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Do antiplatelet drugs increase the risk of bleeding after tooth extraction? A case-crossover study

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Abstract. The aim of this study was to assess the risk of bleeding after tooth extraction in patients taking aspirin or clopidogrel. This case-crossover study evaluated patients taking aspirin (80 mg/day) or clopidogrel (75 mg/day) and undergoing tooth extraction. In the first session, extraction was performed without discontinuing aspirin (group 1) or clopidogrel (group 2). In the second session, patients ceased using antiplatelet drugs 5 days prior to tooth extraction. Bleeding was evaluated using a visual analogue scale (VAS) for 72 h after tooth extraction. The platelet function assay (PFA) was performed for group 1 and flow cytometry assessment of vasodilator-stimulated phosphoprotein (VASP) was performed for group 2, in both sessions. Thirty-eight patients were studied: 20 in group 1 and 18 in group 2. Analysis of the data did not demonstrate any difference in bleeding severity between sessions 1 and 2 in either group ($P > 0.05$). There was a significant difference between sessions 1 and 2 in group 1 for the mean collagen/epinephrine membrane closure time (PFA) ($P = 0.001$). A significant difference in platelet reactivity index (flow cytometry for VASP) was noted between sessions 1 and 2 in group 2 ($P = 0.001$). According to this case-crossover study, dental extraction can be performed safely without withdrawal of aspirin or clopidogrel.

Key words: aspirin; clopidogrel; tooth extraction; bleeding.

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Antiplatelet drugs are used for the secondary prevention of cardiac and cerebrovascular diseases, especially in patients with ischemic heart disease, a history of coronary artery bypass, previous myocardial infarction, placement of a stent, non-haemorrhagic stroke, peripheral arterial disease, and transient ischemic attacks[1]. Low-dose clopidogrel and aspirin are the most commonly prescribed antiplatelet drugs for these patients[1]. Aspirin affects the cyclooxygenase pathway and inhibits platelet activity. This effect on platelet activity is irreversible during the lifespan of the platelet (7–10 days)[2]. Clopidogrel bisulfate is a direct inhibitor of adenosine diphosphate (ADP) binding to its receptor. This affects subsequent ADP-mediated activation of glycoprotein GPIIb/IIIa and results in excessive bleeding. The effect of clopidogrel, similar to that of aspirin, lasts for the entire lifespan of the platelet[2].

Several studies have demonstrated the risk of thrombosis and myocardial

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infarction after withdrawal of antiplatelet drugs[3–5]. Previous studies have advocated that patients who are candidates for tooth extraction can continue taking antiplatelet drugs without having an increased risk of excessive bleeding[1,6,7].

The purpose of this study was to address the following question: Do antiplatelet drugs increase the risk of bleeding after tooth extraction? It was hypothesized that the continuation of use of aspirin or clopidogrel would increase the risk of bleeding after tooth extraction. Therefore, the aim of this study was to assess the risk of bleeding after tooth extraction in patients taking aspirin or clopidogrel.

Materials and methods

A case-crossover study was designed. The sample was derived from the population of patients presenting to the Oral and Maxillofacial Surgery Department of Shahid Beheshti University of Medical Sciences between September 1, 2014 and September 31, 2016. The research protocol was approved by the committee of the medical ethics group of Shahid Beheshti University of Medical Sciences. Patients eligible for study inclusion were on aspirin (80 mg/day) or clopidogrel (75 mg/day) and were candidates for bilateral first and second molar tooth extraction. The same molar teeth were removed in the maxilla or mandible. Patients were excluded from the study if they were taking dual antiplatelet drugs or other anticoagulant drugs, did not have permission from their cardiologist to discontinue aspirin or clopidogrel for 5 days, or had a haematocrit <30% and platelet count $<50 \times 10^9$/l. All patients underwent simple extractions without flap elevation. All patients consulted a cardiologist before the study and gained permission to participate, and all provided a signed permission letter.

In the first session, the patients underwent tooth extraction without discontinuing aspirin (group 1) or clopidogrel (group 2). For the second session, patients ceased using their antiplatelet drugs 5 days before the extraction. The gap between the two sessions was 2 weeks.

