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Perioperative Management of the Patient with Hematologic Disorders

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Surgeons of all specialties have an unavoidable interaction with the ability of a patient to heal physical wounds. Whether traumatic or surgically induced, wound healing is a complex process that must occur uninterrupted to achieve what is popularly known as surgical success. Once injury is induced to the tissue, a series of events are triggered aimed at repairing the sequelae of the insult. This orchestrated set of events always starts with the control of any bleeding that may occur at the surgical site. Once injury to tissues takes place and bleeding starts, the body's first step in the intricate process of wound healing is to stop blood loss and stabilize the wound to permit the subsequent series of steps to take place. For this to happen in a predictable fashion, a patient's ability to control and stop bleeding is critically important. This process of bleeding control is called hemostasis. Unfortunately, not all patients possess intact hemostatic ability. What is even more critical is that in some instances, the disorder presents such benign manifestations that an individual may be undiagnosed until a revealing event takes place, such as major trauma or surgery. This occurrence presents a serious problem for the treating surgeon if the first manifestation of the disease is identified on the operating room table. It is important to carry out the preoperative health history in an inquisitive fashion to unmask any underlying condition with which a patient may present.

According to the National Hemophilia Foundation, the incidence of bleeding disorders can be as frequent as 1 in every 10,000 patients [1]. A bleeding disorder is any condition in which an inherited or acquired blood deficiency caused by the absence or inactivity of an essential blood protein or factor causes the body to form unstable blood clots that allow bleeding to continue for a longer period of time than the normal accepted parameters. Depending on the severity of the condition, the clinical implications can range from the nagging wound that continues to ooze and inconvenience a patient for an extended period of time to a serious life-threatening blood volume depletion.

When plasma coagulation factor concentrations are in the range of 5% of normal, neither spontaneous hemarthrosis nor spontaneous bleeding occurs [2]. With trauma or minor surgery, however, severe bleeding may ensue unless coagulation factor levels approach 40% to 50% of normal serum levels for a given coagulation factor. Conversely, major surgery requires 100% of normal clotting activity to prevent intraoperative and postoperative complications as a result of excessive blood loss. After major surgery, replacement of essential coagulation factors is continued for at least 10 days. Oral surgery or minor surgery requires an additional 5 to 7 days of factor replacement [3].

Hemostasis

Hemostasis is the process the body launches for the prevention of blood loss after injury has been caused to the tissues. This process involves a series of complex reactions that are intricately linked with

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each other and occur almost simultaneously. For the purpose of this discussion, we divide these stages of hemostasis into four phases: vascular phase, platelet phase, coagulation phase, and fibrinolytic phase. The process to stop loss of blood is triggered by soft tissue trauma that involves the endothelial wall of blood vessels, and the end product is a clot that acts as a mechanical stop or seal that eventually stops bleeding. The final phase of this process is followed by a fibrinolytic phase, which prevents uncontrolled coagulation beyond the site of injury and dissolves the clot [4,5].

Vascular phase

Normal endothelial cells have a thromboresistant surface that prevents clot formation and allows blood to flow through the vasculature without interruption. Certain proteins contained within the vessel wall also act in the prevention of intravascular coagulation. Thrombomodulin is a molecule contained in the endothelium that inhibits coagulation by activating the natural anticoagulant protein C to bind free thrombin. The endothelium also is capable of stimulating blood clot breakdown or fibrinolysis through the production of tissue-type plasminogen activator [4–6].

The vascular phase of hemostasis starts immediately after a blood vessel is injured. An almost instantaneous reflex of the vessel wall produces constriction of its lumen, which in turn decreases blood flow to the site and reduces the amount of blood that is lost. The injured cells secrete ADP and von Willebrand factor (vWF), which promote platelet adhesion to the subendothelial tissue leading toward the platelet phase. The efficiency of the vascular phase depends to a great extend on the size of the lumen of the injured vessel and the volume and flow of the blood carried through it. Smaller vessels in the venous system are more likely to undergo constriction that allows for spontaneous sequencing of the hemostatic process. Larger vessels in the arterial system in particular require surgical intervention and mechanical clamping to stop blood loss.

