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Perioperative Anticoagulant Management: An Overview of Pharmacological Aspects

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Abstract:

Background: Managing patients on anticoagulant or antiplatelet therapy presents a complex challenge, especially around the perioperative period. These therapies are crucial in preventing thromboembolic events but pose a significant risk of bleeding during surgery. The dilemma for healthcare professionals is to balance the risk of thromboembolic events with the potential for surgical bleeding. This requires careful management to optimize patient safety and surgical outcomes.

Aim: This article aims to provide an overview of pharmacological considerations for perioperative anticoagulant management, focusing on the various medications and strategies used to manage anticoagulation therapy before surgery.

Methods: A comprehensive review of the pharmacology, indications, and clinical management of anticoagulants, antiplatelet agents, and their respective perioperative considerations was conducted. The discussion incorporates key medications, including aspirin, warfarin, direct oral anticoagulants (DOACs), and heparins, highlighting their pharmacokinetics and timing for interruption before surgery.

Results: Anticoagulants and antiplatelet agents differ significantly in their pharmacological properties. For example, aspirin irreversibly inhibits platelet aggregation, and its effects persist throughout the lifespan of platelets, necessitating a cessation period of 5-7 days before surgery. Similarly, warfarin, which inhibits vitamin K-dependent clotting factors, requires careful monitoring and adjustment before surgical procedures. Direct oral anticoagulants, such as rivaroxaban and dabigatran, have a rapid onset and are easier to manage due to their predictable pharmacokinetics, but their use still requires consideration of renal function and potential interactions.

Conclusion: Optimal management of anticoagulants and antiplatelet therapy during the perioperative period is critical in balancing the risks of bleeding and thromboembolic events. Tailored management strategies, considering the patient's specific clinical profile and the surgical procedure, are essential for preventing adverse outcomes. Further research is needed to refine these strategies and ensure safer perioperative management for patients on anticoagulant therapy.

Keywords: Anticoagulation, antiplatelet therapy, perioperative management, bleeding risk, thromboembolism, aspirin, warfarin, DOACs, surgical outcomes, patient safety.

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Introduction:

Managing patients undergoing anticoagulation and antiplatelet therapy presents a significant challenge for healthcare professionals. The interruption of these therapies may increase the risk of thrombotic events, both during and after surgery. However, continuing the therapy without interruption can elevate the risk of bleeding, potentially resulting in a wide range of adverse outcomes, from minor bleeding to life-threatening hemorrhages. The optimal management of these patients involves carefully balancing the risks of thromboembolism and bleeding. Decisions regarding whether to interrupt or continue anticoagulation and antiplatelet therapy before surgery are influenced by multiple factors. Among these are an individual's underlying bleeding risk, the bleeding risk associated with the specific surgical procedure, the timing of interruption and resumption of therapy, and whether bridging therapy should be considered. Each of these factors plays a crucial role in determining the appropriate course of action. Evaluating the overall clinical situation, including a patient's medical history and the type of surgery being performed, is essential in making informed decisions. Furthermore, the management strategy should be personalized, considering the unique risks associated with each patient. These complex issues, involving both medical and surgical considerations, require careful and thoughtful decision-making to ensure patient safety and optimize surgical outcomes. Ultimately, managing anticoagulation therapy around the time of surgery demands a nuanced approach to balance both the thrombotic and hemorrhagic risks, tailoring interventions to the patient's specific clinical needs [1].

Etiology

Anticoagulation therapy is commonly indicated in patients with various medical conditions that predispose them to thromboembolic events. The most frequent

indications for anticoagulation include atrial fibrillation, deep vein thrombosis (DVT), pulmonary embolism (PE), and the presence of prosthetic heart valves. Atrial fibrillation, a common arrhythmia, significantly increases the risk of stroke, which can be mitigated by appropriate anticoagulation therapy. In patients with DVT and PE, anticoagulation prevents the extension and propagation of clots, reducing the risk of potentially life-threatening complications such as pulmonary embolism. Furthermore, after the implantation of prosthetic heart valves, anticoagulation is essential to prevent thromboembolism, as these valves increase the risk of clot formation. In addition to these conditions, patients who have undergone percutaneous coronary interventions (PCI) typically require dual antiplatelet therapy to prevent stent thrombosis. Similarly, individuals with a history of coronary artery bypass grafting (CABG), stroke, or conditions like essential thrombocythemia may also need ongoing antithrombotic therapy. The primary goal of anticoagulation is to reduce the risk of thromboembolic events, which can lead to significant morbidity and mortality if not adequately managed. It is important to tailor anticoagulation therapy based on the specific risk profile of each patient, including the type of underlying condition and the presence of any additional risk factors. Thus, a thorough evaluation is necessary to ensure the most effective and safe anticoagulant regimen for each patient [2].

