



Perspective

Management of patients taking antithrombotic drugs before dental surgery



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Antithrombotic drugs are widely used for the treatment and prevention of thrombosis. However, hemorrhage as the main side effect should be concerned before dental surgery such as tooth extraction, soft tissue excision, and so on. Therefore, we should know how to manage the patients who take antithrombotic drugs before the dental surgery to decrease the risk of hemorrhage and complications after dental surgery.

According to the mechanism of inhibiting thrombosis pathways, antithrombotic drugs are classified into

antiplatelet agents, anticoagulants, and fibrinolytic agents.¹ Fibrinolytic agents are usually used for thrombi degradation in surgery or emergency, while antiplatelet agents and anticoagulants are commonly used in the long-term treatment for prevention of thrombosis. Management of patients taking antithrombotic drugs should be cautious before doing the invasive dental therapy.²

Antiplatelet agents such as aspirin, clopidogrel, ticlopidine, prasugrel, and ticagrelor are common drugs which inhibit platelet activation through different pathways.¹ Assessing platelet activation and bleeding risk is important for patients who take antiplatelet agents. PFA-100 is approved particularly to monitor patients taking aspirin.³ Moreover, both bleeding time and VerifyNow can be used for patients taking aspirin and clopidogrel.^{3,4} Dezsi et al.² reviewed the latest evidence and suggested that the

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alteration or discontinuation of single or dual antiplatelet therapy consisting of aspirin and clopidogrel is not recommended for any dental procedures. For high bleeding risk dental procedures, the use of local hemostatic measures such as mechanical pressure, hemostatic agents (e.g., Gelfoam® or Surgicel®), suturing, and tranexamic acid mouthwash is recommended.² Moreover, there is strong evidence provided by the American Dental Association to suggest that it is not necessary to alter antiplatelet therapy prior to dental intervention for most patients taking antiplatelet agents.⁵

Anticoagulants including vitamin K antagonists (e.g., warfarin), heparins and low-molecular-weight heparins (LMWHs), direct thrombin inhibitors, and factor Xa inhibitors. Warfarin blocks the vitamin K-epoxide reductase to prevent vitamin K-dependent clotting factors, proteins C and S, activation, and interferes with the synthesis of the clotting proteins including factors II, VII, IX and X.⁶ Cessation of the medicine 5 days before the surgery and perioperative evaluation including prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR) is indicated before the surgery. Otherwise, vitamin K, prothrombin complex concentrates, and fresh frozen plasma should be used if in emergency.^{7,8} However, based on the available evidence and extensive clinical experience, the interruption of vitamin K antagonist treatment before dental procedures is not recommended for interventions that are unlikely to cause bleeding, and for low and high bleeding risk procedures if the INR of the patient is ≤ 3.5 24 h before the planned intervention. If $\text{INR} \geq 3.5$, dose adjustment is required, and the procedure should be delayed until the patient's INR has been reduced to less than 3.5. According to current recommendations, this strategy applies for both low and high bleeding risk dental procedures.²

Heparins are divided into two classifications: unfractionated heparin and LMWH. Unfractionated heparin causes anticoagulation effect in multiple ways, but the main mechanism is through elevating the activity of antithrombin III and further contributing to conformational change of coagulation factor Xa and IIa. Unfractionated heparin also leads to inhibition on factors IXa, XI, and XIIa.⁶ Cessation of the medicine 6 h before the surgery and aPTT monitoring before surgery are necessary. Protamine sulfate can be prepared as antagonist if having bleeding emergency. LMWH also binds to antithrombin III but only inhibits factor Xa.⁹ Thus, it is not necessary to monitor aPTT or INR as warfarin and heparin due to the short half-life period which is about 3–4 h for the LMWH. However, cessation of the medicine 12–24 h before the surgery is better if possible.⁹

Direct oral anticoagulants include the direct factor Xa inhibitors (e.g., rivaroxaban, edoxaban, and apixaban) and the direct thrombin inhibitors (e.g., dabigatran).² Factor Xa is crucial during coagulation propagation. It is not only activating factor X but also amplifying coagulation by converting prothrombin to thrombin which further triggers the pathway of coagulation. Therefore, factor Xa inhibitors aim at suppressing factor Xa in indirect or direct way to achieve anticoagulation effect. Direct factor Xa inhibitors (e.g., rivaroxaban, edoxaban, and apixaban) are unnecessary to be discontinued for minor procedures, but should be stopped 1–7 days before surgery depending on

the patient's renal and liver function if massive bleeding during surgery is concerned. Otherwise, aPTT, PT, and anti-factor Xa can be monitored if complete hemostasis is required.¹⁰

Direct thrombin inhibitors (e.g., dabigatran) have the main function in inhibiting intrinsic activity of the thrombin directly. Although there is no linear relation between aPTT and the degree of coagulopathy caused by direct thrombin inhibitor, normal aPTT rules out the significantly abnormal amounts of direct thrombin inhibitor.¹¹

The most recent information suggests that simple surgical interventions with a low bleeding risk such as dental extractions do not require the interruption of direct factor Xa or direct thrombin inhibitors in patients with normal renal function. Where possible, it is recommended that the procedure is performed at trough concentrations of direct factor Xa or direct thrombin inhibitors, i.e. 12 or 24 h after the last intake depending on twice-daily or once-daily dosing. Interventions at peak plasma concentration should be avoided.² For patients taking direct factor Xa or direct thrombin inhibitors who require a dental procedure with a higher risk of bleeding complications, it is recommended to delay the morning dose of once-daily agents (rivaroxaban, edoxaban) on the day of dental treatment, and skip one dose of twice-daily medications (apixaban, dabigatran). For patients usually taking their rivaroxaban or edoxaban dose in the evening, there is no need to modify their medication schedule before dental treatment. If complete hemostasis has been achieved, direct factor Xa or direct thrombin inhibitors can be resumed six-to-eight hours after the intervention.²

In summary, there is general agreement that treatment regimens with older anticoagulants (e.g., warfarin) and antiplatelet agents (e.g., clopidogrel, ticlopidine, prasugrel, ticagrelor, and/or aspirin) should not be altered before dental procedures for most patients. In addition, on the basis of limited evidence, general consensus appears to be that in most patients who are receiving the newer direct-acting oral anticoagulants (i.e., dabigatran, rivaroxaban, apixaban, or edoxaban) and undergoing dental interventions (in conjunction with usual local measures to control bleeding), no change to the anticoagulant regimen is required. The risks (i.e., thromboembolism, stroke, myocardial infarction) of stopping or reducing these medication regimens far outweigh the consequences of prolonged bleeding, which can be controlled with local measures. Any suggested modification to the medication regimen prior to dental surgery should be done in consultation and on advice of the patient's physician.⁵

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

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