Platelet phase

Platelets are cellular components of blood anatomically characterized by the absence of a nucleus. These anuclear cells have an average lifespan in the circulation of approximately 8 to 12 days. The ultracellular structure of platelets includes multiple components that are critical for adequate platelet function, including the glycocalyx, plasma membrane, microfilaments, tubules, and granules. Platelet receptors, such as glycoprotein Ib, which interacts with vWF, and glycoprotein IIb, which binds with fibrinogen, are located in the plasma membrane [7]. If vascular injury exposes the underlying collagen, platelets adhere to the exposed subendothelial tissue as a result of contact activation to begin forming the platelet plug. During this phase, platelets release granules that help attract more platelets to the site and aid in stabilization of the immature plug. This process is referred to as platelet degranulation. The granules released in this process include dense granules, alpha granules, and lysosomes. Platelets also release serotonin, ADP, and thromboxane A_2 as part of the degranulation process. These substances function as strong platelet chemotactic agents and promote aggregation, continued degranulation, and further vasoconstriction, which lead to the formation of a stable platelet plug. Changes in the platelet membrane receptors plus the conversion of coagulation factors strengthen the platelet plug with fibrin, which leads it into a proper and stable blood clot [8,9].

Coagulation phase

Classic model of coagulation

Although it is possible to single out the events of hemostasis, which helps in our understanding of it (eg, platelet agglutination and formation of fibrin), it must be realized that this whole process occurs synergistically [10]. The discovery of thrombin by Schmidt in 1872 [11] and the initial work of Morawitz [12], which focused on delineating the scheme in which blood undergoes clotting, contributed to what is known currently about this process.

Coagulation is a sequential process that involves multiple components in a series of events often referred to as a cascade. Phospholipids, calcium ions, and plasma proteins are the main components involved in this stage of hemostasis [8]. Most of the proteins involved in this process are synthesized in the liver, including fibrinogen, prothrombin, and factors V, VII, IX, X, XI, XII, and XIII. Some of these proteins also depend on the presence of vitamin K to function properly. Vitamin K–dependent factors include factors II, VII, IX, and X. The coagulation cascade is divided into two pathways: the extrinsic and the intrinsic pathways. These pathways converge to form the common pathway at the level in which factor X is activated and ends with the formation of fibrin (Fig. 1).

Extrinsic pathway. The extrinsic pathway is activated by tissue factor (TF), which is released as a result of subendothelial tissue exposure of the injured

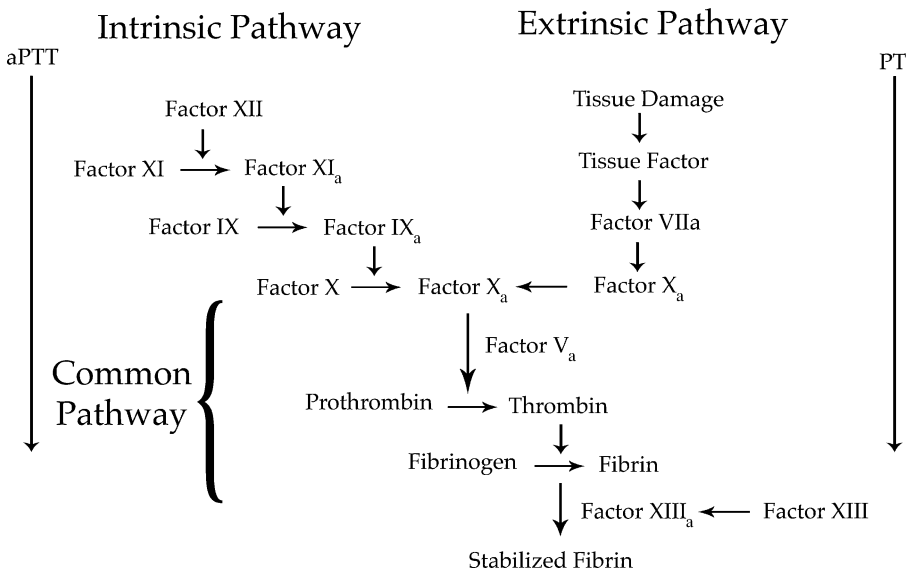

Fig. 1. Classic model of coagulation.

vessel. This factor, which is extrinsic to the coagulation system, activates factor VII to VIIa. Factor VIIa in the presence of ionized calcium activates factor X. The laboratory test used to measure the function of this pathway is the prothrombin time (PT). Normal PT is 11 to 15 seconds. Although this test is sensitive, it is not specific in determining the cause of an abnormal result. An abnormal result can be caused by low levels of blood proteins (clotting factors), a decrease in activity of any of these factors, the absence of any of the factors, or the presence of a substance that blocks the activity of any of these factors.

Intrinsic pathway. The intrinsic pathway starts with contact activation with elastin, collagen, platelets, prekallikrein, high molecular weight kininogens, or plasmin. Factor XII is activated followed by further activation of factor XI and factor IX. Finally, the intrinsic pathway leads to the common pathway when factor IXa activates factor X under the presence of ionized calcium, platelet factor III, and factor VIIIa. The screening laboratory test of choice for this pathway is the activated partial thromboplastin time (aPPT). The normal aPPT is 25 to 35 seconds.

