Recovery Time of Platelet Function After Aspirin Withdrawal

Jeonghun Lee, MD1, Jeong Kyung Kim, MD, PhD1,*, Jeong Hee Kim, MD1, Tsagaan Dunuu, MD2, Sang-Ho Park, MD3, Sang Joon Park, MD4, Ji Yeon Kang, DDS5, Rak Kyeong Choi, MD6, Min Su Hyon, MD7

1 Cardiovascular Interventional Center, Sun General Hospital, Daejeon, Korea
2 Department of Internal Medicine, Soochunhyang University Cheonan Hospital, Cheonan, Korea
3 Intensive Care Unit and Department of Emergency, Shatin Central Hospital, Ulaanbaatar, Mongolia
4 Department of Oral and Maxillofacial Surgery, Sun General Hospital, Daejeon, Korea
5 Interventional Radiology, Department of Radiology, Sun General Hospital, Daejeon, Korea
6 Department of Internal Medicine, Bucheon Sejong General Hospital, Bucheon, Korea
7 Cardiovascular Division of Internal Medicine, Bucheon Sejong General Hospital, Bucheon, Korea

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A B S T R A C T

Introduction: Inappropriate antiplatelet therapy discontinuation increases the risk of thrombotic complications and bleeding after dental procedures. To determine the platelet reactivity recovery time after aspirin withdrawal in vivo, our study was conducted in patients with low-risk cardiovascular disease who can stop aspirin administration following the guidelines stipulated by the American College of Chest Physicians. The time it takes for platelet activity to normalize and the diagnostic accuracy of testing methods were assessed for a residual antiplatelet activity with multiple electrode aggregometry. Our study included patients with clinically indicated hypertension preparing for a dental extraction procedure.

Materials and methods: A total of 212 patients not taking aspirin (control group) and 248 patients with hypertension receiving long-time aspirin treatment at a 100-mg daily dose were prospectively included in the study, which involved stopping aspirin intake before dental extraction. The residual platelet activity and dental bleeding in patients who stopped aspirin intake were analyzed and compared with those of the control group. In addition, platelet reactivity recovery time and bleeding risk in patients who stopped taking aspirin every 24 hours for 0 to 5 days (0–143 hours) before dental extraction was also assessed.

Results: Platelet reactivity normalized 96 hours after aspirin withdrawal. The cut-off value of 49 arbitrary units in the arachidonic acid platelet aggregation test excluded the effect of aspirin with 91% sensitivity and 66% specificity. AUC showed 0.86 (P < 0.001) diagnostic accuracy. The immediate bleeding complications in all treatment groups were similar to those seen in the control group and were successfully managed with local hemostatic measures.

Conclusions: The antiplatelet effects of aspirin disappeared 96 hours after aspirin withdrawal in our study, and dental extractions may be safely performed in this period when appropriate local hemostatic measures are taken. Based on these results, a shorter aspirin intake cessation period may be allowable in complex dental procedures and surgery for which a longer aspirin intake cessation period (7–10 days) is recommended based on the American College of Chest Physicians guidelines.

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Introduction

Platelets play a pivotal role in the pathophysiology of ischemic complications of atherosclerotic cardiovascular disease. Aspirin acts on platelets by acetyling the cyclooxygenase enzyme at position serine 529, resulting in reduced formation of cyclic endoperoxides (prostaglandin G2 and prostaglandin H2) and thromboxane from arachidonic acid. Aspirin is an oral antiplatelet drug commonly used to reduce adverse clinical events across a wide spectrum of patients with atherothrombotic disease.1–3

An increasing number of patients undergoing dental procedures or surgery ingest aspirin. The American College of Chest Physicians (ACCP) recommends that patients scheduled for

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coronary artery bypass grafting continue aspirin intake up to and throughout the time of coronary artery bypass grafting despite published reports of increased risk of perioperative bleeding. Preoperative aspirin administration increases blood loss during bleeding-sensitive operations. Thus, ACCP guidelines suggest that patients about to undergo noncardiac surgery who are at low risk for cardiac disease stop aspirin intake 7 to 10 days before surgery.

The optimal dental management in patients receiving long-term aspirin treatment has yet to be clearly defined. Antiplatelet discontinuation increases the risk of thrombotic complications, whereas uninterrupted antiplatelet therapy is assumed to increase risk of bleeding after dental procedures. The effect of aspirin on the amount of bleeding that occurs during tooth extraction procedures is controversial, and the perioperative guidelines recommend that aspirin administration should not be altered for such procedures. Dental extraction may be safely performed in patients receiving single or dual antiplatelet therapy when appropriate local hemostatic measures are taken.

