

Inhibition of Platelet Aggregation by Combined Therapy with Aspirin and Cilostazol after Off-Pump Coronary Artery Bypass Surgery

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Background: Although off-pump coronary artery bypass (OPCAB) has become an increasingly common surgical procedure, recent concerns have been raised regarding the existence of a hypercoagulable or prothrombotic state associated with OPCAB. To determine the optimal antiplatelet regimen after OPCAB, we investigated the effects of aspirin alone and of combined therapy with aspirin + cilostazol on platelet aggregation in patients after OPCAB. **Material and Methods:** Twenty patients scheduled to undergo OPCAB were randomized to one of two antiplatelet regimens: aspirin alone ($n = 10$) and aspirin + cilostazol ($n = 10$). Antiplatelet agents had not been received for at least 1 week before surgery and were initiated on the afternoon of postoperative day 1. Platelet aggregability and hemostatic parameters were evaluated at four time points: before and 3, 7, and 14 days after OPCAB. We measured agonist- and shear stress-induced platelet aggregation (SIPA) using a modified cone-plate viscometer. **Results:** No complications resulting from postoperative antiplatelet therapy-related bleeding were seen in either group. Collagen- and arachidonate-induced platelet aggregation and SIPA were significantly inhibited in the aspirin + cilostazol group compared with the aspirin-alone group (collagen- and arachidonate-induced aggregation, $p < 0.0001$; SIPA, $p = 0.0367$). Adding cilostazol to aspirin augmented the inhibitory effects on platelet aggregation induced by collagen and arachidonate. adenosine diphosphate (ADP)-induced platelet aggregation tended to be inhibited in the aspirin + cilostazol group compared with the aspirin-alone group ($p = 0.0534$).

Conclusion: The results of this study suggest that combined therapy with aspirin + cilostazol is more effective than aspirin monotherapy in reducing platelet aggregation in patients after OPCAB. This combination therapy may represent a new therapeutic option for an anti-thrombotic regimen in patients after OPCAB. (*Ann Thorac Cardiovasc Surg* 2008; 14: 230–237)

Key words: platelet aggregation, antiplatelet drug, off-pump coronary artery bypass surgery, cardiopulmonary bypass

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Introduction

Off-pump coronary artery bypass (OPCAB) has become an increasingly common surgical procedure with proven short- and midterm efficacy and safety.^{1,2)} The main advantages of OPCAB are the opportunity to avoid the use of cardiopulmonary bypass (CPB) with its damaging effects and to improve and expedite patient

recovery. Furthermore, after OPCAB, hemostasis is preserved and postoperative bleeding is significantly reduced compared with procedures using CPB.³⁾ However, recent concerns have been raised regarding the existence of a hypercoagulable or prothrombotic state associated with OPCAB, which could increase the risk of perioperative venous and arterial thrombosis and potentially endanger the patency of coronary anastomoses.⁴⁻⁷⁾

Antiplatelet therapy is an essential part of management therapy for patients undergoing coronary artery bypass surgery. Aspirin has been shown to effectively increase survival and reduce morbidity in patients with ischemic heart disease.⁸⁾ In particular, the beneficial effects of aspirin in the prevention of graft occlusion have been well established in patients undergoing conventional on-pump coronary artery bypass.⁹⁾ However, more aggressive postoperative antithrombotic therapy has been suggested to prevent procoagulant activity in patients after OPCAB,¹⁰⁾ and efficacy in this regard has been reported for combined therapy with aspirin and clopidogrel, an adenosine diphosphate (ADP) receptor antagonist.¹⁰⁾

Cilostazol, a specific inhibitor of cyclic adenosine monophosphate (cAMP) phosphodiesterase III, has both an antiplatelet function and vasodilating effects.¹¹⁾ It has been shown to be effective in the treatment of patients with intermittent claudication¹²⁾ and in the secondary prevention of stroke.¹³⁾ It has also been reported that cilostazol prevents the occurrence of restenosis after coronary angioplasty and stenting.^{14,15)} Furthermore, it was demonstrated that combined therapy with aspirin + cilostazol inhibited increased platelet aggregability in patients with acute myocardial infarction undergoing primary coronary angioplasty compared with aspirin alone.¹⁶⁾ Interestingly, cilostazol added to aspirin does not alter the bleeding time compared with aspirin alone, whereas clopidogrel added to aspirin prolongs the bleeding time compared with either agent alone.¹⁷⁾

With the increased use of OPCAB, it is necessary to determine the optimal postoperative antiplatelet regimen. Therefore in the present study, we compared the effects of aspirin alone and of a combined therapy with aspirin + cilostazol on platelet aggregation in patients after OPCAB.

