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Platelet function in pregnant women receiving aspirin and dipyridamole

Keiko Kinouchi[1], Tomio Fujita[2], Chie Narahara[2], and Seiji Kitamura[1]

Departments of [1] Anesthesiology and [2] Maternal Medicine, Osaka Medical Center and Research Institute for Maternal and Child Health, 840 Murodo-cho, Izumi, Osaka 594-1101, Japan

Abstract

Purpose. This study was undertaken to evaluate the hemostasis and coagulation profile of pregnant women receiving antiplatelet therapy with low-dose aspirin and dipyridamole for prevention of preeclampsia, intrauterine growth retardation, or pregnancy losses.

Methods. Twenty-three pregnant women who received antiplatelet therapy with combined aspirin (40 mg·day^{-1}) and dipyridamole (150 mg·day^{-1}) were enrolled in the study. Platelet aggregation and coagulation tests were performed before the start of aspirin and dipyridamole, during medication, and at 3 days and 6 days after cessation of medication.

Results. Collagen-induced platelet aggregation was decreased during medication (25 ± 26%, $P < 0.001$) and at 3 days after cessation of medication (46 ± 35%, $P < 0.001$) compared with that before the start of medication (89 ± 7%). ADP-induced platelet aggregation was decreased during medication compared with that before medication (66 ± 18% *vs* 92 ± 7%, $P < 0.001$). The platelet count, prothrombin time, activated partial thromboplastin time, bleeding time, and levels of fibrinogen and antithrombin III did not change over time. The blood loss of these patients during vaginal delivery and cesarean section did not differ from that of normal women during vaginal delivery and repeat cesarean section, respectively.

Conclusion. At the doses used in this study, aspirin and dipyridamole inhibited platelet aggregation for up to 3 days after cessation of medication. This abnormality of aggregation was not detected by the bleeding time and was not associated with clinically abnormal bleeding.

Key words Aspirin · Dipyridamole · Platelet aggregation · Pregnant women

Address correspondence to: K. Kinouchi
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Introduction

Antiplatelet therapy with low-dose aspirin, with or without dipyridamole, has been reported to be effective in the prevention of preeclampsia, intrauterine growth retardation (IUGR), and pregnancy losses, and its prophylactic use in patients at high risk has become increasingly popular [1–5]. Daily oral intake of aspirin and dipyridamole is usually started before pregnancy or in the first trimester and continued up to 30–37 weeks of gestation. These patients often end up with a preterm delivery or cesarean section during antiplatelet therapy or within a few days after the cessation of medication. It is important for anesthesiologists to know about possible bleeding tendencies while performing spinal or epidural anesthesia in these patients. In this study, the hemostasis and coagulation profile of pregnant women receiving low-dose aspirin and dipyridamole was investigated.

Materials and methods

Pregnant women who received antiplatelet therapy with combined aspirin (40 mg·day^{-1}) and dipyridamole (150 mg·day^{-1}) between July 1995 and October 1996 were studied. After informed consent had been obtained, platelet aggregation and coagulation tests were scheduled to be performed before the start of aspirin and dipyridamole (control data), during medication (later than 8 weeks after the start of medication), and at 3 days and 6 days after the cessation of medication, whenever possible. Patients who received heparin treatment along with aspirin and dipyridamole were excluded from the study.

Platelet count, bleeding time, prothrombin time (PT), and activated partial thromboplastin time (aPTT) were measured. Two types of platelet aggregation tests were performed, which used collagen-induced and ADP-

induced methods. Platelet aggregation was measured according to the method of Born and O'Brien [6,7] by using an automatic platelet aggregometer (Hema Tracer 801, MC Medical, Tokyo, Japan). Briefly, platelet-rich plasma (PRP) containing approximately 250000 platelets·μl^{-1} was used with one of the following aggregation-inducing agents at the indicated final concentrations: collagen (2 $\mu g \cdot ml^{-1}$) or ADP (3 μM). The light transmission obtained with PRP before the addition of this agent was set at 0%, and the light transmission obtained with platelet-poor plasma (PPP) was set at 100%. The amount of platelet aggregation was estimated from the change in light transmission after addition of the aggregation-inducing agent to PRP. The normal ranges of collagen- and ADP-induced platelet aggregation in nonpregnant subjects are 45%–95% and 35%–85%, respectively.

Bleeding time was measured by making an incision (1 mm deep and 5 mm long) in the earlobe with a surgical blade and blotting the wound every 30 s until it was dry. The bleeding time was defined as the interval from incision to cessation of bleeding.

