REVIEW

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State of the art regarding anticoagulant and thrombolytic therapy in dental procedures

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Abstract

Patients with anticoagulant therapy have a high thromboembolic risk. Due to the rich oro-maxillofacial vasculature and the fact that some dental procedures may cause a bleeding, the physician should be able to correlate this risk with the hemorrhagic risk. Dental procedures are a trigger for psychic stress. One of the most important changes in acute stress is in cardiovascular system. In healthy patients, these changes are reversible and have no significant consequences, but in patients with cardiovascular diseases, the response to the catecholamine stress can cause organic lesions resulting in an acute myocardial infarction or stroke. This review explores in a concise manner the biochemical changes concerning anticoagulation and thrombolytic treatment in dental procedures.

Keywords: anticoagulants, hemostasis, heparin, thrombolytic therapy.

Introduction

Anticoagulation medication is one of the most commonly used treatment methods in patients presenting in the medical service. Cardiovascular, neurological diseases or conditions requiring interventions with prolonged bed immobility are currently increasing their prevalence rates. In the case of an unfavorable status of the oral cavity, the manifestations of these conditions may worsen, which is why the dentist frequently encounters situations in which he has to deal with this type of patient.

Patients with anticoagulant therapy have a high thromboembolic risk. Due to the rich oro-maxillofacial vasculature and the fact that some dental procedures may cause bleeding, the dentist should be able to correlate this risk with the hemorrhagic risk. Dental procedures are a trigger factor for psychic stress. The fear of pain caused by injection, extraction, and possible complications during dental treatments will increase these conditions, causing anxiety and sometimes-even depression. One of the most important changes in acute stress is related to cardiovascular system. In healthy patients, these changes are reversible and have no significant consequences, but in patients with cardiovascular disease, the response to the catecholamine stress reaction can cause organic lesions resulting in an acute myocardial infarction or stroke [1].

Coagulation mechanism

Coagulation involves the interaction of several components: vascular endothelium, platelets and plasma glycoproteins (GPs). It is related to a positive and negative feedback mechanism and counterbalanced by the fibrinolytic system. Endothelium plays an important role in maintaining blood flow and limiting clot formation only locally. After producing a vascular lesion, endothelial cells release procoagulant factors, such as tissue factor (TF), plasminogen activator inhibitor (PAI), von Willebrand factor (vWF), and protease-activated receptors (PARs). In order to inhibit clot formation, it releases tissue factor pathway inhibitor (TFPI), heparan sulfate, thrombomodulin, protein C endothelial receptor, tissue plasminogen activator (tPA), ecto-adenosine diphosphatase (ADPase), prostacyclin, nitric oxide, A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), metalloproteinase with the role of limiting the procoagulant activity of vWF [2–4].

Platelets exhibit several roles during hemostasis, such as: adhesion, degranulation, aggregation, fusion and procoagulant [3]. After endothelial injury, the subendothelial matrix rich in vWF and collagen is exposed, which promote platelet adhesion through GP (Ib) IX/V and Ia/IIa and initiation of activation [4]. During adhesion, GP IIb/IIIa platelet receptors, which bind to fibrinogen and vWF, are activated, resulting in platelet aggregation. The activated platelets release the content of alpha and dense granules into the extracellular space. The degranulation process is dependent on the synthesis of prostaglandins. Following degranulation, platelets release procoagulant material into the extracellular space, such as: vWF, factor V, β-thromboglobulin, platelet factor 4 (PF4), fibrinogen, adenosine diphosphate (ADP), serotonin, calcium, etc. Released substances, especially ADP, facilitate a positive feedback loop that accentuates the release of ADP and thromboxane A2, resulting in secondary aggregation [4]. This physiological process aims at forming the thrombus and stopping hemorrhage, followed by its dissolution and restoration of circulation in the injured vessel. Hemostasis is divided into

three stages: primary hemostasis, secondary hemostasis and fibrinolysis [5].

Primary hemostasis

The first stage of hemostasis begins at the time of vascular injury and is performed with the participation of four constituents: vascular wall, platelets, vWF and fibrinogen, the latter two having a role in the adhesion and aggregation of the platelets.

