Bleeding Disorders: Characterization, Dental Considerations and Management

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ABSTRACT

Hemostasis is a finely balanced process in which an insult to a blood vessel wall, either by injury or surgical intervention, stimulates a pair of parallel, yet associated, pathways that lead to the termination of blood loss. The coagulation cascade is initiated by the interaction between exposed subendothelial tissue factor and circulating blood and includes a series of amplification steps that result in thrombin generation. Concurrently, exposed subendothelial collagen stimulates platelets, which, in the presence of thrombin, are consolidated by fibrin to form a blood clot, thus terminating blood loss. Multiple inherited and acquired abnormalities in these pathways can seriously compromise hemostasis. Furthermore, several drugs, including over-the-counter preparations, also adversely affect hemostasis. These present significant concerns to the dentist conducting invasive procedures as they can prolong postoperative bleeding, impair wound healing and increase risk of infection. In this article, we review the current knowledge of bleeding abnormalities and discuss preoperative systemic precautions and intraoperative hemostatic measures.

MeSH Key Words: blood coagulation/physiology; blood coagulation disorders/complications

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Dental procedures, such as extractions and periodontal surgery, are among the most common invasive procedures in Canada. Many dental procedures are associated with postoperative bleeding, which, in most cases, is self-limiting and nonproblematic. However, a small but significant segment of the population has an increased risk of bleeding due to inherited bleeding disorders, in which even relatively minor invasive procedures can precipitate a prolonged bleeding episode. Excessive bleeding in these patients is not only distressing for the patient, but also hinders the completion of the procedure (e.g., suture insertion) and can compromise wound healing. More common are patients with hemostatic defects secondary to underlying disease or medication. The dental management of such indiviuals presents a significant challenge; however, the onus is very much on the dental practitioner to maintain clear and frequent communication with the patient's primary physician, hematologist or both to assess the risk and plan appropriate management.

Normal Hemostasis

Under normal conditions, hemostasis (or the arrest of bleeding) occurs through 2 independent, but related processes: the coagulation cascade (**Fig. 1**)[1] and the platelet activation pathway (**Fig. 2**).[2] Blood vessels are lined with a continuous layer of endothelial cells that allow the passage of gases, soluble nutrients, etc., but prevent contact between blood components and the subendothelial matrix and interstitial tissues. However, when the integrity of the endothelial layer is compromised, the interaction of the blood with previously inaccessible stimuli initiates both arms of the hemostatic process.