Epidemiology

Anticoagulation therapy is primarily used for managing conditions that pose a high risk of thromboembolism, such as atrial fibrillation, deep vein thrombosis, and pulmonary embolism. In the United States, approximately 3 to 5 million people suffer from atrial fibrillation (AF), a figure expected to rise to 8 million by 2050 [1]. AF is one of the leading causes of stroke, and its prevalence is increasing with the aging population. Anticoagulation therapy plays a crucial role in preventing stroke in patients with AF, significantly reducing the risk of thromboembolic events. Similarly, deep vein thrombosis and pulmonary embolism are common indications for anticoagulation, as these conditions can lead to severe complications, including death, if untreated. In the United States, nearly 250,000 patients annually require discontinuation of anticoagulation therapy for surgery, as anticoagulants increase the risk of bleeding during invasive procedures [2]. This highlights the importance of balancing anticoagulation therapy with the need for surgery, as inappropriate management can lead to adverse outcomes. The increasing prevalence of conditions requiring anticoagulation therapy and the growing number of patients needing surgical interventions underscore the challenges healthcare professionals face in managing these complex cases. It is essential to develop strategies to optimize anticoagulation therapy, minimize thrombotic and bleeding risks, and ensure that patients undergoing surgery receive the appropriate care based on their unique clinical situation. As the population ages, these challenges are expected to become even more prevalent.

Pathophysiology

The physiological hemostasis, which is responsible for stopping bleeding after injury, can be disrupted by a variety of factors, including genetic disorders, malignancy, sepsis, surgery, and pharmacological agents, particularly those used for anticoagulation and antiplatelet therapy. Under normal circumstances, the body maintains a delicate balance between pro-coagulant and anticoagulant factors to ensure proper blood clotting and prevent excessive bleeding. However, certain conditions, such as genetic defects in coagulation factors, can predispose individuals to either bleeding or thrombosis. Malignancy and sepsis further complicate this balance by triggering inflammatory responses that can alter coagulation pathways. In the context of surgery, the physical trauma and inflammatory response can also disrupt hemostasis, requiring careful management of anticoagulation therapy. Drugs used for anticoagulation, such as warfarin and direct oral anticoagulants (DOACs), and antiplatelet medications, such as aspirin and clopidogrel, interfere with clot formation, which is critical for controlling bleeding during surgery. As a result, understanding the mechanisms of anticoagulation and antiplatelet therapy is crucial for managing patients during the perioperative period. A pharmacological review of these medications is essential, as it provides valuable insights into how different drugs affect the coagulation system and how they should be managed to minimize bleeding risks. Given the complexity of hemostasis and the variability in patient response to anticoagulants, a tailored approach to perioperative anticoagulation is vital to ensure optimal patient outcomes during surgical procedures [3].

Aspirin (Acetylsalicylic Acid)

Aspirin is the most widely prescribed antiplatelet agent for the prevention of cardiovascular events. Its therapeutic effect is attributed to the irreversible inhibition of cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2. These enzymes are crucial for converting arachidonic acid into prostaglandin (PG) H2, which is further transformed into several bioactive prostanoids, including thromboxane A2. Thromboxane A2 is a potent vasoconstrictor and a key inducer of platelet aggregation. Although aspirin has a relatively short half-life (3 to 6 hours), its irreversible inhibition persists throughout the lifespan of the platelet, which is typically 8 to 9 days. Following cessation of aspirin therapy, platelet function gradually recovers at a rate of approximately 10% per day, contingent upon platelet turnover [3][4].

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs exert their therapeutic effects by inhibiting COX enzymes, with some drugs selectively targeting COX-2, the enzyme primarily responsible for pain and inflammation. By selectively inhibiting COX-2, these agents minimize the adverse effects associated with the inhibition of COX-1. The impact of NSAIDs on platelet function is generally transient, normalizing within 3 days, although this duration can vary between specific drugs within the class. For short-acting NSAIDs such as ibuprofen, diclofenac, and indomethacin, platelet function recovers to 50% within 6 hours of the last dose, reaching baseline levels within 24 hours [4][5].