Common pathway. The common pathway consists of the convergence point of the intrinsic and the extrinsic pathways. Factor X is transformed to factor Xa and, along with factor V, activates prothrombin (factor II) to thrombin (factor IIa). Thrombin is an enzyme with four key functions: (1) removal of small fibrinopeptides from the large fibrinogen precursor, which favors the polymerization of fibrinogen into strands of fibrin, (2) activation of factor XIII to XIIIa (XIIIa is the fibrin-stabilizing factor, which in the presence of calcium ions interlinks fibrin strands), (3) activation of platelets, and (4) activation of protein C (an antithrombotic plasma enzyme).

At the same time that thrombin activates fibrinogen to form fibrin, it also stimulates the production of more factor VIII and activates factor XIII, which is responsible for cross-linking the fibrin monomers and stabilizing the clot [9].

Cell-based model of coagulation

The in vivo process of coagulation occurs in a synergistic fashion rather than in a sequentially separated cascade of events. Hoffman and colleagues [13–15] determined that this classic model inadequately explains how coagulation happens. Many questions about disorders in this process are left unanswered as to whether coagulation truly consists of an intrinsic and extrinsic pathway. For example, why does the extrinsic pathway not compensate for the lack of factor VIII and IX? Why do patients who lack activators of the intrinsic pathway (factor XII, high molecular weight kininogens, prekallikrein) not present with major clinical bleeding but reflect a prolonged aPPT? In an attempt to answer these and other relevant questions, investigators came to the conclusion that there is an interrelationship between intrinsic and extrinsic pathways, and they developed a model to explain how coagulation occurs in vivo. The

model consists of three interrelated processes: initiation, amplification, and propagation. It is also based on the evidence that coagulation takes place in two cell surfaces: TF-bearing cells and platelets (Fig. 2).

Initiation phase. The initiation phase takes place on the surface of the TF-bearing cell, which, under normal circumstances, is isolated from the blood. When tissue injury occurs, plasma is allowed to come in contact with these TF-bearing cells and functions as a receptor for factor VII. The TF in plasma activates factor VII and forms the FVIIa/TF complex, which in turn activates small amounts of factors IX and X. Factor Xa interacts with its cofactor Va and forms thrombin. The amount of thrombin formed at this point is not enough to form a fibrin clot. It is enough to promote platelet activation and factor VIII formation as part of the amplification phase, however. The FVIIa/TF complex not bound to the cell surfaces can become easily inhibited by the TF pathway inhibitor and antithrombin III.

Amplification phase. The small amount of thrombin produced in the initiation phase activates platelets and triggers the production of a large amount of factor VIII. In this process, the activation of the platelets exposes the receptor sites for more coagulation factors. The factor VIIIa is activated by dissociation of the FVIII/vWF complex, which allows vWF to promote more platelet adhesion and aggregation. Factors V and XI are activated on the platelet surface. The role of factor XI is to increase the amount of factor IXa on the platelet surface to increase the amount of surface available for factor Xa in the propagation phase. At the end of this phase the final product is an activated platelet with factors Va, VIIIa, and XIa on its surface.

Propagation phase. Factor IXa activated during the initiation phase diffuses from the TF-bearing cell to the activated platelets surfaces and binds to factor VIIIa to form FVIIIa/FIXa complex (tenase) on the platelet surface. Factor Xa cannot move from TF environment. It must be brought directly to the platelet surface. In this phase, plasma factor X is activated by factor IX, and factor Xa associates with its cofactor Va on the platelet surface to create complex FXa/Va (prothrombinase), which is capable of producing sufficient thrombin to create cleavage of fibrinogen to form the fibrin clot.

Fibrinolytic phase

The fibrinolytic phase is a vital component of hemostasis. Its main function is to avoid thrombotic occlusion of the blood vessel and propagation of the

