Review of Inherited Coagulation Disorders

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Most invasive dental procedures elicit some degree of bleeding which ultimately leads to clotting and eventual hemostasis. However, patients with inherited coagulation disorders may exhibit prolonged or, in some cases, excessive bleeding requiring multiple perioperative interventions. Von Willebrand disease is the most common inherited coagulopathy and often manifests via easy bruising, epistaxis, or prolonged bleeding. Hemophilia A (factor VII) and B (factor IX) are factor deficiencies that are clinically indistinguishable and managed according to severity and the required dental treatment. Other coagulopathies are rare (ie, inheritance is autosomal recessive) and may only become evident in homozygotes or compound heterozygotes. Current lab values and medical consultation with the patient's hematologist are imperative prior to rendering invasive dental treatment. There are a myriad of sedation and general anesthesia considerations, including risks for epistaxis with nasal instrumentation and bruising with improper patient positioning. Preoperative treatment with desmopressin or factor replacement may be required and generally should facilitate normal hemostasis. Additional therapies should be considered to help ensure adequate postoperative hemostasis, including pressure dressings, resorbable clotting materials, laser therapy, and oral rinses.

Key Words: Von Willebrand disease; Hemophilia; Factor deficiencies; Clotting cascade; Anesthesia considerations; Dental considerations.

Hemostasis is the complex process of preventing and stopping bleeding from a damaged blood vessel. This mechanism involves an intricate series of events designed to seal a ruptured blood vessel quickly and effectively and is essential for preventing excessive blood loss and facilitating wound healing. Coagulation can be summarized in 4 major steps: vasoconstriction, formation of a platelet plug, activation of the clotting cascade, and formation of a fibrin clot that will gradually be dissolved once the damaged blood vessel is repaired.

HEMOSTASIS AND COAGULATION

Current understanding of normal hemostasis includes a series of well-regulated steps and a balanced system of proteolytic reactions.[1] Blood vessels are lined with endothelial cells which allow for the passage of fluids and solutes into the extracellular spaces but separate interstitial tissues from the blood.[2] When injury occurs to this endothelial layer, a chain of events that comprises the hemostatic process is initiated. Called *primary hemostasis*, this process results from exposure of the extracellular matrix in the injured vessel's epithelium. This highly thrombogenic environment attracts quiescent platelets which become activated and then release secretory granules that recruit additional platelets to aggregate, eventually forming a hemostatic plug. These secretory granules, understood now to fall within categories of dense granules or α-granules, contain more than 300 other substances involved in anti-inflammatory and proinflammatory processes, coagulation, and anticoagulation mechanisms.[2,3] There are 2 theories on how coagulation occurs in vivo: the *clotting cascade* and the *cell-based model* of coagulation. The clotting cascade is the classical paradigm that presents clotting as 2 distinct pathways that meet downstream to form a common pathway. The cell-based model paradigm, more physiologically accurate, describes the role of platelets and proposes that clotting occurs on the surface of tissue factor (TF)–presenting cells and on platelets.[4]

Coagulation Cascade

This classical paradigm was proposed in the 1960s and consists of sequential activation steps resulting in thrombin generation to form a blood clot. This cascade involves the extrinsic and intrinsic pathways (Figure), which are presented as being separate and distinct. The extrinsic pathway, which occurs outside the circulating blood, starts with the exposure of TF and activated factor VII (FVIIa). The

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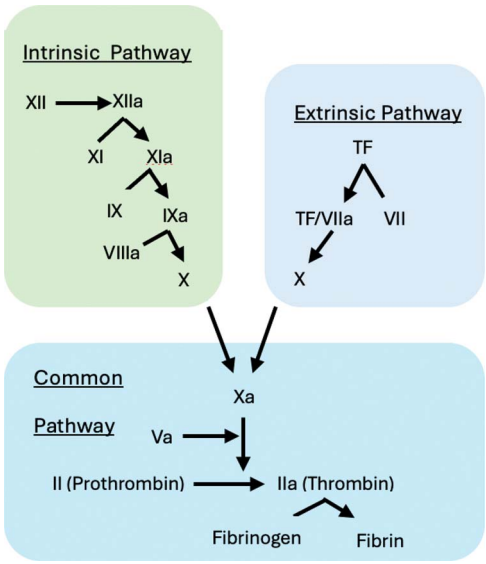
Figure. Coagulation Cascade



The classic coagulation cascade model of hemostasis consisting of the intrinsic, extrinsic, and common pathways.

