GENERAL REVIEW

UDC: 615.03:615.273]:616.31
https://doi.org/10.2298/VSP170719128B

Dental management of patients taking antiplatelet, oral anticoagulant and novel anticoagulant medications

Stomatološko zbrinjavanje pacijenata na terapiji antitrombocitnim, oralnim antikoagulantnim i novim antikoagulantnim lekovima

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Key words:
tooth diseases; fibrinolitic agents; anticoagulants; oral surgical procedures; treatment outcome.

Ključne reči:
zub, bolesti; fibrinolitici; antikoagulansi; hirurgija, oralna, procedure; lečenje, ishod.

Introduction

Antiplatelet and anticoagulant drugs are used widely in the long-term prevention and treatment of arterial and venous thrombosis. Oral surgery in the patients taking these drugs is always challenging and the risk of bleeding needs to be balanced against the risk of thromboembolic complication in case of treatment cessation.

Recently, a group of drugs, referred to as new oral anticoagulants (NOACs), including direct thrombin inhibitors and factor Xa (FXa) inhibitors, have started to be in clinical use. These drugs are mostly indicated to prevent a stroke and systemic embolisms in patients with atrial fibrillation, and for prevention of thrombosis after the elective hip and knee surgery [1, 2]. It is likely that NOACs will be increasingly used in the coming years. Therefore, it is very important for dentists to be familiar with the mechanisms of action of the drugs, their interaction with the drugs commonly prescribed in dentistry, possible bleeding complications and their prevention and treatment.

The aim of this article is to show basic characteristics of antiplatelet, oral anticoagulants and NOACs, and based on the literature review, to present current recommendations regarding the dental treatment of patients taking these medications.

Dental treatment of patients taking antiplatelet drugs

Low doses of aspirin, clopidogrel, ticlopidine and dipyridamole are the most frequently administered antiplatelet drugs. The most common indications for a long-term antiplatelet therapy are ischemic cardiovascular and cerebrovascular diseases and peripheral arterial disease [3, 4]. The mechanisms of action of these drugs are different. Aspirin irreversibly inactivates cyclo-oxygenase, the enzyme necessary for synthesis of thromboxane A_2, which is important for platelet aggregation. Thienopyridines (clopidogrel, ticlopidine and prasugrel) are inhibitors of adenosine-diphosphate receptors. Like aspirin, these drugs affect the activity of platelets during their lifetime (7–10 days). Dipiridamole inhibits the reuptake of adenosine and increases cAMP [5].

The patients taking antithrombotic agents may have prolonged bleeding time, but this test is not reliable enough to predict the bleeding risk after oral surgical procedures. Moreover, despite using antithrombotic agents, the bleeding time may be within the normal range [6]. The platelet aggregation test is more sensitive, but it is not in use in everyday practice [6, 7]. That is the reason why any platelet function test is not commonly recommended to the patients taking antiplatelet drugs before the dental surgical procedure.

For fear of prolonged and excessive bleeding, discontinuation of antiplatelet drugs several days before a dental surgery was often recommended in the past. This therapeutic approach can expose patients to the risk of thromboembolism [8–11]. According to the current recommendations based on numerous researches, there is no need to stop antiplatelet medications before most dental surgical procedures, including tooth extraction [6, 7, 12–15].

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A recently published review of the literature have showed that of at least 1,283 patients receiving single or dual antiplatelet medications who underwent at least 2,343 dental surgical procedures, including at least 2,308 simple and surgical tooth extractions in at least 1,334 visits, no more than 35 patients (2.7% of patients and 2.6% of visits) had bleeding complications requiring local measures for hemostasis and only 2 patients (0.2%) needed more than local measures to control hemorrhage. On the other hand, there were several reports of thrombotic complications when antiplatelet drugs were stopped due to dental procedures. The author concluded that bleeding is a rare complication after tooth extractions in the patients taking antiplatelet medications and, therefore, there is no need to discontinue these drugs for a dental surgery [16].

Due to the different mechanisms of action, a combined use of antiplatelet drugs may have a synergistic effect. The combination of low-dose aspirin and clopidogrel is increasingly used. The most common indication for a dual antiplatelet treatment is prevention of thrombotic complications after percutaneous insertion of a coronary stent [5, 17]. As recommended by the American College of Chest Physicians, a dual antiplatelet therapy should not be interrupted perioperatively within 6 weeks of placement of a metal stent or within 6 months of placement of a drug-eluting stent [18]. Premature discontinuation of a dual antiplatelet therapy is well recognized as a risk factor for stent thrombosis [17].