Normally, platelets have a diameter of 2–5 μm and live 5–7 days [6]. Thrombopoietin is synthesized in bone marrow and smooth muscle cells and plays an important role in platelet formation. Thrombopoietin elimination from the bloodstream occurs due to its uptake into platelets [7]. Thrombocytes have no nucleus, but their ability to respond to a variety of stimuli is largely due to a high content of alpha granules and dense granules. These alpha granules contain the following important components in the process of primary hemostasis: fibronectin, platelets derived from growth factors, transforming growth factor-beta (TGF-β), PF4, β-thromboglobulin, factors V and VIII, fibrinogen, adhesive proteins, such as vWF and factor X. The dense granules in platelet composition contain ADP, adenosine triphosphate (ATP), epinephrine, serotonin, histamine, and calcium ions [8]. In addition to all of the above factors, platelets also contain myosin, contractile proteins, actin, mitochondria, fibrin stabilizers (factor XIII), enzymatic systems, smooth muscle cells and fibroblasts, vascular endothelial cell growth factors, lattices, endoplasmic and Golgi apparatus [7]. Symbiosis between chemical and physical factors prevents platelet adhesion to normal endothelial cells. Thus, biochemical factors encompass the synthesis of various antithrombotic substances of endothelial vascular cells, such as heparin-like glycosaminoglycans, coagulation inhibitors, platelet inhibitors and fibrinolysis activators [9]. Physical factors are characterized by the rejection of forces resulting from the negative electrical charge of endothelial cells and platelets. Releasing these inhibitors into the bloodstream is intended to prevent their adhesion to the normal endothelium [10].

Exploratory tests of primary hemostasis

Exploration of primary hemostasis can be performed through a series of tests, such as bleeding time – considered normal at values ranging from 2 to 4 minutes. There are two ways to achieve the test: (*i*) Duke – involves making a 1.5/3 mm incision at the earlobe and measuring the time required to stop bleeding; (*ii*) Ivy – a 2/2 mm incision is made on the forearm. The difference between the two is that, unlike the first method, the second method includes the application of an arm at the arm, and the incision place of the two methods is different. Capillary fragility test consists of assessing the number of petechiae from applying a pressure to the skin by using a strain gauze. The most common is the Rumpel–Leede method. Platelet count – the normal value is between 150 000–400 000/mm^3. Decreasing below normal is considered a thrombocytopenia, and elevation over normal is thrombocytosis. Dosage of fibrinogen (with normal values of 200–400 mg/dL) and vWF [5, 11, 12].

Secondary hemostasis

Secondary hemostasis or coagulation itself is the cascade activation process of coagulation plasmas in order to convert soluble fibrinogen into insoluble fibrin, thereby forming the fibrin network that will strengthen platelet aggregates and achieve efficient hemostasis [5] (Table 1).

Table 1 – ***Nomenclature of coagulation factors [13]***

No.	Name	Role
I	Fibrinogen	Clot formation
II	Prothrombin	Activation of factors I, V, VII, VIII, XI, XIII, protein C and platelets
III	Tissue factor	Cofactor VIIa
IV	Calcium	Role in binding of phospholipid coagulation factors
V	Proaccelerin	Cofactor of X – prothrombinase complex
VI		Activated form of V
VII	Proconvertin	Enables factors IX and X
VIII	Antihemophilic factor A	Cofactor of IX complex
IX	Antihemophilic factor B or Christmas factor	Enables factor X, forms the complex tensor with factor VIII
X	Stuart–Prower factor	Forms the prothrombinase complex together with factor V, which will activate factor II
XI	Antecedent of plasma thromboplastin	Activates factor IX
XII	Hageman factor	Enables factors XI, VII and prekallikrein
XIII	Fibrin stabilizing factor	Creating cross-links between fibrin monomers
XIV	Prekallikrein – Fletcher factor	Precursor of kallikrein
XV	HMWK – Fitzgerland factor	Cofactor
XVI	von Willebrand factor	Role in platelet adhesion; it is linked to factor VIII
XVII	Antithrombin III	Inhibits IIa, Xa and other proteases
XVIII	Heparin cofactor II	Inhibits IIa
XIX	Protein C	Inactivates factors Va and VIIIa
XX	Protein S	Cofactor for activated C protein

HMWK: High-molecular-weight kininogen.