For patients preparing to undergo a dental procedure, detection of the degree of residual-aspirin-induced suppression of platelet activity in accordance with the duration of aspirin withdrawal could not only result in appropriate postponement of complex or bleeding-sensitive dental procedure but also prevent the unnecessary postponement of a simple dental procedure.

Multiple electrode aggregometry (MEA) is a newly developed technique for testing platelet function in whole blood based on classic whole-blood impedance aggregometry. It has been used to study the effects of aspirin and clopidogrel on platelet aggregation. MEA does not require a specialized coagulation laboratory and may be useful for point-of-care analysis. Up to now, no information has been available regarding the use of MEA for the determination of the time course of platelet inhibition after the ingestion of a single 100-mg dose of aspirin.

To determine the platelet reactivity recovery time after aspirin withdrawal in vivo, our study was conducted among patients with low-risk cardiovascular disease who can stop aspirin intake following the ACCP guideline. The residual-aspirin-induced suppression of platelet activity with MEA was assessed in patients who needed to stop aspirin intake before dental extraction. Results of the time course assessment of the antiplatelet effects and the bleeding risk after cessation of a single oral dose of 100 mg aspirin was examined with MEA before dental extraction in patients with hypertension, which is associated with low risk for ischemic cardiac disease. The diagnostic value of MEA in the assessment of residual platelet reactivity after the cessation of aspirin intake was also determined.

Materials and Methods

Study population

All patients older than age 18 years consecutively referred for dental extractions were prospectively screened from October 2011 to April 2013 at 2 centers. The control group, those who were not taking aspirin, and the patients who had been taking 100 mg aspirin and antihypertensive medication daily were included at each center. These patients were randomly assigned to 6 groups that were to stop aspirin intake for 0 to 5 days before dental extraction. Based on the findings in the aspirin-treated healthy volunteers in a study conducted by Jambor et al., it was hypothesized that the platelet function in patients who stopped aspirin intake before the dental procedure would gradually normalize, with wide interindividual variation on Days 3 and 4 (between 48 and 96 hours) after the final ingestion of aspirin.

On Day 5 and thereafter (after 96 hours), no detectable aspirin effect was expected. Thus, our study was designed to assess the platelet activity recovery time and the bleeding risk in patients who stopped taking aspirin 0 to 5 days (0–143 hours) before dental extraction. Our study was conducted according to Good Clinical Practice and in accordance with the Declaration of Helsinki and all its subsequent amendments. The ethics committee or institutional review board of each participating center approved the protocol, and all study participants gave written informed consent during enrollment.

Dental procedures

Anterior mandibular and maxillary teeth were extracted under local anesthetic injection in the buccal and palatal or lingual aspect of the teeth. Posterior mandibular teeth were extracted under a combination of inferior alveolar nerve block anesthesia and anesthesia infiltration done buccally and lingually. A solution of 2% lidocaine 1.8 mL with epinephrine 1:80,000 was infiltrated into each extraction site to ensure similar local hemostatic effects of epinephrine.

Patients were instructed to bite on a pressure pack for 30 minutes after the dental extractions. In patients in whom bleeding was still present, a piece of oxidized regenerated cellulose gauze was sutured over the inlet of the postextraction socket (these sutures were removed on Day 6). The patients then bit on a pressure pack for 30 minutes for a second time, and were evaluated before leaving the hospital. All patients were given appropriate postoperative instructions and were advised to immediately report the occurrence of any hemorrhagic problem. The patients were interviewed by telephone at the end of the extraction day, and bleeding complaints were recorded.

Estimation of bleeding after dental procedure

The bleeding complications after dental extraction were classified according to the time of occurrence as immediate (occurring during the extraction session at the clinic) or late (occurring any time thereafter). Prolonged immediate bleeding was defined by the need to use hemostatic gauze when the blood extended beyond the tooth socket after 30 minutes of biting on a pressure pack. Late bleeding complications were defined as clinically significant when they extended beyond 12 hours, made the patient call or return to the dental practitioner or to an emergency department, resulted in hematoma or ecchymosis within the oral soft tissues, or required blood transfusion.

