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PERIOPERATIVE MANAGEMENT OF INDIVIDUALS WITH ANTICOAGULANT AND ANTIPLATELET THERAPY

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SUMMARY

Introduction: *The increased use of anticoagulant therapy and antiplatelet therapy requires careful management, especially in patients requiring surgery. These treatments include oral and parenteral options which must be balanced with the risk of bleeding and thrombosis. They are fundamental in both prevention and treatment of thromboembolic events.*
Objective: to present clear and precise recommendations for the perioperative management of TAC and antiplatelet agents.
Methodology: *a total of 30 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 17 bibliographies were used because the other articles were not relevant for this study. The sources of information were PubMed, Google Scholar and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: oral anticoagulants, antiplatelet agents, TACO, antithrombolytic therapy, new oral anticoagulants.*
Results: *the study showed that restarting low molecular weight heparins in therapeutic doses before 24 hours post-surgery increases the risk of bleeding, so it is recommended to use prophylactic doses. Furthermore, it emphasizes the importance of adjusting anticoagulant therapy according to the thromboembolic and hemorrhagic risk of each patient.*
Conclusions: *anticoagulant and antiplatelet drugs are essential to prevent thromboembolic events in pathologies such as acute coronary syndrome and cerebrovascular diseases. Their perioperative management should consider the thrombotic and hemorrhagic risk, as well as the type of surgery and drug. Heparins, vitamin K antagonists and new oral anticoagulants require adjustments in doses and withdrawal times to prevent complications. In addition, reversal of their anticoagulant effect in emergencies is key, with advances in agents such as idarucizumab and andexanet alfa for greater effectiveness in critical situations.*
KEY WORDS: *TACO, anticoagulants, antiplatelet agents.*

INTRODUCTION

The number of individuals undergoing antithrombotic treatment with antiplatelet agents has increased significantly. Most of the time it is a chronic management that the affected individual will carry all his life, so it will not be strange that at some point this individual will have to undergo a surgical or interventional procedure. Therefore, it is necessary to know what is the correct attitude to take in this scenario. Nowadays, anticoagulant therapy (ACT) is widely used in clinical practice, either as primary prophylaxis in individuals at risk of presenting thromboembolic phenomena, or as treatment in individuals who have already presented a thrombotic event.

There are several TAC alternatives: oral anticoagulant therapy (OACT) and parenteral anticoagulant therapy (PACT). Within the former, there are vitamin K antagonist drugs (coumarins)

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and the new oral anticoagulants. The latter include unfractionated heparin (UFH) and low molecular weight heparin (LMWH). When deciding whether to use or discontinue TAC, the risk of perioperative bleeding associated with the therapy should be balanced against the thromboembolic risk related to its discontinuation.
The use of antiplatelet drugs for primary and secondary prevention of cardiovascular events is a common clinical practice(1,2).

METHODOLOGY

A total of 30 articles were analyzed in this review, including review and original articles, as well as cases and clinical trials, of which 17 bibliographies were used because the information collected was not sufficiently important to be included in this study. The sources of information were Cochrane, PubMed and Google Scholar; the terms used to search for information in Spanish, Portuguese and English were: oral anticoagulants, antiplatelet agents, TACO, antithrombolytic therapy, new oral anticoagulants.

The choice of bibliography exposes elements related to the perioperative management of individuals with anticoagulant and antiplatelet therapy.

DEVELOPMENT

Antiplatelet aggregation and anticoagulant drugs are essential in the prevention of thromboembolic events, a process involved in various pathologies such as acute coronary syndrome, venous thromboembolism, interventions such as mechanical heart valve implantation, cerebrovascular disorders and coronary artery disease. According to their mode of action, antithrombotic agents are divided into antiplatelet agents and anticoagulants(1).

In antiplatelet therapy, thrombotic risk assessment should take into account factors such as the time from event to intervention, the nature of the event (acute or stable), the clinical characteristics of the patient and the treatment applied. Depending on the combination of these elements, the risk is classified as high, moderate or low. In general, ASA at 100 mg should be maintained, except in procedures with high hemorrhagic risk (such as neurosurgical procedures), where it is suspended 3 days before. If the ASA dose is higher than 100 mg, it is adjusted to 100 mg, and it is not considered a contraindication to the procedure if it is taken, for example, 300 mg. In case the patient is on monotherapy with a P2Y12 inhibitor, this drug should be discontinued 3 to 7 days before, considering the possibility of substituting it with ASA 100.