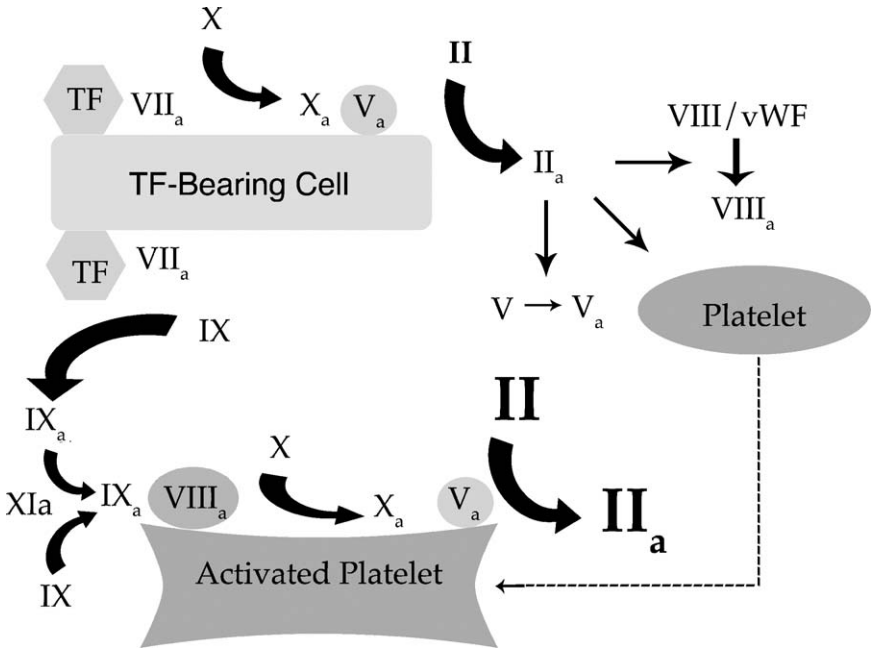

Fig. 2. Cell-based model of coagulation. (*Adapted from* Hoffman M. Remodeling the blood coagulation cascade. J Thromb Thrombolysis 2003;16(1–2):18; with permission.)

coagulation throughout the entire vascular system. The process starts early during the coagulation process and consists of the activation of plasminogen, a normal plasma protein that is converted into plasmin by the action of enzymes called plasminogen activators. The most important plasminogen activator is tissue-type plasminogen activator, which is found in the vascular endothelium. Plasmin is broken down into small fragments called fibrin degradation products that exert an anticoagulant effect. The action of this fibrinolytic system is regulated by naturally occurring inhibitors and antiplasmins [8,9].

Screening laboratory tests

Laboratory tests are useful in identifying specific problems of the hemostasis process. These tests help to establish a diagnosis but cannot predict actual bleeding during surgery.

Ivy bleeding time

This test is performed by placing a blood pressure cuff on a patient's arm and inflating it to 40 mm Hg. A small incision is made on the patient's arm, and every 30 seconds the blood is blotted gently with filter paper until bleeding has stopped. The filter paper must not touch the wound. This test is intended to measure platelet function, but it is neither sensitive nor specific. For this reason, its use is declining and at some institutions has been eliminated completely. Platelet counts <100,000/microL, low hematocrit, aspirin, other platelet inhibitory drugs, and certain other medications can prolong the bleeding time. Many variables influence the result, including skin thickness, temperature, blood vessel characteristics, type of blade, orientation of the incision (horizontal versus vertical), location of the incision, handedness, and other features.

Prothrombin time

PT evaluates the formation of thrombin and fibrin through the extrinsic pathway. The test consists of adding thromboplastin as an activating agent to the sample. The factors measured in this test are I, II, V, VII, and X. Some of them are vitamin K dependent, such as factors II, V, and VII, which are also depressed by warfarin sodium. The normal value range is 11 to 15 seconds [8].

International normalized ratio

The accuracy of the PT is known to be system dependent. Because of this dependency, the World Health Organization has addressed this system variability problem by (1) the establishment of primary and secondary international reference preparations of thromboplastin and (2) the development of a statistical model for the calibration of thromboplastins to derive the International Sensitivity Index (ISI) and the INR. The INR uses the ISI to equate all thromboplastins to the reference thromboplastin through the following equation

$$\mathrm{INR} = (\text{patient PT}/\text{mean normal PT})^{\mathrm{ISI}}$$

Thus, the INR can be calculated using the working PT ratio once the ISI of the thromboplastin is known. Documented differences in PT results in several interlaboratory trials led the International Committee on Thrombosis and Hemostasis to make a joint recommendation in 1983 to express all PTs as INRs and request that manufacturers indicate the ISI of their thromboplastin reagents [16].

Activated partial thromboplastin time

The aPTT measures the time required to generate thrombin and fibrin via the intrinsic and common pathway. The normal aPTT ranges from 25 to 35 seconds. The clinical application of these tests involves screening for deficiency of prekallikrein, high molecular weight kininogens, and factors I, II, V, VIII, IX, X, XI, and XII, XI, IX.

PTT reagent (phospholipid with an intrinsic pathway activator, such as silica, celite, kaolin, ellagic acid) and calcium are added to patient plasma, and the time until clot formation is measured in seconds. Phospholipid in the PTT assay is called "partial thromboplastin" because TF is not present. TF is present with phospholipid in (complete) thromboplastin reagents that are used for PT assays [17]. The aPTT is also the test of choice for controlling heparin therapy.

