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Original Report

Platelet and Leukocyte Deactivation After Intracoronary Stent Placement in Patients Receiving Combined Antiplatelet Therapy

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Summary: Activated platelets and leukocytes have been demonstrated to play a role in the development of stent thrombosis, and coronary angioplasty has been shown to result in activation of platelets, leukocytes, and endothelial cells. We aimed to evaluate the effects of intracoronary stent placement and aspirin plus ticlopidine treatment on platelets, leukocytes, and endothelial cells via observing the serial changes in the circulating soluble forms of adhesion molecules in 54 patients with coronary artery disease, who had elective coronary angioplasty and stent implantation for a single lesion of the left anterior descending artery. After stent placement, intravenous heparin infusion was administered only for 24 hours, and aspirin plus ticlopidine treatment was applied for 1 month. Venous blood samples were drawn before stent placement, and repeated 24 and 48 hours after the procedure. Patients were excluded if they had had recent cardiovascular events or any illness that might influence platelet, leukocyte, and endothelial cell function. The plasma level of sL-selectin was significantly decreased 48 hours after coronary stenting (636 ± 110 ng/mL vs 567 ± 93 ng/mL; $P = 0.001$, respectively). Likewise, the plasma level of sP-selectin was also decreased significantly 48 hours after the procedure (260 ± 61 ng/mL vs 233 ± 83 ng/mL, $P = 0.01$). The sE-selectin level was found to be significantly increased 24 hours (31 ± 9 ng/mL vs 39 ± 12 ng/mL, $P = 0.0001$) and 48hours(31 ± 9 ng/mL vs 42 ± 15 ng/mL, $P = 0.001$) after coronary stenting. The results of our study suggest that significant platelet and leukocyte deactivation take place in patients treated with combined antiplatelet therapy after stenting; endothelial cell activation also occurs during this treatment. **Key Words:** Adhesion molecules—Intracoronary stents—Leukocytes—Platelets—Ticlopidine.

Elective implantation of intracoronary stents was shown to improve early and long-term clinical success of coronary angioplasty in selected patients (1,2). Although two limitations of stent implantation are acute and subacute stent thrombosis, the incidence of thrombosis declined after the improvement of implantation techniques and pharmacological interventions of procedure protocols. Accordingly, the patients were put on antithrombotic prophylaxis via combined antiplatelet therapy with aspirin and ticlopidine after stenting (3,4).

Activated platelets and leukocytes have been shown to play central roles in the development of thrombosis (5–10). Selectins are important adhesion molecules in cell-to-cell interaction, involving circulating neutrophils and monocytes in the blood and the association with endothelium and activated platelets and leukocytes at the sites of tissue injury (11–13). P-selectin, which is found in the α-granules of platelets and Weibel-Palade bodies of endothelial cells, is redistributed to the cell surface upon cell stimulation (14–16). P-selectin mediates adhesion of monocytes and neutrophils. L-selectin, which is constitutively expressed on leukocytes, is a ligand for P-selectin and E-selectin and mediates neutrophil-neutrophil cells, neutrophil-endothelial cells, and neutrophil-platelet interactions (17,18). E-selectin is expressed on activated endothelial cells and mediates adhesion of leukocyte to endothelial cells (19,20). Because the adhesion molecules are shed from activated cells, increased levels of circulating soluble P-selectin, E-selectin, and L-selectin can be used as activation markers of platelets, endothelial cells, and leukocytes, respectively (21–24).

Coronary angioplasty has been shown to result in activation of platelets, leukocytes, and endothelial cells, despite aspirin and anticoagulant therapy (4,6,7,25–31). Meanwhile, in patients receiving combined aspirin and

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ticlopidine therapy, platelet and leukocyte deactivation was shown (4,32). Accordingly, circulating soluble selectin levels after coronary stent placement were investigated to examine the effects of ticlopidine plus aspirin treatment and intracoronary stents on platelets, leukocytes, and endothelial cells.

