Anticoagulants in dermatological surgical practice

Anticoagulantes na prática cirúrgica dermatológica

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ABSTRACT

Introduction: In the last decades, anticoagulants have become more frequent in the population and younger age groups.

Objective: This article aims to address the risk of the most used anticoagulant medications in dermatological surgeries. Methods: We reviewed the most common anticoagulant medications.

Results: The pre-surgical consultation performed correctly, emphasizing the patient's clinical history (including renal function in cases of use of new oral anticoagulants), the anatomical site addressed, and the surgical treatment schedule is essential for a satisfactory outcome.

Conclusions: The use of anticoagulant medications is increasingly common in medical practice. In patients receiving anticoagulant medications, strict adherence to good surgical practices is essential. Special attention to adequate hemostasis of the surgical field, adequate and compressive dressings and postoperative care must be given. The patient should be adequately informed about the most significant risks to which he is subject.

Keywords: Dermatology; Anticoagulants; Surgery

RESUMO

Introdução: *Nas últimas décadas, o uso de anticoagulantes vem se tornando mais frequente na população e em faixas etárias mais jovens.*

Objetivo: *O objetivo desse artigo é abordar o risco das medicações anticoagulantes mais utilizadas em cirurgia dermatológica.*

Métodos: *Foi realizada revisão das medicações anticoagulantes mais utilizadas. Resultados: A consulta pré-cirúrgica realizada adequadamente, com ênfase ao histórico clínico do paciente (incluindo função renal nos casos de uso dos novos anticoagulantes orais), a localização anatômica abordada e a exata programação do tratamento cirúrgico são essenciais para um desfecho adequado.*

Conclusões: *A utilização de medicações anticoagulantes é cada vez mais frequente na prática médica. Em pacientes recebendo medicações anticoagulantes é essencial a estrita adesão às boas práticas cirúrgicas, com especial atenção à hemostasia adequada do campo cirúrgico, aos curativos adequados e compressivos e aos cuidados pós-operatórios, sendo o paciente devidamente informado sobre os maiores riscos aos quais está sujeito.*

Palavras-chave: *Anticoagulantes; Centro cirúrgico hospitalar; Dermatologia*

Review Articles

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INTRODUCTION

In the last decades, anticoagulant use has become more frequent in the population and younger age groups. This class of drug, which was initially limited to vitamin K inhibitors and acetylsalicylic acid (ASA), grew with the introduction of new antiplatelet agents and new oral anticoagulants (NOAC). These new medications have their pharmacological profile and drug interactions, and they are very different from their predecessors. The dermatological literature on the anticoagulant's impact on the surgical procedures performed by dermatologists is scarce. Furthermore, the international "guidelines" on anticoagulation are unspecific, considering all procedures as low bleeding risk, which, in the end, can lead to inappropriate conduct in the face of more invasive interventions performed by the dermatological surgeon. This article aims to review of the most used anticoagulant medications and their risks for dermatological surgeries.

Warfarin

Warfarin is a vitamin K epoxy reductase (VKOR) inhibitor. It starts to act in 90 minutes and has a half-life from 36 to 42 hours (Table 1).[1] It has been one of the most widely used anticoagulants for decades. However, due to the narrow therapeutic window and the INR volatility, recent studies showed that only 61% of patients undergoing treatment remained on the desired therapeutic target.[2,3] Due to its intense protein binding and metabolism by cytochrome P2C9, many drugs and supplements interfere with its action. Administration of vitamin K or fresh frozen plasma can reverse its effect.

Hemorrhagic events are the most frequent adverse event, and their occurrence is closely linked to INR values, especially when they are higher.[4,5] Previous studies suggest that dermatological surgeries can be performed with a lower risk of hemorrhagic complications in patients using warfarin, provided that the INR value is lower[3,5] (Table 2), with special attention to intraoperative hemostasis.[4] Two other studies assessing patients who underwent surgery with a low bleeding rate using warfarin found a risk of bleeding ranging from 2.28% to 2.5%.[5,6]

For many years, warfarin suspension and the use of bridging therapies with heparin have been recommended preoperatively. Currently, the literature strongly recommends not using these substitutions for dermatological surgeries due to the increased bleeding risk (9.6% vs. 2.5% while maintaining warfarin) and thromboembolic phenomena.[6,7]