Material and Methods

Subjects and study protocol

The subjects for this study were 20 Japanese patients, scheduled to undergo OPCAB at Mie University Hospital, who had not been receiving aspirin or other agents known to alter platelet function for at least 1 week prior to surgery. The study was approved by the Ethics Committee of Mie University, and written informed consent was obtained from each patient.

All patients were randomly assigned to one of two treatment groups, each comprising 10 patients: an aspirin-alone (100 mg/day) group and an aspirin (100 mg/day) + cilostazol (200 mg/day) group. Exclusion criteria were the presence of any associated cardiac disease requiring surgical treatment, including the use of CPB (e.g., left ventricular aneurysm or valvular disease), myocardial infarction either evolving or acute (within 48 h) or recent (within 2 weeks), and severe depressed ventricular function (ejection fraction: <35%). The preoperative use of intravenous heparin was also considered an exclusion criterion.

The OPCAB surgical technique was standardized with the use of the Octopus Tissue Stabilizer (Medtronic, Inc., Minneapolis, MN). In all patients, a full midline sternotomy was performed, and the left internal mammary artery was harvested, together with additional graft material (saphenous vein and/or radial artery). The patients were heparinized for an activated clotting time (ACT) of more than 300 s, and protamine was administered after the procedure until ACT returned to about 150 s. Mediastinal and pleural drains were inserted before chest closure and left in situ until drainage was less than 20 mL during 2 consecutive hours after a period of 18 h.

Administration of the antiplatelet drugs (aspirin alone or aspirin + cilostazol) was begun on the afternoon of postoperative day 1 according to the protocol. No other anticoagulant drugs were administered after surgery.

Blood sampling

Blood samples were carefully taken from a peripheral vein at four time points: (a) preoperative (but after induction of anesthesia), (b) 3 days, (c) 7 days, and (d) 14 days after surgery. Blood was mixed with 3.8% sodium citrate solution at a ratio of 10:1 (v/v). Platelet-rich plasma was prepared by centrifugation at 900 rpm for 15 min at room temperature. To standardize the aggregation

Table 1. Patient background characteristics

	ASA (n = 10)	ASA + CIL (n = 10)	p value
Age (year)	64.2 ± 9.8	67.7 ± 8.8	0.412
Male	10	9	1.00
Coronary risk factors			
Cigarette smoking	5 (50%)	6 (60%)	1.00
Diabetes mellitus	4 (40%)	3 (30%)	1.00
Systemic hypertension	6 (60%)	8 (80%)	0.682
Hypercholesterolemia	4 (40%)	4 (40%)	1.00
Number of bypasses	2.2 ± 0.9	2.0 ± 0.8	0.613
Graft patency	100%	100%	1.00
CVA	2 (20%)	2 (20%)	1.00
ASO	1 (10%)	2 (20%)	1.00

CVA, cerebral vascular accident; ASO, arteriosclerosis obliterans; ASA, aspirin; CIL, cilostazol.

experiments, platelet count was adjusted to $3 \times 10^5 \mu\text{L}$ using homologous platelet-poor plasma obtained by centrifuging the blood at 3,700 rpm for 8 min. The aggregation experiments were completed within 3 to 4 hours after blood sampling.