MATERIALS AND METHODS

Study population

The study group consisted of 54 consecutive patients scheduled for elective one-vessel (left anterior descending) percutaneous transluminal coronary angioplasty and stent implantation. All patients had stable exertional angina and a positive exercise stress test, and also had significant proximal left anterior descending coronary artery stenosis (> %70), classified as either a type A or type B lesion. Patients had elective implantation of an uncoated AVE stent (AVE stent, Arterial Vascular Engineering Inc, Santa Rosa, CA) and uncoated NIR stent (Scimed, Boston Scientific Corporation, Galway, Ireland). All stents were implanted successfully immediately after angioplasty. All patients gave written informed consent.

Patients with recent myocardial infarction (< 6 weeks), unstable angina, small vessels (< 2.5mm), and coronary artery bypass grafting within 6 months were excluded. Patients with any illness known to influence adhesion molecule levels, including infections, diabetes mellitus, malignancy, chronic liver disease, renal insufficiency, and connective tissue disease, and patients taking antiinflammatory and anticoagulant drugs, were also excluded from the study.

Stent procedure and poststenting management of patients

Percutaneous transluminal coronary angioplasty was performed by use of standard procedures and via the femoral approach. After initial coronary angiography, 10,000 IU of intravenous unfractionated heparin was given just before the catheter system was inserted. The dilatation procedure was performed with multiple balloon inflations, using steerable nonperfusion balloon dilatation catheters ranging in diameter from 3.0 to 3.5 mm when inflated. None of the patients developed abrupt vessel closure, threatened closure, or dissection during coronary angioplasty. After balloon angioplasty, an uncoated AVE stent or NIR stent was placed in the patient. All stents used in the study were premounted.

After stent placement, intravenous heparin was infused for 24 hours at a rate of approximately 1000 IU/h to maintain an activated partial thromboplastin time (APTT) of between 80 and 100 seconds. All patients had been on long-term treatment with aspirin before entering the study and received an additional oral dose of 300 mg of aspirin on the morning of the procedure. Aspirin treatment was continued indefinitely. Ticlopidine treatment began on the day of intervention, just before the procedure, and continued in a dosage of 250 mg twice daily for 1 month. No patient received other anti-thrombotic treatment, including glycoprotein IIb/IIIa inhibitors, either during or after the procedure

Blood sampling

Blood samples for measurement of adhesion molecules were drawn from an antecubital vein before and 24 and 48 hours after the procedure, separated by centrifugation, and immediately frozen and stored at −80°C. Concentrations of sE-selectin, sP-selectin, and sL-selectin in stored plasma were measured with enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Abington, United Kingdom). The concentrations in plasma were expressed in ng/mL. Routine laboratory analysis was performed immediately using standard methods.

Statistical analysis

The distribution of numeric variables was examined by the Kolmogorow-Smirnow (KS) test. Because the KS test confirmed a normal distribution of the variables studied, i.e., E-selectin, P-selectin and L-selectin, parametric tests were used for the remainder of the statistical analysis. Time-dependent changes were tested via repeated measures analysis of variance (ANOVA). Significant results of repeated measures of ANOVA were compared post-hoc by a paired samples t test, with a significance level adjusted downwards to 0.017, i.e., the number of paired comparisons. Data were expressed as mean ± SD for numeric variables, and as n (%) for nominal variables. Except for paired comparisons following repeated measures of ANOVA, significant P values were assigned to be less than 0.05.

RESULTS

Study population

Fifty-four patients with significant proximal left anterior descending artery were enrolled in the study (41 men, 13 women; mean age, 56 ± 7 years). Although the group who had the AVE stent consisted of 28 patients, the group who had the NIR stent consisted of 26 patients. The major baseline and preprocedural laboratory variables of study patients, including the plasma soluble adhesion molecule levels, are shown in Table 1. Procedural characteristics, such as number of dilatations, maximum pressure of dilatations, total dilatation time, maximal duration of dilatations, and last-used balloon diameter were given in Table 2.