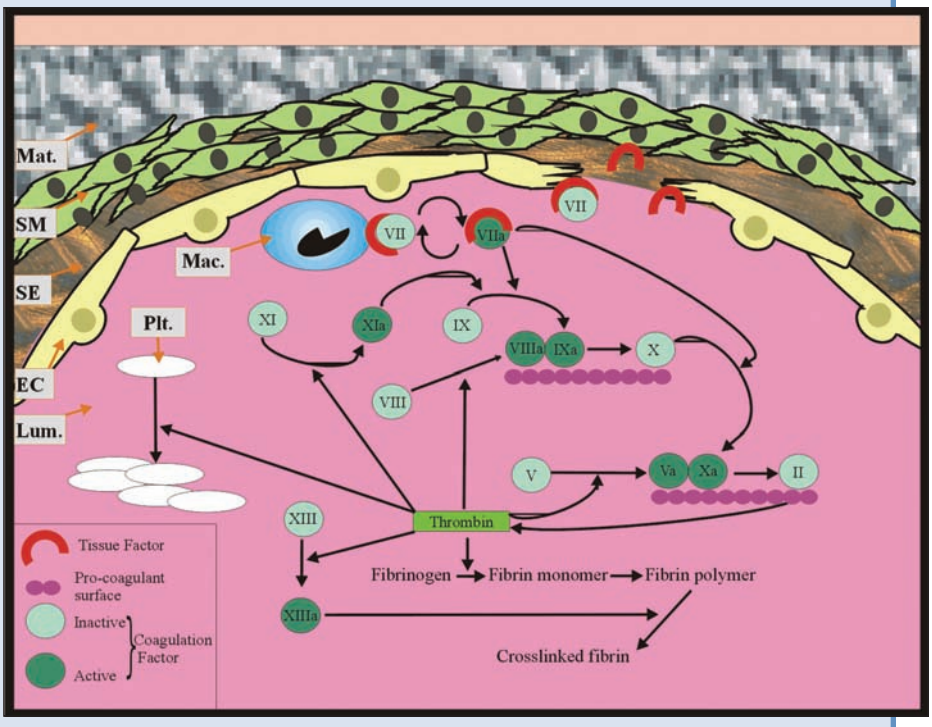

Figure 1: Coagulation cascade initiated by vascular damage leads to the expression of tissue factor and culminates in the generation of thrombin and cross-linked fibrin. EC = endothelial cells; Lum. = lumen; Mac. = macrophage; Mat. = matrix ; Plt. = platelet; SE = subendothelial matrix; SM = smooth muscle.

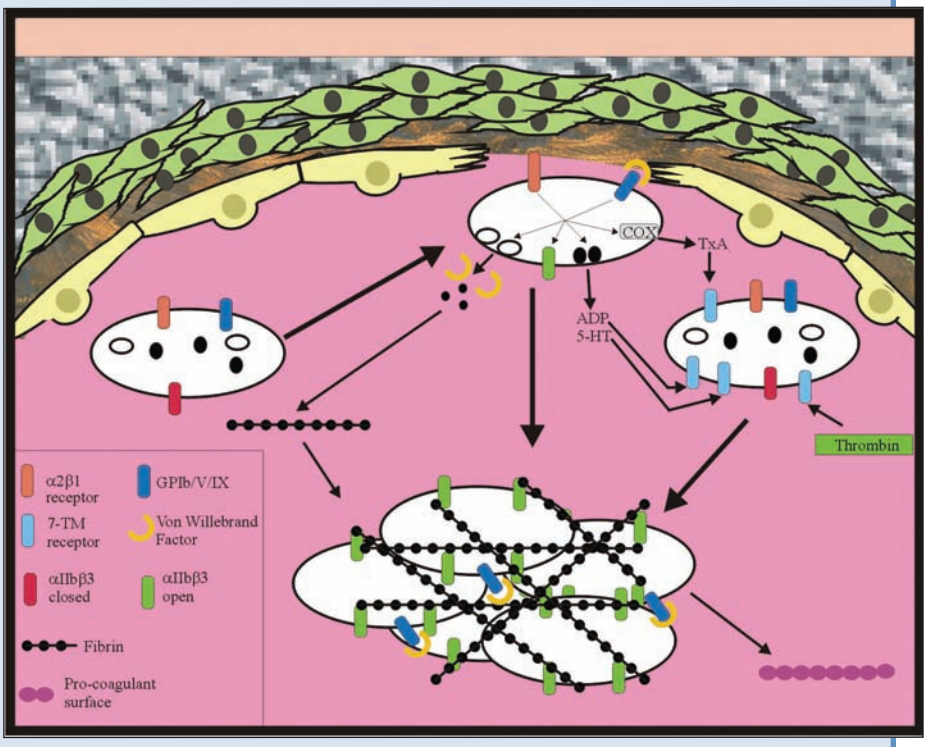

Figure 2: Platelet activation, initiated by vascular damage exposing subendothelial von Willebrand factor and collagen, culminates in platelet aggregation. ADP = adenosine diphosphate; COX = cyclooxygenase; 5-HT = serotonin; TxA = thromboxane A.

