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REVIEWS

PERIOPERATIVE PREPARATION FOR ORAL SURGERY IN PATIENTS ON ANTICOAGULANT OR ANTIPLATELET THERAPY

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ABSTRACT

The most common cause of deviation in coagulation status is the systemic administration of anticoagulants (ACs) and antiplatelet drugs (APs). The two types of drugs act at different stages of the coagulation cascade. Knowledge of their pharmacokinetics and pharmacodynamics is a prerequisite for adequate preoperative planning and postoperative control. The present review aims to investigate and discuss perioperative management in patients on anticoagulant and antiplatelet therapy undergoing oral surgery. The Web of Science, PubMed, Scopus, and Google Scholar databases were searched for appropriate studies using the following keywords: anticoagulants, antiplatelet drugs, perioperative management, and oral surgery. Perioperative management of patients on anticoagulant and antiplatelet therapy depends on the type, volume, and duration of the surgical intervention, the class and type of medication administered, and some patient-related factors, such as age, comorbidity, individual risk of spontaneous hemorrhage, congenital coagulopathy, etc. The approach in these patients is multidisciplinary and requires the assessment of the specialist who prescribed the treatment (cardiologist, neurologist, vascular surgeon, etc.) and the oral surgeon and anesthesiologist. Some deviations in the coagulation status require prolonged inpatient follow-up. Therefore, it is necessary to perform a careful and thorough analysis of whether the surgery can be performed in an ambulatory setting or a hospital unit.

Keywords: *anticoagulants, antiplatelet drugs, perioperative management, oral surgery*

INTRODUCTION

Coagulation is a physiological process that protects the body from significant blood loss. This process is influenced by many factors associated with the available blood cells and the clotting factors in the blood plasma [1]. Regarding the surgical site, increased coagulability is not subject to postoperative care. The possible high risk of systemic coagulation is subject to monitoring and correction by specialists managing the treatment of the underlying disease (hematological, oncological, etc.). Deviations in the normal coagulation status with an increased risk of bleeding can be due to congenital and acquired conditions [2].

Patients with congenital coagulopathy associated with abnormalities in plasma factors and congenital thrombocytopenia are subject to consultation with a hematologist and extensive preoperative preparation. Due to the high risk of postoperative bleeding, surgical interventions should be performed in a hospital setting [2, 3]. Patients with acquired coagulopathy associated with abnormalities in plasma factors and acquired thrombocytopenia are subject to consultation with an internal medicine specialist and/or a specialist monitoring the patient. Patients

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with a history of systemic administration of certain medications are subject to more careful monitoring due to an increased risk of intra- and postoperative bleeding [4, 5]. These medications are direct and indirect anticoagulants, antiplatelet drugs, chemotherapeutics, monoclonal antibodies, immunomodulators, immunosuppressants, non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, selective serotonin and noradrenaline reuptake inhibitors, carbamazepine, enzyme phytoextracts (Nattokinase, Bromelain) [5].

The most common cause of deviation in coagulation status is the systemic administration of anticoagulants (ACs) and antiplatelet drugs (APs). The two types of drugs act at different stages of the coagulation cascade and thrombocyte aggregation [6]. Knowledge of their pharmacokinetics and pharmacodynamics is a prerequisite for adequate preoperative planning and postoperative control.

AIM

The present review aims to investigate and discuss perioperative management in patients on anticoagulant and antiplatelet therapy undergoing oral surgery.

MATERIALS AND METHODS

The Web of Science, PubMed, Scopus, and Google Scholar databases were searched for appropriate studies using the following keywords: anticoagulants, antiplatelet drugs, perioperative management, and oral surgery.

RESULTS AND DISCUSSION

Anticoagulant Therapy

Anticoagulants are divided into vitamin K antagonists, heparins, and direct oral anticoagulants. Direct ACs inactivate coagulation factors in blood plasma, while indirect ones suppress the production of factors II, VII, IX, X, and proteins C and S in the liver. The former include inhibitors of factors IIa and Xa, while indirect ACs are vitamin K antagonists (VKAs), conventional heparin, and low-molecular-weight heparins (indirect thrombin inhibitors) [7–9].

Vitamin K antagonists (coumarin derivatives) are a group of drugs that inhibit coagulation by reducing the active form of vitamin K by inhibiting the enzyme vitamin K epoxide reductase. The most commonly used drugs in this group are warfarin, acenocoumarol, and phenprocoumon [10], with warfarin and phenprocoumon having limited use in Bulgaria. When using coumarin anticoagulants, several days are needed to achieve a therapeutic effect since they suppress the formation of new factors but do not affect the number of already existing ones. Their therapeutic effect is assessed by the international normalized ratio (INR) laboratory indicator [11].

