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Recovery Time of Platelet Function After Aspirin Withdrawal

Jeonghun Lee, MD[1], Jeong Kyung Kim, MD, PhD[1,*], Jeong Hee Kim, MD[1], Tsagaan Dunuu, MD[2], Sang-Ho Park, MD[3], Sang Joon Park, MD[4], Ji Yeon Kang, DDS[5], Rak Kyeong Choi, MD[6], Min Su Hyon, MD[7]

[1] *Cardiovascular Interventional Center, Sun General Hospital, Daejeon, Korea*
[2] *Intensive Care Unit and Department of Emergency, Shastin Central Hospital, Ulaanbaatar, Mongolia*
[3] *Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Cheonan, Korea*
[4] *Interventional Radiology, Department of Radiology, Sun General Hospital, Daejeon, Korea*
[5] *Department of Oral and Maxillofacial Surgery, Sun General Hospital, Daejeon, Korea*
[6] *Cardiovascular Division of Internal Medicine, Bucheon Sejong General Hospital, Bucheon, Korea*
[7] *Department of Internal Medicine, Soonchunhyang University, College of Medicine, Cardiovascular Institution, Seoul, Korea*

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ABSTRACT

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 acetylating 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

* Address correspondence to: Jeong Kyung Kim, MD, PhD, Cardiovascular Center, Sun General Hospital, 29 Mokjung-ro, Jung-gu, Daejeon 301-725, Republic of Korea.
E-mail address: dr_kairo@naver.com (J. K. Kim).

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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.[4,5] Preoperative aspirin administration increases blood loss during bleeding-sensitive operations.[6–8] 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.[9]

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.[10,11] MEA does not require a specialized coagulation laboratory and may be useful for point-of-care analysis.[12–14] 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 reactivity 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 Jámbor et al,[15] 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/nL 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.[16]

Compliance

To optimize the compliance of patients whose last aspirin intake doses were documented, face-to-face interviews were conducted.

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