Acetylsalicylic acid

The acetylsalicylic acid (ASA) is an irreversible inhibitor of cyclooxygenase,1 which hinders platelets from producing thromboxane A2, promoting their aggregation, vasoconstriction, and increased activation.8 It has a rapid onset of action (30-40 minutes) and a short half-life (three hours) (Table 1). The effect is reversible only after platelet renewal. Although some authors have described an increased risk of postoperative bleeding with ASA,9 others found a slight risk (1.42%)6 or did not find increased bleeding when using acetylsalicylic acid and other non-hormonal anti-inflammatory drugs.[5,10]

Clopidogrel

Clopidogrel is an irreversible platelet adenosine diphosphate P2Y12 receptor inhibitor, activated after vascular injuries or plaque ruptures. It has an onset of action in two hours and a half-life of six hours.

Drugs metabolized by cytochrome P450 interfere with clopidogrel metabolism by decreasing antiplatelet activity (e.g., proton-pump inhibitors).

Some authors describe a 28-fold increased risk of severe bleeding in patients using clopidogrel compared to non-anticoagulants, and a six-fold increased risk compared to patients using acetylsalicylic acid.[9] Studies comparing the association of clopidogrel with other antiplatelet agents (ASA) found an eight-fold increased risk of severe bleeding complications, compared to monotherapy.[8] Koenen *et al.*, in a prospective multicenter study with 9,154 surgical procedures, found a bleeding risk of 3.57% in individuals taking two anticoagulants (ASA and clopidogrel); 2.13% for the association of ASA and coumarins; and 1.32% for of ASA combined with heparin. Moreover, those not anticoagulated presented a risk of hemorrhagic complications of 0.55%.[11]

Ticagrelor

Ticagrelor is a P2Y12 receptor inhibitor with the onset of action (15-30 minutes) and recovery of platelet function (72 hours) faster than clopidogrel. However, some studies suggest a higher risk of hemorrhagic events (central nervous system and gastrointestinal tract). It presents a 6-8 hour half-life (Table 1).[8]

Prasugrel

Prasugrel is another irreversible platelet receptor P2Y12 inhibitor, also with faster action than clopidogrel. It has an onset of action in 15-30 minutes and a half-life of 2-15 hours (Table 1). Its maximum antiplatelet effect occurs within 48 hours, and recovery occurs gradually after two days of medication suspension.[8]

Dipyridamole

Dipyridamole is a phosphodiesterase inhibitor used as a coronary vasodilator. It has an antiplatelet effect due to decreased platelet aggregation and vasodilation. As a single agent, it does not increase the risk of bleeding.[8]

NEW ORAL ANTICOAGULANTS

Rivaroxaban

Rivaroxaban is a direct factor Xa inhibitor, reversibly blocking the conversion of prothrombin to thrombin.[12] It has an onset of action between two and four hours and a half-life of 5-12 hours (Table 1). Its elimination is mainly renal.[8]

It is administered in fixed doses and does not require routine control due to predictable pharmacodynamic and pharmacokinetic characteristics.[8]

There are no specific laboratory tests for monitoring, but, in emergencies, the activated partial thromboplastin time (APTT) and the prolonged prothrombin time (PT) can be used qualitatively to assess Factor Xa inhibitors.[1]

Table 1: Pharmacological characteristics of anticoagulants

Anticoagulant	Onset of action	Half-life
Warfarin	90 minutes	36 to 42 hours
Acetylsalicylic acid	30 minutes	3 hours
Clopidogrel	150 minutes	6 hours
Ticagrelor	15 minutes	6 to 8 hours
Prasugrel	15 minutes	2 a 15 hours
Dipyridamole	10 minutes	3 hours
Rivaroxaban	120 minutes	5 to 12 hours
Apixaban	60 minutes	10 to 15 hours
Edoxaban	60 minutes	10 to 15 hours
Dabigatran	120 to 180 minutes	8 to 17 hours