intrinsic pathway, which is an intravascular process, occurs via activation of FXII, FXI, and FIX.[2,4,5] The importance of the intrinsic coagulation cascade is evident in many patients with congenital bleeding disorders due to deficiencies in clotting factors, like hemophilia A (FVIII), hemophilia B (FIX), or FX deficiency.[1,2,5] At the juncture of the 2 pathways, activated FVIII (FVIIIa) is required to activate FX (FXa) and FV (FVa) which ultimately convert FII (prothrombin) to activated FII (thrombin). FI (fibrinogen) is converted by thrombin into activated FI (fibrin) which then helps cross-link platelets and strengthen the platelet plug.[1,5]

Cell-Based Model of Coagulation

The coagulation cascade describes clotting neatly and correlates well with laboratory tests such as prothrombin time (PT), which measures extrinsic pathway activity, and activated partial thromboplastin time (aPTT), which measures intrinsic pathway activity. However, it does not adequately explain coagulation in vivo because it does not describe coagulation as it occurs on the surface of fibroblasts, endothelial cells, and platelets.[1] Therefore, the cell-based model of coagulation was proposed to describe blood clotting in 3 overlapping phases—initiation, amplification, and propagation.

TF-bearing cells, such as fibroblasts and endothelial cells, are the site of the initiation phase. TF is an integral membrane protein that stays localized on the cell in which it was synthesized. In the initiation phase, TF binds to FVII and becomes activated whenever a vascular injury occurs.[4] The activated TF/FVIIa-complex then activates FIX and FX. FXa, in turn, activates FV which then converts a small amount of prothrombin into thrombin.

The amplification phase begins as circulating platelets are exposed to extracellular matrix proteins at the site of injury and begin to adhere. Platelet adhesion involves the binding of platelet surface glycoprotein (GP) Ib/IX to von Willebrand factor (vWF). In addition to activation of TF/FVII, vascular injury also causes the conformational conversion of vWF from its inactive, globulated configuration to its active, linear form. This activation exposes the GPIb-binding site on vWF, which is pivotal in thrombus formation. Additionally, FVIII is activated and binds to vWF and is then cleaved by thrombin to release it from vWF. The activated platelet now has FVa and FVIIIa bound on its surface, allowing for a significant amount of thrombin to be generated.

During the propagation stage, the Xase complex (activated FVIII/FIX) activates FX on the platelet surface, which binds to its cofactor FVa and generates the large amounts of thrombin required to convert fibrinogen to fibrin. Thrombin also activates FXIII, which cross-links adjacent fibrin monomers to one another and stabilizes the fibrin meshwork.[4]

Platelet Activation

The interaction between coagulation factors and platelets is integral to thrombus formation. Additionally, the initial thrombin generation from the TF/FVII pathway is important for converting the quiescent platelet into its active state. Subendothelial vWF, which is exposed by the vascular injury and endothelial damage, binds to platelet GPIb/IX/V, resulting in platelet adhesion to the damaged endothelium. The thrombin produced from the TF/FVII pathway then binds to protease-activated receptors on the platelet surface and results in the conversion of GPIIb/IIIa from a quiescent to an active state. This further attracts internal GPIIb/IIIa molecules to the platelet surface. Activated GPIIb/IIIa molecules bind to fibrinogen, linking activated platelets to one another and allowing for platelet aggregation and platelet plug formation. Certain molecules such as thromboxane A_2 (TX-A_2), serotonin, and adenosine diphosphate (ADP) help stabilize platelet aggregation. TX-A_2 binds to its receptors on the platelet surface and induces "inside-out" signal transduction of GPIIb/IIIa, which in turn amplifies platelet aggregation. ADP is then released from the platelet granules, contributing to the signal transduction for GPIIb/IIIa activation and binding to the G protein–coupled receptor P2Y12. This ADP release stabilizes and stimulates platelet plug formation, generating platelet aggregation and platelet plug formation.[4]

INHERETED COAGULOPATHIES

Building on the understanding of normal coagulation, it is crucial to explore inherited coagulopathies that represent deviations from the typical process. Inherited coagulopathies, such as von Willebrand disease (vWD) and hemophilia, arise from genetic mutations that affect different clotting factors. The severity and nature of these coagulopathies can vary widely, largely depending on the specific deficiency. Additionally, the pattern of inheritance, whether autosomal dominant, autosomal recessive, or X-linked, plays a crucial role in determining the likelihood and presentation of these disorders within families. Understanding these variances is essential for diagnosing and managing affected individuals.