Exclusion criteria

Patients were excluded if they had a history of bleeding diathesis, chronic oral anticoagulation treatment, <30% hematocrit, a <80/mL platelet count, or any known congenital or acquired hemostasis disorder, with the exception of aspirin-induced platelet dysfunction. Patients with a history of acute myocardial infarction, unstable angina, stable angina with coronary artery stenting, stroke, and concomitant administration of other antiplatelet or nonopioid anti-inflammatory agent were also excluded.

As in previous reports assessing the bleeding risk of multiple extractions in patients receiving oral anticoagulation who needed multiple extractions (>3 teeth), surgical extractions, extractions in deferent quadrants, or deciduous teeth were excluded.

Compliance

To optimize the compliance of patients whose last aspirin intake doses were documented, face-to-face interviews were conducted.
Standard pill count was used to assess adherence. At each visit, the pills remaining in the containers were counted. Adherence was defined by the number of pills taken (dispensed pills – returned pills) in relation to the theoretical prescribed doses.

**Blood sampling and intervention**

Blood was sampled from the antecubital vein without stasis using a 21G butterfly needle. The first 2 mL blood was discarded. Blood was then collected in 4.5-mL tubes containing 25 μg/mL hirudin (Dynabyte, Munich, Germany) as an anticoagulant according to the manufacturer's recommendations. After blood drawing at baseline, all participants in the control group took 1 tablet of 100 mg aspirin (Aspirin Protect; Bayer, Leverkusen, Germany) in the presence of a study advisor, followed by extraction of additional blood samples. The hematocrit, leukocytes, and platelet count were determined from the EDTA blood samples using an SF 3000 analyzer (Sysmex Corp, Kobe, Japan).

**Platelet aggregation test**

Platelet function analysis was performed using the Multiplate analyzer, a novel whole-blood impedance aggregometry device (Dynabyte, Munich, Germany). The device has 5 MEA test cells for parallel testing, and each test cell incorporates 2 independent sensor units. One unit consists of 2 silver-coated, highly conductive copper wires. Analysis was based on the platelet adhesion upon activation, a property that results in aggregation onto the metal sensor wires in the test cell, thus increasing the electrical impedance between the wires. For measurement, 300 μL preheated saline (37°C) and 300 μL hirudin-anticoagulated whole blood were placed in the test cell, and the sample was stirred using a Teflon (DuPont Company, Wilmington, Delaware)-coated electromagnetic stirrer (800 revolutions/min) over a 3-minute incubation period. Platelet aggregation was initiated using arachidonic acid (arachidonic acid test, 0.5 mM), the reagent supplied by the manufacturer (Dynabyte, Munich, Germany). Increased impedance due to platelet aggregation [ASPI] test, 0.5 mM), the reagent supplied by the manufacturer (Dynabyte, Munich, Germany). Increased impedance due to the attachment of platelets to the electrodes was continuously measured using a 2 electrode pairs and the differences between the AUC values detected by the sensor unit and the mean AUC were calculated. When the values were outside the acceptable range (correlation coefficient < 0.98 or difference from the mean curve > 20%), the results were flagged and the measurement was repeated.

The institutional reference range was defined as between the 10th and 90th percentiles of the control group (no aspirin intake) for each assay. An aspirin effect was excluded if the value was within the institutional reference ranges, or more precisely, above the 10th percentile of the control group in the ASPI test. Aspirin resistance was determined to be present if the measurement value for the full-aspirin-effect group was within the institutional reference range.

The variability of measurements was quantified using the mean of the SDs of the 3 consecutive measurements with 17 healthy subjects after 100 mg aspirin intake, and were expressed as percentages of the mean values (% CV).

**Statistical analysis**

Statistical analysis was performed using NCSS for Windows version 2007 (NCSS, Kaysville, Utah). The Kolmogorov-Smirnov test was used to check for the normal distribution of the continuous data. The result was expressed as mean (SD) if normally distributed, and as median (25th, 75th percentile) if not. The categorical variables were compared using the χ² test. One-way ANOVA on ranks was used to detect the differences among the groups. In the case of significant differences in group medians, a post hoc multiple-comparison procedure versus the control group was applied according to Dunn's method. Categorical data were compared using the χ² test. To detect significant differences in platelet aggregation as 15.0 AU and 80% statistical power (α = 0.05 [20]), the sample size needed to be at least 29 for each aspirin withdrawal group.

