

Prasugrel Versus Clopidogrel: A Comparative Examination of Local Bleeding After Dental Extraction in Patients Receiving Dual Antiplatelet Therapy

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Purpose: To study the effects of various parameters on local hemostasis after dental extraction in patients receiving different combinations of medications who had previously confirmed effective dual inhibition of platelet aggregation.

Materials and Methods: A total of 129 patients were enrolled. They underwent acute or planned percutaneous coronary intervention and their stomatological examination disclosed teeth that could have acted as foci and thus had to be removed. All patients took acetylsalicylic acid 100 mg and clopidogrel or prasugrel. Lidocaine with or without epinephrine was used for local anesthesia, and a gauze swab or suture was applied to help hemostasis.

Results: Bleeding time was significantly longer by an average of 10 minutes (+21%) in patients taking prasugrel ($P < .05$) compared with those taking clopidogrel. Use of a suture resulted in a significantly shorter bleeding time after anesthesia with or without epinephrine ($P < .05$). A considerably longer bleeding time was observed when anesthesia with no epinephrine was combined with gauze. In smokers, the bleeding time was shorter by 15% on average.

Conclusion: This study is the first to analyze differences in bleeding times between clopidogrel and prasugrel treatments during dental extraction. In general, prasugrel is associated with a considerably longer bleeding time; nevertheless, dental extraction can be performed safely with either combination.

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Coronary heart disease is one of the most common causes of death worldwide. Percutaneous coronary intervention (PCI) is the most widespread and effective therapy for coronary heart disease. It includes the implantation of a stent, extending a mesh of metal wire, and subsequent dilation of a narrowed segment of the vessel using a balloon catheter.¹ However, this ther-

apeutic modality poses new challenges for general dentists and oral and maxillofacial surgeons, because dual antiplatelet therapy (DAPT) is invariably required after PCI in the postoperative period after stent implantation, which increases the risk of bleeding associated with dental interventions. These patients receive combined clopidogrel and acetylsalicylic acid (ASA) every

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day to prevent acute stent thrombosis, which carries the risk of sudden cardiac death. If no effective inhibition of platelet aggregation is seen with this combination, another antiplatelet agent, prasugrel, can be introduced.

Dentists and oral and maxillofacial surgeons need to have a clear understanding of all the effects and rules of discontinuation of medications used in these patients.² This is necessary because, on the one hand, there is an increased risk of perioperative and postoperative hemorrhage occurring in the area of operation. On the other hand, even a transient discontinuation of the medicines might be associated with acute stent thrombosis. Only a few studies have been published on how to achieve effective hemostasis in patients undergoing dental extraction who receive DAPT. Several comparative studies have been performed in connection with the effects of clopidogrel and prasugrel³⁻⁶; however, to date, no study has examined the issue of hemostasis after dental extraction.

During PCI, patients receive a single oral loading dose of ASA 500 mg and clopidogrel 600 mg. After the intervention, patients have to take ASA 100 mg once a day for their entire lifetime and clopidogrel for months, depending on the type of stent. With a bare metal stent, patients must take clopidogrel for 1 to at least 6 months; with a drug-eluting stent, they must take it for 9 to 12 months; and after an event of acute coronary syndrome, they must take it for 12 months at a dose of 75 mg once a day.⁷ For endothelial progenitor cell capture stents, endothelialization of the stent occurs much sooner, so that DAPT can be withdrawn safely after only 6 weeks.⁸ However, a case has been reported in which an endothelial progenitor cell capture stent was implanted in a patient with a known gastric tumor because of severe coronary stenosis and then, after having confirmed complete endothelialization of the stent with optic coherence tomography, surgery could be performed successfully after 2 weeks, with no complication after discontinuation of DAPT.⁹

However, unjustified early discontinuation of DAPT is associated with an increased risk of stent thrombosis, which cannot be decreased even by the use of heparin. Discontinuation of DAPT is not recommended until complete endothelialization of the stent (usually 6 to 12 months). Interventions that cannot be delayed during this period should be performed only with maintained therapy. Transient use of clopidogrel 75 mg twice a day for a few weeks has been associated with clinical benefits¹⁰; therefore, clopidogrel treatment with increased doses also can be recommended as a temporary alternative for patients receiving ASA therapy or with an allergy to ASA.