All stents were successfully deployed in all patients, and no angiographically detectable dissection was present. None of patients developed chest pain, echocardio-

TABLE 1. *Baseline clinical characteristics and preprocedural laboratory variables of the study patients*

Patients, *n*	54
Sex, M/F	41/13
Age, y, mean ± SD	53 ± 8.5
Prior PTCA, %	4
Coronary risk factors	
Hypertension, *n* (%)	27 (50)
Hypercholestrolemia, *n* (%)	22 (40)
Active smoking, *n* (%)	22 (40)
Family history, *n* (%)	16 (30)
Obesity, *n* (%)	5 (10)
Total cholesterol, mmol/L, mean ± SD	5.18 ± 1.26
Triglycerides, mmol/L, mean ± SD	3.47 ± 1.29
HDL cholesterol, mmol/L, mean ± SD	1.03 ± 0.23
LDL cholesterol, mmol/L, mean ± SD	3.62 ± 0.95
Leukocyte count, $\times 10^3/\mu L$, mean ± SD	7.296 ± 1.107
Platelet count, $\times 10^3/\mu L$, mean ± SD	217.741 ± 45.282

F, female; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M, male; PTCA, percutaneous transluminal coronary angioplasty; SD, standard deviation.

graph (ECG) changes, or cardiac enzyme elevation during the course of 48 hours of hospital stay after stent implantation. Exercise tests performed 1 month after the procedure resulted in negative scores in all patients. Therefore, no evaluated patients developed stent thrombosis within the 1-month observation period of the study.

Changes in the soluble adhesion molecule levels after stent placement

The serial changes in circulating sP-selectin, sE-selectin, and sL-selectin levels before and after stent implantation are shown in Table 3. The sP-selectin level was found to be significantly decreased 48 hours after stent implantation ($P = 0.01$) (Fig. 1).

Comparing the prestent sL-selectin concentrations to levels measured at hours 24 and 48 after stenting, significant decrease was found 48 hours after the procedure ($P = 0.001$) (Fig. 2). The level of sE-selectin was significantly increased 24 hours and 48 hours after stent implantation ($P = 0.0001$ and $P = 0.001$, respectively) (Table 4).

Comparison of adhesion molecules levels among patients with AVE stent and NIR stent before and after stent placement

Comparing the soluble P-selectin, sE-selectin, and sL-selectin levels measured before and after stent implantation between two stent groups, no significant difference was found (Table 4).

TABLE 2. *Procedural characteristics of the stent groups*

Stent length, mm	15.5 ± 4.4
Number of dilatations	3.5 ± 0.7
Maximum pressure of dilatations, atm	11.9 ± 1.8
Total dilatation time, s	164.7 ± 36.8
Maximum duration of dilatations, s	63.5 ± 12.6
Last used balloon diameter, mm	3.2 ± 2.8

Data are expressed as mean ± standard deviation.

TABLE 3. *Changes in the soluble adhesion molecule levels after stent placement*

	Before procedure	24 h after procedure	48 h after procedure
sP-selectin, ng/mL	260 ± 81	247 ± 99	233 ± 83*
sE-selectin, ng/mL	31 ± 9	39 ± 12†	42 ± 15‡
sL-selectin, ng/mL	636 ± 110	596 ± 90	567 ± 93‡

Values are expressed as mean ± standard deviation.
* P, 0.01; †P, 0.0001; ‡P, 0.001, versus baseline levels.

Relation between soluble adhesion molecules and stent placement procedures

No correlation was found between the soluble adhesion molecule levels measured 24 and 48 hours after stent placement and the procedural characteristics, such as number of dilatations, maximum pressure of dilatations, total dilatation time, maximal duration of dilatations, or last used balloon diameter.

DISCUSSION

The results of the present study demonstrate that the plasma levels of sP-selectin and sL-selectin decreased, whereas sE-selectin increased, after coronary stent implantation in patients receiving combined antiplatelet therapy.

