ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

Periprocedural Management of Patients on Antithrombotic Therapy

Robert D. McBane, MD
Vascular Medicine Division
Gonda Vascular Center
Mayo Clinic
Rochester, Minnesota

H&O How common is it for surgical patients to be on an antiplatelet or anticoagulant agent?

RM Antiplatelet therapy includes aspirin and the P2Y12 antagonists clopidogrel, ticagrelor, and prasugrel. An estimated 50 million patients in the United States are taking an antiplatelet agent. This estimate is derived from the vast prevalence of coronary artery, cerebrovascular, and peripheral artery disease in this country. The most common antiplatelet agent for these patients is aspirin, followed by clopidogrel and a growing number of people taking ticagrelor. Some patients are on dual antiplatelet therapy with a P2Y12 antagonist plus aspirin.

An additional 6 million people in the United States take an anticoagulant, such as warfarin, heparin, or a direct oral anticoagulant (DOAC); the DOACs include rivaroxaban, apixaban (Eliquis, BMS/Pfizer), dabigatran, and edoxaban (Sayvasa, Daiichi Sankyo). The most common conditions that prompt the use of an anticoagulant are atrial fibrillation, which affects 4 million people in this country, and venous thrombosis, which affects 1 million people a year. The third most common reason for anticoagulant therapy is the presence of a mechanical heart valve. Some patients require dual antithrombotic therapy with an antiplatelet plus an anticoagulant.

An estimated 10% of patients who are on one of these agents require an invasive procedure each year, which translates to approximately 5 million people. Most invasive procedures are elective, but approximately 5% are emergent or urgent, complicating management.

H&O What special concerns exist for patients undergoing a procedure while on an antithrombotic agent?

RM The risks that we worry about in these patients are major bleeding, thrombosis, and mortality. We use the definition of major bleeding from the International Society on Thrombosis and Hemostasis (ISTH).[1] The ISTH also has a definition for major surgery-related bleeding, but that has not been as widely adopted.[2] Thrombotic events are defined by the American Heart Association, the American College of Chest Physicians (ACCP), and the ISTH. The American Heart Association and American Stroke Association have provided definitions of heart attack[3] and stroke.[4] To diagnose recurrence of a venous thrombotic event, a comparison of prior images is important to establish clearly that the new thrombus is truly new and distinct from prior thrombi. Another important outcome is clinically relevant nonmajor bleeding, which is bleeding that does not meet the ISTH criteria for major bleeding but requires that the patient either stop their medication or interact with health care providers.[5] Clinically relevant nonmajor bleeding changes patient management, at least in the short term, and is more than just nuisance bleeding. This form of bleeding can have significant clinical ramifications. The overall goal of periprocedural antithrombotic management is to promote adequate procedural hemostasis while avoiding bleeding or thrombotic outcomes, which may increase mortality.

H&O How should physicians estimate the risk of thrombosis or bleeding in these patients before a procedure?

RM Estimating the risk of thrombosis or bleeding is challenging. Fortunately, guidelines from the ACCP define the risk of thrombosis, whether it be from venous thromboembolism, atrial fibrillation, or a mechanical heart valve.[6] Patients are at high risk for venous thromboembolism if a venous thrombus has occurred within the past 3 months or in the context of cancer or a severe thrombophilia, such as antiphospholipid syndrome. The CHA2DS2-VASc score is used to determine the risk of thromboembolism in patients with atrial fibrillation. The patients at highest risk are those who have valvular atrial fibrillation or a CHA2DS2-VASc score of at least 7, or who have had a stroke or transient ischemic attack (TIA) within the past 3 months.[6] Regarding mechanical heart valves, the risk of thrombosis depends on the location of the valve—mitral, aortic, tricuspid, or pulmonary—and the generation of the valve. A patient who has a mechanical bileaflet heart valve in the aortic position is considered to be at low risk if no other risk factors are present, such as atrial fibrillation, prior stroke or TIA, prior valve thrombosis, rheumatic heart disease, hypertension, diabetes mellitus, heart failure, or advanced age (≥75 years). For those with a mechanical heart valve in any other location or multiple mechanical valves, the risk is high. For patients with older-generation valves, such as caged ball or tilting-disc valves in any position, the risk also is high.