Von Willebrand Disease

Present in 1% to 3% of the global population, vWD is the most common inherited bleeding disorder. VWD is a coagulopathy that result from quantitative or qualitative abnormalities of vWF and there are more than 20 distinct types of vWD. VWF is the largest circulating protein found in the blood plasma and is made up of multimers, or subunits, of varying sizes. In the absence of vWF, approximately 10% of circulating FVIII is present.[2,6] As a critical adhesive link in the process of platelets adhering to the damaged blood vessel in primary hemostasis and as a carrier for FVIII in secondary hemostasis, its role is clearly imperative if adequate clotting is to occur. This factor is stored in Weibel-Palade bodies in vascular endothelium or in alpha granules in megakaryocytes or platelets.[7] VWF functions by binding to GPIb receptors on platelets and subsequently to GPIIb/IIIa receptors on damaged vessel subendothelium.[6] Mucocutaneous bleeding is the most common clinical manifestation. Treatment for vWD is dependent upon the type and history as well as the clinical situation (ie, spontaneous vs surgical bleeding).

The gene coding for vWF is located on chromosome 12p13.3.[6] VWF is produced in endothelial cells and megakaryocytes and appears to have higher stored concentrations in the brain and lungs in comparison with the kidneys and liver.[6] Stimulation for endothelial secretion of vWF occurs in the presence of thrombin, fibrin, histamine, and complement factors C5b-9.[6] Presence of estrogen and circulating catecholamines is typically coupled with higher levels of vWF.[6] Type O blood experiences a 25% to 30% reduction in vWF and a mean antigen level of 75%; type AB blood has a mean antigen level of 123%.[6]

Type 1 vWD is of autosomal dominant inheritance and is the most common form, accounting for roughly 70% to 80% of diagnoses.[2] It accounts for approximately 1% of the general population, and clinically significant disease is seen in 1:1000 patients with type 1 vWD.[6,7] This type experiences a reduced quantity of vWF, 20% to 50% less than normal values, but a structurally and physiologically normal protein.[6] There is also an association of decreased levels of vWF antigen, FVII coagulant, and ristocetin (an additional agglutination cofactor).[6] Clinical manifestations of type 1 include epistaxis, easy bruising and/or hematomas, menorrhagia, gingival bleeding, and gastrointestinal bleeding.[6]

Type 2A vWD also has an autosomal dominant inheritance pattern but differs from type 1 in that it is a qualitative defect involving the loss of both intermediate and large plasma multimers, which are the functionally active subunits.[6] This loss appears to be related to retention within endoplasmic reticulum and proteolysis of the multimer proteins within the intracellular plasma. Type 2B vWD, also inherited via autosomal dominance, is classified separately with thrombocytopenia and loss of large vWF multimers.[6] Pseudo-vWD resembles type 2B. There is a mutation in GPI at the vWF binding site; mucocutaneous bleeding is a common presentation.[6] Type 2N vWD (Normandy) has an X-linked recessive inheritance pattern with decreased binding of FVIII to vWF. This diminished binding drastically reduces the half-life of FVIII coagulant from 12 hours to 1 hour, mimicking hemophilia A.[6] Type 2M vWD exhibits a decrease in the binding of vWF and platelet GPIb.

Type 3 vWD has an autosomal recessive inheritance that exhibits low to undetectable levels of plasma and platelet vWF antigen, diminished ristocetin cofactor activity, and significantly reduced levels of FVIII.[6] Clinical manifestations include spontaneous hemarthroses and muscle hematoma.[6]

Acquired forms of vWD also exist and are associated with lymphoproliferative diseases, tumors, autoimmune disease, hypothyroidism, and some medications like valproic acid or ciprofloxacin.[6] Probable mechanisms include decreased synthesis, rapid destruction and proteolysis, and tumor cell disruption.[6] Treatments for these acquired conditions depend on the mechanism of disruption and include cryoprecipitate, desmopressin, and fresh frozen plasma (FFP); however, these are only limited treatments, as they typically have a 3- to 5-hour working time.[6]

Hemophilia A (FVIII Deficiency)

Discovered in 1952, hemophilia A is an X-linked congenital bleeding disorder caused by a deficiency of FVIII.[5,6] Hemophilia is the most common severe bleeding disorder; it affects 1 in 5000 males in the United States, and affects all ethnicities.[5,8] The FVIII gene is one of the largest genes found in the human body, spanning 186 kb of genomic DNA and located on Xq28. Specifically, intron 22 of this gene is large and prone to inversion mutations, contributing to approximately 50% of all severe hemophilia A cases. The

other 50% of cases are caused by inversions, deletions, insertions, or point mutations of the other introns.[2,8,9]

FVIII, a component of the extrinsic pathway, is synthesized on hepatic and reticuloendothelial cells.[10] It is a single-chain polypeptide with 3 A domains (A1, A2, and A3), a large central B domain, and 2 C domains. The C2 domain is important for binding to vWF, thrombin, and FXa.[6] VWF protects FVIII from proteolytic degradation in the plasma and concentrates FVIII at the site of injury. The A2 and A3 domains are important sites for binding to activated FIX (FIXa). The B domain can be deleted without any consequences.[5,6,8]