Thienopyridines (Clopidogrel and Prasugrel)

Thienopyridines, including clopidogrel and prasugrel, are antagonists of the adenosine diphosphate (ADP) P2Y12 receptor on platelets. ADP binding to this receptor typically triggers an increase in intracellular calcium, activating the GpIIB/IIIa receptor and enhancing platelet aggregation through fibrinogen binding. Both clopidogrel and prasugrel are prodrugs, and their active metabolites irreversibly modify platelet function in a dose- and time-dependent manner. A daily dose of 75 mg clopidogrel results in a 60% reduction in platelet activity within 3 to 5 days, while a 600 mg loading dose achieves maximal platelet inhibition within 6 to 8 hours. Similarly, a 60 mg loading dose of prasugrel results in steady-state inhibition within 2 hours of administration. Due to their irreversible action, these agents should be discontinued 5 to 7 days before elective non-cardiac surgery [3][4].

Non-thienopyridines (Ticagrelor and Cangrelor)

Ticagrelor and cangrelor represent a newer class of antiplatelet drugs with distinct mechanisms of action. Ticagrelor, a reversible, non-competitive ATP analog, binds to the P2Y12 receptor, blocking its activation and subsequent signaling. Following a loading dose of ticagrelor, peak antiplatelet effects are observed within 2 hours, with a plasma half-life of 8 to 12 hours. Steady-state concentrations are typically reached within 2 to 3 days. Due to its reversible effect, ticagrelor should be suspended 5 days before surgery. In contrast, cangrelor is a direct, intravenously administered, reversible inhibitor of the P2Y12 receptor. It exerts near-complete platelet inhibition (95% to 100%) within 2 minutes of administration. Cangrelor’s short plasma half-life (3 to 6 minutes) facilitates the recovery of 80% to 90% of platelet function within 60 to 90 minutes after discontinuation of the infusion [7].

Vitamin K Antagonists (Warfarin, Acenocoumarol, Phenprocoumon)

Vitamin K antagonists, commonly referred to as coumarins, include the widely used drug warfarin, which has been in clinical use for over 50 years. Warfarin's mechanism involves inhibiting the 2,3-epoxide reductase enzyme, which is essential for the cyclical reduction of vitamin K. This reduced form of vitamin K serves as a cofactor for the carboxylation of glutamic acid at the N-terminus of clotting factors. Without this modification, clotting factors II, VII, IX, and X cannot bind to the required calcium ions for activation. This inhibition also affects the production of the anticoagulants protein C and S, which have shorter half-lives than clotting factors II and X. As a result, an initial transient procoagulant state may arise, particularly with high doses of warfarin during the initiation of therapy [8]. Warfarin exists as a racemic mixture of the R and S isomers, with the S isomer being 3 to 5 times more potent than the R isomer. The half-life of warfarin is typically 36 to 42 hours, with the S isomer having a shorter half-life of 29 hours and the R isomer 45 hours. However, warfarin's pharmacokinetics are influenced by numerous factors, including drug interactions and genetic variations, making its dosing complex and necessitating regular monitoring [9].

Direct Inhibitors of Factor Xa (Rivaroxaban, Apixaban, Edoxaban, Betrixaban)

Direct oral anticoagulants (DOACs), such as rivaroxaban, apixaban, edoxaban, and betrixaban, function by binding directly to the active site of factor Xa, thereby inactivating it and preventing thrombin activation and clot formation [10]. These agents offer several advantages, including their rapid onset of action and relatively short half-life, which facilitates easier interruption and re-initiation of anticoagulation, particularly following surgery. Additionally, DOACs are associated with a lower risk of bleeding compared to traditional vitamin K antagonists, and they do not require routine coagulation monitoring [11]. However, the pharmacokinetics of DOACs can be influenced by a patient's renal and hepatic function, which may alter their therapeutic effect and safety profile.

Direct Inhibitors of Thrombin (Dabigatran)

Dabigatran, the sole direct thrombin inhibitor, acts by directly binding to thrombin, thus preventing the conversion of fibrinogen to fibrin and inhibiting clot formation. This drug has a rapid onset of action (0.5 to 2 hours) and is metabolized by non-specific plasma esterases. The plasma half-life of dabigatran is approximately 12 hours, but its elimination is primarily renal (80%) and significantly affected by renal function. Patients with impaired renal clearance (CrCl < 30 ml/min) should avoid dabigatran due to the increased risk of drug accumulation and bleeding complications [11].

Fondaparinux

Fondaparinux is a synthetic Penta saccharide that functions as an indirect factor Xa inhibitor. It binds reversibly to antithrombin, enhancing its ability to inactivate factor Xa. Fondaparinux has a plasma half-life of approximately 15 to 17 hours, and its anticoagulant effect persists for up to 2 to 4 days after the last dose in individuals with normal renal function [11].