In the first arm, the stimulus is the glycoprotein tissue factor, which is expressed on the surface of subendothelial cells.[3] Following an insult to the endothelial layer, the subendothelial tissue factor comes into contact with circulating blood (**Fig. 1**). Additional tissue factor is expressed on the surface of endothelial cells following injury and on macrophages following stimulation by soluble factors, such as cytokines and bacterial products. The presence of small amounts of tissue factor initiates a succession of proteolytic events, termed the coagulation cascade — the sequential activation of a series of soluble enzymes. Amplification at each step results in the generation of large amounts of important hemostatic proteins (**Fig. 1**).[1]

Initially, tissue factor interacts with Factor VII, leading to its conversion to the active form, Factor VIIa. The tissue factor–Factor VIIa complex proteolytically converts Factors IX, X and additional VII to their active forms IXa, Xa and VIIa. Factor Xa then converts Factor II (or prothrombin) to thrombin, which has several critical functions.[4] First, thrombin proteolytically activates Factors V (to Va), VIII (to VIIIa) and XI (to XIa), amplifying steps in the coagulation cascade. Second, thrombin converts fibrinogen to the fibrin monomer and activates Factor XIII (to XIIIa), which catalyzes the cross-linking of fibrin, both crucial steps in the consolidation of the hemostatic plug. Finally, thrombin is a powerful, locally produced platelet activator.[4]

The second hemostatic pathway engaged following vascular injury is the platelet activation process (**Fig. 2**). Platelets are

Table 1 Classification of von Willebrand disease

Type 1	Partial deficiency (80% of those with vWD)
Type 2	Qualitative defects
A	Decreased function; absent medium and high-molecular-weight multimers
B	Increased affinity for platelet GPIb; decreased high-molecular-weight multimers
M	Decreased function; variable multimer pattern
N	Decreased affinity for FVIII
Type 3	Severe deficiency; autosomal recessive

the smallest cells in circulating blood; derived from megakaryocytes,[5] their turnover rate is 10–12 days. Structurally, they are anucleate, but they contain several types of storage granules, notably alpha granules and dense granules.[2,6] Alpha granules contain a range of proteins, including adhesive material, such as fibrinogen and von Willebrand factor (vWF), several coagulation factors and growth factors. The dense granules contain soluble platelet-activating molecules such as ADP and serotonin (5-HT). Platelets also possess surface receptors that mediate platelet adhesion and activation.[2,6]

Damage to the endothelial lining initiates the adhesion of platelets to, and their activation by, a number of components of the subendothelium (**Fig. 2**). vWF is a large adhesive protein stored in endothelial cells (from which it is secreted into the subendothelial space) and platelets.[7] Under the high shear stress in the microvasculature, subendothelial vWF binds to, and stimulates, platelets via the glycoprotein Ib–V–IX complex on the platelet surface. In larger vessels, subendothelial matrix proteins, notably collagen, are exposed, which activates platelets via the α2β1 receptor on the platelet surface.[2]

Once activated, platelets undergo significant structural and functional changes. The contents of both dense and alpha granules are expelled. Dense granule-derived 5-HT and ADP act on their respective receptors to stimulate production of additional platelets and recruit them to the site of injury, whereas alpha-granule-derived vWF and fibrinogen both serve to solidify platelet–platelet interactions.[2,6] Activated platelets synthesize, by the cyclooxygenase 1 (COX-1) pathway, thromboxane A_2 (TxA_2) which acts as a soluble platelet agonist responsible for significant amplification of the platelet response and as a vasoconstrictor, reducing local blood flow and, therefore, blood loss at the site of injury.[2,6]

Following activation, platelets shed phosphatidylserine-rich, negatively charged membrane fragments or microparticles (**Fig. 2**), which provide the necessary platform for the activities of components of the coagulation cascade (**Fig. 1**).[8]

The principle receptor that mediates platelet–platelet interaction is the αIIbβ3 integrin.[9] This glycoprotein is present on the surface of circulating platelets, but in a closed form. Following activation by any platelet agonist, the structure of the αIIbβ3 complex is rearranged into an open configuration that promotes the binding of several adhesive proteins, most notably cross-linked fibrin (**Fig. 2**), which mediate platelet–platelet aggregation. The end result of these processes is that the initially fragile adherent platelet monolayer formed at the site of injury is consolidated by additional platelets and the cross-linking action of fibrin into a stable clot (**Fig. 2**).