Exploratory tests of secondary hemostasis

Activated partial thromboplastin time (aPTT) evaluates the intrinsic pathway and has normal values between 25–39 seconds [11]. This is achieved by initiating the coagulation cascade following application to a specific artificial surface of factor XII, prekallikrein and high-molecular-weight kininogen (HMWK) [14]. Prothrombin time or Quick time evaluates the extrinsic path and the common path, has normal values between 12–15 seconds [5, 11, 12]. International Normalized Ratio (INR) defined as the ratio between the patient's prothrombin index (PI) and the reference PI of the laboratory – normal values between 0.8–1.2 [5, 11]. Dosage of fibrinogen – normal values between 200–400 mg/dL [7]. Dosage of coagulation factors [12]. Thrombin time is the clotting time of platelets in the platelets when thrombin is added. The normal value is approximately 15–18 seconds [5].

Fibrinolysis

Physiological fibrinolysis is the process of proteolytic degradation of fibrin under the action of plasmin in order

to avoid thrombotic obstruction of blood vessels. It is the main antithrombotic physiological mechanism [5]. The formed clot will have a certain architecture dependent on the diameter and geometric layout of the fibers, which will influence the development of fibrinolysis [15]. This process is controlled by the plasmin that acts on fibrin and fibrinogen. Plasmin is obtained by the activation of plasminogen, whose cleavage is triggered by certain activators, such as the tissue activator (present in the endothelium), urokinase and streptokinase [12]. Fibrinolysis prevents spontaneous formation and pathological propagation of the clot formed. It is activated in parallel with coagulation and removes clots at the same time as the lesion healing and tissue repair. Fibrinolysis can be activated in two ways: (*i*) by tissue, by releasing tPa favored by vascular lesions and friction forces; (*ii*) in the pathway of the kinin system, by kallikrein, which also intervenes in coagulation activation and induces the formation of urokinase [16]. Activators of fibrinolysis trigger plasminogen activation in plasmin, which is responsible for the lysis of the previously formed clot. This reaction occurs in the presence of fibrin and results in fibrin degradation products with anticoagulant effect and interfering with fibrin polymerization [3]. Plasmin is a proteolytic enzyme which, released in the circulation, can have systemic fibrinolytic effects and reduces platelet adhesion by decreasing number of platelet receptors [17]. Its action is controlled by circulating inhibitors of the α_2-antiplasmin type, whose action is replicated by pharmacological agents, such as Tranexamic acid (TA), Epsilon-aminocaproic acid (AEAC) and Aprotinin. The fibrinolytic system also has other inhibitors, such as tPA inhibitors [3]. Exploratory tests of fibrinolysis are dosage of degradation products of fibrinogen and fibrin. Dilute blood clot lysis time, with normal 150–300 minutes [2]. Lysis time of undiluted blood clot with normal values greater than 24 hours [12]. Lysis time of the euglobulin clot, with normal values between 150–180 minutes. D-dimer test, with normal values <250 ng/mL. Increased levels occur in myocardial infarction, deep vein thrombosis and in pregnancy. Plasma dosing of fibrinolysis proteins [5].

Anticoagulant and thrombolytic treatment

It is associated with an increased risk of bleeding during dental operations. It is recommended to discontinue or replace it 2–4 days before an invasive act. Heparin is the most well known anticoagulant, being shown to reduce intravascular thrombosis. It works by forming an antithrombin (AT) complex that inhibits thrombin and, to a lesser extent, factors IX, XI, XII. Generation of thrombin is prevented by inhibition of factors X, V and VIII. It also induces endothelial release of TFPI that reduces factor VIIa activity. Anticoagulants are classified according to their mode of administration in: intravenous anticoagulants – this class includes unfractionated and low molecular weight heparins; oral anticoagulants – classical anticoagulants (vitamin K antagonists) and new generation oral anticoagulants, some of which are still in the experimental stage [18].