Mechanical disruption in the atherosclerotic plaque during the dilatation of coronary stenosis with balloon angioplasty and stent implantation may lead to activation of platelets, endothelial cells, leukocytes, and the coagulation system (5,7–9). The foreign stent material itself also may contribute to alterations of platelet, leukocyte, and endothelial cell function and activation of comple-

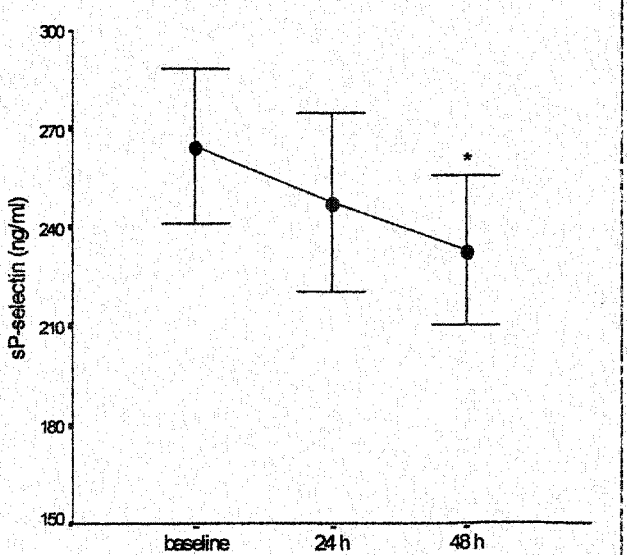

FIG. 1. Serial changes in circulating sP-selectin after coronary stenting. Data are mean ± standard deviation. *P = 0.01 versus baseline.

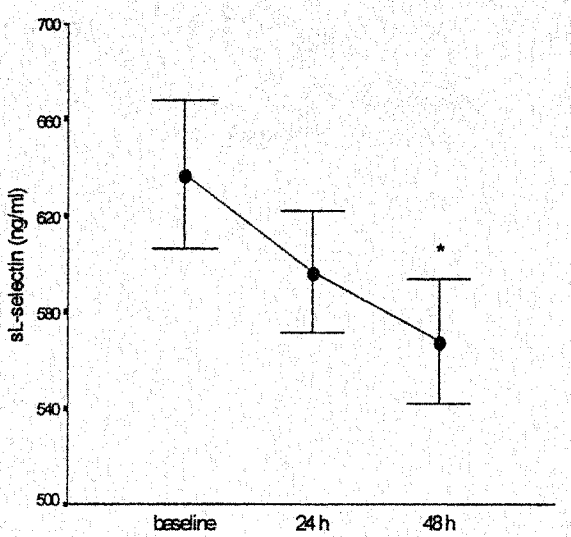

FIG. 2. Serial changes in circulating sL-selectin after coronary stenting. Data are mean ± SD. *P = 0.001 versus baseline.

ment and coagulation systems, and this may play an additional important role in the pathogenesis of stent thrombosis (33,34).

In previous studies, focusing on the platelet function after coronary angioplasty and stent implantation revealed platelet activation in patients receiving aspirin and heparin therapy (5–7,24–29). However, in recent studies, platelet deactivation was shown in patients taking combined aspirin and ticlopidine after stent placement (4,32,35). In accordance with these studies, we found that plasma sP-selectin levels decreased significantly after stent implantation in patients receiving combined antiplatelet therapy. Because ticlopidine is a potent antiplatelet drug and inhibits platelet functions in many steps, platelet deactivation found in the present study can be ascribed to the ticlopidine therapy.

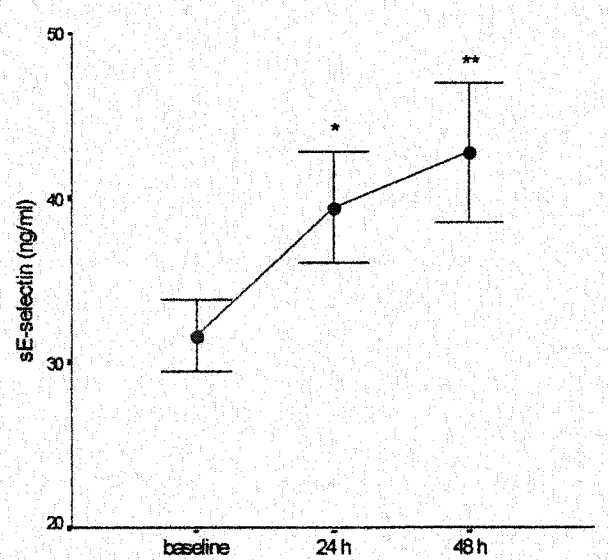

FIG. 3. Serial changes in circulating sE-selectin after coronary stenting. Data are mean ± SD. *P = 0.0001 versus baseline; **P = 0.001 versus baseline

Coronary angioplasty has been shown to result in leukocyte activation in patients receiving aspirin and heparin (24,26,29,31). In the present study, we found a significant decrease in the soluble L-selectin level after stenting in patients taking combined antiplatelet therapy. This result is consistent with the previous study that showed leukocyte deactivation in patients taking combined antiplatelet therapy after stent placement (32).