The INR values between 0.8 and 1.2 are considered a physiological norm [12], while values between 2.0 and 3.0 are in the therapeutic range for treating and preventing thromboembolism in patients with high embolic risk [13]. In some conditions, such as the presence of mechanical heart valves, the target therapeutic values are higher than 3.0 [14]. However, values of 3.0–4.0 are associated with higher bleeding risk [15].

Oral anticoagulants (OACs) are a common therapy in patients with implanted artificial heart valves, total heart failure, absolute arrhythmia in paroxysmal atrial fibrillation, deep vein thrombosis of the extremities, and pulmonary thromboembolism. Although coumarin OACs provide effective prophylaxis against life-threatening thromboembolism, the long period of residual hypocoagulability after discontinuation of their use and the significant risk of postoperative bleeding during this period are serious disadvantages of their use [16].

Direct oral anticoagulants (DOACs, previously known as novel/non-vitamin K-dependent oral anticoagulants (NOACs)) are first-line medications in the treatment of all cardiovascular diseases with a high thromboembolic risk, the prevention of ischemic strokes, and thromboembolic prophylaxis after orthopedic surgery for total joint replacement. This class of drugs has been preferred over coumarin anticoagulants because of their greater efficacy and safety. They have been demonstrated to pose a lower risk of spontaneous non-traumatic bleeding than vitamin K antagonists, particularly warfarin. Another advantage of DOACs is that there is no need for frequent titration of the therapeutic dose, although laboratory monitoring is still recommended in some cases [17]. Direct oral anticoagulants are factor IIa (thrombin) or factor Xa (thrombokinase) inhibitors. They achieve rapid therapeutic effects, have a short

half-life, and do not usually require routine monitoring [18].

Due to the increased risk of intra- and postoperative bleeding in patients on systemic anticoagulant therapy, preoperative preparation is mandatory, including detailed laboratory monitoring and therapy correction in terms of its type, dosage, and regimen. Complete cessation of the treatment without adequate substitution increases the risk of massive focal intravascular/intracardiac thrombosis with subsequent thromboembolism and vascular obstructive accidents [19, 20].

There is no standardized protocol for the perioperative management of patients on OACs undergoing minor surgical interventions. Literature data support that anticoagulant therapy should not be interrupted during surgery due to the unjustified risk of vascular accidents [21]. This statement is supported by numerous medical and dental societies in the USA—the American Dental Association, the American Heart Association, the American Society of Anesthesiology, the American College of Cardiology, etc. [22]

The recommendations of the European Society of Cardiology and the European Society of Anesthesiology are that non-cardiac surgery can be performed at INR < 1.5, and accordingly most oral surgery procedures can be performed without stopping the systemic administration of DOAC (or only by omitting a single dose immediately before the intervention), but with the use of local hemostasis agents [23]. According to the German Society of Cardiology, dentoalveolar surgery can be performed at INR values between 1.8 and 2.0 [24].

Antiplatelet Therapy

Antiplatelet drugs are part of the first-line medication in patients with cardiovascular diseases and high arterial thrombotic risk.

According to their mechanism of action, these drugs are divided into cyclooxygenase 1 ($COX_{1)}$ inhibitors (acetylsalicylic acid (ASA)), P2Y12 inhibitors (with irreversible blockade—clopidogrel, prasugrel; with reversible blockade—ticagrelor, cangrelor), and glycoprotein IIB/IIIA inhibitors (eptifibatide, tirofiban) [25,26].

In patients taking ASA as primary prophylaxis of arterial thrombosis, the increased risk of intra- and postoperative bleeding depends directly on the half-life of platelets with sustained inhibition of aggregation. There are no randomized studies analyzing the risks and benefits of stopping/continuing systemic ASA therapy in patients with the need for non-cardiac surgery and comorbidities requiring its administration. There is no scientific data on a proven method of drug transition with a reduced risk of both bleeding and massive local thrombosis. The behavior is strictly individual and requires an assessment of the risk of bleeding with continued therapy and the ischemic risk when it is interrupted. This decision is interdisciplinary, involving a surgeon to assess the risk of prolonged and profuse bleeding and a cardiologist/angiologist to assess the risk of organ-threatening and/or life-threatening thrombosis.

Perioperative Management of Patients on Anticoagulant or Antiplatelet Therapy

Perioperative management of patients on anticoagulant and antiplatelet therapy depends on the type, volume, and duration of the surgical intervention, the class and type of medication administered, and some patient-related factors, such as age, comorbidity, individual risk of spontaneous hemorrhage, congenital coagulopathy, etc. [23].

Prolonged intra- and postoperative bleeding requiring additional measures beyond local hemostasis is rarely observed in oral surgery. The decision whether to discontinue anticoagulant therapy should be based on the indications for its administration and the history of previous thromboembolism. Discontinuation may be necessary for dental procedures with a moderate or high risk of bleeding [21]. In patients on low-molecular-weight heparin therapy, the behavior is determined by whether their dose is prophylactic or therapeutic. Discontinuation of the anticoagulant is not necessary if prophylactic doses are used. If the doses are therapeutic, a consultation with the specialist who prescribed the medication is mandatory. In Bulgaria, the standard prophylactic doses of low-molecular-weight heparins are: dalteparin—2,500–5,000 IU/d; enoxaparin—2,000–4,000 IU/d (20–40 mg); fondaparinux (a synthetic derivative)—2.5 mg/d.