Despite its benefits, a dual antiplatelet therapy increases the risk of spontaneous and postoperative bleeding [16]. A small number of studies with a limited number of patients were conducted in order to estimate the risk of bleeding after oral surgical procedures in the patients taking dual antiplatelet drugs. However, the results of all these studies suggested that dental extractions can be safely done without interrupting a dual antiplatelet therapy applying only local hemostatic measures [12, 13, 15, 16, 19, 20].

Dental treatment of patients taking oral anticoagulant drugs

Oral anticoagulants are coumarin derivatives and vitamin K antagonists. These drugs inhibit vitamin K epoxide reductase, an enzyme responsible for the cyclic interconversion of vitamin K. The lack of the active form of vitamin K which is necessary for carboxylation of the glutamic acid residue on coagulation factors II, VII, IX and X results in the production of biologically inactive coagulation factors [2].

The most common indications for oral anticoagulant therapy (OAT) are atrial fibrillation, the mechanical prosthetic heart valves, deep vein thrombosis and pulmonary embolism [21]. The International Normalized Ratio (INR) is the test used to monitor the effect of OAT. The therapeutic range of the INR values is 2.0 to 3.0 in most cases. For the patients with the highest risk of thromboembolism, for example those with the mechanical prosthetic heart valves, higher INR values, up to 3.5 or even 4.0, are recommended [21–23].

Acenocoumarol, warfarin and phenprocoumon are the most commonly used oral anticoagulants. All these drugs are used orally and they are rapidly absorbed from the gastrointestinal (GI) tract. They have high bioavailability and circulate mostly bounded to plasma proteins, mainly albumin. They are metabolized by the liver via cytochrome P-450 enzyme system, mostly by hydroxylation, and excreted through urine. Half-lives of these drugs are different (acenocoumarol 8–11 h, warfarin 36–42h, phenprocoumon 5–6 days). Coumarin derivatives have a slow onset of action because their antithrombotic effect requires reduction of vitamin K-depending coagulation factors in the plasma and depends on half-lives of these factors. Half-lives of vitamin K-depending factors are different (4–6 hours for FVII, 18–30 hours for FIX, 48 hours for FX and 60–72 hours for FII). Following the administration of OAT, it takes usually 2–3 days for the initial effect on the INR value. On the other hand, the effect of these drugs lasts for several days after cessation of OAT. This time it is necessary to have a complete excretion of the drug from the body for synthesis of new vitamin K-dependent factors [2, 24, 25].

The most serious complication of OAT is bleeding. Depending on the INR levels and severity of the bleeding complication, several therapeutic approaches are recommended: to reduce or temporarily interrupt OAT, or to introduce vitamin K orally or by slow IV infusion. Life-threatening bleeding could be treated by fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), or recombinant factor VIIa (rVIIa) [2, 24, 25].

Many drugs can increase or decrease the anticoagulant effect of oral anticoagulants. The most commonly used drugs in dentistry which can interact with OAT are: carbamazepine, metronidazole, erythromycin, sulphonamides, tetracycline and miconazole (oral gel). Except carbamazepine, all mentioned drugs increase the effect of OAT [25–27]. Due to the risk of bleeding, aspirin and other nonsteroidal anti-inflamatory drugs (NSAIDs) should be avoided. Paracetamol is considered to be the drug of choice for pain relief in the patients taking OAT.

The oral surgical procedures in the patients taking OAT have been studied a lot. The results of most studies show that dental extractions can be performed safely without discontinuing OAT if INR is within the therapeutic range (INR $\leq$ 4.0) and if appropriate local hemostatic measures are provided [14, 28–38]. The most commonly used local hemostatic agents and measures are: oxidized regenerated cellulose, absorbable gelatin or collagen sponges, fibrin glue, antifibrinolytics applied directly into the wound or in the form of a solution as a mouthwash and wound suturing [39–41].

A recently published review of the literature showed that over 99% of anticoagulated patients who continued OAT had no postoperative bleeding requiring more than local hemostatic measures. In more than 5,431 patients who underwent over 11,381 surgical procedures, bleeding that required more than local hemostasis occured only in 31 (~0.6%) of patients. Many of these patients had higher INR therapeutic levels than currently recomended. On the other hand, among at least 2,673 patients whose OAT was reduced or withdrawn for at least 2,775 visits for the dental procedures, there were 22 embolic complications (0.8% of cessations), including 6 fatal events (0.2% of cessations). The authors concluded that

the thromboembolic risk in the patients whose OAT was interrupted for a dental surgery exceeded the risk of significant bleeding in the patients whose anticoagulation is continued [38].