Measurement of platelet aggregation

Agonist-induced platelet aggregation was monitored photometrically at 37°C by the turbidimetric method using an aggregometer (AG-10, Kowa, Tokyo, Japan), as previously described.¹⁸⁾ The agonists used were 2.3 μM ADP (Sigma, St. Louis, MO), 1.2 $\mu\text{g/mL}$ of collagen (Nycomed, Munich, Germany), and 0.83 mM sodium arachidonate (Sigma). Continuous monitoring of shear stress-induced platelet aggregation (SIPA) was performed by a turbidimetric technique using a modified cone-plate viscometer, as previously described.¹⁹⁾ To measure SIPA, 400 μL of platelet-rich plasma was applied to the chamber, and the cone was rotated by a computer-controlled rotor motor that generated constant shear stress. Platelet-rich plasma was exposed to a gradient of 6 to 108 dyne/cm² over 6 min, and aggregation was continuously monitored from the start of application of shear force by recording the intensity of the light transmitted through the platelet-rich plasma. For each type of induced aggregation, the aggregation response was quantified as the maximum extent of aggregation.^{18,19)}

Plasma von Willebrand factor activity and fibrinogen level

Plasma von Willebrand factor level was measured by the aggregometer as the ristocetin cofactor activity using a von

Willebrand factor reagent test kit (Behring Diagnostics, Marburg, Germany).¹⁶⁾ Plasma von Willebrand factor activity (expressed as the percentage of the normal activity level) was read from a calibration curve constructed from serial dilutions of normal pooled plasma (100%) with isotonic saline to a final von Willebrand factor activity of 100%, 50%, 25%, 12.5%, and 6.3%. The normal value was $112.5\% \pm 18.7\%$ [mean \pm standard deviation (SD)]. Plasma fibrinogen level was measured by a clotting method using Multifibren U (Behringwerke, Marburg, Germany).

Statistical analysis

All data were expressed as the mean \pm SD and analyzed using StatView version 5.0 (SAS Institute, Cary, NC). Differences in the distribution of patient background characteristics between the two groups were examined by χ^2 test and Fisher's exact test. Differences between the two groups for repeatedly measured variables were analyzed by analysis of variance (ANOVA). One-way ANOVA was used to compare differences between the four measurement time points within each group. Two-tailed nonparametric tests were used to analyze differences between the two groups at single time points (Mann-Whitney U test) and changes within each group to detect time interactions (Wilcoxon test). A *p* value of <0.05 was considered statistically significant.

Results

Patient background characteristics are shown in Table 1. There were no significant differences in age or pre-operative risk factors between the two groups. All pa-

tients received antiplatelet drugs on the afternoon of postoperative day 1 according to the protocol, because no patients had chest tube drainage that would suggest the need for reexploration.

Effects of OPCAB on platelet count, von Willebrand factor activity, and plasma fibrinogen level

There were no significant differences in platelet count or von Willebrand factor activity between the aspirin-alone group and the aspirin + cilostazol group (Fig. 1). Platelet count transiently decreased at postoperative day 3, tended to increase at day 7, and significantly increased at day 14 in both treatment groups compared with the preoperative platelet count (Fig. 1A). Plasma von Willebrand factor activity significantly increased at postoperative day 3 in both treatment groups compared with the preoperative activity, whereas no significant differences were observed at days 7 and 14 (Fig. 1B). Plasma fibrinogen level significantly increased at days 3, 7, and 14 in both treatment groups compared with the preoperative level (Fig. 1C).

Effects of antiplatelet therapy on agonist-induced platelet aggregation

Treatment with aspirin alone showed a statistically significant inhibitory effect on collagen-induced platelet aggregation at postoperative days 7 and 14 (Fig. 2A). However, combined therapy with aspirin + cilostazol showed significant inhibition of collagen-induced aggregation from postoperative day 3, and the inhibitory effect in the aspirin + cilostazol group was significantly greater than that in the aspirin-alone group ($p < 0.0001$). These results indicated that cilostazol augmented the inhibitory effect of aspirin on collagen-induced platelet aggregation.

Arachidonate-induced aggregation was also significantly inhibited in the combined therapy group compared with the aspirin-alone group ($p < 0.0001$), though there were no significant differences between the preoperative value and the values at days 3 and 7 for aspirin + cilostazol therapy (Fig. 2B).