Unfractitious heparin

The anticoagulant effect of heparin is evidenced by interaction with AT. A specific pentasaccharide sequence from heparin binds to AT lysine, thereby producing AT conformational modifications and transformation from a slow and progressive thrombin inhibitor into a rapid inhibitor of different coagulation enzymes. Heparin/AT complex also inactivates other coagulation factors, such as Xa, IXa and XIIa. The most sensitive to this complex are thrombin and factor Xa. Heparin is given parenterally because it is poorly absorbed by the gastrointestinal tract. The unfractionated heparins bind nonspecifically to proteins and cells. It presents a large individual variability of the anticoagulant response, called heparin-resistance, and is due to heterogeneity of heparin and its neutralization by circulating plasma factors and proteins released by activated platelets [19]. It is hepatically eliminated and the antidote is protamine [20]. It is indicated in: acute ST segment elevation coronary syndrome in patients with fibrinolytic therapy; coronary syndrome without ST segment elevation; deep vein thrombosis as treatment or prophylaxis; pulmonary embolism; ischemic stroke; chronic limb arteriopathy therapy. Response to heparin therapy is monitored by aPTT or activated clotting time (ACT). Adverse reactions, such as thrombocytopenia, spontaneous bleeding, cutaneous necrosis and osteoporosis, may occur. Discontinuation of heparin therapy may result in a relapse with an increase in ischemic events [21].

Low molecular weight heparins

They are obtained by chemical or enzymatic depolymerization of standard unfractionated heparins and the selection of those with low molecular weight. They combine factors IIa and Xa inhibition. The anticoagulant effect is the same as for unfractionated heparin, through the unique pentasaccharide sequence that binds to AT lysine. They bind less to plasma proteins, so they have a higher bioavailability at low doses and a more predictive anticoagulant response. They are eliminated in the urine, so dose reduction is recommended in patients with renal impairment. It presents a number of advantages compared to unfractionated heparin, such as: a more intense anti-factor Xa activity; increased and constant release of TFPI; PF4 has no neutralizing function; thrombocytopenia or osteoporosis rarely occurs as an adverse reaction; administered subcutaneously; does not require therapy monitoring.

Oral anticoagulation therapy

Vitamin K antagonists

It is delayed and is not recommended to be used in the acute phase. In the long run, they reduce the mortality rate and the occurrence of new myocardial infarctions. The effectiveness of oral anticoagulants is evidenced by INR. In healthy patients, INR should be <1 and in patients undergoing anticoagulation should be maintained between 2 and 3, thus decreasing the incidence of coronary events [21] (Table 2).

Proteins C, S and coagulation factors II, VII, IX and X are synthesized in the liver by the vitamin K-dependent elements. Reduced vitamin K, *i.e.*, Hydroquinone, is intended to mediate the carboxylation of these elements

by activating them, eventually returning to the original structure due to chemical processes, taking part in a new chemical cycle. Vitamin K antagonists, coumarin or indandione derivatives, inhibit the carboxylation of the four factors and block the return of vitamin K compounds to the initial form and the resumption of the metabolic cycle [23, 24]. Their effect depends on the half-life of different types of antagonists, the different intestinal absorption of patients, food and nutritional factors, other concomitant medications and their interaction with each other, resulting in a varied response to treatment. Also, these drugs have a small therapeutic window, their effect appears and disappears slowly, and increase the risk of patients suffering from intracranial hemorrhage. In conclusion, it requires frequent monitoring of the treatment.

Table 2 – ***Attitude in patients with supra-therapeutic or bleeding INR [22]***

INR	Treatment recommendations
INR <5, without significant bleeding	Reduction or omission of AVK dose. More frequent monitoring. Lower dose resumption when INR reaches the therapeutic area. If the increase in INR is minimal, the dose should not be reduced.
INR >5 but <9, without significant bleeding	One or two doses are omitted. More frequent monitoring. Lower dose resumption when INR reaches the therapeutic area. If the risk of bleeding is increased, dose omission and VK1 <12.5 mg administered orally. If a faster reversal is required in case of an emergency intervention, VK1 <5 mg orally is given to decrease the INR within the next 24 hours. If INR is still increased, 12 mg of VK1 is also given.
INR >9, without significant bleeding	Stop AVK. Take VK1 510 mg orally to reduce INR in 24–48 hours. More frequent monitoring. If necessary, supplement the VK1 dose. Lower dose resumption when INR reaches the therapeutic area.
Important bleeding, regardless of INR increase	Stop AVK. VK1 10 mg is slowly given as an infusion. It can be repeated at 12 hours if INR is kept up. Supplement treatment with FFP or PCC, depending on the urgency of the situation. rFVIIa may be administered as an alternative to PCC.
Life-threatening bleeding and INR increased, regardless of value	Stop AVK. FFP, PCC or rFVIIa are administered. Supplemented with 10 mg slow infusion VK1, which is repeated according to INR.