The diagnostic accuracy of the platelet function assays in identifying aspirin-induced platelet inhibition was calculated using receiver operating characteristic (ROC) curves. For the generation of ROC curves, the data of the 1- to 5-day aspirin-intake-skipping

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### Table 1

Baseline characteristics.

| Variable* | Control | 0-23 | 24-47 | 48-71 | 72-95 | 96-119 | 120-143 | P† |
|-----------|---------|------|-------|-------|-------|--------|---------|----|
| Patients  | 212     | 42   | 40    | 45    | 44    | 41     | 46      |    |
| Age, y    | 62 (13.4) | 64.4 (10.2) | 63.4 (11.2) | 62 (13.4) | 64 (14.4) | 65 (11.4) | 67 (14.7) | 0.14 |
| Male      | 51      | 47   | 49    | 51    | 47    | 54     | 52      | 0.66 |
| Weight, kg| 61.7 (14.7) | 58.3 (13.2) | 60.3 (15.2) | 61.7 (14.7) | 59.4 (15.1) | 60.5 (14.9) | 57.7 (15.4) | 0.63 |
| Height, cm| 168 (8.1) | 167 (8.3) | 168 (8.7) | 162 (8.6) | 163 (9.1) | 160 (9.4) | 158 (9.6) | 0.52 |
| Body mass index | 25.2 (22.0/29.1) | 25.3 (22.3/28.9) | 25.7 (23.1/27.9) | 26.5 (21.4/29.5) | 25.2 (22.0/29.1) | 25.6 (21.1/29.2) | 26.9 (23.0/30.1) | 0.12 |
| Platelet count, n/L | 226 (192/280) | 228 (189/278) | 225 (196/273) | 227 (193/271) | 239 (190/274) | 226 (192/280) | 220 (197/279) | 0.13 |
| Hematocrit, % | 41.1 (36.9/45.7) | 40.8 (36.7/45.4) | 40.1 (36.5/44.7) | 37.8 (32.9/41.7) | 38.3 (35.0/41.7) | 39.1 (36.1/44.5) | 37.4 (32.0/43.7) | 0.23 |
| Leucocytes, n/L | 6.2 (5.4/8.6) | 6.5 (4.4/8.1) | 6.1 (4.7/8.0) | 6.8 (5.2/8.5) | 6.2 (5.4/8.6) | 6.2 (5.3/8.5) | 6.4 (5.5/8.6) | 0.70 |
| Smoking   | 62 (29.1) | 31 (13.2) | 12 (29.6) | 13 (29.4) | 14 (31.6) | 11 (27.1) | 12 (25.8) | 0.09 |
| No. of teeth extracted | 325 | 50 | 51 | 56 | 53 | 51 | 52 | |
| Indication for extraction | | | | | | | | |
| Periodontitis | 155 (47.7) | 24 (48.0) | 22 (43.1) | 25 (44.6) | 24 (45.3) | 26 (510) | 23 (44.2) | 0.55 |
| Radicular lesion | 39 (12.0) | 6 (12.0) | 8 (15.7) | 6 (10.7) | 5 (9.4) | 4 (7.8) | 5 (9.6) | 0.11 |
| Severe decay | 126 (38.8) | 20 (40.0) | 21 (41.2) | 23 (41.1) | 24 (45.3) | 20 (39.2) | 24 (46.2) | 0.12 |
| Other      | 5 (1.5) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | NA |

NA = not applicable.

* Data are expressed as mean (SD) or median (25th/75th percentile), according to the distribution of the data. Characteristics are expressed as absolute numbers and percentage values.

† P value indicates controls versus all of aspirin withdrawal groups.
aspirin groups and the control group were included. The area under the ROC curve, sensitivity (true positives / [true positives + false negatives]), and specificity (true negatives / [true negatives + false positives]) of the assays were calculated. Relative risk (RR) was defined as the ratio of bleeding incidence between 2 groups, and a corresponding 95% CI was reported for the comparison of the bleeding risk between groups. The level of statistical significance was set at P < 0.05.

Results

A total of 470 patients meeting the inclusion and exclusion criteria were enrolled in the study. A total of 212 patients were included in the control group, and 258 patients who were taking aspirin were randomized into 6 groups according to the set duration of aspirin intake cessation. The medication adherence of the patients in our study was analyzed to be 97%, a high adherence rate according to the medication possession ratio of 80% to 100%. The patients' demographic and procedural characteristics were similar, as shown in Table I. The results obtained with MEA were consistent and reproducible, with 9% assay imprecision values, within the range of modern laboratory point-of-care testing.