Platelet count

The circulating platelet count can be determined accurately in a blood sample using an electronic particle counter or manual methods. Examination of a stained blood film provides a rapid estimate of platelet numbers. Normally, there are 8 to 20 platelets per 100× (oil) immersion field in a properly prepared smear (in which the erythrocytes barely touch or just overlap). At least ten different fields should be ex-

amined carefully for platelet estimation. The average number (eg, 14) can be multiplied by a factor of 20,000 to arrive at an approximation of the quantitative platelet concentration. If an average number of 14 platelets is multiplied by 20,000, the approximate platelet concentration would be 280,000 or 280 X 10^9/L. Although estimation of platelets from a blood smear does not replace an actual quantitative measurement, it should be done as a cross-check of the quantitative measurement [18].

Platelet function analyzer 100

The platelet function analyzer 100 was developed as a platelet function screen with the idea of having a more reliable way to assess function than with bleeding time. This test mimics the clotting process in vitro and allows for a more accurate determination of platelet function. Once blood is drawn from a patient, a sample is placed in a test cartridge. A vacuum is applied to the test cartridge through a thin glass to draw the blood. This fine tube is coated previously with collagen and with either epinephrine or ADP. This coating activates the platelets present in the sample and promotes adherence and aggregation. The time it takes for a clot to form and occlude it to prevent further blood flow is measured and reported as a closure time. An initial screen is performed with collagen/epinephrine coating. If the closure time is normal, the likelihood of platelet dysfunction is almost nonexistent. The collagen/ADP test is performed only to confirm an abnormal collagen/epinephrine test. If both test results are abnormal, it is likely that the patient has a platelet dysfunction and further testing for inherited or acquired conditions is indicated. If the collagen/ADP test results are normal, then the abnormal collagen/epinephrine test results may be the result of aspirin ingestion. This is the most common reason why the result may be altered in an otherwise healthy patient with no history of bleeding disorders.

Perioperative management

As with many other disease entities, prevention in the management of patients who have bleeding disorders is the best way to complete surgical treatment on this patient group without regrets and complications. The number of patients with these types of deficiencies is not necessarily uncommon. In 1989, Rhodus and colleagues [19] reported that 2.3% of 1500 adult patients with medically compromising conditions treated in a dental school had significant bleeding problems. Surgical management of individuals with these conditions can be as simple as using topical agents and sutures for routine procedures. More complex cases may require combined attention with a hematologist and possible in-hospital treatment and postoperative stay.

The rainbow of hematologic disorders is vast, and one could dedicate a complete book to that topic. In the interest of time and space, however, we limit this discussion to the most commonly found entities that oral and maxillofacial surgeons may encounter in their practice.

Inherited coagulation disorders

Hemophilia A

Classic hemophilia (hemophilia A) is an X-linked recessive disorder that results in deficiency of plasma factor VIII coagulant activity [20]. It is the most severe of all inherited bleeding disorders and accounts for eight of every ten cases of hemophilia diagnosed every year. Women are carriers of this trait. Fifty percent of the male offspring of female carriers have the disease, and 50% of their female offspring are carriers. In contrast to this, all female children of a male parent with hemophilia are carriers of the trait.

Its severity is classified according to the level of activity of factor VIII present. Factor VIII levels between 50% and 150% are considered normal. Patients are considered as having mild hemophilia A cases if their factor VIII level is between 5% and 30%. Individuals whose factor level approaches the bottom end of this range rarely have unprovoked bleeding episodes, but surgery or injury may cause uncontrolled bleeding, which can be fatal. Milder cases of hemophilia may not be diagnosed at all, although some patients whose clotting activity is 10% to 25% of normal may have prolonged bleeding after surgery, dental extractions, or a major injury. Generally, the first bleeding episode occurs before 18 months of age, often after a minor injury. A child who has hemophilia bruises easily. Even an intramuscular injection can cause bleeding that results in a large hematoma. Moderate cases are those with levels between 1% and 5%, and severe cases correspond to factor VIII level of less than 1% [21]. This last group of patients is significantly more prone to spontaneous bleeding. Recurring bleeding into the joints and muscles ultimately can lead to crippling deformities with significant functional limitations for patients. Bleeding can elevate the floor of the mouth and push

the base of the tongue against the posterior pharyngeal wall until it blocks the airway, which makes breathing difficult. Minor head trauma can trigger substantial intracranial hemorrhage, which can cause brain damage and death [1].

