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ENHANCED STRATEGIES FOR PREVENTION AND MANAGEMENT OF BLOOD LOSS IN SPECIAL, UNUSUAL, AND UNEXPECTED SURGICAL SITUATIONS

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Introduction

Typically, surgical and anesthesia teams work together in the operating room to control blood loss by thoroughly evaluating bleeding risk preoperatively and by using their training in the treatment of intraoperative blood loss. As a result, most bleeding is usually well controlled. In many cases a hematologist is consulted for recommendations preoperatively or, in urgent situations, even while the patient is in the operating room. In the end, however, it is usually the surgeons and anesthesiologists making decisions about how best to control bleeding. What follows is an update on currently available options in the management of surgical bleeding (Table 1).

Strategies for Management of Surgical Bleeding

Preoperative	Intraoperative	Postoperative
A. Anatomic vs. coagulopathic history	A. Dilutional coagulopathy	A. Anatomic
B. Cessation of anticoagulants	B. Disseminated intravascular coagulation (DIC) management	B. Drugs
C. Cessation of antiplatelet agents	C. Fibrinolysis • Diagnosis • ε-aminocaproic acid/tranexamic acid • Thromboelastograph (TEG)	C. von Willebrand's disease
D. Treatment for von Willebrand's disease	D. Cell-saver techniques	D. Factor XIII deficiency
E. Use of DDAVP	E. Recombinant factor VIIa	

Table 1. Strategies for management of surgical bleeding.

Preoperative Evaluation of Bleeding

The preoperative evaluation for surgical bleeding usually begins when the surgeon first sees the patient in the office or the hospital prior to a planned procedure. Many times the patient will have a defined coagulation disorder and provide specific details, or an internist or hematologist will have described it in the chart or a letter. Note should be taken, however, that some patients will identify themselves as being "bleeders" without providing any supporting evidence. While a patient's description of being a bleeder needs to be taken seriously, past bleeding may have been anatomic or related to preoperative use of certain medications, and past operative notes or prior laboratory testing may need to be reviewed. A less frequent but more surprising scenario is that patients sometimes have a surgical bleeding history or even a significant defined coagulation defect but do not tell the surgeon, whom they incorrectly assume has already received this information. Anesthesiologists will routinely evaluate patients more extensively for any bleeding risk closer to the time of surgery, make certain that appropriate medications have been held, check the results of recent coagulation testing, or ask that the patient be seen by a hematologist, which may require delaying the procedure.

The preoperative evaluation should also include specific questioning to detect the presence of von Willebrand's disease (VWD) — the most common hereditary bleeding disorder, affecting 1–2% of the U.S. population with both sexes affected equally.[1, 2] This is important since bleeding associated with VWD is often subtle, and historical information may be more revealing than laboratory testing in leading to a VWD diagnosis. Preoperative treatment for VWD is usually successful in reducing or preventing bleeding.

Usually antiplatelet medications are held for 5–7 days preoperatively to avoid bleeding, and delaying surgery for an appropriate period is usually recommended rather than trying to correct the defect with platelet transfusions. Exceptions include minor surgery, where the bleeding risks and consequences are felt to be low, or procedures such as coronary bypass, where patient outcomes overall have been shown to be better with prior antiplatelet therapy. Many patients who have been on chronic Coumadin therapy are bridged to surgery with low-molecular-weight heparin for 4–5 days preoperatively in an attempt to reduce perioperative thrombotic risk. To avoid bleeding, current recommendations are that the last dose of preoperative enoxaparin or dalteparin low-molecular-weight heparins should be given 24

hours before the procedure without checking an anti-Xa level.[3] If the patient is not being bridged from Coumadin with low-molecular-weight heparin, Coumadin is usually held for 3–4 days preoperatively, and the prothrombin time/international normalized ratio can be checked prior to the procedure to be certain that the Coumadin effect has largely resolved to reduce bleeding risk. If IV unfractionated heparin is being used, the usual recommendation is to hold it for 3 hours before the procedure. If fondaparinux is used for bridging or if the patient is on fondaparinux and needs semi-urgent surgery, the last dose should probably be given at a longer time (at least 36–48 hours) before the procedure due to its longer half-life, although there is no specific evidence-based current recommendation. Preoperative desmopressin acetate (DDAVP) nasal spray is commonly used for most types of VWD after a prior DDAVP challenge has shown a good response. For some rarer types of VWD, especially type 2B VWD, or for major surgeries where maintenance of normal von Willebrand's factor will be necessary for prolonged periods, the plasma-derived product Humate-P® can be used to get around the tachyphylaxis associated with multiple doses of DDAVP over a short time. Preoperative DDAVP can also be used in patients with platelet dysfunction associated with renal failure and liver disease to help prevent bleeding. Dosing can be done with IV DDAVP over 30 minutes immediately before the procedure or with the intranasal preparation of desmopressin (Stimate), often given 1 hour preoperatively. In some cases, DDAVP can also be used to raise factor VIII:C (hemophilic factor) to acceptable levels for surgery in patients with mild hemophilia A. Lastly, some patients with severe liver disease and a hepatic synthetic defect may benefit from having plasma infusions preoperatively because of the increased risk of mortality from these patients undergoing surgery.[4, 5]