INR: International Normalized Ratio; AVK: Anticoagulation with antivitamin K; VK1: Vitamin K1; FFP: Fresh frozen plasma; PCC: Prothrombin complex concentrate; rFVIIa: Recombinant activated factor VII.

They are administered orally and are used for unstable angina pectoris, vascular accidents, cardiac arrhythmias, acute myocardial infarction, primitive pulmonary hypertension, profound limb thrombophlebitis, prophylaxis of thromboembolism in dilatative cardiopathy and valvulopathy [25, 26].

New generation oral anticoagulants

Most are in clinical trials. The only ones used so far are Fondaparinux and Bivalirudin. Anticoagulant therapy targets one of the three stages of coagulation: initiation, propagation and formation of fibrin. The initiation focuses on factor VIIa/TF complex that activates factors IX and X. Coagulation is performed by factors IXa and Xa, together with activated factors VIIIa and Va factor. In third stage, thrombin converts fibrinogen into fibrin [21]. Factor VIIa/TF inhibitors are: *Tifacogin* – a recombinant form of TFPI. Under his influence, patients have a higher risk of bleeding. TF formation and release is the trigger point for initiating coagulation in patients with sepsis. *Nematode anticoagulant protein c2* (*NAPc2*) is an initially isolated polypeptide of *Ancylostoma canninum*. It binds factor Xa by inhibiting factor VIIa in factor VIIa/TF complex. It is injected subcutaneously and has a half-life of 50 hours, so it would benefit from a two-day administration. Based on some studies, it has promising results in patients with deep vein thrombosis, unstable angina, acute myocardial infarction without ST elevation, and those with percutaneous coronary intervention. It may be associated with Aspirin, heparin or low molecular weight heparin therapy, but bleeding discomfort may result from these accumulations of drugs in the body due to prolonged half-life. *rFVIIa* is a recombinant form of factor VIIa, attenuating coagulation initiation by factor VIIa/TF complex. It was used in a study in patients with percutaneous coronary intervention with insignificant effects on predetermined targets: stroke, myocardial infarction, emergency revascularization and vascular occlusion. Due to these unpromising results, studies have been canceled. *Factor IXa inhibitors* can be used either orally and parenterally. They were administered parenterally in the cardiopulmonary surgical bypass. *Factor Xa inhibitors* blocks factor Xa directly and indirectly. Directly by binding to the active sites of factor Xa inhibiting free and plaque form. Indirectly by AT catalyzing factor Xa inhibition. There are two types of factor Xa inhibitors: indirect and direct inhibitors [21].

Indirect factor Xa inhibitors

Fondaparinux is a selective synthetic inhibitor with a half-life of 17 hours. Inhibition is mediated by plasma AT. Decreases thrombin generation and fibrin formation. It can be administered subcutaneously or intravenously, one dose/day. It has a predictable response and does not require dose monitoring. It is eliminated by renal pathway, so its use is limited to patients with severe renal impairment. It exerts a dose-dependent antithrombotic effect. It does not present thrombocytopenia as an adverse reaction. Following studies, the efficacy of Fondaparinux was determined in the acute treatment of venous thromboembolism and in the treatment of acute coronary syndrome. *Idraparinux* is a derivative of Fondaparinux, binds to AT, and its half-life is 80 hours, similar to AT.