During routine minor surgical procedures (ie, simple extractions, small biopsies), minor cases can be managed with a combination of topical agents to stimulate early formation of a blood clot followed by systemic administration of an antifibrinolytic agent. Topical products routinely used in our clinic include absorbable collagen wound dressing (Collaplug), absorbale gelatin sponge (Gelfoam), absorbable oxidized cellulose (Surgicel), and topical thrombin (Thrombin-JMI). Patients typically follow their surgical treatment with oral administration of epsilon aminocaproic acid. This drug acts as an effective inhibitor of fibrinolysis by inhibiting plasminogen activator substances and, to a lesser degree, through antiplasmin activity. It has the advantage of rapid absorption after oral administration, which makes self-administration at home a viable option for this patient group. The typical protocol calls for an initial dose of 5 g, followed by hourly 1-g doses, not to exceed 30 g in a 24-hour period. Tranaxemic acid acts in a similar way and can be used for this purpose.

In patients who have mild to moderate levels of the disorder, 1-deamino-8D-arginine vasopressin (DDAVP) can be used to raise factor VIII to hemostatic levels [22,23]. This synthetic analog of the antidiuretic hormone vasopressin causes release of von Willebrand's factor from storage sites in the endothelial cells, which increases factor VIII levels twofold to threefold. The biggest advantage for this patient subset is that it substitutes plasma-derived coagulation products and avoids the risk for infection with blood-borne viruses. The recommended dose is 0.3 μg/kg in 50 mL of normal saline given intravenously over 15 to 30 minutes or subcutaneously. Peak effect occurs 30 to 60 minutes after administration, with an average duration of 4 hours. Dosing can be repeated every 12 hours for three to four doses [20,24]. Over the last few years, the use of high-concentration intranasal DDAVP spray has made this therapy even more user friendly. Seremetis and Aledort [25] reported 90.2% rating of excellent or good results in a group of 184 patients who used this treatment modality.

Patients with more severe levels of hemophilia A require factor VIII replacement before any surgical procedure. Available clotting factor concentrates consist mainly of recombinant products (Recombinate, Bioclate, and Helixate) and plasma-derived products (Hemophil-M, Hyate C, and Koate DVI). These concentrates are intended to provide patients with a plasma level of at least 50% for minor surgical procedures and 80% to 100% for major surgery [2,26]. Patients are routinely dosed 1 hour before surgery, with redosing at 12 and 24 hours postoperatively. The main disadvantages of this therapy include risk of transmission of viral diseases [27], development of inhibiting antibodies that neutralize factor VIII, and cost (care of an average person who has hemophilia from age 3 to 50 is estimated at $5 million) [28].

Use of topical agents at the time of surgery is also highly recommended. This therapy can be augmented by the use of cryoprecipitate, DDAVP, or antifibrinolytic therapy [29].

Hemophilia B

Hemophilia B (also called "Christmas disease" after Stephen Christmas, a British boy in the twentieth century who was first diagnosed with it) is a bleeding disorder that results from a deficiency in clotting factor IX (plasma thromboplastin component) and is inherited as an X-linked recessive trait. It is one fourth as prevalent as factor VIII, but clinically they cannot be differentiated [30]. A factor IX assay is required to separate the two. Classification and clinical problems are the same as for hemophilia A.

Replacement therapy for mild deficiencies consists of fresh frozen plasma (one unit factor IX/mL) or prothrombin complex concentrates (factors II, VII, IX, and X). Factor IX replacement therapy for more severe cases is the same as that for factor VIII, with the huge advantage that inhibitors to factor IX are rare. The desired factor IX level for minor surgery is 30% to 50%, with levels more than 50% carrying the risk of thromboembolic disease and disseminated intravascular coagulation.

Unlike factor VIII, which is maintained within the circulatory system, factor IX enters the extravascular spaces [31]. It exhibits a two-phase disappearance: (1) rapid initial disappearance (half-life of 4.5 hours) that occurs as an equilibrium with the extravascular spaces and (2) second-phase disappearance (half-life of 32 hours) [32]. Local hemostatic measures are indicated, and Amicar (epsilon aminocaproic acid) can be used with plasma replacement therapy but is contraindicated with prothrombin complex concentrates [33].

von Willebrand's disease

In 1926, Erik von Willebrand first described a hemorrhagic disorder characterized by a prolonged bleeding time and an inheritance pattern that distin-

guished the disease from classic hemophilias. Unlike hemophilia, von Willebrand's disease is not sex-linked and is autosomal dominant. It can occur via a number of genetic abnormalities or it can be an acquired disorder. The deficit is in von Willebrand's factor, more specifically with vWF gene on chromosome 12, but in some patients the coexistence of an impaired response to plasminogen activator and telangectasia suggests the presence of a regular defect or more extensive endothelial abnormalities.