Inherited Coagulation Disorders

Von Willebrand Disease

Von Willebrand disease (vWD) is considered the most common inherited bleeding disorder, affecting up to 1% of the general population and resulting in mucocutaneous and operative bleeding. Easy bruising, epistaxis, menorrhagia and bleeding with oropharyngeal surgery are the most common manifestations.[10] vWD results from quantitative or qualitative defects in vWF, an important protein in hemostasis (see above). vWF is also the carrier of Factor VIII in plasma; its deficiency may, therefore, result in low levels of Factor VIII.[11]

Inherited vWD is subdivided into 3 categories: Types 1 and 3 represent partial and complete deficiency of vWF, respectively; Type 2 variants represent qualitative abnormalities of vWF (**Table 1**). Type 1 vWD is the most common, occurring in 80% of vWD patients; it is usually inherited in an autosomal dominant mode, although variable penetrance can result in some family members being asymptomatic.[10,11]

Diagnosis of vWD, particularly Type 1, can be challenging because laboratory diagnosis requires a battery of tests, the interpretation of which is limited by the heterogeneity of the disease, physiologic variation in levels of vWF and Factor VIII and the limitations of the available laboratory assay. Personal and family bleeding history are important in assigning patients a diagnosis of vWD. Laboratory testing includes quantitative measures of vWF, functional assays of vWF (the ristocetin cofactor assay, ristocetin-induced platelet aggregation or collagen-binding assay) and multimer analysis. The results of these assays help to make the diagnosis and define the subtype. Discrimination among the subtypes is important because of the clinical and therapeutic implications. Repeat testing is often required to confirm a diagnosis, particularly in Type 1 patients with mild deficiencies, as their plasma levels of vWF may fluctuate.[10]

The approach to treatment will depend on the subtype of vWD. Most Type 1 and some Type 2A and

Table 2 Classification of hemophilia

Severe	< 0.01 IU/mL or < 1%	Spontaneous joint, muscle and internal bleeding; excessive bleeding with trauma or surgery
Moderate	0.01–0.05 IU/mL or 1% to 5%	Bleeding into joints or muscles with minor trauma; excessive bleeding with surgery
Mild	0.05–0.35 IU/mL or 5% to 35%	No spontaneous bleeding; delayed onset bleeding after trauma or surgery or dental extractions

2M patients respond well to desmopressin acetate, a synthetic analogue of vasopressin, which stimulates release of vWF from storage pools in endothelial cells, transiently raising plasma levels of vWF and Factor VIII by 3–5-fold, for 8–12 hours and improving primary hemostasis.[12] Desmopressin can be administered intravenously, subcutaneously or as an intranasal spray. The onset of action is immediate and reaches maximum at 30–60 minutes.[13,14] Side effects are primarily the result of vasodilation and include flushing, tachycardia, hypotension and headache. Other side effects include hyponatremia (water intoxication in severe cases) resulting from desmopressin's antidiuretic effects and thrombosis in patients with pre-existing risk factors. Patients for whom desmopressin is being considered as the primary therapeutic or prophylactic therapy should have a trial period to confirm a hemostatic response.

For patients who do not respond to desmopressin and those with Type 2B and Type 3 vWD, vWF replacement is required. The currently available replacement is vWF-containing Factor VIII concentrates derived from pooled human plasma and pasteurized to inactivate viruses.[14–16] As the half-life of vWF is long, once a day dosing is adequate for most bleeding episodes or surgical procedures.

Hemophilia

Hemophilia is an inherited X-chromosome-linked bleeding disorder caused by deficiencies of either Factor VIII (hemophilia A) or Factor IX (hemophilia B). The prevalence of hemophilia is 1 in 5,000 males; 85% to 90% have type A disorder and 10% to 15% have type B. Hemophilia A and B are not clinically distinguishable; they are characterized by easy bruising, spontaneous muscle and joint hemorrhage and excessive bleeding following trauma and surgical procedures. Diagnosis must be confirmed by specific laboratory assay. The severity of bleeding is related to the measured residual factor concentration and is classified as mild, moderate or severe (**Table 2**). This classification often predicts the bleeding risk and the required therapy.[17]

Factors VIII and IX are both initially required for the activation of Factor X in the coagulation cascade that leads to formation of a fibrin clot. The pivotal role played by these 2 factors is underlined by the significant hemorrhagic diathesis caused by deficiency of either protein (**Fig. 1**).