ADP-induced aggregation tended to be enhanced after OPCAB in the aspirin-alone group ($p = 0.0766$). However, ADP-induced aggregation tended to be inhibited, though not significantly ($p = 0.0534$), in the aspirin + cilostazol group compared with the aspirin-alone group (Fig. 2C), and at day 14 it was significantly lower in the aspirin + cilostazol group than in the aspirin-alone group ($p = 0.0211$).

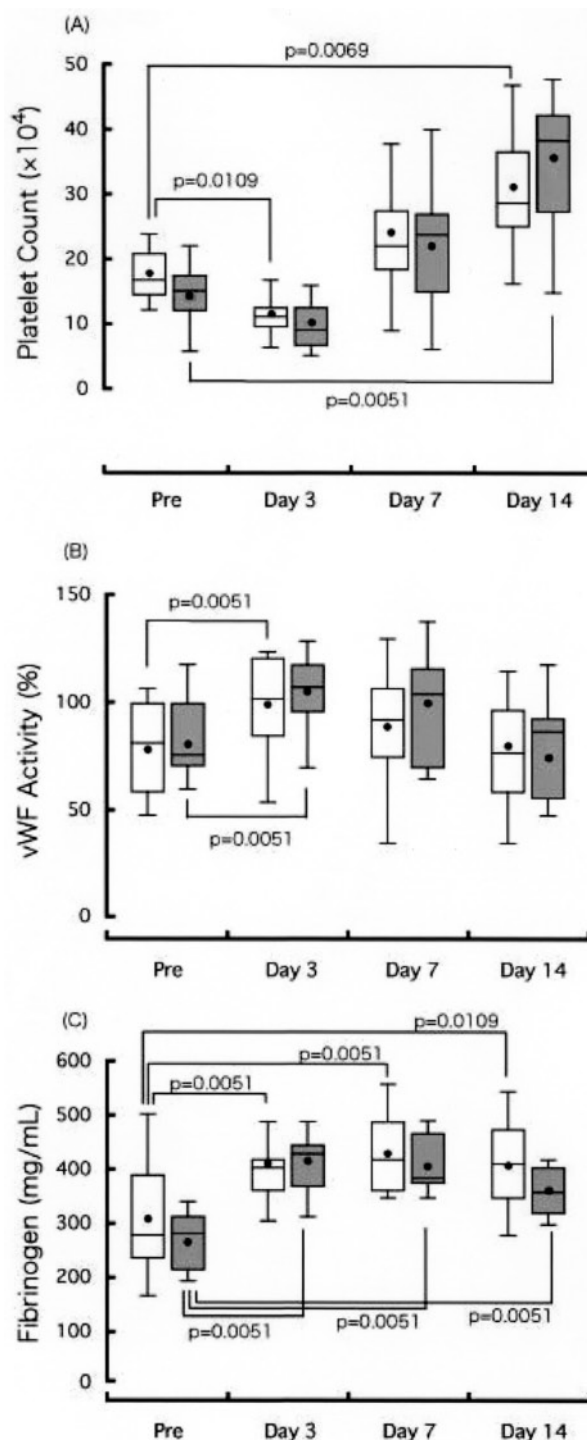


Fig. 1. Effects of aspirin alone (white boxes) and aspirin + cilostazol (black boxes) on platelet count (A), plasma von Willebrand factor (vWF) activity (B), and plasma fibrinogen level (C) in patients after OPCAB.

Box-and-whisker plots show mean (black circles) and median (horizontal lines) values, 25th and 75th percentiles (boxes), and 10th and 90th percentiles (error bars). Pre, preoperatively; Day 3, 3 days after surgery; Day 7, 7 days after surgery; Day 14, 14 days after surgery.