Von Willebrand's factor binds and stabilizes factor VIII in circulation and mediates platelet adhesion. The amount of bleeding seen in a patient with this disorder can vary from day to day. Often administration of desmopressin before a procedure, which causes the release of von Willebrand's factor and plasminogen activator from the endothelial cells, suffices to prevent bleeding [34]. When patients who have von Willebrand's disease are given a single injection of desmopressin (0.4 μg/kg body weight), there is a considerable increase in platelet reactivity. On flow cytometry, increased glycoprotein Ib/IX expression in the platelets was found after the desmopressin injection when phycoerythrin-marked anti-CD62 antibodies were used. Apart from the rise in the vWF, this could explain the increased platelet reactivity [35]. A hematologist, through dosing and measurements of factor levels, determines the correct dosage of desmopressin necessary for each patient. As with hemophilia, supplemental topical agents might be useful.

There are more than 20 distinct clinical and laboratory subtypes of von Willebrand's disease. Most of these variants can be catalogued in three different broad subtypes, however, of which 70% to 80% are considered to be type 1. Type 1 is characterized by a partial quantitative decrease of qualitatively normal vWF and factor VIII. Typically, a proportional reduction in vWF activity, vWF antigen, and factor VIII exists.

Approximately 15% to 20% of patients who have von Willebrand's disease have type 2, which is a variant of the disease with primarily qualitative defects of vWF. It can be either autosomal dominant or recessive. Of the five known type 2 subtypes (ie, 2A, 2B, 2C, 2M, 2N), type 2A is the most common. Type 2A is inherited as an autosomal dominant trait and is characterized by normal to reduced plasma levels of factor VIIIc and vWF. Analysis of vWF multimers reveals a relative reduction in intermediate and high molecular weight multimer complexes. These abnormalities are likely the result of in vivo proteolytic degradation of the vWF. The ristocetin cofactor activity is greatly reduced, and the platelet vWF reveals multimeric abnormalities similar to those found in plasma [36].

Type 2B is also inherited as an autosomal dominant trait. This type is characterized by a reduction in the proportion of high molecular weight vWF multimers, whereas the proportion of low molecular weight fragments is increased. These patients have a hemostatic defect caused by a qualitatively abnormal vWF and intermittent thrombocytopenia. The platelet count may fall further during pregnancy, in association with surgical procedures, or after the administration of desmopressin. Measurements of factor VIIIc and vWF in plasma are variable; however, studies involving the use of titered doses of ristocetin reveal that aggregation of normal platelets is enhanced and induced by unusually small amounts of the drug [37].

In individuals who have type 2C, which is inherited as a recessive trait, the proportion of high molecular weight multimers is reduced and the individual multimers are qualitatively abnormal. Increases in small multimers also are evident in most cases of type 2C. Ristocetin cofactor activity may be decreased out of proportion to reductions in vWF.

A small number of patients who have type 2M disease have laboratory results similar to certain patients who have type 2A. Type 2M is characterized by a decreased platelet-directed function that is not caused by a decrease of high molecular weight multimers. Laboratory findings show decreased vWF activity, but vWF antigen, factor VIII, and multimer analysis are found to be within reference range [38].

Type 2N von Willebrand's disease is also rare and is characterized by a markedly decreased affinity of vWF for factor VIII, which results in factor VIII levels reduced to approximately 5% of the reference range. Other vWF laboratory parameters are usually normal. The factor VIII binding defect in these patients is inherited in an autosomal-recessive manner.

Type 3 is the most severe form of von Willebrand's disease. In the homozygous patient, it is characterized by marked deficiencies of vWF and factor VIIIc in the plasma, the absence of vWF from platelets and endothelial cells, and a lack of the secondary transfusion response and the response to DDAVP [39,40]. It is also characterized by severe clinical bleeding and is inherited as an autosomal-recessive trait. Consanguinity is common in kindreds with this variant. Less severe clinical abnormalities and laboratory abnormalities may be identified in occasional heterozygotes; however, such cases are difficult to identify. Multimeric analysis of the small amount of vWF present yields variable results, in some cases revealing only small multimers [41].

Platelet aggregation disorders

There are three clearly identified groups of platelet dysfunction disorders depending on their etiology. These hematologic alterations can be acquired, drug-induced, or hereditary. Acquired platelet function defects can occur as a result of a blood plasma inhibitory substance, which is the case in conditions such as myeloproliferative syndromes, uremia, paraprotein disorders, liver disease, and pernicious anemia [8]. The most common mechanism of drug-induced platelet dysfunction is through interference with the membrane or membrane receptor sites. The most common offenders in this group are aspirin chlorpromazine, cocaine, xylocaine, cephaloptin, ampicillin, penicillin, and alcohol. Hereditary platelet dysfunctions can be subdivided into surface membrane defects (eg, Bernarrd-Soulier syndrome, Glanzmann's thrombasthenia, collagen receptor defect, and platelet-type von Willebrand's disease) and defects of granule storage (eg, alpha granule deficiency–Gray platelet syndrome, dense granules–Wiskott-Aldrich syndrome, Hermanky-Pudlak syndrome, Chédiak-Higashi syndrome, and thrombocytopenia-absent radius baby syndrome).