Intraoperative Bleeding

Intraoperative bleeding may be anatomic but can also be due to a dilutional coagulopathy if bleeding has been massive, or it can occur unexpectedly from activated processes such as disseminated intravascular coagulation or primary fibrin(ogen)olysis. A dilutional coagulopathy can occur from massive anatomic bleeding, such as from hypervascular tumors or in liver transplantation, unless a replacement ratio of 1 unit of fresh frozen plasma (FFP) is given for every unit of red blood cells (RBC) transfused[6] along with enough platelets to maintain an adequate platelet count. Dilution could also occur in patients with any underlying coagulopathy, such as from liver disease or the uncorrected use of warfarin, prior to undergoing cardiac bypass due to the effect of the initial pump prime used in this procedure. In these situations, blood loss may also be tempered by cell-saver techniques, if available, at a slight risk of bacterial contamination from the surgical field. Disseminated intravascular coagulation (DIC) commonly occurs in sepsis but is probably less often present in surgical settings since infection may preclude the patient from going to surgery. In DIC, the underlying problem is inappropriate activation of coagulation in the microvasculature and overproduction of thrombin that leads to microvascular clot formation and consumption of clotting factors; this leads to clinical bleeding despite its actual underlying thrombotic pathophysiology. DIC also occurs in a variety of special clinical settings including acute promyelocytic leukemia, snake bite, or in women with obstetric complications where the incidence of DIC is especially high and may represent 3–4% of all cases seen by a coagulation laboratory.[7] Treating the underlying provoking disease and using coagulation parameters to guide blood product replacement remain the longstanding tenets of treating DIC. In particularly difficult situations where there is active DIC with uncontrolled bleeding, using antithrombin III concentrate — in addition to replacing RBCs, FFP, platelets, and cryoprecipitate — could be beneficial since antithrombin III is a natural anticoagulant that antagonizes the elevated thrombin produced by the DIC process. The concentrates have been shown to improve some hematologic parameters and may limit end-organ damage due to DIC, but they have not as yet been shown to reduce mortality.[8, 9]

A less-common activated process that could cause significant bleeding in special surgical situations is primary fibrinolysis or fibrinogenolysis. Here the inappropriate activation is in the fibrinolytic cascade, where enhanced activation of plasminogen causes overproduction of plasmin. This overwhelms plasmin's natural inhibitor, alpha-2 antiplasmin, and leads to excessive destruction of its primary target, fibrin. The more advanced form of fibrinolysis may lead to fibrinogenolysis, where higher levels of unopposed plasmin destroys not only fibrin but also fibrinogen and clotting factors V and VIII. As a result, one may observe clots forming in the operative field initially but lysing in several minutes and causing uncontrolled bleeding rather than lysing slowly over the usual period of several days.

The clinical settings in which fibrinolysis may occur include mouth surgery, where there is localized release of unusual plasminogen activator into the oral cavity; genitourinary (GU) tract surgery, where the excessive release of urokinase from the urothelium activates the fibrinolytic cascade; and liver surgery, especially liver transplant surgery, where there is an excessive release of tissue plasminogen activator from the vascular endothelium. In mouth surgery, the diagnosis of fibrinolysis is usually made clinically rather than in the laboratory since the effect is not usually systemic; the result is prolonged intra- or postoperative oral cavity bleeding that is more often an annoyance to the surgeon and patient rather than a life-threatening condition. This is usually managed in patients with historically normal hemostasis by giving oral or IV ε-aminocaproic acid or tranexamic acid when oral cavity bleeding occurs; these medications are competitive inhibitors of plasmin that block its action on fibrin. More recently, the use of localized "swish and spit" ε-aminocaproic acid or tranexamic acid preparations have been helpful, especially in children and for outpatient use. In patients with a history of VWD or mild hemophilia A, where bleeding is more likely, antifibrinolytic therapy is routinely given postoperatively to prevent bleeding. Cryoprecipitate is an additional therapy for fibrinolysis since it is a concentrated source of both fibrinogen and factor VIII. Finally, ε-aminocaproic acid has an additional advantage in localized GU tract bleeding; since it is excreted through the GU tract, lower nonsystemic doses will concentrate there and can adequately treat bleeding without causing as much systemic effect. This can be useful in patients with localized GU tract bleeding who need to be protected from thrombosis elsewhere, for example, in patients who have a prosthetic valve or are undergoing neurosurgery.