H&O How does the risk differ according to the specific procedure a patient is undergoing?

RM Some examples of procedures that carry a low risk of bleeding are gastrointestinal endoscopy without polypectomy, dermatologic procedures, many dental procedures, some ultrasound-guided biopsies, and implantation or reimplantation of a pacemaker or implantable cardioverter defibrillator. High-risk procedures include most neurologic procedures, major general surgeries, gastrointestinal polypectomy, ophthalmologic surgeries involving the orbit or retina, orthopedic joint replacement, and many ear, nose, and throat surgeries. For a more comprehensive list, I would refer the reader to an article that our group published in *The New England Journal of Medicine* in 2013.[7] When questions arise regarding the risk of bleeding for any specific procedure, it is important to contact the surgeon or proceduralist well beforehand to discuss perioperative management, including anticipated bleeding rates. One factor that is especially concerning is the use of neuraxial anesthesia or a regional block. With neuraxial anesthesia, even a small amount of bleeding can be catastrophic.[8] It can be challenging to predict what type of anesthesia will be used for any specific procedure. To avoid these bleeding complications, it is important to ensure that the antithrombotic is completely metabolized before the surgery.

H&O In what situation should antiplatelets or anticoagulants be discontinued before a procedure?

RM A clear plan for the periprocedural management of all antithrombotic medications should be established well ahead of the planned procedure. This plan should include the precise timing of antithrombotic discontinuation, periprocedural deep vein thrombosis prophylaxis, and timing of the reintroduction of each antithrombotic medication after the procedure. Each team member should be familiar with the plan. Clear written and verbal instructions must be provided to the patient with "teach-back" education so that complete comprehension of the plan is accomplished. Decision making is highly procedure-specific, and the strategy should be determined at least 7 to 10 days before an elective procedure. This decision making is often shared by the surgeon/proceduralist and the health care team managing the antithrombotic therapy. At the planning session, the indication for antithrombotic therapy, risk of thromboembolism, and risk of procedure-related bleeding should be carefully assessed. Useful laboratory testing at the planning session may include a complete blood cell count, the creatinine clearance to measure renal function, and the baseline international normalized ratio (INR) if the patient is taking warfarin.

> Decision making regarding periprocedural management for emergency procedures can be challenging.

Warfarin is generally stopped 5 days before a procedure on the basis of results from the BRIDGE trial.[9] For those patients at high risk of thromboembolism, bridging therapy with low-molecular-weight heparin (LMWH) can be implemented 3 days before the procedure if the creatinine clearance is acceptable. LMWH is cleared by the kidney, and a threshold creatinine clearance of 30 mL/min is usually required for its use. For patients with high-

risk atrial fibrillation or a high-risk mechanical heart valve, the dose of enoxaparin is 1 mg/kg twice daily. The final dose of LMWH is given on the morning of the day before the procedure, and the INR is checked the morning of the procedure to confirm that warfarin has been completely metabolized. Warfarin administration can be resumed on the night of the procedure if adequate hemostasis is achieved. If bridging is being used, the administration of therapeutic LMWH should be delayed for at least 48 hours after the procedure to ensure adequate hemostasis. For patients being treated with one of the DOACs, it is equally important to define the periprocedural antithrombotic strategy carefully, including precise verbal and written patient education. For patients receiving this class of anticoagulant, periprocedural bridging with LMWH is rarely if ever indicated, and decision making rests on the anticipated risk of bleeding associated with the planned procedure. This risk must also include the type of anesthesia to be used and whether neuraxial anesthesia is anticipated. For patients undergoing a procedure associated with a minor risk of bleeding, DOACs are typically held for 24 hours before the procedure and restarted 24 hours afterward, once hemostasis is ensured. For those undergoing procedures associated with a major bleeding risk, DOACs are held for 48 hours preoperatively. Postprocedural resumption of DOACs may be delayed by at least 48 to 72 hours and requires complete hemostasis. For patients taking dabigatran, the decision making is more nuanced and depends on the creatinine clearance. If the creatinine clearance is at least 50 mL/min, the 24- and 48-hour hold rule before procedures can be used. If the creatinine clearance is less than 50 mL/min, dabigatran should be held for 48 hours before a procedure with a low bleeding risk and 96 hours before a procedure with a high bleeding risk. When neuraxial anesthesia is to be administered, one extra day should be added to the hold time to ensure that all drug is completely metabolized.[8] For further insight into the timing of DOAC interruption, a review of the PAUSE trial strategy may be useful.[10]