Bleeding disorders that result from platelet abnormalities also can be the result of a low number of circulating platelets or thrombocytopenia, which is almost always an acquired condition. The normal laboratory value is anywhere from 150 to 400 $\times$ 10^9/L. Bleeding is rarely a problem if the platelet count is above 50, however. The platelet shortage can be caused by bone marrow depression after irradiation, the administration of certain drugs or chemicals, or a deficiency of B_{12} complex or folic acid. Specifically, thrombocytopenic disorders may be caused by decrease platelet production, increased platelet destruction, increased platelet use, or platelet dilution [42]. The most common causes for a low platelet count include idiopathic thrombocytopenic purpura, hypersplenism, and disseminated intravascular coagulation [43].

During the acute management of trauma patients, massive blood loss and replacement can create a problem with platelet function. Adult patients with platelet counts of 100,000 who have received 15 to 20 U of blood can develop severe bleeding because of thrombocytopenia. In some cases of massive bleeding, other factors may contribute to thrombocytopenia besides the relationship between blood transfused and platelet count. These factors include soft tissue damage, severe hypotensive shock, hypoxemia, and sepsis. The most useful parameter for estimating the need for platelet transfusion under these circumstances is simply looking at the platelet count. Bleeding times and other platelet function tests under emergency conditions either in the operating room or in the emergency department are impractical and often do not reflect clinical bleeding problems [44].

Preoperative correction of the causative agent for thrombocytopenia is the main goal for elective surgical patients. Under emergency conditions, however, the main goal is to maintain ideal platelet count level (ie, >100,000/uL).

There are two types of platelet concentrates used for transfusion: (1) pooled platelet units (usually six) harvested from individual random, whole blood donations, which are commonly called a "six pack" and (2) a unit from a single donor harvested by apheresis. The number of platelets in each type is comparable; both types of platelets are suspended in plasma. Platelets may be stored a maximum of 5 days; shortages of this blood component are much more common than with other components [45]. The dose of platelets needed depends on the change desired in the platelet count. In general, a pool of six whole blood platelets (six pack) or a single unit of apheresis platelet increases the count by approximately 30,000/μL for a 70-kg person.

Patients who are Rh negative, especially if they have child-bearing potential, should receive platelets from Rh-negative donors whenever possible to prevent alloimmunization. If this is not possible, 300 μg Rh immunoglobulin should be administered intramuscularly after the transfusion (no later than 72 hours after the transfusion) [46].

Prophylactic transfusion is not recommended in idiopathic thrombocytopenic purpura or untreated disseminated intravascular coagulation. There is evidence of increased risk of thrombosis if platelets are transfused into patients who have thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia. Patients who have thrombocytopenia from septicemia or hypersplenism are not likely to respond to platelet transfusions [47].

Two other common causes for increased bleeding during the acute management of trauma patients are hypothermia and acidosis. Hypothermia associated with severe trauma is correlated with significant worse prognosis than either trauma or hypothermia alone [48]. Isolated hypothermia of 32.2°C leads to a 23% mortality rate, whereas trauma-induced hypothermia of less than 32°C is associated with 100% mortality [49–51]. The primary risk of hypothermia is abnormal bleeding. Several factors have been proposed to contribute to this coagulopaththy, including reduced activity of coagulation enzymes and platelets, activation of fibrinolysis, and endothelial injury [52].

Acidosis is also associated with worse survival in trauma and surgical patients because of metabolic derangements that may develop. Excess lactic acid production associated with tissue hypoxia is the best recognized cause. It is the end product of anaerobic metabolism, and its level is related to oxygen availability [53]. Acidosis can impair coagulation and worsen the risk of serious hemorrhage. Massive transfusion can exacerbate acidosis caused by the decreased pH of banked blood, which makes it a cyclic problem [54].

Summary

Bleeding at the time of surgery has the potential to become a serious complication. Careful patient assessment and review of history are of the utmost importance if this situation is to be avoided on the operating table. Unfortunately, many patients, particularly younger individuals with little to no previous exposure to surgery, are unaware of underlying bleeding disorders that they may have. Understanding the basic pathophysiology and management of these conditions becomes critical for the treating surgeon. For patients who have known conditions, close interconsultation with the treating hematologists and careful observation of preoperative, intraoperative, and postoperative established protocols reduces the risk of complications for patients and makes the possibility of success a reality for these individuals.

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