Residual antiplatelet effects with MEA

Results of the aspirin-induced platelet reactivity in the ASPI test are presented in Table II and Figure 1. All patients in the control group after aspirin intake, and patients who had stopped taking aspirin for < 96 hours showed significant differences in terms of platelet activity when compared with the control group. There were significant differences between the platelet aggregation analyses performed after aspirin withdrawal, 24 to 47 hours after aspirin withdrawal, 48 to 71 hours after aspirin withdrawal, 72 to 95 hours after aspirin withdrawal, and 96 to 119 hours after aspirin withdrawal, except 120 to 143 hours after aspirin withdrawal. Seventy-two hours after aspirin withdrawal, the platelet activity gradually reached a point near the value of the controls, and there was no difference after more than 96 hours when compared with the control group.

Diagnostic value of MEA

Quantifying the diagnostic accuracy of MEA with ROC analysis in detecting residual aspirin effect showed the AUC was 0.86 (P < 0.001) (Figure 2). An AUC value ≥ 49 AU in the ASPI test indicated a recovered antiplatelet effect of aspirin with 91% sensitivity and 66% specificity, as shown in Table III.

The results obtained with MEA were consistent and reproducible, with 9% assay imprecision values, within the range of modern laboratory point-of-care testing.

Bleeding risk after each period of aspirin intake discontinuation

One patient (0.5%) had prolonged immediate bleeding in the control group and there was 1 patient with prolonged bleeding in each aspirin intake discontinuation group (0–23 hours [2.4%; RR = 6.8; 95% CI, 0.6–69.2; P = 0.21], 24–47 hours [2.5%; RR = 7.1; 95% CI, 0.9–69.4; P = 0.17], and 72–95 hours [2.3%; RR = 6.5; 95% CI, 0.6–67.4; P = 0.22]). Immediate bleeding occurred in 1 patient in the control group (0.5%) and there was 1 patient with immediate bleeding in each aspirin withdrawal group (48–71 hours [2.2%; RR = 6.3; 95% CI, 0.7–65.7; P = 0.25], 96–119 hours [2.4%; RR = 6.9;
Some studies linked MEA data to bleeding\textsuperscript{12,25} or thrombotic outcomes.\textsuperscript{26} A very recent investigation of 100 patients undergoing cardiac surgery suggested that the preoperative ASPI test in MEA may be a more sensitive predictor of platelet transfusion than patient self-reporting on aspirin intake.\textsuperscript{12}

Within 72 hours after aspirin intake, more than 80% suppression of aspirin-induced platelet aggregation was observed in all patients. The platelet function was gradually normalized 72 hours after drug withdrawal. This suppression was consistent with the results reported for MEA during long-term aspirin treatment.\textsuperscript{11} The antiplatelet effect time course of aspirin assessed using MEA in our study was in accordance with the results obtained using other monitoring techniques, such as thromboxane B2 production\textsuperscript{27} or PFA-100,\textsuperscript{28} considering that the administered doses in these studies were in fact lower. Results of our study suggest an important clinical implication in deciding the appropriate duration of aspirin cessation before dental extractions without postponing the procedures. Although ACCP recommends 7- to 10-day aspirin intake cessation before surgery in patients with low cardiovascular risk, the results of our study suggest that aspirin intake cessation not longer than 96 hours can be adequate.

The recommendation to stop aspirin intake for 7 to 10 days is based only on the concern for the mature platelets during exposure to aspirin. There are some mechanisms that may modulate the antiplatelet effects in the presence of aspirin and after aspirin cessation. First, immature platelets, which are reticulated and larger, have less attenuated and more elevated platelet activity than mature platelets in the presence of aspirin. Moreover, the inhibition of human megakaryocyte cyclooxygenase with low doses of aspirin is incomplete, and megakaryocyte cyclooxygenase seems to recover within 12 hours after aspirin ingestion.\textsuperscript{29,30} Second, interruption of the platelet function by aspirin results in the production of new platelets, presumably through the action of a feedback system controlling thrombocytopenia.\textsuperscript{31} With the newly formed platelets from the bone marrow in the absence of aspirin, these mechanisms may affect the platelet activity recovery time faster than the life span of the mature platelets.

### Study limitations

This study has some limitations. First, it was not designated as an in vivo study. It could not be determined if low or high platelet reactivity as determined by the ASPI test actually results in increased prothromboembolic events. Although platelet reactivity is a well-validated predictor of the clinical outcomes of thrombotic ischemic heart disease, large-scale and long-term trials powered for clinical outcomes will be necessary. Second, the results of our study are based on measurements using only MEA, but various studies reported that MEA measurements correlate with light transmission aggregometry\textsuperscript{13,14} and flow cytometry.\textsuperscript{15} Finally, biochemical measurement to verify aspirin compliance, such as urinary thromboxane level, was not designated. Instead, standard pill count was used to assess adherence.