It undergoes hepatic metabolism through the cytochrome CYP3A4/5 and CYP2J2 pathways, revealing important drug interactions. Azoles, cyclosporins, and erythromycin increase the anticoagulant effects. Phenytoin and rifampicin have the opposite effect, reducing this action. Also, P glycoprotein (P-gp) inhibitors lead to prolonged and increased anticoagulant action (verapamil, amiodarone, and quinidine) due to the competitive inhibition of renal clearance.[12]

There is no specific antidote, but prothrombin complex concentrate can be administered in emergencies.[1] Two new agents for reversing anticoagulant effects are under investigation (andexanet alfa and ciraparantag), the first of which has already been approved by the Food and Drug Administration (FDA) in May 2018.[1,13,14]

Apixaban

Apixaban is a direct reversible factor Xa inhibitor, whose mechanism of action is identical to rivaroxaban and edoxaban.[1,8] It has fast absorption (1-3 hours) and a half-life of 10 to 15 hours (Table 1). Its excretion is renal (25%) and biliary, and cytochrome P 450/3A4 and enzymatic pathway P-gp metabolizes it. Therefore inhibitors of these pathways increase blood levels of the medication (interactions similar to rivaroxaban).[1,8] It also does not require routine monitoring, and patients with mild or moderate renal and hepatic dysfunction do not need dose correction. Andexanet alfa recently obtained authorization as a reverse agent from the FDA.[1,13]

Edoxaban

Edoxaban is the newest direct factor Xa inhibitor.[1,12] It has an identical mechanism of action to other factor Xa inhibitors. However, cytochrome P 450 poorly metabolizes it, thus reducing the risk of drug interactions.[1,12] Furthermore, medicines that are metabolized by the enzymes of the P-gp system interfere with their effectiveness.

Dabigatran

Dabigatran is a direct thrombin inhibitor by constraining factor IIa1 and reversibly blocking the fibrinogen conversion to fibrin.[1,8,12] It starts to act in 1-3 hours and has a half-life of 8-17 hours (Table 1). The kidneys excrete it (80%) and, thus, renal dysfunctions can prolong its half-life, being contraindicated in severe renal changes (creatinine clearance <30 ml/min).[1,8,12] Cytochrome P does not metabolize it; however, the glycoprotein P (P-gp) inhibitors can raise its plasma levels.

Like other new oral anticoagulants, routine monitoring is unnecessary, but the thrombin time (TT) can be used to infer its effect.[1] In emergencies, hemodialysis can be used to reduce its action. More recently, idarucizumab has been approved in Europe as a reversing agent.[1,15] Ciraparantag has also been suggested for this purpose.[14]

ANTICOAGULANTS AND ANTIPLATELETS IN SURGICAL PRACTICE

The use of anticoagulant medications is increasingly common in medical practice. Consequently, the dermatological surgeon faces daily the need for invasive procedures in patients using one of these medications. In this context, careful preoperative anamnesis focused on daily medications and clinical indications for such use is essential. It's vital to measure the complexity of the planned procedure, together with the bleeding risk.

There is significant controversy in the literature about the degree of complexity of surgical procedures performed by the dermatologist. However, in general, we must consider those with large detachments and with large tissue movements as procedures with higher bleeding risk. Anatomical location is also directly linked to this risk, with the incidence of bleeding complications in the nose being much more frequent than in other areas of the head and neck region (21% x 6%).16

There are no specific criteria in the dermatological literature on the definition of surgical bleeding. Some authors consider everything from mild events, such as changing the dressing, to severe events, ranging from surgical revision and necrosis to blood transfusion. [11] It can explain different numbers and different interpretations. In general, it is accepted that the risk of bleeding in dermatological surgeries performed on patients who are not using any medication is low, being estimated at approximately 1%.[8,11,13] The highest bleeding risk is demonstrated in patients undergoing surgical procedures under the use of anticoagulants.[8,11] The literature describes that the association of two or more agents significantly increases hemorrhagic events.[8,11,12] However, the increased risk of thromboembolic events associated with discontinuation of anticoagulant medications is well documented.[17,18,19] The magnitude of potential events that present high morbidity and mortality dramatically surpasses the risk of hemorrhagic complications at the surgical site in dermatological surgery.