FVIII circulates in the blood bound to vWF, is a cofactor for FIX, and allows for the activation of FX in the coagulation pathway. The normal coagulation pathway results in the conversion of fibrinogen to fibrin, stabilizing the clot at the site of injury. In hemophilia A, a deficiency or absence of FVIII produces a profound abnormality in the coagulation pathway, as FVIII is required for amplifying the production of FXa. In addition, FXa, which is generated by TF/FVIIa, is insufficient because this pathway is inhibited by TF pathway inhibitor as part of a negative feedback loop. Despite an abnormal coagulation pathway, the primary platelet plug formation and the initiation phases of coagulation are normal. Any clot that is formed from the initiation phase is friable and porous.[8]

The diagnosis of hemophilia A is often made following a bleeding episode or due to family history; however, 50% of cases show no family history of hemophilia A. Normal plasma levels of FVIII are 50% to 150%. Thus, hemophilia A is classified as mild (>5%), moderate (1%-5%), or severe (<1%). In patients with hemophilia A, approximately 65% have severe disease, 15% have moderate disease, and 20% have mild disease.[5,9] Most cases of severe disease show signs and symptoms by 4 years of age. Cases of moderate or mild disease are often diagnosed later in life following bleeding after trauma or surgery. Diagnosis of hemophilia A can also be made in the first trimester using chorionic villus sampling and gene analysis. In the second trimester, fetal blood sampling can be done.[8]

Hemophilia A and B are clinically indistinguishable, and thus specific factor assays are performed to differentiate and confirm the diagnosis. The PT, platelet function analysis (PFA)–100, and fibrinogen activity are normal.[6] The aPTT is prolonged when FVIII levels are less than 30%.[6,8]

Female carriers of the mutated gene may be asymptomatic unless extreme lyonization results in low FVIII levels. If FVIII levels are less than 40% in these female carriers, they are considered to have hemophilia A. If FVIII levels are at or above 40% in these female carriers, they are truly considered to be just carriers. Carriers are then further classified as symptomatic (ie, with bleeding manifestations) or asymptomatic. However, even carriers with an FVIII level of 40% to 60% may still experience bleeding episodes (eg, heavy menstrual bleeding, postpartum hemorrhage, or joint bleeding).[5,9] Asymptomatic females may become symptomatic with the onset of menarche. FVIII levels increase throughout pregnancy and drop to prepregnancy levels following delivery.[8]

Patients with severe hemophilia A often experience hemarthrosis (ie, bleeding in a joint) which can occur spontaneously or with minimal trauma. Hemarthrosis usually begins as mild joint pain and tenderness but rapidly progresses to excruciating pain, swelling, warmth, and muscle spasms.[5,9,10] A long-term effect of recurrent hemarthrosis is hemophilic arthropathy, which is characterized by synovial thickening and chronic inflammation, resulting in repeated hemorrhage. Common sites of target joints include the knees, elbows, ankles, hips, and shoulders. Joint stability may worsen due to disuse atrophy of surrounding muscles, thereby limiting the joint range of motion.[8]

Another characteristic includes muscle hematomas that can lead to compartment syndrome and can eventually cause fibrosis and peripheral nerve damage. Commonly, iliopsoas bleeds are accompanied by pain and flexion deformity, whereas gastrointestinal bleeding and hematuria are less common.[6] Intracranial hemorrhage rarely occurs but carries a 10% recurrence rate and is the leading cause of mortality in patients with hemophilia. Although most newborns with severe hemophilia do not experience complications following delivery, vaginal vacuum extraction is associated with an increased risk in central nervous system bleeds. The incidence of intracranial hemorrhage in newborns with hemophilia is 1% to 4%.[8]

The pattern of bleeding in hemophilia A tends to be coagulopathic rather than mucosal. Coagulopathic bleeding is often delayed in onset, meaning deep bruising is common and petechiae are rare. In the hemophilias, excessive bleeding from minor skin injuries is rare, but significant postsurgical bleeding is expected.[8]

Hemophilia B (FIX, Christmas Factor Deficiency)

Clinically, hemophilia B mimics hemophilia A with easy bruising, spontaneous muscle or joint hemorrhage, and excessive bleeding with trauma or surgical procedures. An X-linked, recessive coagulopathy, hemophilia B is a deficiency in FIX clotting. Prevalence is 1 in 25,000 to 30,000 male births.[6] Carriers are typically asymptomatic, as they retain greater than 50% of FIX activity, with exceptions being Turner syndrome, X-chromosome inactivation, X-mosaicism, and testicular feminization.[6] Bleeding episodes are similar to those found in hemophilia A. Severe disease is associated with less than 1% of normal factor activity, moderate is 1% to 5%, and mild is 5% to 40%. Inhibitors to FIX develop in less than 3% of patients who are severely affected.[6]

The gene for FIX is located on chromosome Xq27 and is responsible for encoding the vitamin K–dependent,

single-chain GP. Hemophilia B can be caused by point, frameshift, or deletion mutations resulting in either structural or functional changes to the FIX protein. The zymogen, or inactive, FIX becomes activated when cleaved by TF/FVIIa or FXIa, yielding FIXa.[6] In the presence of a phospholipid surface (such as platelets) and FVIIIa, FIXa will in turn activate FX.[6] Lab studies will typically yield normal PT, normal bleeding time, prolonged aPTT, and low FIX levels. Treatment typically involves FIX replacement.