Heparins

Heparin enhances the activity of antithrombin, which, in turn, inhibits factors IIa (thrombin) and Xa. Heparin has been extensively used in clinical practice, with various indications and dosing regimens. One notable adverse effect is heparin-induced thrombocytopenia (HIT), although it remains a relatively rare complication, typically dependent on dose, administration route, and the specific heparin type. In patients with renal impairment (CrCl < 30 ml/min), low molecular weight heparins (LMWH) should be avoided or dose-adjusted, with unfractionated heparin (UFH) being a preferable option. Heparin can be used therapeutically for high-risk thromboembolic patients (e.g., enoxaparin 1 mg/kg twice daily or dalteparin 100 units/kg twice daily) or for prophylaxis in bridge therapy (e.g., enoxaparin 40 mg once daily or dalteparin 5,000 units once daily) [12].

Evaluation

Several prominent guidelines recommend a multifaceted approach for assessing thromboembolic risk in patients undergoing elective surgery, emphasizing four key factors to guide clinical decision-making [13].

Assessment of Thromboembolic Risk

The three primary conditions associated with elevated thromboembolic risk include atrial fibrillation, prosthetic heart valves, and recent thromboembolism, whether venous or arterial. The thromboembolic risk in atrial fibrillation can be quantified using clinical variables through the CHA2DS2VASc score [14]. For patients with prosthetic valves, risk stratification involves considering the type, location, and number of prosthetic valves, as well as the presence of additional cardiac risk factors. Regarding thromboembolism, the timing of the event and likelihood of recurrence are critical in risk classification. Venous thromboembolism (VTE) can be categorized as provoked (induced by identifiable risk factors, such as congestive heart failure, malignancy, or inherited thrombophilia) or unprovoked (no clear cause) [15].

Evaluation of Procedural Bleeding Risk

When determining bleeding risk, the type of surgery and the patient's clinical profile must be considered. The HAS-BLED score (Hypertension, Abnormal liver/kidney function, Stroke, Bleeding history, Labile INR, elderly, drugs, alcohol) is a tool used to assess this risk. A score higher than 3 suggests a significant bleeding risk. The BNK Online Bridging Registry (BORDER) study identified the HAS-BLED score as a reliable predictor of perioperative bleeding [16]. Surgical risks are typically categorized into low (0-2% two-day major bleeding risk) or high (2-4% two-day major bleeding risk). Special caution is required for intracranial, cardiac, and neuraxial surgeries due to severe potential complications and poor outcomes [17].

Deciding on Anticoagulation or Antithrombotic Therapy Interruption

The decision to interrupt anticoagulation therapy involves balancing the risks and benefits, requiring clinical judgment in the absence of standardized tools. Patients with a high bleeding risk may benefit from discontinuing anticoagulation, while those with high thromboembolic risk may require bridging therapy and a shorter duration of therapy interruption. For example, patients undergoing potentially curative cancer surgery might require bridging therapy. In some cases, deferring elective surgery can be an appropriate strategy after weighing risks. For patients with a recent VTE episode (less than one month), the recurrence risk can be as high as 40% in the following month. Elective procedures should be postponed for up to 3 months after VTE when feasible. In cases of recent acute ischemic stroke, the risk of major cardiovascular events post-surgery is elevated, particularly within the first three months, and surgery may be deferred for up to 9 months [18].

A frequent clinical scenario involves patients with coronary stents, the majority of whom are on dual antiplatelet therapy. Approximately 5% of these patients require surgical intervention within one year of stent placement. If interruption of aspirin and

thienopyridine is necessary during the perioperative period, elective surgery should be postponed for 6 weeks in patients with bare-metal stents and 6 months in those with drug-eluting stents [4][12]. However, if surgery cannot be delayed, dual antiplatelet therapy should be maintained throughout the perioperative course [21][22]. Despite limited supporting evidence, certain low-bleeding-risk procedures, such as dental interventions, may justify continuation of anticoagulation therapy. Studies involving warfarin patients within the therapeutic INR range indicate that continuing anticoagulation during dental procedures, including extractions, is safe, and that bridging therapy could increase bleeding complications [23][24]. A cross-sectional study of direct oral anticoagulants (DOACs) revealed no significant bleeding risk associated with continued anticoagulation.