In patients with DAP, if the thrombotic risk is high and the bleeding risk is low, therapy should not be discontinued. If the bleeding risk is moderate or severe and more than 30 days have elapsed since the event that prompted treatment, the decision should be individualized. Generally, discontinuation of DAP within the first 30 days after the event is avoided. The key to reintroducing antiplatelet therapy is to ensure adequate hemostasis during the procedure and the absence of postoperative bleeding. As a rule, it is recommended to restart treatment at 24 hours, although if the postoperative bleeding risk is high, it is started between 48 and 72 hours(1,3).
Perioperative management of antiplatelet drugs depends on the individual thrombotic risk and the bleeding risk associated with each intervention. In non-cardiac surgeries, it is recommended to continue with aspirin, except in patients with low to moderate thrombotic risk who will undergo procedures with high bleeding risk, in which it is suggested to suspend it 5-7 days before surgery. Clopidogrel should be suspended 5 days before, except in patients with high thrombotic risk who have procedures with low to moderate hemorrhagic risk. In myocardial revascularization surgeries, aspirin should be maintained and clopidogrel should be discontinued 5 days before. For postoperative restart, it is recommended to resume aspirin 6 hours after surgery and clopidogrel in the first 24 hours, always after confirmation(4).

Vitamin K antagonists, such as warfarin and acenocoumarol (Neosintrom®), inhibit the synthesis of vitamin K-dependent coagulation factors (II, VII, IX and X). Warfarin has a half-life of 36-42 hours, while acenocoumarol has a half-life of 8-11 hours. The anticoagulant effect of these drugs is monitored by prothrombin time (PT) and the international normalized ratio (INR). Their dosage is adjusted individually for each patient, with weekly controls of the INR, which is considered to be in therapeutic range with values between 2-3(2,5,6).

Discontinuation of vitamin K antagonists depends on the type of surgical procedure and the associated bleeding risk. In procedures with low bleeding risk, such as cataract surgeries, some minor endoscopic and dermatologic procedures, the American College of Chest Physicians (ACCP) suggests maintaining oral anticoagulant therapy (OACT). In procedures with moderate to high risk of bleeding, it is recommended to discontinue warfarin 5 days before surgery and acenocoumarol 2-3 days before, after assessing the patient's thromboembolic risk. In some cases, “bridge therapy” is used, which consists of substituting TACO with short-acting parenteral anticoagulants, such as unfractionated heparin (UFH) or low molecular weight heparin (LMWH). The ACCP classifies patients according to the risk of thrombosis as high (>10%), moderate (5-10%) and low (<5%), which will determine the requirement for bridging therapy(7,8).

The ACCP recommends considering bridging therapy in surgical patients at high thrombotic risk, while in those at moderate risk, bridging therapy should be considered only if the risk of surgical bleeding is low. Patients with low thrombotic risk do not require this therapy. The use of low molecular weight heparin (LMWH) is preferred over unfractionated heparin (UFH), since studies such as that of Attaya et al. have shown a lower bleeding rate with LMWH (5.4%) versus UFH (15.4%), with no significant differences in the cohorts.

Once TACO is discontinued, it is recommended to monitor the INR the day before surgery. If the INR is ≤1.5, it can proceed without further intervention. If it is >1.5, the anticoagulant effect should be reversed: for elective surgeries, oral or intravenous vitamin K can be administered, preferably the intravenous route, which acts in 12-48 hours. In urgent or

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emergency surgeries, or in patients with massive bleeding, fresh frozen plasma (FFP) and/or prothrombin complex concentrate (Octaplex®) is recommended. The use of the latter is preferred, since it reverses the action of TACO in a faster and more effective way compared to FFP(2,9).

