelet agents due to coronary stenting, do not appear to be associated with thrombotic risk.

Limitations

The current study recruited young healthy volunteers instead of old patients at risk for developing cardiovascular disease. In the setting of atherosclerosis, suppression of PGI₂ production in endothelial cells by celecoxib is pronounced, since COX-2 plays a greater role as a source of PGI₂.²⁸⁾²⁹⁾ As a result, celecoxib might have a more profound effect on prostanoic balance under atherosclerotic conditions, promoting platelet-dependent thrombosis.³⁰⁾

The number of volunteers allocated to each treatment group was rather small. However, previous reports evaluating effects of celecoxib on antiplatelet activity and prostanoids had similar numbers of subjects. And results of platelet function tests in this study were consistent with those from previous studies.

Conclusion

Celecoxib does not interfere with the antiplatelet action of dual antiplatelet therapy, and it does not affect the balance of prostacyclin and thromboxane production. Recent evidence suggests that celecoxib may increase cardiovascular events in high risk patients and that aspirin may not be protective. Since patients with coronary artery stenting take aspirin and clopidogrel together, and some of them take it indefinitely, our study results are worth consideration. Celecoxib can be administered safely in these patients during coverage of dual antiplatelet therapy. Current warnings for celecoxib now mandate larger clinical trials that evaluate the safety of celecoxib during dual antiplatelet therapy following stenting.

Acknowledgments

This study was partly supported by a grant [Circulation Multicenter 2005-1] from the Korean Circulation Society. This study was also supported by

grants from the Korea Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea (0412-CR02-0704-0001), from the SNUH Research fund (04-2005-049) and from the Innovative Research Institute for Cell Therapy (IRICT: A062260).

REFERENCES

- 1) Silverstein FE, Faich G, Goldstein JL, et al. *Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA* 2000;284:1247-55.
- 2) Steinbach G, Lynch PM, Phillips RK, et al. *The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med* 2000;342:1946-52.
- 3) Koo BK, Kim YS, Park KW, et al. *Effect of celecoxib on restenosis after coronary angioplasty with a Taxus stent (COREA-TAXUS trial): an open-label randomised controlled study. Lancet* 2007;370:567-74.
- 4) Bresalier RS, Sandler RS, Quan H, et al. *Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med* 2005;352:1092-102.
- 5) Solomon SD, McMurray JJ, Pfeffer MA, et al. *Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med* 2005;352:1071-80.
- 6) Fitzgerald GA. *Coxibs and cardiovascular disease. N Engl J Med* 2004;351:1709-11.
- 7) Hawk E, Viner JL. *The adenoma prevention with celecoxib and prevention of colorectal sporadic adenomatous polyps trials: stepping stones to progress. Cancer Epidemiol Biomarkers Prev* 2007;16:185-7.
- 8) ADAPT Research Group. *Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). PLoS Clin Trials* 2006;1:e33.
- 9) Chae SC. *Antiplatelet agents in high-risk patients with coronary artery disease. Korean Circ J* 2004;34:23-7.
- 10) Kim SS, Jeong MH, Sim DS, et al. *Very late thrombosis of a drug-eluting stent after discontinuation of dual antiplatelet therapy in a patient treated with both drug-eluting and bare-metal stents. Korean Circ J* 2009;39:205-8.
- 11) Park JC, Jeong MH, Kim JH, et al. *Clinical characteristics of coronary interventions in old aged patients. Korean Circ J* 1998;28:256-61.
- 12) Fiorina P, Perseghin G, De Cobelli F, et al. *Altered kidney graft high-energy phosphate metabolism in kidney-transplanted endstage renal disease type 1 diabetic patients: a cross-sectional analysis of the effect of kidney alone and kidney-pancreas transplantation. Diabetes Care* 2007;30:597-603.
- 13) McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, Fitzgerald GA. *Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci U S A* 1999;96:272-7.
- 14) Fitzgerald GA, Patrono C. *The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med* 2001;345:433-42.
- 15) Arrebola MM, De la Cruz JP, Villalobos MA, Pinacho A, Guerrero A, Sanchez de la Cuesta F. *In vitro effects of clopidogrel on the platelet-subendothelium interaction, platelet thromboxane and endothelial prostacyclin production, and nitric oxide synthesis. J Cardiovasc Pharmacol* 2004;43:74-82.
- 16) Leese PT, Hubbard RC, Karim A, Isakson PC, Yu SS, Geis GS. *Effects of celecoxib, a novel cyclooxygenase-2 inhibitor, on platelet function in healthy adults: a randomized, controlled trial. J Clin Pharmacol* 2000;40:124-32.
- 17) Van Ryn J, Kink-Eiband M, Kuritsch I, et al. *Meloxicam does not affect the antiplatelet effect of aspirin in healthy male and female volunteers. J Clin Pharmacol* 2004;44:777-84.
- 18) Wilner KD, Rushing M, Walden C, et al. *Celecoxib does not affect the antiplatelet activity of aspirin in healthy volunteers. J Clin Pharmacol* 2002;42:1027-30.
- 19) Renda G, Tacconelli S, Capone ML, et al. *Celecoxib, ibuprofen, and the antiplatelet effect of aspirin in patients with osteoarthritis and ischemic heart disease. Clin Pharmacol Ther* 2006;80:264-74.
- 20) Yang HM, Kim HS, Park KW, et al. *Celecoxib, a cyclooxygenase-2 inhibitor, reduces neointimal hyperplasia through inhibition of Akt signaling. Circulation* 2004;110:301-8.
- 21) Wang K, Tarakji K, Zhou Z, et al. *Celecoxib, a selective cyclooxygenase-2 inhibitor, decreases monocyte chemoattractant protein 1 expression and neointimal hyperplasia in the rabbit atherosclerotic balloon injury model. J Cardiovasc Pharmacol* 2005;45:61-7.
- 22) Steffel J, Hermann M, Greutert H, et al. *Celecoxib decreases endothelial tissue factor expression through inhibition of c-Jun terminal NH2 kinase phosphorylation. Circulation* 2005;111:1685-9.
- 23) Nieswandt B, Watson SP. *Platelet-collagen interaction: is GPVI the central receptor? Blood* 2003;102:449-61.
- 24) Solomon SD, Wittes J, Finn PV, et al. *Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: the cross trial safety analysis. Circulation* 2008;117:2104-13.
- 25) McGettigan P, Henry D. *Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA* 2006;296:1633-44.
- 26) White WB, West CR, Borer JS, et al. *Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials. Am J Cardiol* 2007;99:91-8.
- 27) Johnsen SP, Larsson H, Tarone RE, et al. *Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAIDs: a population-based case-control study. Arch Intern Med* 2005;165:978-84.
- 28) Belton O, Byrne D, Kearney D, Leahy A, Fitzgerald DJ. *Cyclooxygenase-1 and -2-dependent prostacyclin formation in patients with atherosclerosis. Circulation* 2000;102:840-5.
- 29) Kobayashi T, Tahara Y, Matsumoto M, et al. *Roles of thromboxane A(2) and prostacyclin in the development of atherosclerosis in apoE-deficient mice. J Clin Invest* 2004;114:784-94.
- 30) Antman EM, DeMets D, Loscalzo J. *Cyclooxygenase inhibition and cardiovascular risk. Circulation* 2005;112:759-70.