It is given once a week. It has been tested in deep vein thrombosis with a fall in recurrence, but with increased bleeding. The bleeding effect is dose-dependent. *SSR12517E* is a form of Idraparinux. It is administered once a week. The effect can be neutralized by intravenous Avidin. It is used in studies in patients with pulmonary embolism and deep vein thrombosis. *SR123781A* binds to AT. It has a heparin-like action of inhibiting factor Xa and thrombin. It does not bind to platelets or fibrin factor IV, so do not induce thrombocytopenia. It can be administered subcutaneously. Renal elimination is eliminated. It has been used in patients with orthopedic disorders.

Direct factor Xa inhibitors

DX-9065a is a direct synthetic factor X inhibitor. It is administered parenterally, with a dose-dependent half-life of between 40 minutes and five hours and is renal eliminated. It is used in patients with acute coronary syndrome without ST segment elevation and in patients with percutaneous coronary intervention, with favorable outcomes in less than half of patients. *Otamixaban* is given intravenously. It has a half-life of two to three hours, it is excreted in the urine, and the metabolites are excreted through the feces. It is associated with heparin in patients with acute myocardial infarction without ST segment elevation, resulting in a potent antithrombotic effect and dose-dependent bleeding. Razaxaban is used in prophylaxis of thrombosis following knee replacement (Table 3).

Factor Xa inhibitors administered orally

Apixaban is a direct factor X inhibitor. It has a half-life of 12 hours. It can be renal or hepatic eliminated. Following clinical trials, patients treated with Apixaban exhibit fewer pulmonary embolism and less bleeding. It has favorable results in the treatment of deep and unfavorable venous thrombosis in acute coronary syndromes. *Rivaroxaban* has a half-life of nine hours; 65% is excreted in the urine, the rest of the bile or feces. It is considered an easy way to treat deep vein thrombosis and prevent recurrent venous thromboembolism. No dose–effect studies have been demonstrated, but the increase in the dose increases the bleeding rate. *Edoxaban* is a new direct factor Xa inhibitor given orally. It has an anticoagulant effect that is dose-proportional and fast onset of action. It is eliminated by both urine and feces. It is analyzed for the prevention and treatment of venous thromboembolism. *LY-517717* has a half-life of 25 hours and can be given once a day. Studies have been performed on patients with hip or knee arthroplasty, with good efficacy at high dosages. *YM150* was used in once-daily patients with arthroplasty, without a major dose-to-bleed relationship. It has a half-life of 19 hours, and for high-dose venous thrombosis prophylaxis, high doses are used.

Factor Va inhibitors

Factor Va degraded and inactivated by protein C is a cofactor for thrombin generation. *Drotrecogin alfa* is a recombinant form of activated C protein. It is used in patients with sepsis. *ART-123* is a recombinant analogue of thrombomodulin. It binds to thrombin and turns it into a potent protein C activator. It has a half-day half-life and is administered by the subcutaneous route. Clinical trials have been shown to be effective in patients with arthroplasty in the prevention of venous thrombosis, and bleeding is dose-dependent.

Table 3 – ***New generation oral anticoagulants [21]***

Indirect factor Xa inhibitors	Direct factor Xa inhibitors	Factor Xa inhibitors administered orally	Factor Va inhibitors	Thrombin inhibitors
Fondaparinux	DX-9065a	Apixaban	Drotrecogin alfa	Hirudin
Idraparinux	Otamixaban	Rivaroxaban	ART-123	Bivalirudin
SSR12517E	Razaxaban	Edoxaban		Argatroban
SR123781A		LY-517717		Flovagatran
		YM150		Permusirudin
				Dabigatran etexilate
				Odiparcil

Thrombin inhibitors

Hirudin is a direct bipolar thrombin inhibitor. It is superior to unfractionated heparin during drug administration. It is used in prophylaxis of deep vein thrombosis and for the care of thrombocytopenic patients receiving heparin therapy. *Bivalirudin* is a synthetic peptide with a half-life of 36 minutes. It binds to reversible thrombin and has a dose-dependent effect. After administration of Bivalirudin, bleeding complications are reduced. *Argatroban* is a thrombin inhibitor indicated in patients with heparin-induced thrombocytopenia. It has a half-life of 40 minutes. Administering infusions to patients with unstable angina does not cause a relapse, but after stopping the infusion, resting angina may occur. *Flovagatran* has a short half-life, has been studied as an alternative to heparin in patients during hemodialysis and in the final stage of chronic kidney disease. Permusirudin is a derivative of altered Hirudin for prolonging half-life. Studies have been performed in patients with end-stage renal disease under chronic hemodialysis treatment. *Dabigatran etexilate* inhibits free and thrombin bound to the clot. It has a half-life of up to 17 hours. It is given orally. Provides antithrombotic protection and at high doses decreases stroke/systemic embolism without major bleeding. In some cases, it produces dyspnea. *Odiparcil* indirectly inhibits thrombin. It presents a delayed action of two or three days. It has been tested for orthopedic disorders for low-efficacy thrombosis prophylaxis. In order to restore coagulation time, Protamine sulphate may be administered.