The blood loss of the patients during vaginal delivery was compared with that of normal parturients without known hemostatic disorders or abnormal placental implantation who gave birth in January 1996. The blood loss of the patients during cesarean section was compared with that of normal parturients who underwent repeat cesarean section in January or February 1996.

All measurements are reported as means ± SD. Differences among the times of measurement were assessed by one-way analysis of variance and Bonferroni's post-hoc comparison tests. Blood loss of the patients and the normal parturients was compared by the Mann-Whitney U test. A value of $P < 0.05$ was considered significant.

Results

Platelet aggregation was tested in 23 patients, consisting of 2 primigravidas and 21 multigravidas. The patients' mean age was 31.3 ± 3.6 years. Fourteen patients had vaginal deliveries and 9 had cesarean sections. All the patients had live births. The mean gestational age was 38.3 ± 2.8 weeks. Three patients had premature deliveries with gestational ages of 28 weeks 6 days, 33 weeks 5 days, and 36 weeks 1 day. There were three cases of IUGR. All patients who had cesarean deliveries received spinal anesthesia. Indications for cesarean section were repeat cesarean section in five patients, repeat cesarean section and toxemia in two, fetal distress in one, and arrested labor in one. Spinal anesthesia was administered without any complications. In two patients vaginal delivery was complicated by toxemia. There was one case of atonic bleeding after vaginal delivery, but there were no cases of placental abruption or neonatal bleeding abnormality.

In all cases, aspirin and dipyridamole were started and discontinued simultaneously. In four patients, aspirin and dipyridamole intake was started before pregnancy, and control data were not obtained. In the other patients aspirin and dipyridamole intake was started at gestational ages of 5 to 15 weeks (10.0 ± 2.7 weeks) and discontinued at gestational ages of 20 to 37 weeks (34.2 ± 4.1 weeks). Of nine patients who underwent cesarean section under spinal anesthesia, five patients underwent spinal anesthesia within 7 days after discontinuing medication.

The indications for aspirin and dipyridamole treatment among the patients are shown in Table 1. In six patients, prednisolone was used in combination with aspirin and dipyridamole. Levothyroxine sodium was administered to two patients and insulin to two patients.

Platelet aggregation data are shown in Table 2. In some patients, platelet aggregation was tested at 4 days instead of 3 or 6 days after cessation of medication. These data are included in Table 2. Collagen-induced platelet aggregation was decreased during the treatment (25 ± 26%, $P < 0.001$) and at 3 days after cessation of medication (46 ± 35%, $P < 0.001$) compared with control values (89 ± 7%). ADP-induced platelet aggregation was decreased during medication compared with the value before medication (66 ± 18% *vs* 92 ± 7%, $P < 0.001$).

The PT was greater than 100% in all measurements in all patients. There were no differences, over time in measurements of aPTT, fibrinogen, antithrombin III, and bleeding time (Table 3). There were no abnormal values of bleeding time, PT, or aPTT in any patient at any time.

The mean blood loss in women who delivered vaginally ($n = 13$) was 265 ± 115 g, which was not different from that of normal parturients (288 ± 135 g, $n = 90$). The data from the patient with atonic bleeding were not included in this comparison. The loss of blood and amniotic fluid in women who delivered by cesarean section

Table 1. Indications for aspirin and dipyridamole treatment

Indication	No. of patients
Hypertension	8
History of IUGR (or IUFD) and preeclampsia	6
History of IUGR (or IUFD)	4
Positive antiphospholipid antibodies	3
Systemic lupus erythematosus	2
Total	23

IUGR, intrauterine growth retardation; IUFD, intrauterine fetal death

Table 2. Platelet aggregation data (mean % ± SD)

Measurement	Before medication ($n = 9$)	During medication ($n = 21$)	3 days after medication ($n = 7$)	4 days after medication ($n = 5$)	6 days after medication ($n = 7$)
Collagen-induced platelet aggregation[a]	89 ± 7	25 ± 26[b,c,d]	46 ± 35[b,c]	69 ± 24	87 ± 8
ADP-induced platelet aggregation[e]	92 ± 7	66 ± 18[b,c]	73 ± 19	85 ± 11	92 ± 6

[a] Normal range, 45%–95%
[b] $p < 0.001$ *vs* data before medication
[c] $p < 0.01$ *vs* data 6 days after medication
[d] $p < 0.001$ *vs* data 4 days after medication
[e] Normal range, 35%–85%

Table 3. Hemostatic and coagulation profile (means ± SD)

Measurement	Before mediation	During medication	3 days after medication	6 days after medication
Platelet count (×1000/μl)	215 ± 57	216 ± 55	197 ± 53	208 ± 29
Bleeding time (min)	1.7 ± 0.8	1.5 ± 0.9	2.5 ± 2.1	—
aPTT (s)	34 ± 5	35 ± 4	34 ± 2	32 ± 3
Fibrinogen ($mg \cdot dl^{-1}$)	328 ± 88	383 ± 108	434 ± 16	380 ± 22
Antithrombin III (%)	106 ± 12	106 ± 12	97 ± 13	108 ± 6

aPTT, activated partial thromboplastin time

($n = 9$) was 840 ± 312 g, which was not different from that of normal parturients who underwent repeat cesarean section (930 ± 446 g, $n = 23$).