Other Factor Deficiencies

FII Deficiency. Also known as hypoprothrombinemia or dysprothrombinemia, a deficiency in FII (prothrombin) is often unmasked by mild to moderate mucocutaneous and soft-tissue bleeding.[6] The gene responsible for this deficiency is found on chromosome 11p11-q12. Homozygotes of hypoprothrombinemia have less than 10% of normal quantity and homozygotes of dysprothrombinemia range from 1% to 20% of normal. Prothrombin is a protein synthesized in the liver and is vitamin K dependent. It is responsible for conversion of fibrinogen to fibrin, platelet aggregation, plasminogen activation, and activation of FV, FVIII, FXI, and FXIII, and protein C (when thrombomodulin is present).[6] A prothrombin level of 5% to 50% of normal is indicative of excessive bleeding only with surgery or trauma.[6] Lab values will show prolonged aPTT, prolonged PT, and a normal thrombin time.

FV Deficiency. A deficiency in FV is inherited in an autosomal recessive pattern. Clinical presentation includes ecchymosis, epistaxis, gingival bleeding, menorrhagia (in females), and excessive bleeding in the presence of trauma.[6] Coding for this factor is located on chromosome 1q21-25 and has some homology to FVIII. FV is produced in the liver and has a half-life of 12 to 15 hours. When activated, FV combines with FXa on the phospholipids of the platelets to create the prothrombinase complex, which is responsible for the conversion of prothrombin to thrombin.[6]

FVII Deficiency. FVII deficiency is rare with an autosomal recessive inheritance found on chromosome 13q34. Another vitamin K–dependent factor, FVII is secreted by the liver. This zymogen is activated by FXa, FIXa, FXIIa, thrombin, and FVIIa and is enhanced in the presence of TF.[6] The FVII half-life is 5 hours. Factor levels less than 1% of normal will mimic severe hemophilia A and B, and levels around 5% will have more mild symptoms such as epistaxis, gingival bleeding, menorrhagia, and easy bruising.

FX Deficiency. An autosomal recessive inherited disorder, FX deficiency can be qualitative or quantitative in nature. Clinical presentation includes spontaneous hemarthrosis, soft tissue and mucosal bleeding, or unusual bleeding following trauma. The gene coding for FX is located on chromosome 13q34 and is also vitamin K dependent. When activated, it will convert prothrombin to thrombin in the presence of a platelet-phospholipid surface, divalent calcium, and FVa.[6] Heterozygotes are typically able to maintain levels of more than 50% of normal and are therefore asymptomatic. Lab values will demonstrate normal thrombin time, prolonged PT and aPTT, diminished to absent FX levels, and a prolonged Russell viper venom time.[6] Acquired FX deficiency can be associated with amyloidosis, spindle cell thymoma, fungicide toxicity, renal or adrenal adenocarcinoma, and the use of methylbromide.[6]

FXI Deficiency (Rosenthal). Common amongst those of Ashkenazi Jewish descent and with an incidence of approximately 1:450, FXI deficiency is an autosomal recessive disorder. It affects both the intrinsic coagulation and fibrinolytic pathways. Located on chromosome 4q34-35, this factor is a GP that activates FIX via proteolysis. FXI plays a critical role of thrombin-activatable fibrinolysis inhibitor complex, which is initiated in the presence of thrombin.[6] This inhibitor downregulates fibrinolysis by disallowing binding of plasminogen to fibrin by removing the C-terminal lysine residues on partially degraded fibrin. Bleeding severity is related to the genotype. Spontaneous hemorrhage is rare, but mild to moderate bleeding is generally associated with injury.[6]

ANESTHETIC CONSIDERATIONS

The perioperative risks of patients with congenital coagulopathies undergoing surgery and sedation or general anesthesia include prolonged, and potentially fatal, hemorrhage and closed-space bleeding leading to nerve injury, vascular damage, or airway obstruction.[11] A hematologist must be involved during the perioperative care of patients with coagulopathies prior to undergoing surgery with or without sedation or general anesthesia. It is important to have a detailed plan to both measure and replace deficient factors as appropriate. Special care should be taken regarding airway maintenance. Video laryngoscopy is the preferred method when endotracheal intubation is required. Laryngeal mask airways should also be considered, if appropriate for the surgical procedure, to limit potential trauma to and bleeding in the airway. Any nasal cannulations (eg, passage of endotracheal or nasogastric tubes) should be avoided. For minor surgeries, noninvasive blood pressure monitoring is preferred; however, if multiple blood gases or labs are required throughout the procedure, invasive monitoring and site bleeding risk should be considered.