Defects in the Factor VIII gene include deletions and point mutations; intrachromosomal inversion of intron 22 is present in almost 50% of patients with severe hemophilia A. More than 250 missense mutations in the Factor VIII gene have been identified.[18] Defects in the Factor IX gene may also be due to either large deletions or point mutations. Patients with large deletions and absent protein may be at risk of anaphylaxis when treated with Factor IX replacement. Mutations in the Factor VIII or IX genes manifest as hemophilia in males and as the carrier state in females. In carrier females, the levels of Factors VIII and IX vary widely and may sometimes be low enough to result in clinical bleeding problems.

Treatment for hemophilia is by intravenous replacement of Factor VIII or IX using purified plasma-derived concentrates or, preferably, recombinant factor concentrates. The required dose, frequency and duration of therapy depends on the severity of the bleeding episode.[17,18] For surgical procedures, patients receive preoperative doses of factor concentrate to raise plasma concentrations to hemostatic levels. These are then maintained postoperatively by repeated intermittent doses or by continuous infusion.

In mild hemophilia A only, desmopressin can be used to raise levels of Factor VIII to approximately twice baseline, which may result in adequate hemostasis for minor bleeds or procedures.

Inhibitors (allo-antibodies) develop in up to 20% to 30% of patients with hemophilia A and 5% of those with hemophilia B, usually as an immune response to factor replacement therapy. Inhibitors are seen more frequently in patients with severe hemophilia, particularly those with large gene deletions. The risk of inhibitor development is also influenced by inherited differences in the immune response.[19] The presence of inhibitors complicates treatment, as simple factor replacement is often not effective and alternative bypassing agents, such as recombinant Factor VIIa, are used to promote hemostasis. Immune modulation, with continuous exposure to the factor in conjunction with immunosuppressive drugs, is used to induce immune tolerance and reduce inhibitor titres.[17,18]

Table 3 Rare coagulation abnormalities[a]

Deficiency	Prevalence of severe deficiency (× 10^{-6})[b]	Treatment options
Fibrinogen	1	Cryoprecipitate Fibrinogen concentrate
Prothrombin	0.5	Fresh frozen plasma Prothrombin complex concentrate
Factor V	1	Fresh frozen plasma
Factor VII	2	Factor VII concentrate Recombinant Factor VIIa
Factor X	10	Fresh frozen plasma
Factor XI	1	Fresh frozen plasma Factor XI concentrate
Factor XIII	0.5	Factor XIII concentrate Cryoprecipitate or plasma

[a]*Data from Bolton-Maggs,[17] Peyvandi,[20] Di Paolo[21]*
[b]*Factor concentrations < 10%*

Rare Coagulation Factor Deficiencies

Congenital deficiencies in coagulation factors, other than Factor VIII and Factor IX, are very rare. Factor XI deficiency in the Ashkenazi Jewish population has a prevalence of 1 in 1,000; however, the prevalences of fibrinogen, prothrombin and Factors V, VII, X and XIII deficiencies are in the order of only 1 in 0.5–1 million. These disorders are inherited as autosomal recessive traits and manifest clinically in homozygotes or compound heterozygotes.[20] Although, with some exceptions, the bleeding manifestations in these disorders are less severe than hemophilia, patients may require coagulation factor replacement before dental surgery. Specific factor concentrates are available for some deficiencies (e.g., Factor VII); fresh frozen plasma is used as the source for others (e.g., Factor V) (**Table 3**).[20,21]

Acquired Coagulation Abnormalities

Patients on long-term anticoagulation therapy with either warfarin or heparin are at increased risk of bleeding with trauma or surgical procedures. The risk of bleeding is relative to the intensity of anticoagulation. In cases of acute bleeding or in preparation for major surgery, these anticoagulants may need to be discontinued temporarily. However, their role in the treatment or prevention of thromboembolic disease should be carefully considered before interruption of therapy, as the patients may be placed at a significantly increased risk of a thrombotic event.