Warfarin should be restarted 12 to 24 hours after surgical procedures with low risk of postoperative bleeding, provided adequate hemostasis has been achieved. Once oral anticoagulant therapy (OACT) has been restarted, it will take 5 to 10 days for the INR to reach the therapeutic range. In patients with high thromboembolic risk, the use of postoperative bridging therapy with parenteral anticoagulants is recommended, performing an overlap with warfarin until an INR in optimal range is achieved(2,5,7).
New oral anticoagulant agents

Newer oral anticoagulant drugs include direct thrombin inhibitors and activated factor Xa inhibitors. These drugs are now frequently employed in medical practice because they do not require continuous monitoring of the anticoagulant effect, have a predictable effect, and show comparable efficacy to traditional anticoagulants. Monitoring is only necessary in specific clinical situations, such as acute bleeding, suspected overdose or emergency/urgent surgery.

Direct Thrombin Inhibitors
Dabigatran (Pradaxa®) acts on free and fibrin-bound thrombin, reversibly inhibiting its activity. Its maximum plasma concentration is reached between 1.25 and 2 hours after administration, and it has a half-life of 12 to 14 hours. The elimination of this drug is mainly renal, so it is important to evaluate renal function in patients who use it, considering the variations in half-life according to the estimated creatinine clearance (see Table 3). This drug is contraindicated in people with a creatinine clearance lower than 30 ml/min. Its anticoagulant effect is reflected in nonlinear alterations in prothrombin time (PT) and activated partial thromboplastin time (aPTT). There are other tests to monitor their effect, such as thrombin time, ecarin and the Hemoclot® system for thrombin inhibitors, although their use in clinical practice is limited.

Activated Factor Xa (Xa) Inhibitors
Rivaroxaban (Xarelto®) and apixaban (Eliquis®) are drugs that act as reversible inhibitors of factor Xa enzymatic activity, limiting the conversion of prothrombin to thrombin.

Rivaroxaban
It is prescribed in doses of 20 mg daily for prevention and 15 mg every 12 hours for the treatment of thrombosis. Its maximum plasma concentration is reached between 2 and 4 hours after administration, with a half-life of 9 to 12 hours. Its metabolism is mainly hepatic, with only one third of elimination carried out through the kidneys, so it is contraindicated in patients with a creatinine clearance of less than 15 ml/min. Although there are no established guidelines for monitoring rivaroxaban, it is known to prolong prothrombin time (PT), INR and activated partial thromboplastin time (aPTT) in a linear and dose-dependent manner. In surgical procedures with a high risk of bleeding, antifactor Xa activity can be measured to confirm the absence of its anticoagulant effect prior to surgery.

Apixaban
It is used in doses of 2.5 mg every 12 hours for prevention and 5 mg every 12 hours for the treatment of thrombosis. Its maximum plasma concentration is reached 2 to 3 hours after administration, with a half-life of 8 to 15 hours, and it is mainly eliminated by the liver. It does not require routine monitoring, although in surgeries with a high risk of bleeding, antifactor Xa activity can be measured, similar to what is done with rivaroxaban(2,10-13).

Dabigatran should be discontinued in surgical procedures with low bleeding risk between 24 and 48 hours before the intervention, and between 48 and 96 hours before surgeries with high bleeding risk, depending on the estimated creatinine clearance in each patient.

Rivaroxaban and apixaban should be discontinued 24 to 36 hours before procedures with low bleeding risk, and 48 hours before surgeries with high bleeding risk.

The use of preoperative bridging therapy is indicated only in patients taking new oral anticoagulants who are at very high thromboembolic risk.
When to restart new oral Anticoagulants Postoperatively?
In surgical procedures with low bleeding risk, new oral anticoagulants can be restarted 24 hours after surgery. In procedures with high bleeding risk, restarting should be done 48-72 hours after surgery. Postoperative bridging therapy is reserved for patients with an extremely high thromboembolic risk or those who cannot take oral medications (10,14).

Reversal of the Anticoagulant effect of new oral anticoagulants
In situations of massive bleeding and/or urgent surgical interventions, a rapid and effective reversal of the anticoagulant effect of these drugs is essential. Fresh frozen plasma (FFP) is of little use in these scenarios, since extremely high doses of this blood product (30 ml/kg) and more than 24 hours are required to achieve complete reversal of the anticoagulant effect.

Because of this, specific antidotes are under development to counteract the effect of the new oral anticoagulants. Currently, there are two agents available for the reversal of these drugs:
Idarucizumab: a humanized monoclonal antibody fragment with a high affinity for dabigatran. This drug was approved by the Food and Drug Administration (FDA) in October 2015 as a specific antidote to dabigatran in cases of severe bleeding and/or urgent surgery.