Large prospective studies have shown that more than 20% of patients show no appropriate response to therapeutic doses of clopidogrel. These patients

have a 5- to 10-fold increased risk of stent thrombosis, stroke, and recurring myocardial infarction. If ineffective antiplatelet therapy is found in patients taking clopidogrel plus ASA, prasugrel instead of clopidogrel is recommended.¹ Its single loading dose is 60 mg, and it should be taken at a maintenance dose of 10 mg daily, with continued ASA.

Hemorrhages after dental extractions can be stopped in most cases by compressing the alveolar borders and placing a sterile gauze swab on the extraction wound, on which the patient has to bite. Although antiplatelet therapy can cause increased bleeding in patients undergoing dental extraction, no discontinuation of medications is recommended in patients receiving ASA monotherapy¹¹⁻¹³ or DAPT (ASA and clopidogrel).^{14,15} There have been only a few studies on effective hemostasis in such cases.¹⁶

In the present study, the authors examined bleeding times after dental extraction in patients receiving DAPT by comparing the results in patients receiving, in addition to ASA 100 mg once daily, clopidogrel at normal or increased doses (75 mg once or twice daily, respectively) or prasugrel (10 mg once daily). They also examined the possible effects of the anesthetic method of choice (lidocaine with or without epinephrine) and physical hemostasis.

Materials and Methods

PATIENTS

A total of 129 patients who underwent acute or planned PCI were enrolled in this study. Only patients whose antiplatelet therapy effectiveness (area under curve, ≤ 42) was confirmed by Multiplate analyzer (Roche Diagnostics International Ltd., Rotkreuz, Switzerland) aggregometry¹⁷ were enrolled.

In the total sample, 74% of patients were men ($n = 95$) and 26% were women ($n = 34$). Seventy percent of patients were 50 to 69 years old (11%, <49 yr old; 19%, >69 yr old). Diabetes mellitus was present in 34% of patients ($n = 44$), including patients with a known history of type 2 diabetes mellitus receiving therapy (diet with or without tablets with or without insulin) and those with fasting blood glucose levels of at least 7 mmol/L and glycated hemoglobin levels of at least $\geq 7\%$ despite no known history of or treatment for diabetes mellitus. When patients were divided into 4 categories based on body mass index (BMI), only 27% ($n = 35$) of the enrolled patients had a normal BMI; the others were classified as overweight ($n = 52$), moderately obese ($n = 36$), or severely obese ($n = 6$).

Blood pressure and heart rate were measured immediately before and after dental extractions. If blood pressure exceeded 160/95 mmHg, then patients were given sedative (alprazolam 0.25 mg) and antihypertensive (captopril 25 mg) tablets to chew. Dental

extraction was performed only when blood pressure decreased to lower than 160/95 mmHg.

Patients were divided into 2 groups: group 1 included 63 patients taking clopidogrel plus ASA and group 2 included 66 patients taking prasugrel plus ASA. Group 1 was divided into 2 subgroups: those receiving clopidogrel 75 mg twice a day ($n = 28$) and those receiving clopidogrel 75 mg once a day ($n = 35$). Prasugrel was taken at a dose of 10 mg/day (once a day). The 2 groups received ASA 100 mg. Other groups were formed based on the number of dental radices (≥ 1). Cases in which several teeth were extracted were studied separately (total, 37 cases).

The results were studied not only as a function of the methods of hemostasis and anesthesia (see below), but also according to BMI, blood pressure, smoking, potential accompanying diseases (diabetes mellitus or mild renal failure [decreased glomerular filtration rate]), certain medications taken by the patients (eg, β -blockers),¹⁸ and demographic variables.

Exclusion criteria included lack of consent to participate; concurrent use of agents that could influence hemostasis; lack of response or resistance to ASA, clopidogrel, or prasugrel; spontaneous international normalized ratio of at least 1.8; any known neoplastic or hematopoietic disease; oral infections; and febricity.

This study was approved by the regional science and research ethics committee of the Petz Aladár County Teaching Hospital (Győr, Hungary), and the study design conformed to the Declaration of Helsinki in all respects.