Warfarin is a vitamin K antagonist, inhibiting the γ-carboxylation of glutamic acid residues on the clotting factor zymogens II, VII, IX and X. The absence of this modification inhibits calcium-dependent binding to anionic phospholipid, which is required for assembly of the coagulation enzyme complexes on cell surfaces (**Fig. 1**).[22] Warfarin's effect is monitored by the international normalized ratio (INR; a standardization of the prothrombin time assay). The therapeutic INR range varies depending on the indication, but is 2.0–3.0 for most patients requiring protection from venous or arterial thromboembolism.[23]

Heparin is a proteoglycan that functions as a cofactor of the naturally occurring anticoagulant antithrombin, accelerating inhibition of the serine proteases of the coagulation cascade, particularly Factors IIa and Xa. Because the half-life of unfractionated heparin (3kD to 30kD) is short (1 hour), therapeutic levels are maintained by intravenous bolus followed by infusion. The therapeutic range is usually monitored by appropriate prolongation of the activated partial thromboplastin time (aPTT). Low molecular weight heparin (LMWH) (5kD) exerts its anticoagulation effects via antithrombin, particularly on Factor Xa with less effect on IIa. It has a longer half-life than unfractionated heparin and, therefore, can be delivered subcutaneously only once or twice a day.[24] Most patients on long-term therapy do not require laboratory monitoring; when monitoring is required, an anti-Xa assay is used, as aPTT is not prolonged.[25]

Platelet Disorders

The large number of platelet-related defects, both inherited and acquired, can be broadly categorized as defects of number (thrombocytopenia) or of function. This classification is somewhat arbitrary as some platelet disorders are characterized by both decreased number and function.

Table 4 Inherited thrombocytopenias

Small platelets	Normal-sized platelets	Large platelets
Wiskott-Aldrich Syndrome X-linked thrombocytopenia	Glanzmann thrombocytopenia Familial platelet disorder associated with a predisposition to myelodysplastic syndromes Congenital amegakaryocytic thrombocytopenia Thrombocytopenia with absent radii Autosomal dominant thrombocytopenia	Bernard Soulier syndrome Velocardiofacial syndrome Mediterranean thrombocytopenia Paris-Trousseau-Jacobsen's syndrome May-Haegglin anomaly Sebastian syndrome Fechtner syndrome Epstein syndrome Gray platelet syndrome Montreal platelet syndrome

Table 5 Acquired thrombocytopenias

	Nonimmune-related	
Immune-related	Impaired production	Destructive
Immune thrombocytopenic purpura Drug-induced thrombocytopenia Neonatal immune thrombocytopenia Post-transfusion purpura	Drug-induced bone marrow depression Viral or bacterial infections Alcoholism Aplastic anemia Myelodyplastic syndromes Leukemia, lymphoma, myeloma Solid tumour infiltrating bone marrow	Disseminated intravascular coagulopathy Thrombotic thrombocytopenic purpura Hemolytic uremic syndrome Heparin-induced thrombocytopenia Splenomegaly, splenic sequestration

Thrombocytopenias

Blood platelet levels normally fall within the broad range of 150–400 × 10^9/L, although for any given person the range is much narrower.[26] These levels are preserved by the fine balance between synthesis of platelets in the bone marrow and their removal by the spleen. Disturbing this balance by reducing production or increasing removal (either by splenic uptake or platelet activation) results in thrombocytopenia, which may be considered mild (100–150 × 10^9/L), moderate (50–100 × 10^9/L) or severe (< 50 × 10^9/L).[26] In general, thrombocytopenias fall into 2 categories: inherited (**Table 4**)[26,27] and acquired (**Table 5**).[26] Inherited thrombocytopenias are rare, are often associated with alterations in platelet size and, in many cases, are considered to be 1 component of a syndrome.[27]

Acquired thrombocytopenias can be classified as those of immune origin and those of nonimmune origin. Of the immune causes, immune thrombocytopenic purpura (ITP) is likely the most common and can occur in association with infection or as part of an auto-immune syndrome. Nonimmune acquired thrombocytopenias are most often secondary to drug toxicity or another underlying disease.[26] In particular, most chemotherapeutic agents can cause thrombocytopenia, and aggressive multi-agent regimens routinely cause myelosuppression, of which thrombocytopenia can be the dose-limiting factor.