### Conclusions

The antiplatelet effects of aspirin can be expected within 96 hours after the final ingestion of aspirin. Similar bleeding complications occurred compared with the control group within such period. The platelet function generally recovers if the aspirin cessation period exceeds 96 hours. With these results, a shorter aspirin intake cessation period may be needed in complex dental procedures and surgery for which a longer aspirin intake cessation (7–10 days) is recommended by the ACCP guidelines. The ASPI test might be the preferred diagnostic method for determining the

### Table III

| Diagnostic accuracy of multiple electrode aggregometry. | ASPI test, U |
|--------------------------------------------------------|-------------|
| Control group 10th percentile                           | 49          |
| Control group 90th percentile                           | 117         |
| Cutoff                                                 | 49          |
| Sensitivity, % (95% CI)                                 | 91 (86–94)  |
| Specificity, % (95% CI)                                 | 66 (55–71)  |
| AUC ROC (95% CI)                                        | 0.86 (0.81–0.88) |
| P                                                      | < 0.001     |

ASPI = arachidonic acid platelet aggregation; CI = confidential interval; ROC = receiver operating characteristic.

Cutoff value of the ASPI test for the exclusion of aspirin-induced platelet activity, as determined by the 10th or 90th percentiles of the values obtained by the control group (without aspirin intake) (n = 212), with respective sensitivities and specificities of the tests for the exclusion of aspirin-induced platelet activity. Diagnostic values are characterized by the AUC ROC.

95% CI, 0.7–68.1; P = 0.2], and 120–143 hours [2.2%; RR = 6.2; 95% CI, 0.5–65.6; P = 0.26]). All cases of immediate bleeding were successfully treated with hemostatic gauze and suturing after dental extraction. Patients with immediate bleeding did not significantly differ in gender, age, and number or type of extracted teeth across the different treatment groups. None of the controls or patients who stopped aspirin intake for 1 to 5 days developed any late hemorrhagic complication.

### Discussion

The main finding of our study is that aspirin-induced platelet aggregation in South Korean patients gradually increased 72 hours after cessation of aspirin intake and returned to the baseline values 96 hours after the cessation of aspirin intake before dental extraction. All the immediate bleeding complications in all the treatment groups were similar to those in the patients without aspirin intake. The diagnostic accuracy of platelet function assay with MEA showed the area under the ROC curves as 0.86 for the ASPI test, and 91% and 66% sensitivity and specificity, respectively. This indicates the usefulness of the method in assessing aspirin-induced platelet activity in patients with low cardiovascular risk before dental extraction. The ASPI test was found to have a degree of diagnostic accuracy similar to the results obtained by Jâmbar et al\textsuperscript{17} that involved aspirin-withdrawn patients preparing for surgery in Europe. Their study showed the area under the ROC curves as 0.81 for the ASPI test, and the sensitivity and specificity as 88% and 71%, respectively, in preoperative patients.

For the choice of aspirin dose, it has been determined that high-dose aspirin (500–1500 mg daily) is no more effective than medium-dose aspirin (160–325 mg daily) or low-dose aspirin (75–150 mg daily) for long-term use.\textsuperscript{32} A dose of 100 mg daily was selected in our study because it corresponds to the typical dose of aspirin ingested as long-term therapy for the primary and secondary prevention of cardiovascular disease in patients with low cardiovascular risk factors.\textsuperscript{18} Aspirin caused near-complete inhibition of aspirin-induced platelet aggregation with the ASPI test, as shown in this study.\textsuperscript{19,20} The incidence of aspirin nonresponse was reported to be 5% to 50%, with remarkably different values with different platelet function tests.\textsuperscript{21–23} In our study, aspirin resistance was detected in 10% of patients using MEA.

In a recent study involving healthy volunteers and patients with coronary artery disease, the comparison of light transmission aggregometry, Platelet Function Analyzer (PFA-100) with Collagen-Epinephrine (COL-EPI) (Dade-Behring, Marburg, Germany), ASPI test, and VerifyNow (Accumetrics Inc, San Diego, CA) aspirin assay, revealed that MEA is the most sensitive platelet function assay for aspirin.\textsuperscript{24}
residual effects in patients who need aspirin intake cessation for a dental procedure or surgery.

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All authors contributed equally and are responsible for the content and writing of this paper.

Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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