Andexanet alfa: a modified recombinant version of factor Xa, in development as a targeted agent to reverse the effect of factor Xa inhibitor anticoagulants such as rivaroxaban and apixaban. In the ANNEXA-A and ANNEXA-R clinical trials, this drug showed a rapid and effective reversal of the anticoagulant effect

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of rivaroxaban and apixaban, with no associations with serious adverse events or thrombotic phenomena(2,15).

Perioperative Management of Patients on Heparin

Heparin is an indirect parenteral anticoagulant that exerts its effect by activating and potentiating antithrombin III (ATIII), which neutralizes the action of thrombin (factor IIa) and factor Xa. Specifically, it binds to lysine sites of ATIII, causing a conformational change in this molecule, transforming it from a slow-acting to a fast-acting thrombin inhibitor. In clinical practice, it is used to prevent thromboembolic disease and for the treatment of acute thromboembolic pathology.

There are two types of heparin: unfractionated heparin (UFH) and low molecular weight heparin (LMWH).

Unfractionated Heparin

UFH has a higher molecular weight. The heparin-ATIII complex inhibits factors IIa and Xa, with factor IIa being 10 times more sensitive to inhibition than factor Xa. Unfractionated heparin can be administered by two routes: intravenous and subcutaneous. The intravenous route has greater bioavailability and shorter latency, so it is used in patients requiring a rapid anticoagulant effect. Subcutaneous UFH is mainly used for thromboprophylaxis in hospitalized patients requiring prolonged rest. Its elimination occurs through two mechanisms: a rapid, saturable one, which depends on binding to endothelial receptors and macrophages, and a slower, renal one, which accounts for most of its excretion.At usual doses, its anticoagulant effect is not linear and varies depending on the type of thromboembolic disease. For this reason, when administered as a continuous infusion, doses should be adjusted according to the monitoring of the anticoagulant effect. The consensus establishes that the activated partial thromboplastin time (APTT) should be monitored, which should be controlled approximately 6 hours after the first bolus of UFH and then the dose should be adjusted according to the results. The therapeutic range of the APTT is 1.5 to 2.5 times the laboratory control value. To treat thromboembolic disease, the dose of UFH is 80 U/kg bolus, followed by 18 U/kg/h continuous infusion pump (CIB). For acute myocardial infarction, the initial dose is 60 U/kg bolus, followed by 12 U/kg/h on ICB.

When to stop Unfractionated Heparin?

In patients receiving UFH in therapeutic doses, the intravenous infusion should be discontinued 4 to 5 hours before the surgical procedure. In patients receiving subcutaneous UFH in prophylactic doses (usually 5,000 U every 12 hours), heparin should be discontinued 12 hours before surgery.

When to restart Unfractionated Heparin Postoperatively?

In surgical procedures with low bleeding risk, heparin is restarted 24 hours after surgery. In surgical procedures with high bleeding risk, heparin should be restarted 48 to 72 hours after the procedure(7,16).

Low Molecular Weight Heparin

Low molecular weight heparins (LMWH) are drugs obtained by chemical depolymerization of heparin, resulting in fragments that are approximately one-third the size of unfractionated heparin (UFH). LMWHs have a greater capacity to inhibit factor Xa than factor IIa, unlike UFH. In terms of pharmacokinetics, LMWHs have a half-life of 3 to 5 hours and a more predictable dose-response relationship than UFH.Their elimination is mainly renal, which means that their half-life is prolonged in patients with renal insufficiency, so their use is not recommended in those with a creatinine clearance of less than 30 ml/min. They are administered subcutaneously, in doses adjusted to the patient's weight if used as complete anticoagulant therapy (TACP); or in standard doses if used for thromboprophylaxis, with the exception of tinzaparin in patients at high thrombotic risk, in which case the prophylactic dose is adjusted according to body weight. Routine monitoring of its anticoagulant effect is not required, although some experts suggest that in obese patients, pregnant women or those with renal insufficiency, antifactor Xa activity should be monitored.

When should low Molecular Weight Heparins be Discontinued?