In patients having liver surgery or liver transplantation, the diagnosis of a fibrinolytic state will typically need to be made to differentiate it from active DIC since antifibrinolytic therapy may worsen the underlying prothrombotic state in DIC and affect the patient adversely. The diagnosis of fibrinolysis can be made in an appropriate clinical setting by 1) noting clinical lysis in the operative field or in an unanticoagulated laboratory specimen tube at the bedside, or by 2) the laboratory finding of specific destruction of fibrinogen, factor V, and factor VIII without significant thrombocytopenia or destruction of other factors

and possibly with a positive euglobulin lysis time. A faster and perhaps more accurate way to diagnose fibrinolysis is through use of a thromboelastogram (TEG), if available. The TEG is especially effective in liver transplant surgery, where fibrinolysis is common,[10, 11] because it facilitates rapid diagnosis by allowing visualization of the characteristic fibrinolysis pattern on the TEG, which can lead to prediction of response and earlier treatment with antifibrinolytics.[12, 13]

Recombinant human factor VIIa (rhFVIIa) has recently come into widespread use for uncontrolled intraoperative bleeding that is unresponsive to usual measures. While it is only approved for use in patients with congenital factor VII deficiency and for patients with hemophilia A and B inhibitors, recent reports have documented that more than 90% of its use has been for off-label neurosurgical and cardiac surgical bleeding, at great expense and increased risk of thrombosis.[14, 15] The use of rhFVIIa for bleeding is attractive because it rapidly shortens the prothrombin time and activated partial thromboplastin time, but a clear benefit for overall patient outcome has been difficult to demonstrate; therefore, its repeated use — especially at the higher doses — should currently be discouraged. There have been repeated reports, however, of patients with severe platelet defects, particularly Glanzman's thrombasthenia, who have responded well to rhFVIIa where its use might be considered.[16] A final method for controlling local bleeding is the use of a number of thrombin-containing topical tissue sealants. Earlier products contained thrombin, which was often bovine, and were associated with the potentially serious side effect of immune coagulopathy. Newer, recently approved products use recombinant molecules that have shown lower rates of immunogenicity, lessening the concern about their use.[17, 18]

Postoperative Bleeding

Postoperative bleeding may be anatomic or due to an activated process that started during the procedure, a drug effect, or a previously unrecognized congenital disorder, particularly VWD. Activated processes can be diagnosed using the same approach as outlined for intraoperative bleeding. A re-examination of the patient's history regarding preoperative use of antiplatelet drugs or symptoms of VWD may point to them as causes.[19] In addition, the use of ketorolac (Toradol), a parenteral nonnarcotic analgesic sometimes used for pain control in the immediate postoperative period, has antiplatelet effects and should also be considered as a possible cause of bleeding in the postoperative period. Commonly considered as a cause of postoperative bleeding but rarely found is a congenital deficiency of factor XIII, which stabilizes fibrin clots by cross-linking fibrin strands. A congenital deficiency of factor XIII makes fibrin clots more susceptible to degradation and can cause postoperative bleeding and/or delayed healing. Treating a congenital deficiency consists of elevating the circulating level of factor XIII with FFP or cryoprecipitate, the latter being preferred since it is a more concentrated source of the protein. However, the extreme rarity of this disorder, estimated to be 1 in 2 million, makes it an unlikely cause of postoperative bleeding.[20, 21]

Summary

Advances continue to be made in our understanding of coagulation and in the development of new pharmacologic and mechanical therapies. When applied in appropriate and specific surgical situations, these new treatments should enhance our ability to control operative bleeding and lead to a reduction of blood product use.

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