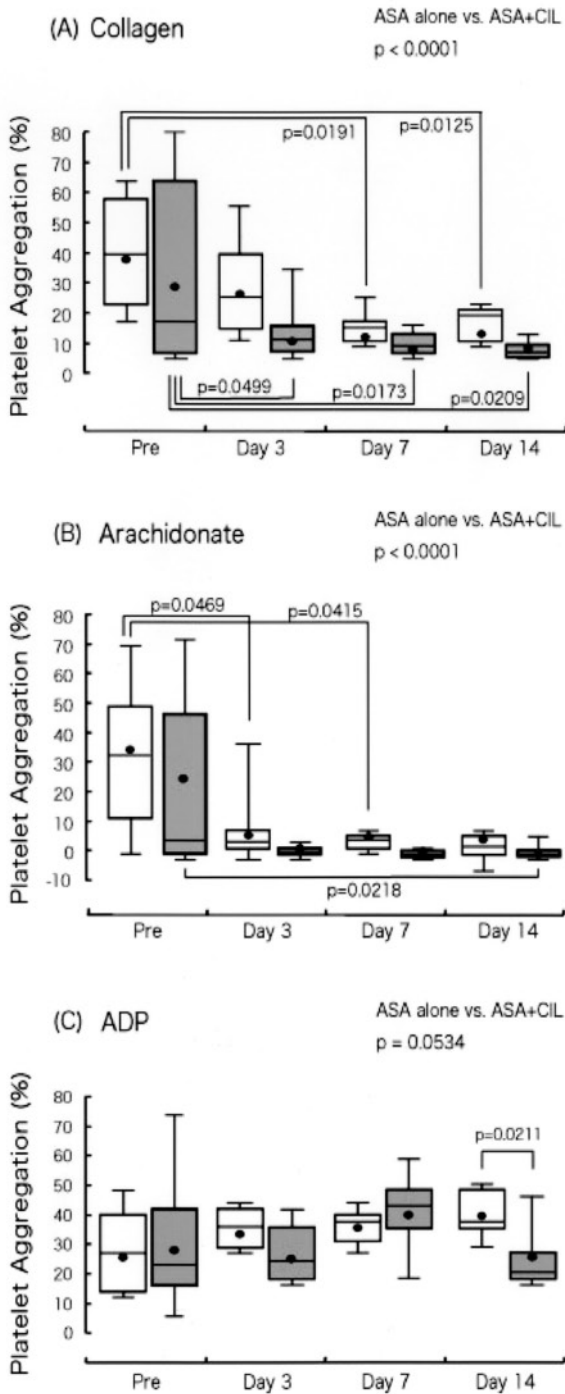


Fig. 2. Effects of aspirin alone (white boxes) and aspirin + cilostazol (black boxes) on platelet aggregation induced by collagen (A), arachidonate (B), and ADP (C) in patients after OPCAB. Box-and-whisker plots show mean (black circles) and median (horizontal lines) values, 25th and 75th percentiles (boxes), and 10th and 90th percentiles (error bars). Pre, preoperatively; Day 3, 3 days after surgery; Day 7, 7 days after surgery; Day 14, 14 days after surgery; ASA, aspirin; CIL, cilostazol.

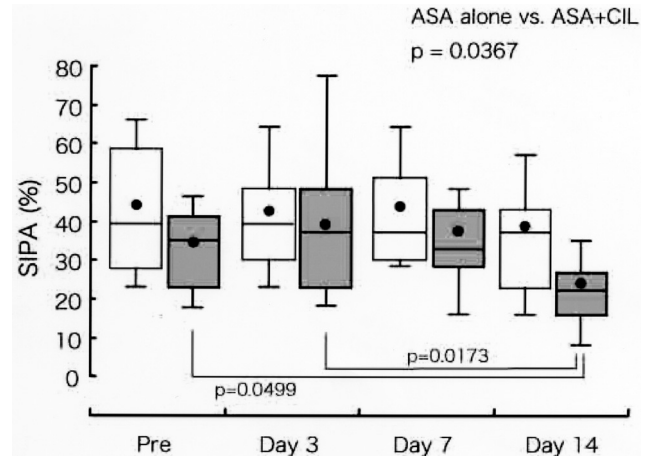


Fig. 3. Effects of aspirin alone (white boxes) and aspirin + cilostazol (black boxes) on SIPA in patients after OPCAB. Box-and-whisker plots show mean (black circles) and median (horizontal lines) values, 25th and 75th percentiles (boxes), and 10th and 90th percentiles (error bars). Pre, preoperatively; Day 3, 3 days after surgery; Day 7, 7 days after surgery; Day 14, 14 days after surgery; ASA, aspirin; CIL, cilostazol.