Endovascular procedures, including venous and arterial angioplasty, angiography, catheter ablation for atrial fibrillation, and atherectomy, were analyzed in a meta-analysis of 20,000 patients on warfarin anticoagulation. The results demonstrated low complication rates in both interrupted and uninterrupted anticoagulation groups [25][26]. Similar outcomes were reported in DOAC studies, such as VENTURE-AF and RE-CIRCUIT, where complications remained low and comparable between groups [27][28]. Additionally, the implantation of prosthetic cardiac devices is considered a high-bleeding-risk procedure. In the BRUISE CONTROL studies, uninterrupted warfarin therapy resulted in fewer pocket hematomas compared to bridging with low-molecular-weight heparin [29]. Furthermore, uninterrupted DOAC therapy in high-thromboembolic-risk patients undergoing electrophysiologic procedures did not outperform therapy interrupted 48 hours prior to surgery [30].

Bridging anticoagulation involves substituting long-acting anticoagulants with shorter-acting agents, such as low-molecular-weight heparin (LMWH), to minimize subtherapeutic anticoagulation and reduce thromboembolic risk [31]. Despite evidence questioning its efficacy, bridging therapy is still used selectively for patients at high thromboembolic risk. Scenarios recommended for bridging therapy include patients with mechanical heart valves, recent thromboembolic events, or those requiring coronary stenting [32]. Notably, a meta-analysis by Sigeal et al. (2012) found no significant difference in thromboembolic events between patients receiving bridging therapy and those who did not; however, the risk of major bleeding was three times higher in the bridging group [32]. Large cohort studies, including the RE-LY trial, indicated that patients on warfarin with bridging therapy had a higher incidence of thromboembolic events and major bleeding compared to those without bridging therapy [33]. The BRIDGE study and PERIOP-2 trial further questioned the benefits of bridging therapy, showing no reduction in thromboembolic events and higher bleeding rates in patients receiving bridging anticoagulation [34].

Treatment:

Our bridging recommendations follow the AT9 guidelines, which align with the 2018 guidelines from the American Society of Regional Anesthesia (ASRA) and are

similar to those from the American College of Surgeons in the same year. During the preoperative period, warfarin should be discontinued 5 days before surgery. Additionally, three days prior to the surgical procedure, subcutaneous low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) should be started at therapeutic doses, with consideration given to the patient's renal function. Two days before surgery, the International Normalized Ratio (INR) should be assessed, and if it is greater than 1.5, vitamin K should be administered at a dose of 1 to 2 mg. LMWH should be discontinued 24 hours before surgery, or 4 to 6 hours prior if the patient is on UFH.

In the postoperative period, if the patient is tolerating oral intake and there are no unexpected surgical issues that would increase the risk of bleeding, warfarin should be restarted 12 to 24 hours after surgery. For patients who received preoperative bridging therapy due to high thromboembolic risk and underwent a minor surgical procedure, LMWH or UFH should be resumed 24 hours after surgery. In contrast, if the patient underwent a major surgical procedure, the resumption of LMWH or UFH should occur 48 to 72 hours postoperatively. It is crucial to always assess the bleeding risk and ensure adequate hemostasis before resuming LMWH or UFH therapy [4][12][18][35].Regarding the management of patients on direct oral anticoagulants (DOACs) undergoing elective surgery, it is important to note that bridging therapy is not indicated for these patients. The predictable pharmacological effects of DOACs allow for a properly timed interruption of anticoagulation therapy before surgery. Several professional societies, including the American College of Cardiology Expert Consensus (2017), the European Heart and Rhythm Association (2018), and the American Society of Regional Anesthesia (ASRA) (2018), have issued recommendations on the timing of DOAC interruption. The appropriate timing of interruption for patients on DOAC anticoagulation is based on the invasiveness and bleeding risk of the procedure, the pharmacokinetic profile of the DOAC, and the clinical characteristics of the patient, such as renal and liver function. As a common recommendation among these guidelines, DOACs should be held 3 half-lives before low-risk procedures and 5 half-lives before high-risk procedures. However, some procedures, such as a colonoscopy without biopsy, which are considered to have minimal bleeding risk, may allow for the continuation of DOAC therapy. Betrixaban, a newer factor Xa inhibitor, is specifically noted by ASRA (2018), which recommends its interruption at least 72 hours before a neuraxial block, and at least 5 hours should pass between catheter removal and reinitiation of the drug [4][19][20].