Discussion

Pregnant women are known to have a higher frequency of hypercoagulability than nonpregnant women [8,9]. In diseased states coagulability is further increased, including placental coagulation leading to uteroplacental insufficiency.

There are several reports showing the efficacy of antiplatelet therapy among selected women deemed to be at high risk for preeclampsia, IUGR, and intrauterine fetal death [1–4]. Other indications for antiplatelet therapy include recurrent spontaneous abortion and the detection of autoimmune antibodies [5].

Low-dose aspirin (30–100 $mg \cdot day^{-1}$) is known to exert an antithrombotic effect by inhibiting platelet cyclooxygenase activity, thus prohibiting the production of thromboxane A_2, which is a potent vasoconstrictor and platelet aggregator. A larger dose of aspirin also inhibits the production in endothelial cells of prostacyclin, which is a vasodilator and an inhibitor of platelet aggregation. In antiplatelet therapy, a small dose is selected to leave the prostacyclin production intact. In preeclampsia, the thromboxane A_2/prostacyclin ratio is increased due to increased production of thromboxane A_2. Administration of low-dose aspirin normalizes the thromboxane A_2/prostacyclin ratio by inhibiting thromboxane A_2 production. Platelets do not synthesize protein, and the inhibition of platelet cyclooxygenase by aspirin lasts throughout the life span of the platelet, which is about 10 days [10]. The effect of aspirin is expected to disappear within a week.

Dipyridamole is also known to exert an inhibitory effect on platelet aggregation by blocking the cellular reuptake and metabolism of adenosine, which is a potent vasodilator and antithrombotic substance, and by increasing the production of prostacyclin [11,12]. At therapeutic concentrations, dipyridamole has been reported to inhibit ADP- and collagen-induced aggregation in whole blood [11]. Both aspirin and dipyridamole exert an effect in the same direction in lowering the thromboxane A_2/prostacyclin ratio and inhibiting platelet aggregation. The contribution of each drug when they are used together has not been clearly delineated. Since the coadministration of two drugs is popular in antithrombotic therapy, we did not try to separate the effects of these two drugs. Prednisolone at the usual therapeutic doses is not known to affect platelet aggregation.

The combination of 40 $mg \cdot day^{-1}$ aspirin and 150 $mg \cdot day^{-1}$ dipyridamole was effective in inhibiting platelet aggregation. Platelet aggregation induced by collagen, ADP, adrenaline, and arachidonic acid in normal pregnancy has been reported by different authors to increase, decrease, or remain the same [13,14]. Because the normal values of collagen- and ADP-induced platelet aggregation in nonpregnant people are 45%–95% and 35%–85%, respectively, collagen-induced

aggregation was decreased below the normal limits by medication in our patients. ADP-induced aggregation was decreased in comparison with control values but remained in the normal range. The collagen-induced aggregation method is more sensitive in evaluating the effect of aspirin.

In this study, aspirin and dipyridamole did not prolong the bleeding time. Previous studies of patients receiving low-dose aspirin have reported prolonged bleeding time, which was not associated with clinical bleeding [15,16]. The explanation of this discrepancy is not clear, but it may be related to the lower dose of aspirin used in our study compared with other studies (40 mg *vs* 50–60 mg), different methods of measurement, and the small number of subjects in our study. Addition of dipyridamole 150 mg·day^{-1} apparently did not cause additional prolongation of the bleeding time. The blood loss during vaginal delivery and cesarean section in the patients was not different from that of normal parturients. Since bleeding time, PT, and aPTT were not prolonged and there was no clinically abnormal bleeding, administration of spinal or epidural anesthesia could be safe during or soon after the cessation of aspirin and dipyridamole treatment at these doses. In other reports dealing with a larger population of parturients or other surgical patients treated with low-dose aspirin, with or without dipyridamole, abnormal bleeding was not detected, and spinal and epidural anesthesia were performed without problems [16–18].

In conclusion, antiplatelet therapy in pregnant women with combined aspirin (40 mg·day^{-1}) and dipyridamole (150 mg·day^{-1}) inhibited platelet aggregation up to 3 days after cessation of medication but was not associated with clinically abnormal bleeding.

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