Anticoagulant interactions with commonly prescribed drugs in dental medicine

Heparins – the most commonly prescribed drugs in dentistry in a patient receiving heparin therapy are

non-steroidal anti-inflammatory drugs (NSAIDs), due to increased hemorrhagic risk. *Oral anticoagulants* – drugs that increase the effect are: Metronidazole, Erythromycin, generation II and III cephalosporins, Fluconazole, NSAIDs, Biseptol and Aspirin. Effect-lowering drugs are: Rifampicin, Carbamazepine and barbiturates [24]. From a chemical point of view, Dabigatran, Rivaroxaban and Apixaban are part of the P-glycoprotein (P-GP) transporter structure, therefore, P-GP inhibitors/inducers, such as Ketoconazole, Rifampicin, Quinidine, Verapamil, Clarithromycin, for Rivaroxaban are not recommended concomitantly [27, 28].

Clinical applications

At the root of diseases requiring anticoagulant treatment is a theory more than 100 years old, the theory of Rudolph Virchow, which claims that their most important etiological factors are hypercoagulability of blood, vascular lesions and blood stasis [29].

Atrial fibrillation

Atrial fibrillation is the abnormal heart rate characterized by rapid and irregular beating [30]. It is the most common tachyarrhythmia among patients, especially in the elderly, with prevalence values being closely correlated with age [31]. It can be classified as: paroxysmal (episode that takes less than a week); persistent (less than a year), permanent (when present for more than one year) [32].

This arrhythmia involves modifying sinus rhythm (dictated by proper functioning of the sinus node) at a frequent, chaotic and irregular rate found at the atria level, whose number of contractions may increase to over 400 beats/min. Hemodynamic changes caused by ineffective and asynchronous contraction of atria lead to the appearance of blood stasis and thrombus formation at this level. Mobilized in the circulation, thromboembolies cause ischemic attacks, atrial fibrillation being one of the major causative factors of ischemic stroke [33]. In advanced stages, atrial arrhythmia maintains a dysfunction including ventricular, especially left ventricular, which aggravates atrial changes by increasing dilation and progressively decreasing their function, increasing the intensity of symptomatology and thromboembolic risk [34].

Treatment of atrial fibrillation aims at converting to a normal cardiac rhythm and preventing thrombosis. Prevention of thrombosis is achieved with anticoagulant therapy that aims to bring INR to 2–3. Anticoagulants commonly used are oral, vitamin K antagonists, but new oral anticoagulants are also commonly used. In emergency cases, unfractionated and low molecular weight heparins may be injected [35]. The prognosis of patients with atrial fibrillation under treatment is favorable, while without treatment, atrial fibrillation can cause vascular accidents, abnormal bleeding, and in severe cases lead to death.

Acute myocardial infarction

This cardiac condition is caused by myocardial death following prolonged ischemia, cell death demonstrated by the presence of troponin cardiac protein and creatine kinase muscle–brain (CK-MB) enzyme in the blood. Suggestive symptoms are the precordial pain that irradiates the neck and left arm, anxiety, dyspnea, arrhythmia, fatigue, nausea, vomiting [20]. In atypical cases, the pain may irradiate including the mandible or lower molars. This ischemic attack occurs most frequently following the breakdown of the plaque of the atheroma, on the surface of which platelets adhere. The thrombus that is finally formed is the result of platelet aggregation as well as an increased secretion of local thrombin (TF) and especially tissue (secretion that has a long duration, including after treatment of the ischemic episode).