Therefore, the pre-surgical consultation performed properly with an emphasis on the patient's clinical history (including renal function in cases of new oral anticoagulants use), the anatomical location addressed, and the exact surgical schedule treatment is essential for a satisfactory outcome. Whenever feasible, it's crucial to consider reconstructions with the least possible detachment,[18] mainly for complex and riskier areas such as the face. At that time, medications used prophylactically can be discontinued for procedures with higher hemorrhagic potential.

Table 2: Recommendations of anticoagulants in dermatological surgical practice

Anticoagulant	Recommendation
General orientations	1. Medicines and supplements with potential anticoagulant and / or antiplatelet action in prophylactic use can be suspended seven days before surgery. 2. Medications used for medical indication (previous heart attack, stroke) should be maintained. 3. Special attention is paid to intraoperative surgical techniques to control bleeding, in addition to occlusive dressings for an adequate time.
Warfarin	1. One week before surgery, request INR. If INR is >3.5, weigh the risk / benefit of the surgery immediately and if possible postpone the procedure until the INR is within the safety margin (2-3, 5).
Acetylsalicylic acid	1. Do not suspend. 2. If prophylactic or analgesic use, it can be discontinued 7- 10 days before the procedure.
Clopidogrel, Ticagrelor and Prasugrel	1. Do not suspend
Dipyridamole	1. Do not suspend
Dabigatran, Rivaroxaban, Apixaban	1. If surgery with greater bleeding potential, discontinue only the dose prior to the day of surgery.

Regarding warfarin, a multicenter study with 9,154 surgical procedures 11 demonstrated the INR value as a significant factor for the bleeding risk in multivariate analysis. In the univariate analysis, the study found that, with a lower INR,[1,3] the risk of bleeding was 0.46%; and with a higher INR,[1,3] the risk of bleeding increased to 3.7% ($p<0.0001$).

Syed *et al.*[4] reported a bleeding risk of 60% with INR >3.5 and 27% for INR <3.5. However, the withdrawal of warfarin increases the risk of thromboembolism, in addition to the rebound hypercoagulability state observed when it is interrupted.[8] Bridging therapies with heparin are a common practice in moments of warfarin suspension. However, there is an extensive demonstration of increased bleeding events,[6,8,20,21] and currently it is not advised in dermatological surgery.[22] It is currently considered that INR <3 does not contraindicate the dermatological surgery, even those with more complex reconstructions such as flaps or grafts.[8,18,25] If the INR is >3, it is suggested to postpone the surgery until the INR can be within the safety margin.[8,18]

The use of clopidogrel increases the risk of hemorrhagic events with data ranging from 2.86% to 9%.[9] Acetylsalicylic acid increased the risk from 1.42% to 2-3%.[8,9] Other authors have not found an increased risk of bleeding with the ASA use compared to controls.[5,10] The risk of severe ischemic events and even death with the interruption of these medications is abundant.[18,23] Therefore, it is currently recommended not to interrupt medication in patients on antiplatelet monotherapy,[5,8,18] except for those with exclusively preventive indication.[8] In such cases, they should be suspended seven to 10 days before the surgery date. In cases of a combination of two antiplatelet agents and procedures with a higher bleeding potential, one should evaluate the possibility of operating after the patient is on monotherapy.[11] If not possible, the surgical procedure is performed without interrupting the medications.[24]

Regarding the new oral anticoagulants, we need to consider three main factors in the pre-surgical evaluation: the extent of the surgical procedure, the bleeding risk, and the patient's renal function. The bleeding risk is similar to that of warfarin. Some guidelines, such as the European Heart Rhythm Association (EHRA), consider unnecessary to interrupt NOAC in superficial surgery in patients with normal kidney function (Table 2).[12,25] For more aggressive surgeries, it is recommended to interrupt the medication 24 hours before the procedure and not restart it before one hour after the procedure, due to predictability and short half-lives.[11,24] In patients with creatinine clearance <30 ml/minute, the medication interruption time should be longer.[1]

Strict adherence to good surgical practices is essential in patients receiving anticoagulant medications, paying particular attention to adequate hemostasis of the surgical field, proper compressive dressings, and postoperative care. It's also important to properly inform the patient about the highest risks they are subject to.

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