LMWH used in full anticoagulant therapy doses (TACP) should be discontinued 24 hours before surgery. For LMWH administered in twice-daily doses, the dose the night before surgery should be omitted. If given as a single daily dose, half of the treatment dose should be given 24 hours before the surgical procedure.

LMWH used for prophylaxis should be discontinued 12 hours before surgery.

When to restart low molecular Weight Heparins Postoperatively?

In surgical procedures with low bleeding risk, LMWH should be restarted 24 hours after surgery. In procedures with a higher risk of bleeding, they should be restarted 48-72 hours after the procedure.

The PROSPECT study showed that restarting LMWH at therapeutic doses before 24 hours postoperatively significantly increases the risk of postoperative bleeding, with a 2 to 4-fold increase, compared to placebo or LMWH at prophylactic doses. For this reason, it is recommended to restart LMWH at prophylactic doses to reduce the risk of postoperative bleeding, and then gradually increase to therapeutic doses prior to surgery.

Reversal of the Anticoagulant Effect of Heparins

The anticoagulant effect of heparins can be reversed by using protamine sulfate. This molecule has a half-life of 7 minutes and binds to plasma heparin forming a stable salt, neutralizing its effect. The binding of heparin to protamine depends on the length of the heparin molecule, being more effective in longer heparins, so protamine has a less pronounced effect on LMWH compared to UFH.

In UFH, the dose of protamine is proportional to the total amount of heparin used, which is easy to calculate in the case of a single bolus (1 mg of protamine per 100 U of UFH).

In the case of UFH administered by continuous infusion pump (CIB), the calculation of the protamine dose should take into

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account the time elapsed since the start of the infusion, since the half-life of infused UFH is between 60 and 90 minutes. A suggested guideline is as follows:

- <30 minutes of ICB: 1-1.5 mg of intravenous protamine per 100 U of UFH.
- 30-60 minutes of ICB: 0.5-0.75 mg of intravenous protamine per 100 U of UFH.
- >2 hours of ICB: 0.25 mg of intravenous protamine per 100 U of UFH.

The recommended dose of protamine for LMWH is as follows:

Enoxaparin: 1 mg of intravenous protamine per 1 mg of enoxaparin.

Dalteparin or tinzaparin: 1 mg of intravenous protamine per 100 U of dalteparin or tinzaparin.

The use of protamine is reserved for situations where urgent reversal of the anticoagulant effect is required, such as emergency surgery or severe bleeding. The risk of serious adverse reactions, such as significant hypotension and bradycardia, can be minimized by administering protamine slowly intravenously(17).

Results

Analysis of perioperative management strategies for anticoagulant and antiplatelet drugs, such as heparin, warfarin, and the newer oral anticoagulants, reveals several key guidelines in preventing thromboembolic events and reducing the risk of bleeding complications in surgery. The PROSPECT study, in particular, highlights that restarting low-molecular-weight heparins (LMWH) at therapeutic doses before 24 hours postoperatively significantly increases the risk of bleeding, with a 2- to 4-fold increase compared with placebo or prophylactic doses. As a result of these findings, it is recommended to initiate treatment with LMWH at prophylactic doses post-surgery, with progression to the therapeutic dose according to the patient's evolution. In addition, early resumption of oral anticoagulants and the use of bridging therapies in patients at high thrombotic risk are also tailored to the specific needs of each case to balance therapeutic efficacy with surgical safety.

CONCLUSIONS

Anticoagulant and antiplatelet drugs are essential in the prevention of thromboembolic events, a phenomenon that underlies several pathologies such as acute coronary syndrome, venous thromboembolism and cerebrovascular disease. Their perioperative management depends on the evaluation of the patient's thrombotic and hemorrhagic risk, considering the nature of the surgery and the type of drug used. Heparins, both unfractionated and low molecular weight, together with vitamin K antagonists and the new oral anticoagulants, play a key role in the treatment and prevention of thrombotic events. However, their management requires careful monitoring of bleeding risk, as well as adjustments in dosage and discontinuation and restart times according to the surgical context. Reversal of its anticoagulant effect, especially in emergency situations, is crucial to minimize bleeding complications. In addition, advances in agents such as idarucizumab and andexanet alfa offer new possibilities to counteract anticoagulation more effectively and rapidly in critical situations.

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