A coagulation profile including platelet count, PT, thrombin time, and aPTT should be performed. For major invasive surgery, point-of-care viscoelastic monitors, such as the thromboelastograph or rotational thromboelastograph, measure blood coagulation intraoperatively and help guide clinicians on the administration of blood products or recombinant

factors. These clinical tests, thromboelastography (TEG) and rotational thromboelastometry, assess platelet function, clot strength, and fibrinolysis.

With TEG, a small sample of the patient's blood is gently rotated in a cup at an angle of 4 degrees and 25 minutes, repeated 6 times a minute to imitate sluggish venous blood flow. A pin is then suspended from a torsion wire into the blood sample. The development of fibrin strands couples the motion of the cup to the pin, which is directly proportional to the clot strength. The increased tension in the wire is picked up by the electromagnetic transducer, and the electrical signal is amplified to create a trace. The shape of the trace generates various measurements to indicate the time and speed of clot formation, clot strength, and fibrinolysis. All these values are then analyzed to help clinicians decide which blood products need to be administered.[12]

Patients with vWD can undergo surgical procedures safely. Many type 1, 2A, and 2M vWD patients have success solely with desmopressin; however, upwards of 20% to 25% may not have an adequate response.[2,6] The typical infusion dose of desmopressin is 0.3 μg/kg (up to 20 μg) diluted into 50 mL of normal saline over 30 to 60 minutes.[6] Intranasal desmopressin (150-300 μg) can be given but has more of a limited response. In patients where desmopressin is insufficient, antifibrinolytics (eg, aminocaproic acid) can be administered rather than plasma products.[6] In patients with type 2B vWD, desmopressin is relatively contraindicated due to a potential to intensify thrombocytopenia.[6]

Patients who are unresponsive to desmopressin and those with types 2B, 2N, and 3 vWD require plasma-derived FVIII concentrates with vWF.[2,6] For major surgery, the ideal level of vWF is 0.8 to 1.0 U/mL or 80% to 100% of normal values; this can be achieved with 50 U/kg of body weight FVIII concentrate.[6] Postoperatively, the targeted vWF concentration is 0.4 U/mL for several days.[6]

Cryoprecipitate is commonly administered because it contains 40% to 70% of the original concentration of vWF. It is dosed at 1 bag/10 kg of body weight every 12 to 24 hours, and the duration of administration is bleeding dependent.[6] Purified plasma–derived vWF/FVIII is a US Food and Drug Administration–approved treatment with 2.5 IU of ristocetin cofactor to 1 U FVIII and a half-life of 11 hours.[6] Preoperatively, a loading dose is 60 to 80 ristocetin cofactor activity/kg body weight administered intravenously (IV) every 8 to 12 hours. Administration is continued for 7 to 10 days for major surgery and 3 to 5 days for minor surgery.[6] In some rare cases of type 3 vWD, patients may have developed alloantibodies to vWF. Combinations of recombinant FVIIIa, antifibrinolytics, and thrombin glue have been successfully administered for oral surgical procedures in these patients.[6]

For hemophilia A, current guidelines recommend that factor replacement therapy increase the preoperative plasma FVIII levels to 40% to 70% for elective surgeries and 80% to 100% for major surgeries.[9,10] After surgery, the target FVIII level is 50% until the surgical wound is healed or for about 6 to 10 days. Dosing calculations are dependent on many factors, including the targeted increase in factor levels, clinical expertise of the consulting hematologist, individual patient-level factors (eg, history of previous bleeding episodes), and hospital protocols. An example of the formula to determine the dose required to increase FVIII levels is as follows: FVIII dose = weight (kg) × 0.5 × (desired absolute percentage increase in factor levels). To rapidly increase FVIII levels to about 100%, the usual dose given is 50 units/kg.