A certain number of patients, mostly those with the highest risk for thrombosis, take OAT and aspirin combined. A strict recommendation for the combined OAT-aspirin therapy was given only to the patients with the prosthetic heart valves [42–44]. However, many patients with atrial fibrillation are receiving the combined OAT-antiplatelet therapy as well [45, 46]. The addition of aspirin to OAT seems a rational therapeutic approach for the patients receiving OAT in whom cardiovascular prophylaxis is indicated. Despite the advantages of this combined therapy, there is a higher risk of experiencing a spontaneous and prolonged, excessive bleeding during and after surgical procedures [34]. There is a lack of data regarding this group of patients who required a dental surgery. The results of the published studies, which comprised a limited number of patients, show that dental extractions can be safely done without interrupting either OAT or antiplatelet therapy if INR is within the therapeutic range, and if proper local hemostatic measures are applied [14, 34].

Dental treatment of patients taking new oral anticoagulants

In the last few years, new oral anticoagulant drugs, direct thrombin inhibitors and FXa inhibitors, are available for clinical use. Compared to vitamin K antagonists, NOACs have certain advantages: rapid onset and direct mode of action, predictable anticoagulant response, wide therapeutic index, limited drug and food interactions and no need for routine monitoring of their effect [47, 48].

Direct thrombin inhibitors

Dabigatranetexilate is a reversible thrombin inhibitor that binds on the thrombin, thus preventing fibrinogen conversion into fibrin. It reversibly inhibits free and clot-bound thrombin. When taken orally, it is rapidly absorbed from the GI tract. After hydrolysis in plasma, it is converted into an active form with a rapid onset of action and reaches the peak plasma concentration after 0.5–4 hours [49]. Its terminal half-life is 12–17 hours and up to 27 hours in the patients with severe renal dysfunction [47–50]. 80%–85% of the drug is eliminated by the kidneys and the rest via the bile. Administered in the common doses of 150 mg, or 110 mg twice daily, dabigatran reaches a stabile concentration in plasma 2–3 days after the initiation of therapy. The duration of its effect is about 22 hours.

The RELY-ABLE multicentre study conducted in 2009 assessed the efficacy and bleeding complications of dabigatran compared to warfarin in the patients with atrial fibrillation. The results of the study showed that patients taking dabigatran in the dose of 150 mg twice daily had lower rates of stroke and systemic embolism, but similar rates of major bleedings. Dabigatran in the dose of 110 mg twice daily showed a similar efficacy in preventing systemic embolism and stroke, but lower rates of major bleedings compared to warfarin [51]. The drug was approved by the European Medicines Agency (EMA), and the Food and Drug Administration (FDA) for the prevention of stroke and systemic embolism in the patients with nonvalvular atrial fibrillation as well as for thromboprophylaxis after the prosthetic hip and knee joint replacement.

A routine coagulation monitoring for the patients taking dabigatran is not required. Thrombin clotting time (TT) and ecarin clotting time are the most sensitive test for monitoring the effect of dabigatran. The activated partial thromboplastin time (aPTT) is less sensitive, but widely available and it can be used to check coagulation in case of emergency. Checking INR is not recommended, because this test is insensitive [47–50].

In case of bleeding in the patients taking dabigatran, a treatment option depends on the severity of a bleeding complication. For minor bleedings, it is recommended to postpone the next dose or discontinue the drug. Any discontinuation of the drug should be carefully considered due to the risk of thromboembolism. In case of a moderate and severe bleeding, treatment options include fluid replacement and hemodynamic support, the use of rVIIa factor prothrombin complex concentrates and hemodialysis [47, 49, 50]. Recently, FDA approved the use of idarucizumab, monoclonal antibody fragment, for reversal of the effect of dabigatran in urgent surgical procedures or in life threatening bleeding situations [49, 52].

There is a risk of prolonged bleeding during and after invasive dental procedures, including dental extractions, in the patients taking dabigatran. It is estimated that there is a similar risk of peri-procedural bleeding in the patients taking dabigatran and warfarin [53, 54]. There is also the opinion that the patients taking dabigatran should be treated similarly to those receiving low-molecular-weight heparins [48]. Up to now, there has been a lack of well-designed clinical trials that would include a number of patients taking dabigatran and require a dental surgery [49, 55, 56].