Effect of antiplatelet therapy on SIPA

In the aspirin + cilostazol group, SIPA was significantly inhibited after OPCAB compared with the aspirin-alone group ($p = 0.0367$) (Fig. 3). Moreover, the combination of aspirin + cilostazol significantly inhibited SIPA at day 14 compared with the preoperative value ($p = 0.0499$) and with the value at postoperative day 3 ($p = 0.0173$).

Postoperative complications

There were no in-hospital deaths, reexplorations for bleeding, gastrointestinal bleeding, stroke, or myocardial infarctions in either group. In the aspirin + cilostazol group, the drains were left in situ until postoperative day 2 in 3 patients with no increase in blood loss resulting from antiplatelet therapy being observed.

Discussion

Traditionally, patients undergoing coronary artery bypass operations by CPB are not considered at risk of venous or arterial thromboembolic complications, since CPB induces clotting disorders and platelet dysfunction.²⁰ Therefore aggressive anticoagulant prophylaxis is generally not recommended during the early postop-

erative period, and aspirin has been the most commonly used postoperative antiplatelet drug. However, because OPCAB lacks the hemostasis-impairing effect of CPB, different postoperative prophylaxis strategies for thrombotic events should be considered.^{7,10} Furthermore, aspirin appears to not always be an effective inhibitor of platelet function, because considerable individual variations in its antiplatelet effects, referred to as "aspirin resistance," have been widely known. Zimmermann et al. reported that aspirin resistance develops in many patients who undergo coronary artery bypass grafting.²¹ In the present study we focused on platelet function in patients undergoing OPCAB and investigated the effects of aspirin monotherapy and combined therapy with aspirin + cilostazol on platelet aggregation during the early postoperative period. A low dose of aspirin inhibits the production of thromboxane A₂ by irreversibly acetylating cyclooxygenase in the platelets. Based on this mechanism, aspirin inhibits platelet aggregation induced by collagen and arachidonate. On the other hand, cilostazol is a specific inhibitor of cAMP phosphodiesterase III, which is strongly expressed in platelets and vascular smooth muscle cells.¹¹ Cilostazol inhibits platelet aggregation induced by ADP as well as by collagen and arachidonate.²² SIPA is also significantly inhibited by cilostazol.²³

In the present study we found that platelet counts were decreased at postoperative day 3 and progressively increased at days 7 and 14 compared with the preoperative count. The increase in platelet count during the postoperative period indicated increased platelet turnover, suggesting the early recovery of platelet aggregability. Plasma von Willebrand factor is derived primarily from endothelial cells, and increased plasma levels are considered to reflect the extent of vascular damage.¹⁶ We found significant increases in von Willebrand factor activity on postoperative day 3 in both groups compared with the preoperative activity. This result may also indicate the early recovery of von Willebrand factor-dependent platelet functions such as platelet adhesion and SIPA.

Our data showed that aspirin suppressed platelet aggregation induced by collagen and arachidonate after OPCAB, and that the addition of cilostazol to aspirin significantly augmented that inhibitory effect. These results may reflect a synergistic effect of two different types of antiplatelet drugs with different mechanisms for inhibiting platelet aggregation.

Aspirin monotherapy did not inhibit ADP-induced

platelet aggregation or SIPA, as previously reported in patients with cardiovascular disease.¹⁶ Rather, ADP-induced platelet aggregation tended to increase postoperatively in the aspirin-alone group. We demonstrated that combined therapy with aspirin + cilostazol was effective in reducing ADP-induced platelet aggregation and SIPA in patients after OPCAB. Significant suppression of platelet aggregability by this combined therapy compared with aspirin alone has been demonstrated in patients with acute myocardial infarction after coronary angioplasty.¹⁶ The present study therefore confirmed the inhibitory effects of combined therapy with aspirin + cilostazol on platelet aggregation in patients undergoing OPCAB.