LOCAL ANESTHESIA

Based on the substances used for anesthesia, 2 groups were defined: 1 group received a 2% lidocaine injection containing no epinephrine and 1 group received a 2% lidocaine injection containing epinephrine 0.01 mg/mL. The latter is the usual anesthetic of choice in clinical practice, because the vasoconstrictor effect of epinephrine allows better bleeding control. In addition, because it inhibits the absorption of lidocaine, epinephrine prolongs the duration of the action of local anesthesia and decreases its toxicity. Epinephrine also has good diffusion ability: it causes an even 3-hour-long numbness when used for conduction and mucosal anesthesia.¹⁹ However, it should not be forgotten that local vasoconstriction can be followed by a reactive vasodilatation that can lead to a secondary hemorrhage. Two different anesthetics were used to study the frequency and extent of this effect.^{19,20}

EXTRACTION, ANTIHEMORRHAGIC PROTOCOL, AND PERIPROCEDURAL OBSERVATION

After removal of the teeth indicated as foci, the 2 different methods of physical hemostasis during

wound care after dental extraction were compared. One method included alveolar compression followed by letting the patients bite on a sterile gauze swab placed on the extraction wound. In the other group, the wound was sutured and then patients bit on a sterile gauze swab placed on the extraction wound. The patients were randomly assigned to 1 of these 2 groups.

Coagulation was checked continuously for 5 minutes and then at 15-minute intervals. If only slight leakage from the alveolus was seen, continuous observation was started again. The complete cessation of leakage was the primary endpoint.

After the bleeding was controlled, all patients were instructed to avoid physical exertion and sudden or prolonged forward bending. Patients were instructed not to smoke, suck on the wound, or poke it with the tongue. Patients were not allowed to eat for 2 hours after the extraction, and they were instructed to chew only on the side of the mouth opposite to the extraction for the remainder of the surgical day.

Patients had provisional bedrest for 24 hours after the extraction, and they were observed for the occurrence of any secondary hemorrhage.

STATISTICAL ANALYSIS

The Mann-Whitney *U* test (MWU) was used for pairwise comparisons, and the Kruskal-Wallis test was used when several groups were compared. The use of nonparametric analyses was justified by the fact that the data did not show a normal distribution in all cases (Shapiro-Wilk test, $P > .05$). Correlation analysis was performed for 2 continuous variables (age and BMI). Statistical calculations were performed using Statistica for Windows (StatSoft, Inc, Tulsa OK).

Results

When comparing all patients taking prasugrel versus clopidogrel, bleeding time was longer by an average of 10 minutes (+21%) in patients taking prasugrel (Table 1). Based on the MWU, this difference was shown to be significant (MWU, 1,603; group 1, $n = 66$; group 2, $n = 63$; $P = .0247$; 2-tailed level of significance, $P < .05$).

No statistical difference in bleeding times was observed by gender, age, or BMI, but there was a minor trend toward an increase in bleeding time with BMI.

The presence or history of accompanying diseases, such as hypertension or diabetes mellitus, and impaired renal function (glomerular filtration rate, >60 or <60 mL/minute) had no material influence on the results in either group.

When patients with diabetes were classified into subgroups (those with newly detected diabetes and

Table 1. BLEEDING TIMES AFTER DENTAL EXTRACTION IN PATIENTS TAKING PRASUGREL VERSUS THOSE TAKING CLOPIDOGREL

Dual Antiplatelet Therapy		Bleeding Time (minutes)			
Drug	Patients, n	Mean	Minimum	Maximum	Standard Deviation
Clopidogrel and aspirin	63	41.03	15.00	60.00	17.16
Prasugrel and aspirin	66	51.36	15.00	130.00	25.68

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those treated with diet with or without tablets with or without insulin), the difference in bleeding time between patients with and those without diabetes did not reach the limit of statistical importance.

Blood pressure immediately before and after the intervention was examined for any effect on bleeding time. Pre-extraction blood pressure values higher than 160/90 mmHg were always lowered by medication to at least the level before the intervention started; thus, blood pressure values no higher than 140/90 mmHg were included in the analysis. No effect on postextraction bleeding was found.

The effect of smoking status on bleeding time was examined. Significantly shorter bleeding times were observed in smokers (MWU, 1,519; group 1, $n = 79$; group 2, $n = 50$; $P < .05$, 2-tailed). When groups of smokers and nonsmokers were compared separately in the prasugrel and clopidogrel groups, no difference in bleeding times could be observed between groups in patients taking prasugrel, leading to the conclusion that the shorter bleeding time in smokers observed in the entire sample occurred only in patients taking clopidogrel.

For the other variables, neither the number of radices nor the dose (2.5 to 10 mg) of β -blockers (nebivolol, bisoprolol) was associated with a statistical difference in bleeding time.