Intramuscular injections are to be generally avoided in these patients.[13] In about 10% of patients, their body may produce an antibody that inactivates FVIII. These acquired anticoagulants are usually composed of immunoglobulin G, are poorly removed by plasmapheresis, and are responsive to immunosuppressive drugs. The use of prothrombin complex concentrates (PCCs) can be lifesaving to bypass this inhibitor.[10] For patients with mild hemophilia A, an IV infusion of desmopressin about 30 to 90 minutes before the procedure may be sufficient. Desmopressin stimulates the release of vWF and FVIII, increasing levels 3- to 5-fold and lasting up to 6 hours.[6,7,10] Inhibitors, or alloantibodies, develop in 20% to 30% of hemophilia A patients and are more common in severe cases. Immunosuppressive agents may need to be administered if alloantibodies develop.[2] Patients on emicizumab should be treated with FVIII concentrate if no inhibitors are present while continuously monitoring FVIII levels. In addition, FFP and cryoprecipitate can also correct FVIII levels.

In patients with hemophilia B, PCCs can be administered; these concentrates provide zymogen as well as activated prothrombin, FVIIa, FXa, and FIXa.[6] Concentrates have been associated with thrombotic events (eg, thrombophlebitis, deep venous thrombosis, pulmonary embolism, and disseminated intravascular coagulation) because of the combination of activated factors. These concentrates should not be administered if the FIX concentration is greater than 50% of normal, as the risk of thromboembolic events outweighs the benefits of infusion.[6] Highly purified FIX infusions can be administered in the perioperative period and have less of a risk of activating systemic coagulation.[6] Dosing is dependent upon whether the coagulant is derived from plasma or if it is recombinant. Recombinant has a lower recovery profile (37.8%) vs plasma derived (52.6%); recombinant is not exposed to human albumin or bovine serum and therefore may be preferred in some patient populations. With FIX replacement each 1 U/kg will increase circulating FIX levels by 0.01 U/mL. In a severely affected patient, approximately 100 U/kg will need to be administered every 12 to 18 hours. Plasma-derived FIX half-life is 17.7 hours, and recombinant FIX half-life is 18.1 hours.[6]

Patients with prothrombin deficiency can receive PCCs of FFP in the perioperative setting. Typically, only one administration is needed, as the half-life of prothrombin is 3 days.[6] The perioperative goal for FV is more than 25% of normal. This can be achieved with a fresh frozen plasma

Table. Factor Management for Coagulation Deficiencies[a]

Bleeding disorder	*Pretreatment for extraction and/or nerve blocks*
Hemophilia A (mild)	Desmopressin, 0.3 μg/kg (max 20 μg) IV over 20-30 min
Hemophilia A (moderate, severe)	Recombinant factor VIII concentrate, 20-25 IU/kg
Hemophilia B (mild, moderate, severe)	Recombinant factor IX concentrate, 40-60 IU/kg
Type 1 vWD	Desmopressin, 0.3 μg/kg (max 20 μg) IV over 20-30 min
Type 2A and 2M vWD	Desmopressin, 0.3 μg/kg (max 20 μg) IV over 20-30 min OR vWF/factor VIII, 50 IU of vWF:RCoF/kg
Type 2B and 3 vWD	vWF/factor VIII, 50 IU of vWF:RCoF/kg
Factor II	FFP
	PCC
Factor V	FFP
Factor VII	Factor VII concentrate
	Recombinant factor VIIa
Factor X	FFP
Factor XI	FFP
	Factor XI concentrate

FFP, fresh frozen plasma; IV, intravenous; max, maximum; PCC, prothrombin complex concentrate; RCoF, ristocetin cofactor; vWD, von Willebrand disease.

[a] Information from Israels et al.[2]

loading dose of 20 mL/kg and 5 to 10 mL/kg every 12 hours for 7 to 10 days.[6] The goal for hemostasis perioperatively is maintaining a level of greater than 25% of normal through administration of PCC and FFP. Recombinant FVIIa therapy has been successful with doses lower than what is required for treatment of hemophilia.[6] In patients with FXI deficiency, factor replacement is not generally required for dental procedures. However, antifibrinolytics are beneficial and should be considered.[6] See the Table for a full list of preoperative management considerations for dental and surgical procedures.

DENTAL CONSIDERATIONS

Determining the mechanism and severity of coagulopathy is important, but the type, location, and extent of the planned dental treatment are also extremely important. Access to the treatment site in question is critical for assessment and control of hemostasis. A simple anterior extraction can be directly visualized and, therefore, is more readily accessible for applying pressure, topical agents, and additional local hemostatic agents. Sinus elevation and bone grafting would create a different scenario in which there is essentially limited to no access to evaluate or control bleeding if hemostasis cannot be achieved. In the latter scenario, systemic factor replacement therapy will play a critical role. Location of surgical intervention (eg, mandibular tori removal elevating the floor of the mouth) can also cause a significant hematoma and subsequent airway obstruction. Administration of local anesthesia for inferior alveolar and posterior superior alveolar nerve blocks (ie, “deep blocks”) can also contribute to airway obstruction from an uncontrolled hematoma. An appropriate alternative to an inferior alveolar block is the Gow-Gates technique.[2] Other safe techniques include local infiltration, periodontal ligament injection, and intrapulpal injection. If these techniques are inadequate, the addition of sedation or general anesthesia can be considered, but these come with their own set of risks.