Furthermore, besides its antithrombotic and vasodilating effects, cilostazol also has an inhibitory effect on vascular smooth muscle cell proliferation.²⁴ Recent clinical studies have demonstrated that cilostazol is useful in preventing restenosis after coronary intervention by suppressing intimal hyperplasia.^{14,15} This effect of cilostazol may potentially suppress intimal hyperplasia at anastomotic sites of coronary artery bypass grafting, as previously shown in experimental studies.²⁵

It has been reported that combined therapy with aspirin and clopidogrel, a potent ADP receptor antagonist, was effective as an aggressive postoperative antithrombotic therapy after OPCAB.¹⁰ However, Wilhite et al. reported that combined therapy with aspirin and clopidogrel in patients with peripheral arterial occlusive disease resulted in a significant increase in bleeding time when compared with either drug alone, whereas cilostazol added to aspirin did not alter bleeding time compared with aspirin alone.¹⁷ In fact, in the current study there were no complications resulting from postoperative antiplatelet therapy-related bleeding in either group, indicating that combination therapy with aspirin + cilostazol is a safe antithrombotic regimen in patients undergoing OPCAB.

There were some limitations to our study. First, because the average life span of platelets is 7 days, the administration of aspirin or other agents known to alter platelet function was stopped at least 1 week before surgery. Although no statistically significant differences in preoperative collagen- and arachidonate-induced platelet aggregation were seen between the two treatment groups, the preoperative values in each group showed large variations. Because this may indicate a difference in the platelet life span among individuals, it would be necessary to stop the administration of aspirin or other

agents known to alter platelet function for longer than 1 week before surgery to obtain preoperative values with less variation. Second, this was a prospective randomized investigation, but not a double-blind study, and a larger, double-blind multicenter trial is required to confirm our preliminary results.

In conclusion, the results of this study suggest that combined therapy with aspirin + cilostazol is more effective than aspirin monotherapy in reducing platelet aggregation in patients after OPCAB, and this combination therapy may represent a new therapeutic option for an antithrombotic regimen in patients after OPCAB.