EFFECTS OF LOCAL ANESTHESIA AND ANTIHEMORRHAGIC PROTOCOL

Prasugrel Group

The effects of different combinations of anesthesia and hemostasis on bleeding time were compared with Kruskal-Wallis analysis of variance. Using epinephrine-containing anesthesia plus gauze hemostasis as the reference, suturing resulted in a significantly shorter bleeding time in those receiving epinephrine-containing anesthesia ($n = 66$; $H_3 = 30.36026$, $P < .001$) and those receiving epinephrine-free anesthesia ($n = 66$; $H_3 = 30.36026$, $P < .05$). Epinephrine-free anesthesia combined with gauze was associated with a considerably longer bleeding time.

Clopidogrel Group

In this group, the bleeding time was examined in categories defined according to daily dose (75 mg once or twice daily). At a dose of 75 mg once daily (with the administration of ASA 100 mg once daily in parallel), the combination of epinephrine-free anesthesia and gauze swab hemostasis proved to be the most effective method. At doses of 75 mg twice daily and ASA 100 mg once daily, the least important prolongation of bleeding time was found with a combination of suturing and epinephrine-free anesthesia.

When the data were analyzed according to dose, statistical differences were observed between the effects of various combinations of anesthesia and hemostasis on bleeding time only in patients taking higher doses of clopidogrel. The combination of suturing and epinephrine-free anesthesia was found to be the most effective (Table 2).

When comparing the 2 treatment groups, the longest bleeding times were seen in those taking Prasugrel exclusively with a gauze swab independent of the epinephrine content of the anesthetic.

Discussion

PROTRACTED BLEEDING WITH PRASUGREL

When comparing groups of patients taking prasugrel or clopidogrel, a considerably longer bleeding time, by an average of 10 minutes (+21%), was observed in patients taking prasugrel. Because of their different mechanisms of action, ASA and clopidogrel or prasugrel perfectly complement each other in the process of inhibiting platelet aggregation. Although ASA is an antiplatelet agent acting through cyclooxygenase-1 and thromboxane A₂,²¹ clopidogrel and prasugrel are specific and potent inhibitors of adenosine diphosphate (ADP)-mediated platelet aggregation; thus, these agents and ASA increase each other's effect in a synergistic way. At the same time, although clopidogrel and prasugrel are thienopyridine derivatives, they are prodrugs and exert their action at the same point of attack as irreversible inhibitors of the thrombocyte P2Y₁₂ ADP receptor.²² Studies have shown that clopidogrel can exert an irreversible effect

Table 2. SIGNIFICANT DIFFERENCES IN BLEEDING TIMES ARE SEEN WITH HIGHER DOSES OF CLOPIDOGREL

	Daily Clopidogrel (mg)	P Values for Comparisons of Different Combinations			
		LE + GS	L + GS	L + S	LE + S
LE + GS	75 × 1		.12	.91	1.00
L + GS	75 × 1	.12		1.00	.33
L + S	75 × 1	.91	1.00		1.00
LE + S	75 × 1	1.00	.33	1.00	
LE + GS	75 × 2		1.00	.0024*	.04*
L + GS	75 × 2	1.00		.0032*	.04*
L + S	75 × 2	.0024*	.0032*		1.00
LE + S	75 × 2	.0465*	.0479*	1.00	

Abbreviations: L + GS, lidocaine anesthesia without epinephrine and with only gauze swab hemostasis; L + S, lidocaine anesthesia without epinephrine and with suture; LE + GS, lidocaine with epinephrine anesthesia and only gauze swab hemostasis; LE + S, lidocaine with epinephrine anesthesia and suture.

* Significant differences.

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on a maximum of 30% of platelets, whereas prasugrel acts on 60 to 70% of them. Its greater efficacy compared with clopidogrel is due to its considerably simpler metabolism, which allows more active metabolites to enter the circulation. Furthermore, effective inhibition can be attained with prasugrel in patients who have not responded appropriately to clopidogrel owing to variability of the CYP450 isoenzyme (nonresponders). However, the stronger effect also is associated with enhanced undesirable effects; in clinical trials, prasugrel considerably increased the rate of major hemorrhages, mainly in elderly patients.²³⁻²⁵

This difference also explains the major differences in bleeding times observed between groups. Based on these differences, when a gauze swab is used for hemostasis, a considerably longer bleeding time is to be expected in patients taking prasugrel than in patients taking clopidogrel.

EFFECT OF CLOPIDOGREL IS NOT PROPORTIONAL TO DOSE

The dose of clopidogrel had no meaningful effect on bleeding time when examined separately. The antiplatelet efficacy of clopidogrel is dependent on, but not proportional to, dose. That is, more rapid and in some cases more effective inhibition can be attained with a higher dose; however, when the dose is increased above a certain level, its positive effect is not proportional and the hemorrhagic (eg, gastrointestinal) complications can increase considerably.