Consultation with a patient’s hematologist prior to any elective dental procedures should include discussions regarding plans for infusions of coagulation factors, blood products, and other measures prior to arrival at an outpatient, ambulatory, or office-based setting. Oftentimes, patients will have IV access established by the hematology service before arrival, and communication regarding using and maintaining the established IV access should focus upon additional anesthesia-related medications through the same access point.

Surgical interventions can occasionally be modified to create a less traumatic surgical field. Examples include electively sectioning a tooth that could be deemed a difficult extraction, limiting the number of teeth extracted in an appointment, avoiding soft tissue flaps whenever possible as they create a larger bleeding surface area that can be difficult to control postoperatively, and attaining primary closure.[2] In some scenarios it may be preferable to perform root canal therapy on unrestorable teeth with poor prognoses so the mucosa can be largely left intact.

Local Measures

There are local measures that can be employed for necessary surgical procedures. Suturing can be helpful to achieve primary closure if multiple adjacent teeth are extracted. However, each additional needle puncture is a potential source for bleeding, so the benefits must outweigh the risks. Electrocautery or CO_2 laser can be used for soft tissue biopsy or

for the purpose of achieving hemostasis, but these come with the risk of tissue necrosis which can become a source of postoperative bleeding. Gelfoam (Pfizer) is one example of an absorbable gelatinous sponge that allows for scaffolding effect for clot formation. It is placed directly into an extraction socket and will resorb over approximately 4 weeks. Gelfoam should not be placed under flaps as it will inhibit epithelial healing.[6]

Tranexamic acid (TXA) can be used as a mouthwash. The IV preparation of TXA can be diluted to 4.8% solution, which is used as a rinse 4 times a day for 7 days postoperatively. Consider contacting a compounding pharmacy for this preperation.[2] Aminocaproic acid is an antifibrinolytic agent available as oral and IV solutions, tablets, and a mouth rinse. Both agents function to inhibit fibrinolysis by blocking the plasminogen-fibrin bond, thereby inhibiting activation to plasmin. Oral mucosa is known to be rich in plasminogen activators, and saliva itself has fibrinolytic activity, which can increase the likelihood of clot breakdown following oral surgery procedures.[2,13] Sometimes these agents can be used as sole treatments (oral rinses are available) or in conjunction with replacement therapies. Combination therapies in more severe coagulopathies have demonstrated a decreased risk of delayed bleeding and reduced need for replacement factors postoperatively.[2] Oral doses can be started prior to surgery and continued 3 to 5 days postoperatively or until the surgical site is healed.[2]

Surgical stents can be fabricated that would allow for pressure to be exerted onto extraction sites.[2] A moist tea bag can also be useful for patients who continue oozing at home. Soaking a black tea bag in warm water, wringing it out, and then applying it as a pressure dressing for 30 minutes provides pressure and the added benefit of the astringent tannic acid (highest in black teas) which vasoconstricts capillaries and accelerates clot formation.

CONCLUSION

Patients with inherited coagulopathies have a wide array of complexities but are likely to require dental care at some time in their lives. Dental treatment can be safely rendered by collaborating with the patient's hematologist to manage and optimize the patient's coagulopathy. Recombinant factor replacement, desmopressin, and FFP are the primary preoperative treatment options for patients with factor deficiencies. However, administration may not be required depending upon the specifics of the procedure and the patient's coagulopathy. Other local measures that should be considered include laser therapy, collagen plugs, and specialized mouth rinses.

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1) Which of the following inherited coagulopathies is the most common bleeding disorder?

   a. Factor II deficiency
   b. Hemophilia A
   c. Hemophilia B
   d. von Willebrand disease

2) Which of the following airway management techniques should be avoided in patients with clinically significant congenital coagulopathies?

   a. Nasotracheal intubation
   b. Natural airway (nonintubated deep sedation/general anesthesia)
   c. Placement of a laryngeal mask airway
   d. Video laryngoscopy

3) For patients with Type 1, 2A, or 2M von Willebrand disease, which of the following agents can be administered to improve coagulation during dental surgery?

   a. Desmopressin
   b. Normal saline
   c. Nonsteroidal anti-inflammatory drugs
   d. Plain local anesthetics

4) Which of the following intraoral local anesthetic techniques would be contraindicated in patients with clinically significant coagulopathy?

   a. Gow-Gates nerve block
   b. Inferior alveolar nerve block
   c. Intrapulpal injection
   d. Supraperiosteal infiltration