In 2019, a new strategy was published through the PAUSE study, a prospective clinical trial evaluating a standardized approach for perioperative management of DOACs. The interruption scheme utilized in this study was simple and based on the bleeding risk of the procedure. For high-bleeding-risk procedures, rivaroxaban, apixaban, and dabigatran were suspended 48 hours before surgery in patients with creatinine clearance (CrCl) greater than 50 ml/min. If renal function was compromised, with CrCl less than 50 ml/min, these drugs were interrupted 4 days before surgery. For low-bleeding-risk procedures, these DOACs were suspended 24 hours before surgery in

patients with CrCl greater than 50 ml/min, or 2 days before surgery in patients with impaired renal function. Regardless of renal function, all DOACs were reinitiated 48 hours after high-bleeding-risk procedures and 24 hours after low-bleeding-risk procedures. The study reported a 30-day postoperative rate of major bleeding at 1.35% (95% CI, 0%-2.00%) and an arterial thromboembolism rate of 0.16% (95% CI, 0%-0.48%), although further research is needed, particularly in patients undergoing high-surgical bleeding risk procedures [37].

Management of Antithrombotic Therapy in Patients Undergoing Elective Surgery

In patients who have recently undergone coronary stent implantation, elective surgery should ideally be deferred during critical post-implantation periods—6 weeks for bare-metal stents and 6 months for drug-eluting stents. Should deferral be impossible, dual antithrombotic therapy should be maintained throughout the perioperative period. For patients at elevated risk of cardiac events, aspirin should continue throughout the perioperative phase, while clopidogrel and prasugrel should be suspended 5 days before surgery and recommend 24 hours postoperatively. Conversely, in patients at low risk of cardiac events, dual antiplatelet therapy may be stopped 7 to 10 days prior to surgery and reinstated 24 hours after the procedure [4].

Considerations for Patients Undergoing Neuraxial Anesthesia

The following guidelines for neuraxial puncture and catheter removal, derived from the European Society of Anesthesiology and the American Society of Regional Anesthesia (ASRA), provide comprehensive timelines for discontinuing and resuming anticoagulant therapy following neuraxial procedures. For patients receiving intravenous unfractionated heparin (UFH), the infusion should be ceased 4 to 6 hours prior to any puncture or catheter manipulation. In cases where UFH is administered subcutaneously, it should be interrupted 8 to 12 hours before the procedure. Regardless of the administration route, UFH may be resumed 1 hour after the puncture or catheter removal. For those on a prophylactic dose of low-molecular-weight heparin (LMWH), it should be withheld for 12 hours prior to puncture or catheter removal, and 24 hours if therapeutic dosing is used. Regardless of the dose, LMWH can be resumed 4 hours after the procedure. If patients are receiving fondaparinux at a prophylactic dose of 2.5 mg/day, it should be stopped 36 to 42 hours before a neuraxial procedure and may be restarted 6 to 12 hours after the intervention. For patients on direct oral anticoagulants (DOACs), the timing for interruption depends on the specific drug. For rivaroxaban at a prophylactic dose (less than 10 mg/day), the drug should be paused 22 to 26 hours before the neuraxial intervention, while apixaban at a prophylactic dose should be discontinued 26 to 30 hours before the procedure. Both rivaroxaban and apixaban can be resumed 4 to 6 hours following the procedure. For patients on coumarin-based anticoagulants, the International Normalized Ratio (INR) must be reduced to below 1.4 before any neuraxial intervention. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, do not require cessation before neuraxial anesthesia, whereas drugs like

cilostazol necessitate a 42-hour interruption prior to the procedure, with resumption possible 5 hours post-puncture or catheter removal [4].

Emergency Reversal of Anticoagulation

The definitions of "emergency" and "urgent" surgery vary slightly across different clinical guidelines. An urgent procedure refers to a surgery that may be postponed for up to 24 hours, allowing time for anticoagulation reversal based on serial coagulation tests. Conversely, an emergent situation requires surgical intervention within an hour, typically due to life-threatening bleeding. In emergent scenarios, there is limited time and fewer opportunities for testing and delaying the procedure to mitigate bleeding risks [38]. In the case of warfarin reversal, conservative management such as halting the drug and administering oral vitamin K is appropriate for non-significant bleeding with INR alterations. For more critical situations, the reversal of warfarin anticoagulation involves the administration of prothrombin complex concentrate (PCC) and fresh frozen plasma (FFP) as follows:

- INR 2-4: PCC 25 IU/kg IV
- INR ≥4-6: PCC 35 IU/kg IV
- INR >6: PCC 50 IU/kg IV
- Vitamin K: 10 mg IV administered slowly
- FFP: 10-20 ml/kg
- Trauma patients: 1 gm of tranexamic acid at arrival, with a repeat dose of 1 gm after 8 hours.