Nonetheless, the transient use of clopidogrel 75 mg 2 times daily for a few weeks might be associated with clinical benefits.¹⁰ At the usual dose of clopidogrel 75 mg once daily, no statistical difference was observed among the various combinations of anesthesia and hemostasis. Interestingly, when the dose of clopidogrel was increased, a combination of suturing and epinephrine-free anesthesia proved to be the most effective procedure. When the clopidogrel group was examined as a whole, the same combination showed important advantages as a means of effective hemostasis. These findings can be explained by the fact that although the local vasoconstrictor effect of epinephrine in the anesthetic is strong, it is only transient and thus cannot support hemostasis in the long-term.

SUTURING IS RECOMMENDED WITH PRASUGREL

As described earlier, suturing resulted in a meaningfully shorter bleeding time with epinephrine-containing and epinephrine-free anesthesia. This finding confirms the necessity of effective and prolonged constriction of the wound margins (ie, the use of a suture) in patients taking prasugrel. In this way, the risk of bleeding can be decreased effectively.

IN SMOKERS, BLEEDING TIME IS DECREASED ONLY WITH CLOPIDOGREL

Bleeding time in smokers was approximately 15.8% shorter on average, and the difference was important. No meaningful shortening of bleeding time was seen in smokers receiving prasugrel plus ASA therapy; however, this shortening was observed in smokers who received clopidogrel plus ASA. Although smoking stimulates platelet activation, its effects on hemostasis are not completely understood.²⁶ Moreover, it was not previously recognized that this effect cannot prevail clinically in patients taking prasugrel. This can be explained by the fact that, unlike clopidogrel, prasugrel can irreversibly inhibit thrombocytes at a much higher rate, effectively compensating for the increased platelet activation caused by smoking and the microangiopathy and vasospasm caused by smoking.

NUMBER OF DENTAL RADICES

The number of dental radices was not associated with a statistical difference in bleeding time in either treatment group regardless of the methods of anesthesia and hemostasis used.

OTHER CLINICAL FACTORS

Bleeding time was not meaningfully influenced by gender, age, BMI, history of hypertension, diabetes mellitus, mild renal impairment, use of β -blockers, or elevated blood pressure in either treatment group.

This finding is somewhat counterintuitive, because some patient groups also examined in this study (those with metabolic syndrome, diabetes mellitus, and high BMI) were found to be characterized by higher-than-average platelet activity.²⁷

SECONDARY HEMORRHAGE

Secondary hemorrhage after coagulation was observed in only 2 cases. The affected patients took clopidogrel, they received gauze swab hemostasis, and the hemorrhage started in the second and third hours after extraction. In these cases, it was the patients' behavior that triggered the bleeding: 1 patient bent forward suddenly and then for a longer time to tie his shoelace and 1 patient climbed stairs too soon after the intervention. The secondary bleeding in these cases is likely to have been a result of a suddenly developed hyperemia in the alveolus and a local increase in pressure. Repeated hemostasis with a gauze swab and positioning the patients at rest stopped the bleeding effectively.

Based on the results of the present study, which is the first to analyze differences in bleeding times after tooth removal in patients taking clopidogrel versus prasugrel, the authors suggest that dental extraction can be performed safely with due precautions, appropriate instruction, and cooperation of patients who receive DAPT (clopidogrel plus ASA and prasugrel plus ASA). No discontinuation of DAPT is indicated in such cases.

With prasugrel, a more intense and delayed bleeding is to be expected that can last up to 2 hours. Accordingly, putting the patient at rest and under observation for several hours is necessary, with special regard to the fact that secondary hemorrhages were observed only with inadequate patient compliance.

After tooth extraction, a method of attaining hemostasis that uses suturing plus a gauze swab represents a safer and more effective method than combinations containing clopidogrel or prasugrel.

In smokers who take clopidogrel, a shorter bleeding time is expected. However, no shorter bleeding time is expected in smokers taking a combination of prasugrel and ASA.

The presence or absence of epinephrine in the anesthetic has no meaningful effect on bleeding time.

It is extremely important to instruct patients to avoid any sudden or long-lasting forward bending and physical efforts, such as prolonged climbing of stairs, for 24 hours. Surprisingly, the number of dental radices seemed to have no effect on bleeding time. In addition, gender, age, BMI, hypertension, diabetes mellitus, mild renal impairment, use of β -blockers, and elevated blood pressure did not influence the bleeding time, regardless of the type of antiplatelet drug taken.

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