Minor surgical procedures with easy bleeding control can be performed without stopping vitamin K antagonists, and the INR should be monitored and

kept at the lower limit of its therapeutic index [27, 28]. Major surgical interventions (according to the European Society of Cardiology (ESC), interventions in the oral cavity are not included here, although the risk should be specified in more detail), requiring INR ≤ 1.5, necessitate discontinuation of vitamin K antagonists and possible replacement with heparin or low-molecular-weight heparins in patients with a high risk of thrombosis. If therapy has been interrupted, it should be resumed 12–24 hours after the intervention if the bleeding is well-controlled, with the restarting dose being equal to the maintenance dose + 50% for 2 days. In patients with heparin replacement therapy and good bleeding control, heparin/low-molecular-weight heparin combined with a vitamin K antagonist should be resumed 24 hours after surgery until therapeutic INR values are reached. In surgical interventions with a high risk of bleeding, therapeutic doses of low-molecular-weight heparin should be postponed for 48–72 hours after establishing hemostasis [23].

In patients with a history of DOAC therapy undergoing emergency oral surgery, the next dose of the drug should be skipped, and, if possible, laboratory tests for the current coagulation status should be performed. Thorough perioperative examinations are mandatory for patients undergoing elective surgery [29,30].

Preoperative assessment of the coagulation status of patients taking DOACs provides information on the expected duration of intra- and postoperative bleeding based on the residual drug concentration. Most oral surgery procedures are associated with a low risk of bleeding. Therefore, they can be performed without DOAC cessation or skipping a single dose, with careful preparation and adequate local hemostasis [23].

The main guidelines for perioperative bleeding control in patients on anticoagulant therapy (with vitamin K antagonists or DOACs) or antiplatelet therapy are:

1. Most oral surgery procedures can be performed safely using local hemostatic agents. Discontinuation of the therapy may result in a vascular event, whereas the risk of continuing therapy is hemorrhage, which can be easily controlled.
2. The clinician must know the medication's characteristics, potential drug interactions, and local hemostasis agents.
3. Selection of the most appropriate hemostatic agent in the specific situation [21].

In 2022, the ESC published guidelines for cardiovascular assessment and management of patients scheduled for non-cardiac surgery. The European Society of Anaesthesiology and Intensive Care (ESAIC) endorsed these guidelines. The management of patients on anticoagulant or antiplatelet therapy is determined individually and should be consistent with the pharmacokinetics and pharmacodynamics of the medications. An interdisciplinary risk assessment (determination of the patient-related risks of ischemia and hemorrhage) by the cardiologist, neurologist, vascular surgeon, or hematologist, and a surgical risk assessment by the surgeon and anesthesiologist are required [23].

According to the ESC, oral surgery interventions do not fall into the high risk of bleeding category, which suggests that the discontinuation of antiplatelet drugs, even in cases of dual antiplatelet therapy , is not necessary.

The recommendations of the ESC for conducting antiplatelet therapy in patients who are about to undergo non-cardiac surgical intervention are summarized as follows:

1. Elective non-cardiac surgical operations should be postponed for 6 months after percutaneous cardiac interventions (PCI) and 1 year after an acute coronary syndrome.
2. If postponement for 6 months is impossible, then it should be after at least 1 month of treatment with a dual antiplatelet therapy .
3. Managing these patients requires a multidisciplinary approach (surgeons, cardiologists, and anesthesiologists).
4. In high-risk patients with recent PCI, at least 3 months of dual antiplatelet therapy should be considered before non-cardiac surgery.
5. In the absence of a high risk of bleeding, it is recommended that patients with prior PCI continue perioperative aspirin.
6. If the risk of bleeding outweighs the risk of ischemia, aspirin should be discontinued for 3 days.

7. If discontinuation of P2Y12 inhibitor therapy is necessary, ticagrelor should be discontinued for 3–5 days, clopidogrel for 5 days, and prasugrel for 7 days before surgery.
8. If antiplatelet therapy is discontinued before surgery, it is recommended that it be resumed as soon as possible (within 48 hours), according to the interdisciplinary risk assessment [23].

CONCLUSION

Some deviations in the coagulation status require prolonged inpatient follow-up. Therefore, it is necessary to perform a careful and thorough analysis of whether the surgery can be performed in an outpatient setting or a hospital unit. The approach in patients on anticoagulant and antiplatelet therapies is multidisciplinary and requires the assessment of the specialist who prescribed the treatment and the surgeon and anesthesiologist. The overall assessment depends on the individual's characteristics, the type of procedure, and the laboratory results.

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