PCC, available commercially, contains heparin and is contraindicated in patients with a history of heparin-induced thrombocytopenia [13]. The reversal time with vitamin K and PCC typically ranges from 6 to 24 hours, with INR correction occurring approximately 15 minutes after a 10-minute to 1-hour infusion. FFP should be administered if bleeding persists or if PCC is unavailable. Complete reversal usually takes up to 32 hours and must be done with vitamin K [39]. For reversal of DOACs, andexanet alfa has been FDA-approved as an antidote for apixaban and rivaroxaban. It is believed to also reverse the effects of betrixaban and edoxaban, although further studies are necessary. Prior to this approval, prothrombin complex concentrate was the primary reversal agent for DOACs, though its efficacy remains debated. As newer specific reversal agents have been approved, their use may supersede PCC in future management. However, the high cost of these agents limits their widespread use, with a full treatment course of andexanet alfa costing approximately $50,000, compared to $5,000 for PCC [40][41].

Differential Diagnosis and Complications:

When managing perioperative anticoagulants, it is essential to consider a comprehensive differential diagnosis, which includes several conditions. These include acute anemia, afibrinogenemia, child abuse, dysfibrinogenemia, epistaxis, factor V

deficiency, factor X deficiency, gastrointestinal bleeding, idiopathic thrombocytopenic purpura, liver failure, Munchausen syndrome, subdural hematoma, and both type A and type B hemophilia.Two significant complications can arise from improper management of perioperative anticoagulation. The first is bleeding, which occurs when anticoagulation therapy is not appropriately interrupted within the recommended timeframe. However, if anticoagulation is halted too early in the perioperative phase, patients are at an increased risk of thromboembolic events, as surgical interventions themselves can induce a hypercoagulable state. Therefore, managing anticoagulation during the perioperative period requires careful balancing between the risks of bleeding and thrombosis, necessitating constant vigilance from the healthcare provider to prevent severe complications.

Enhancing Healthcare Team Outcomes

The management of perioperative anticoagulation is a shared responsibility that involves all disciplines within the healthcare team. Initially, nurses must ensure that the patient's anticoagulation therapy and relevant diagnoses are accurately documented upon admission for preoperative testing and physical examination. During the preoperative visit, the surgeon and anesthesiologist are responsible for confirming this information and determining how the patient will be managed perioperatively. Once a plan is established, it is the physician's responsibility to explain the management strategy in detail, and the nurse must review this information with the patient before discharge. Pharmacists are also available to clarify any questions or reiterate the plan. On the day of surgery, operative nurses, physicians, and pharmacy personnel must fulfill their usual duties, ensuring that the patient receives the appropriate care in accordance with the surgical protocol. Postoperatively, the physician is tasked with placing orders regarding the continuation or cessation of anticoagulation, depending on the medication and the patient's individual circumstances. Nurses in the recovery room and on the hospital floor are responsible for verifying each prescription before administration, in alignment with the patient’s diagnosis. Pharmacy personnel are responsible for reviewing pharmacological reconciliation to ensure accuracy. When preparing for discharge, the physician writes the discharge orders, which may include continuing the same anticoagulation regimen, modifying the dosage, or temporarily discontinuing the medication. These orders should be reviewed by pharmacy personnel. It is the nurse's responsibility to ensure that the discharge instructions are fully understood by the patient. This comprehensive process of interdisciplinary collaboration is critical in reducing morbidity and mortality related to anticoagulation therapy and preventing errors. By working together as an interprofessional team, the risks associated with perioperative anticoagulation can be effectively mitigated [42].

Conclusion:

Perioperative anticoagulant management is a highly nuanced process that demands a personalized approach to balance the risks of bleeding and thromboembolic events in surgical patients. Patients requiring anticoagulation therapy are often at a