Patients with a history of acute myocardial infarction are under platelet antiaggregation. Oral anticoagulants are also recommended to interfere with the effects of increased amounts of thrombin, indicating the use of new anticoagulants that are at lower risk of bleeding than vitamin K antagonists.

In the absence of adequate treatment, approximately 50% of affected patients are found deceased within the first two hours of onset. Early diagnosis of these patients and modern strategies of myocardial reperfusion have now reduced the mortality in acute myocardial infarction [19].

Deep vein thrombosis

Deep vein thrombosis implies the appearance of a thrombus in the deep arteries of the upper or lower limbs, or in the pelvis. This condition occurs predominantly in the lower limbs, manifested by the appearance of superficial vein dilatation, edema, pain, cyanosis following obstruction of a vein. Among its causes are congestive heart failure, cancer, prolonged immobilization, oral contraceptive treatments, hormonal imbalances, etc. One of the most common causes is surgery or trauma in lower limbs [36].

The main intention of the emergency treatment is to reduce the INR to 2–3 and is done with heparin, and lasting with direct thrombin inhibitors, vitamin K antagonists or factor Xa inhibitors. Treatment lasts for several months, depending on the risk of recurrence. The most important risk associated with venous thrombosis is pulmonary embolism [32, 33].

Pulmonary embolism

It is a condition that involves the appearance of a thrombus in a deep vein, most often from the lower limbs, a clot released into circulation, migrates to a pulmonary artery, responsible for its obstruction. This condition is of two kinds: minor, when common manifestations with other conditions make it difficult to diagnose, or major, when complicated with acute pulmonary heart (dyspnea, pain, cyanosis, sudden death). The patient may be accused of respiratory distress with chest pain, tachycardia, anxious and sometimes hemoptysis.

Anticoagulation treatment is similar to that of deep vein thrombosis, duration and succession of medication being conditioned by the type of pulmonary embolism and associated risk (whether or not in shock). The consequences of pulmonary emphysema are acute respiratory failure, circulation and death [37].

Stroke

Stroke is defined as a series of neurological manifestations due to cerebral hypoxia that occurs as a result of a hemorrhagic or ischemic attack (determined by a thrombus).

Symptoms range from hemiparesis, walking disturbances, hemianopsia, aphasia, sensory changes, headaches to rapid

loss of consciousness. Stroke causes include hypertension, dyslipidemias, uncontrolled diabetes, thrombophlebitis, cardiac disorders, arrhythmias, especially atrial fibrillation, in which case studies have shown a higher severity and a more unfavorable prognosis of vascular accidents.

Anticoagulant treatment in the event of stroke is most useful in cases of transient ischemic attacks, which can improve until an almost complete return of the patient. However, the frequent use of this therapy is the prophylactic treatment of thromboembolic disorders.

This condition can affect physically and mentally. As well as disabilities, muscle weakness, paresthesia, pneumonia, urinary incontinence, difficulty in performing daily activities can occur. Of the cognitive deficits, the most common are aphasia, dementia, memory and attention problems. A major and severe stroke leads to coma, or even death [38].

Valvular disorders

Valvulopathy is one of the most common heart conditions after those caused by high blood pressure and ischemic heart disease. These have several causes, and today they are more often degenerative than those of rheumatic origin are. Existing valvulopathies include: mitral stenosis, aortic regurgitation, aortic stenosis, mitral regurgitation, prosthetic valves, etc. [39, 40].

Anticoagulant treatment is particularly indicated in symptomatic valvulopathies associated with dysrhythmias (frequent mitral stenosis with atrial fibrillation) and mandatory for mechanical valves. The INR value is 2–3 in the case of degenerative valvulopathies, but may increase to 3.5–4 in the case of mechanical valves. The treatment is often performed with Warfarin, and the effectiveness of new anticoagulants in case of valvular diseases is being studied [40].

Conclusions

Over a long period of time, anticoagulant treatment has been achieved by administering vitamin K antagonists. It has now evolved due to constant research and the release of new drug on the market. This emphasizes the need for continuous medical education of the dentist regarding the anticoagulant treatments, supported by the many differences between the recommendations of the specialized literature.

Conflict of interests

The authors state that there is no known conflict of interests associated with this publication.

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