In addition to managing anticoagulant therapy, specific recommendations must be established for the timing of antiplatelet interruption. As with anticoagulants, the specific indication for antiplatelet therapy must be understood and documented. If the patient is receiving dual antiplatelet therapy for an intravascular stent (coronary, carotid, mesenteric, renal, or peripheral arteries), it is important to determine when the stent was placed, why, and under what circumstances. If any questions exist regarding the safety of antiplatelet discontinuation, the managing team must contact and discuss the circumstances with the interventionalist who placed the stent. It is also relevant to determine an adequate platelet count in this context. Once this is established, clopidogrel or ticagrelor should be held for 5 days before the procedure. The risk of bleeding is much higher with prasugrel, so this agent is stopped 7 days before the procedure. Recommendations for aspirin interruption are more nuanced and highly procedure dependent. For patients taking dual antiplatelet therapy for a coronary indication, often the clopidogrel is stopped and the aspirin continued throughout the procedure. For procedures requiring aspirin discontinuation (eg, neurosurgery), a 7-day interruption is reasonable to restore complete platelet function.

Decision making regarding periprocedural management for emergency procedures can be challenging. A stepwise approach facilitates a logical framework for managing these patients. First, establish exactly what procedure is going to be performed and assign a bleeding risk for the procedure and thrombotic risk for the patient. Second, document the exact antithrombotic regimen that the patient is taking and the specific indication for each agent. Third, identify the exact timing and dosage of all antithrombotic(s) recently taken. Fourth, determine whether the drug is likely to be metabolized normally. This step requires understanding drug-specific metabolic pathways and then determining whether those pathways are functioning normally for the patient at that time. For example, LMWH and dabigatran are both cleared by the kidneys. Quickly determining whether renal function is normal with creatinine level and creatinine clearance is straightforward. For the oral factor Xa inhibitors and warfarin, drug metabolism is primarily through the liver. Adding liver function testing to the baseline laboratory assessment can be useful here. Are there any drug interactions that may be either promoting or inhibiting drug metabolism? Recruiting pharmacy can be very helpful to discern interactions rapidly. Lastly, bedside providers and interventionalists will have to decide whether a reversal agent is needed. For the oral factor Xa inhibitors and warfarin, 4-factor prothrombin complex concentrate (Kcentra, CSL Behring) may be indicated. Use of this agent requires a careful balance between the risk of major bleeding associated with the procedure and the risk of thrombosis should the reversal agent be used. Randomized trials and meta-analyses have shown a 3.5% to 5.6% rate of thromboembolic events with the use of 4-factor prothrombin complex concentrate.[11,12]

A specific reversal agent, idarucizumab (Praxbind, Boehringer Ingelheim) is available for patients taking dabigatran. No specific reversal agents are available for P2Y12 antiplatelet agents. Platelet transfusion can be attempted but typically is not adequate for hemostasis.

H&O How does the use of additional medications affect decisions about periprocedural antiplatelet and anticoagulant therapy?

RM Not just medications but also supplements can have anticoagulant effects. For each agent, we need to know whether it promotes bleeding or clotting in addition to how it is metabolized. For example, an agent that interferes with the CYP2C9 pathway will interfere with the metabolism of warfarin, whereas an agent that alters the CYP3A4 pathway can either promote or inhibit the metabolism of DOACs. Over-the-counter herbal supplements should also be considered and documented. For example, ginkgo biloba, garlic, ginseng, and turmeric have platelet-inhibiting properties, and St John's wort may affect coagulation.[13]

Disclosures

Dr McBane has consulted for Regeneron and the Bristol Myers Squibb-Pfizer Alliance and owns stock in Lilly, AbbVie, Medtronic, AstraZeneca, Bristol Myers Squibb, Johnson & Johnson, Merck, and Novo Nordisk.

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