heightened risk of thromboembolic events, such as those with atrial fibrillation, deep vein thrombosis, pulmonary embolism, or prosthetic heart valves. However, the presence of anticoagulants complicates the perioperative period due to the increased risk of bleeding during invasive procedures. Therefore, managing these patients involves carefully weighing the risk of thromboembolism if anticoagulation therapy is interrupted against the potential for bleeding complications if continued. The pharmacological properties of various anticoagulants, such as warfarin, direct oral anticoagulants (DOACs), and antiplatelet drugs like aspirin, significantly influence their management in the perioperative setting. Warfarin, for instance, requires a careful dose adjustment and monitoring due to its long half-life and variability in patient response, which makes its management challenging. DOACs, on the other hand, offer advantages like rapid onset and predictable pharmacokinetics, although renal function must be closely monitored due to their renal clearance. Aspirin's long-lasting effects on platelet aggregation require its cessation well in advance of surgery to minimize bleeding risk. Additionally, bridging therapies, such as low-molecular-weight heparin, may be considered in some high-risk patients who temporarily discontinue their oral anticoagulant therapy before surgery. The timing of discontinuation and resumption of anticoagulation therapy is a critical aspect of perioperative management, as it aims to mitigate thromboembolic and hemorrhagic risks. Personalized strategies based on the patient's clinical situation, including underlying conditions and type of surgery, must be developed to optimize outcomes. Despite the current guidelines and therapeutic approaches, the increasing prevalence of conditions requiring anticoagulation therapy, combined with the growing number of surgeries performed, presents an ongoing challenge. Continued research into safer, more effective management strategies for anticoagulated patients during the perioperative period is essential. Improving our understanding of drug interactions, pharmacokinetics, and bridging therapies will ultimately lead to better outcomes for these patients, minimizing both thrombotic and bleeding risks.

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إدارة مضادات التخثر حول الجراحة: نظرة عامة على الجوانب الدوائية

الملخص:

الخلفية: إن إدارة المرضى الذين يتلقون علاجًا بمضادات التخثر أو الأدوية المضادة للصفيحات يمثل تحديًا معقدًا، خاصة في فترة ما قبل وبعد الجراحة. تعتبر هذه العلاجات ضرورية في الوقاية من الأحداث الخثارية، ولكنها تشكل خطرًا كبيرًا للنزيف أثناء الجراحة. يكمن التحدي أمام مقدمي الرعاية الصحية في موازنة خطر الأحداث الخثارية مع احتمال حدوث نزيف جراحي. يتطلب ذلك إدارة دقيقة لتحسين سلامة المرضى ونتائج الجراحة.

الهدف: يهدف هذا المقال إلى تقديم نظرة عامة حول الاعتبارات الدوائية لإدارة مضادات التخثر حول الجراحة، مع التركيز على الأدوية المختلفة والاستراتيجيات المستخدمة لإدارة علاج مضادات التخثر قبل الجراحة.

المنهج: تم إجراء مراجعة شاملة للدوائيات، والمؤشرات السريرية، والإدارة السريرية لمضادات التخثر، والأدوية المضادة للصفيحات، واعتباراتها حول الجراحة. تدمج المناقشة الأدوية الرئيسية، مثل الأسبرين، والوارفارين،

ومضادات التخثر الفموية المباشرة (DOACs)، والهيبارينات، مع تسليط الضوء على الحركية الدوائية لهذه الأدوية ووقت إيقافها قبل الجراحة.

النتائج: تختلف مضادات التخثر والأدوية المضادة للصفيحات بشكل كبير في خصائصها الدوائية. على سبيل المثال، يقوم الأسبرين بتثبيط تجمع الصفيحات بشكل لا رجعة فيه، وتستمر آثاره طوال عمر الصفيحات، مما يستدعي فترة توقف تتراوح بين 5-7 أيام قبل الجراحة. وبالمثل، يتطلب الوارفارين، الذي يثبط عوامل التجلط المعتمدة على فيتامين ك، مراقبة دقيقة وتعديلًا قبل الإجراءات الجراحية. أما مضادات التخثر الفموية المباشرة مثل ريفاروكسابان ودابيجاتران، فتعتمد على بداية سريعة وسهولة في الإدارة بفضل حركتها الدوائية القابلة للتنبؤ، لكن استخدامها يتطلب أيضًا أخذ وظيفة الكلى في الاعتبار والتفاعل المحتمل مع الأدوية الأخرى.

الخلاصة: إن الإدارة المثلى لمضادات التخثر والأدوية المضادة للصفيحات خلال فترة ما حول الجراحة أمر حاسم في موازنة مخاطر النزيف والأحداث الخثارية. إن استراتيجيات الإدارة المصممة خصيصًا بناءً على الملف السريري الخاص بالمريض والإجراء الجراحي أمر ضروري لمنع النتائج السلبية. هناك حاجة إلى مزيد من البحث لتطوير هذه الاستراتيجيات وضمان إدارة أكثر أمانًا للمرضى الذين يتلقون علاجًا بمضادات التخثر خلال فترة ما حول الجراحة.

الكلمات المفتاحية: مضادات التخثر، العلاج المضاد للصفيحات، الإدارة حول الجراحة، خطر النزيف، الخثار، الأسبرين، الوارفارين، DOACs، نتائج الجراحة، سلامة المرضى.