Activated leukocytes may play a significant role in the pathogenesis of thrombosis by activating several important pathways (9,10,36–38). Those cells initiate the extrinsic pathway of coagulation via surface expression of tissue factors. Moreover, activated leukocytes rapidly show enhanced surface expression of integrins that convert factor X to Xa, leading to fibrin formation. In addition, activated leukocytes release a variety of promotors of acute inflammatory response (39,40). Leukocytes also may initiate and potentiate platelet activation, which commonly occurs after coronary angioplasty as a result of arterial injury (41–43). Accordingly, the involvement of leukocytes in coronary artery thrombosis has been demonstrated. We found that combined antiplatelet therapy causes reduction of leukocyte activation; therefore, this may contribute to a decreased risk for thrombotic events after intracoronary stenting.

The potent inhibition of platelet function with combined antiplatelet therapy might be considered as a potential means of inhibiting detrimental systemic inflammatory response after intervention. Ticlopidine administration already has been shown to reduce plasma fibrinogen levels (44). The potential indirect anti-inflammatory effect of antiplatelet therapy might be one of the mechanisms for sL-selectin decrease after stenting.

Leukocyte–platelet association could contribute to the development of thrombotic processes, because platelets and leukocytes have been shown to influence each other functionally (41–43,45,46). Platelets adhere to leukocytes in an activation-dependent manner and modulate the activation state of leukocytes (47). Activated platelets adhere to leukocytes through P-selectin (45). P-selectin leads to the capture of circulating leukocytes into the area of tissue injury. As a result of our study, decreases in the circulating sP-selectin, reflecting platelet deactivation, could result in decreased binding of platelets to leukocytes, which potentially attenuates the inflammatory process and causes thrombogenesis. This observation might be one of the mechanisms for sL-selectin decrease after stenting.

In previous studies, sE-selectin levels were found to be increased after coronary balloon angioplasty (26,30). Balloon angioplasty and stent implantation mechanically disrupt the atherosclerotic plaque, and, consequently, produce endothelial injury. In our present study, the in-

TABLE 4. *Comparison of adhesion molecules levels among patients with AVE stent and NIR stent before and after stent placement*

	Before procedure		24 h after procedure		48 h after procedure	
	AVE stent	NIR stent	AVE stent	NIR stent	AVE stent	NIR stent
sP-selectin, ng/mL	262 ± 99	266 ± 65	242 ± 111	252 ± 86	227 ± 97	239 ± 67
sE-selectin, ng/mL	30 ± 8	33 ± 7	38 ± 14	40 ± 10	41 ± 18	43 ± 12
sL-selectin, ng/mL	653 ± 111	635 ± 126	603 ± 83	588 ± 99	573 ± 89	561 ± 100

Values are expressed as mean ± standard deviation.
None of the differences was found to be significant among two stent groups.

crease in sE-selectin levels after stent implantation could be caused by direct balloon-induced injury of vascular endothelial cells.

In conclusion, in patients receiving combined antiplatelet therapy (aspirin and ticlopidine), increased levels of soluble E-selectin and decreased levels of sL-selectin and sP-selectin were observed in the patient's peripheral circulation after coronary stenting. Our results indicate that combined antiplatelet therapy effectively depresses the activity of platelets and leukocytes, however, and does not affect endothelial cells. The beneficial effects of this therapy in preventing stent thrombosis might be caused by not only its antiplatelet effects but by antileukocyte effects as well. New agents that either inhibit endothelial cells directly, or inhibit endothelial cells via blockading the adhesion molecules, such as anti–E-selectin antibodies, should be developed to eliminate not only stent thrombosis, but also restenosis.

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