For group 1 patients, the platelet function assay (PFA) was used to monitor the antiplatelet effect of aspirin. Blood (2.7 ml) was collected for the PFA-100 test. Patients with a haematocrit level >55% had a special tube made to adjust for the haematocrit. All tests were done within 4 h after sampling. The PFA was done using a collagen/epinephrine membrane (Col/Epi closure time).

In group 2, a flow cytometry-based assay was performed to measure the activity of platelets (recorded as the platelet reactivity index, PRI) according to the phosphorylation state of an intracellular platelet protein known as vasodilator stimulated phosphoprotein (VASP). The PRI was tested before the first and second sessions in group 2.

Bleeding was evaluated using a visual analogue scale (VAS) for 72 h after the tooth extraction: a score of 1–3 indicated minimal bleeding, a score of 4–6 indicated moderate bleeding (patient needs to place a wet gauze on the extraction site), and a score of 7–10 indicated severe bleeding (patient needs to return to clinic for additional treatments such as suturing and use of coagulation substances).

The simple extractions were performed by an oral and maxillofacial surgeon without any additional procedure.

Statistical analysis

The statistical analyses were performed using IBM SPSS Statistics version 19.0 (IBM Corp., Armonk, NY, USA). The paired *t*-test was used to evaluate PRI and PFA before and after the withdrawal of antiplatelet drugs. The independent *t*-test was used to assess and compare bleeding between the two sessions.

Results

Thirty-eight patients were studied in the two groups (20 patients in group 1 and 18 patients in group 2). The mean age of the patients in group 1 was 59.9 ± 6.50 years and in group 2 was 63.16 ± 5.07 years.

There was a significant difference between sessions 1 and 2 in group 1 for Col/Epi closure time ($P = 0.001$, Table 1). The results demonstrated a significant change in Col/Epi closure time with continued aspirin and holding it for 5 days.

A significant difference in PRI was noted between sessions 1 and 2 in group 2 ($P = 0.001$, Table 1). The results of this analysis demonstrated a significant change in PRI with continue of clopidogrel and holding it for PRI.

No significant difference in bleeding was noted between sessions 1 and 2 in group 1 based on the VAS for bleeding severity after extraction ($P = 0.09$). Analysis of the data did not reveal a significant difference between sessions 1 and 2 in group 2 for severity of bleeding after extraction according to the VAS ($P = 0.10$) (Table 2).

Discussion

The continuous administration of antiplatelet drugs is tremendously important for patients at high risk of thromboembolic events[8]. Antiplatelet drugs have a protective effect against acute myocardial infarction or angina pectoris, cerebrovascular accident, and atrial fibrillation[9,10]. There is a reported higher risk of thrombosis of a stent after the withdrawal of antiplatelet drugs[11]. Also, it has been reported that the discontinuation of aspirin increases the incidence of cerebrovascular accidents by 3.4-fold as compared to its continuation[12]. Patients using antiplatelet drugs are considered high risk with regard to invasive oral surgery[7,13].

The effect of antiplatelet drugs disappears 96 h after withdrawal[14]. Konrad et al. reported that the effect of aspirin on platelets was detected at 3 h and lasted for the following 3 days[15]. Cahill et al. advocated the discontinuation of aspirin therapy 5 days before elective surgery[16].

Table 1. Comparison of the collagen/epinephrine membrane closure time (PFA) between sessions 1 and 2 in group 1 (aspirin group) and of PRI (flow cytometry for VASP) between sessions 1 and 2 in group 2 (clopidogrel group).

Group	Session 1	Session 2	Paired *t*-test
Group 1: Col/Epi closure time (aspirin group)	199.4 ± 10.32 s	170.1 ± 6.01 s	$P = 0.001$
Group 2: PRI (clopidogrel group)	34.33 ± 5.49%	54.27 ± 10.46%	$P = 0.001$

Col/Epi, collagen/epinephrine membrane; PFA, platelet function assay; PRI, platelet reactivity index; VASP, vasodilator-stimulated phosphoprotein.

Table 2. Comparison of bleeding severity between sessions 1 and 2 in the two groups.

Group	Bleeding severity in session 1	Bleeding severity in session 2	Paired *t*-test
Group 1 (aspirin group)	4.6 ± 0.82	4.35 ± 0.58	$P = 0.09$
Group 2 (clopidogrel group)	5.33 ± 0.76	5.01 ± 0.47	$P = 0.10$

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