Some authors suggested skiping the dose on the morning of the procedure [57]. However, most authors suggested that dabigatran should be continued in case of a minor dental surgery, including simple dental extractions [47, 48, 50, 52, 58–60]. To minimize the risk of postoperative bleeding, the procedure should be performed as long after the last dose of dabigatran as possible, trying to avoid the surgery when the drug has a maximal anticoagulant effect. The procedure should be carried out as atraumatic as possible, applying proper local hemostatic measures. Discontinuation of dabigatran, usually 24 hours before the surgery, should be discussed with a patient´s physician and considered only in case of a high risk procedure. Discontinuation of the therapy depends on the risk of postoperative bleeding, the risk of thromboembolism and renal function. Interruption of dabigatran increases the risk of stroke or systemic embolism and if necessary, the drug should be resumed as soon as possible, usually 24–48 hours after the procedure. Paracetamol should be prescribed for pain relief in the postoperative period. Aspirin and other NSAIDs should be avoided. Drugs that decrease the effect of dabigatran such as rifampicin, dexamethasone and car-

bamazepine, or increase its effect such as ketoconazole, itraconazole, erythromycin and clarithromycin, should be avoided or prescribed carefully [47–49, 55].

Factor Xa inhibitors

Rivaroxaban is a reversible direct inhibitor of FXa that catalyzes activation of prothrombin into thrombin. Rivaroxaban is administered orally, once daily. It has a rapid onset of action and reaches the peak plasma concentration after 2.5–4 hours. Its terminal half-life is 5.7–9.2 hours that can be prolonged up to 12–13 hours in the patients > 75 years old. About 66% of the drug is excreted in the urine and the rest in the feces [47–50]. Indications for the use of rivaroxaban include thromboprophylaxis after the prosthetic hip and knee joint replacement. ROCKET-AF, clinical trial showed that rivaroxaban was noninferior to warfarin for the prevention of stroke and systemic embolism in patients with atrial fibrillation [61, 62].

The patients taking rivaroxaban slightly prolonged prothrombin time (PT) and aPTT. The anti-factor Xa assay is considered to be the most accurate test for monitoring the effect of dabigatran, but a routine monitoring of coagulation, similarly to other NOACs, is not required. There is no specific reversal agent for rivaroxaban. In case of a minor bleeding, discontinuation of the drug could be sufficient because duration of the drug effect is short. In case of more serious bleeding complications, rVIIa or prothrombin complex concentrate can be used [47–49].

Drugs that are cytochrome P450 inhibitors such as erythromycin, ketoconazole, itraconazole, voriconazol and posaconazole may increase the risk of bleeding by increasing the concentration of rivaroxaban. Opposite to this, drugs that are cytochrome P450 inducers such as rifampicin may decrease the effect of rivaroxaban [47–49].

Apixaban is recently introduced reversible direct inhibitor of FXa with the same therapeutic indications. The results of the apixaban for Reduction in Stroke and Other Thromboembolic Events (ARISTOTLE) trial showed that apixaban was as effective as warfarin in the prevention of stroke and embolism in the patients with atrial fibrilation with fewer bleeding complications [63]. The drug is administered orally, twice a day. It reaches the maximum plasma concentrations in 3 hours. The half-life of the drug is about 12 hours. About 75% of the drug is eliminated in the feces and 25% in the urine. As for rivaroxaban, the anti-factor Xa assay is considered to be the most accurate test for monitoring its effect and there is no specific antidote. In mild cases of bleeding, discontinuation of the drug could be sufficient, while in more serious cases, the rVIIa or prothrombin complex concentrate can be used [49].

There is insufficient data in the literature about the safety of dental surgical procedures in patients taking FXa inhibitors [49, 54, 56, 59, 64]. However, similar recommendations given for dental treatment of the patients taking dabigatran are applicable to the patients taking FXa inhibitors [47, 48, 50, 52, 58].

Conclusion

Based on the results of the studies, there are clear recommendations in the literature that minor oral surgical procedures, including tooth extractions, can be safely performed in the patients taking antiplatelet and oral anticoagulant drugs without therapy interruption if the proper local hemostatic measures are applied. Similar recommendations were given for the dental treatment of patients taking NOACs. However, these recommendations are mainly based on the experts' opinion, rather than on the results of clinical studies. Therefore, further researches of the safety of dental extractions in the patients taking NOACs are necessary.

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Received on July 19, 2017.
Revised on August 30, 2017.
Accepted on September 11, 2017.
Online First September, 2017.