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References

- van Dijk D, Nierich AP, Jansen EW, Nathoe HM, Suyker WJ, et al. Early outcome after off-pump versus on-pump coronary bypass surgery: results from a randomized study. *Circulation* 2001; **104**: 1761–6.
- Sabik JF, Blackstone EH, Lytle BW, Houghtaling PL, Gillinov AM, et al. Equivalent midterm outcomes after off-pump and on-pump coronary surgery. *J Thorac Cardiovasc Surg* 2004; **127**: 142–8.
- Puskas JD, Williams WH, Duke PG, Staples JR, Glas KE, et al. Off-pump coronary artery bypass grafting provides complete revascularization with reduced myocardial injury, transfusion requirements, and length of stay: a prospective randomized comparison of two hundred unselected patients undergoing off-pump versus conventional coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2003; **125**: 797–808.
- Mariani MA, Gu YJ, Boonstra PW, Grandjean JG, van Oeveren W, et al. Procoagulant activity after off-pump coronary operation: is the current anticoagulation adequate? *Ann Thorac Surg* 1999; **67**: 1370–5.
- Cartier R, Robitaille D. Thrombotic complications in beating heart operations. *J Thorac Cardiovasc Surg* 2001; **121**: 920–2.
- Kurlansky PA. Is there a hypercoagulable state after off-pump coronary artery bypass surgery? What do we know and what can we do? *J Thorac Cardiovasc Surg* 2003; **126**: 7–10.
- Quigley RL, Fried DW, Pym J, Highbloom RY. Off-pump coronary artery bypass surgery may produce a hypercoagulable patient. *Heart Surg Forum* 2003; **6**: 94–7.
- Gum PA, Thamilarasan M, Watanabe J, Blackstone EH, Lauer MS. Aspirin use and all-cause mortality among patients being evaluated for known or suspected coronary artery disease: a propensity analysis. *JAMA* 2001; **286**: 1187–94.
- Gavaghan TP, GebSKI V, Baron DW. Immediate post-operative aspirin improves vein graft patency early and late after coronary artery bypass graft surgery. A placebo-controlled, randomized study. *Circulation* 1991; **83**: 1526–33.
- D'Ancona G, Donias HW, Karamanoukian RL, Bergsland J, Karamanoukian HL. OPCAB therapy survey: off-pump clopidogrel, aspirin or both therapy survey. *Heart Surg Forum* 2001; **4**: 354–8.
- Tanaka T, Ishikawa T, Hagiwara M, Onoda K, Itoh H, et al. Effects of cilostazol, a selective cAMP phosphodiesterase inhibitor, on the contraction of vascular smooth muscle. *Pharmacology* 1988; **36**: 313–20.
- Dawson DL, Cutler BS, Meissner MH, Strandness DE Jr. Cilostazol has beneficial effects in treatment of intermittent claudication: results from a multicenter, randomized, prospective, double-blind trial. *Circulation* 1998; **98**: 678–86.
- Gotoh F, Tohgi H, Hirai S, Terashi A, Fukuuchi, Y, et al. Cilostazol stroke prevention study: a placebo-controlled double-blind trial for secondary prevention of cerebral infarction. *J Stroke Cerebrovasc Dis* 2000; **9**: 147–57.
- Tsuchikane E, Fukuhara A, Kobayashi T, Kirino M, Yamasaki K, et al. Impact of cilostazol on restenosis after percutaneous coronary balloon angioplasty. *Circulation* 1999; **100**: 21–6.
- Douglas JS Jr, Holmes DR Jr, Kereiakes DJ, Grines CL, Block E, et al. Cilostazol for Restenosis Trial (CREST) Investigators. Coronary stent restenosis in patients treated with cilostazol. *Circulation* 2005; **112**: 2826–32.
- Tanigawa T, Nishikawa M, Kitai T, Ueda Y, Okinaka T, et al. Increased platelet aggregability in response to shear stress in acute myocardial infarction and its inhibition by combined therapy with aspirin and cilostazol after coronary intervention. *Am J Cardiol* 2000; **85**: 1054–9.
- Wilhite DB, Comerota AJ, Schmieder FA, Throm RC, Gaughan JP, et al. Managing PAD with multiple platelet inhibitors: the effect of combination therapy on bleeding time. *J Vasc Surg* 2003; **38**: 710–3.
- Nishikawa M, Hidaka H. Role of calmodulin in platelet aggregation. Structure-activity relationship of calmodulin antagonists. *J Clin Invest* 1982; **69**: 1348–55.
- Ikeda Y, Handa M, Kawano K, Kamata T, Murata M, et al. The role of von Willebrand factor and fibrinogen in platelet aggregation under varying shear stress. *J Clin Invest* 1991; **87**: 1234–40.
- Tabuchi N, de Haan J, van Oeveren W. Rapid recovery of platelet function after cardiopulmonary bypass. *Blood* 1993; **82**: 2930–1.
- Zimmermann N, Wenk A, Kim U, Kienzle P, Weber

- AA, et al. Functional and biochemical evaluation of platelet aspirin resistance after coronary artery bypass surgery. *Circulation* 2003; **108**: 542–7.
22. Ikeda Y, Kikuchi M, Murakami H, Satoh K, Murata M, et al. Comparison of the inhibitory effects of cilostazol, acetylsalicylic acid and ticlopidine on platelet functions ex vivo. Randomized, double-blind cross-over study. *Arzneimittelforschung* 1987; **37**: 563–6.
23. Minami N, Suzuki Y, Yamamoto M, Kihira H, Imai E, et al. Inhibition of shear stress-induced platelet aggregation by cilostazol, a specific inhibitor of cGMP-inhibited phosphodiesterase, in vitro and ex vivo. *Life Sci* 1997; **61**: PL383–9.
24. Takahashi S, Oida K, Fujiwara R, Maeda H, Hayashi S, et al. Effect of cilostazol, a cyclic AMP phosphodiesterase inhibitor, on the proliferation of rat aortic smooth muscle cells in culture. *J Cardiovasc Pharmacol* 1992; **20**: 900–6.
25. Takai S, Jin D, Nishimoto M, Sakaguchi M, Kirimura K, et al. Cilostazol suppresses intimal formation in dog grafted veins with reduction of angiotensin II-forming enzymes. *Eur J Pharmacol* 2001; **411**: 301–4.