Increased bleeding is rarely an issue unless platelet counts are < 50 × 10^9/L. The management will vary depending on the etiology of the thrombocytopenia, but platelet counts can usually be raised transiently to support hemostasis if necessary for surgical procedures. Patients receiving chemotherapy should have platelet counts evaluated immediately before dental procedures to ensure that there has been bone marrow recovery before proceeding.

Adhesion Defects

The primary platelet adhesive receptor is GPIb–V–IX, a complex of 4 proteins: GPIbα, GPIbβ, GPV and GPIX,[6] each the product of an individual gene.[28] Bernard Soulier syndrome (BSS) is an autosomal recessive disorder caused by genetic defects in GPIbα, GPIbβ or GPIX.[29] It is characterized by giant platelets and thrombocytopenia and symptoms include mucosal bleeding, easy bruising and surgical bleeding.[28] Several molecular defects have been associated with BSS, but almost all result in a deficiency in the expression of the mature, functional GPIb–V–IX complex.[28,29]

Table 6 Common drugs affecting platelets

Functional impairment	Thrombocytopenia	
Aspirin	Heparin or analogues	Digoxin
NSAIDs	Chemotherapeutic agents	Diclofenac
Ticlopidine, clopidogrel	Quinidine	Indomethacin
Tricyclic antidepressants	Quinine	Phenylbutazone
Clofibrate	Trimethoprim–sulfamethoxazole	Isoretinoin
Sulphinpyrazone	Methyldopa	Gold
Dipyridamole	Furosemide	Procainamide
Propranolol	Acetaminophen	Hydrochlorothiazide
Histamine H_1 antagonists	Cephalosporins	Ranitidine
Penicillin	Vancomycin	Diphenylhydantoin
Ampicillin	Carbamazapine	
Nitroglycerin	Valproic acid	
	Chlorpropamide	

NSAIDs = nonsteroidal anti-inflammatory drugs

Management of bleeding episodes or preparation for surgery usually requires platelet transfusion, although the use of an activated coagulation factor concentrate, recombinant Factor VIIa, has been useful in some patients.[30]

Aggregation Defects

Glanzmann thrombasthenia (GT) is an autosomal recessive disorder caused by qualitative or quantitative defects in 1 of the proteins in the αIIbβ3 integrin, the complex whose structural reorganization following platelet activation is critical to platelet–platelet interaction and clot formation. Essential diagnostic features are a normal platelet count and morphology, but the absence of platelet aggregation in response to stimulants in vitro.[28] In addition to compromising platelet–platelet interaction, clot retraction is also affected which contributes to delayed wound healing.

The signs of GT occur early in life and include easy bruising, epistaxis and prolonged bleeding from relatively minor injuries. Epistaxis, menorrhagia, post-partum bleeding and surgical bleeding can be life-threatening.[31,32] At a molecular level, GT is an extremely complex, heterogeneous condition with multiple deletions and mutations of the genes encoding the αIIbβ3 integrin.[28,31,32]

Management of bleeding episodes in GT patients usually requires platelet transfusion, the use of recombinant Factor VIIa or both. Ancillary therapies include antifibrinolytics and hormonal therapy, and topical measures may be required for specific local sites (see below).[30,31]

Granule Defects

As outlined above, platelets contain 2 important types of storage granules, alpha granules and dense granules, whose released contents following platelet activation are critical to a competent hemostatic system. Deficiencies in both granule types have been reported and they have significant negative effects on hemostasis.

Gray platelet syndrome is mainly an autosomal recessive condition characterized by large platelets and reduced levels of alpha granules.[29] Patients with this syndrome often have mucocutaneous bleeding and associated mild thrombocytopenia. Quebec platelet disorder is an autosomal dominant condition marked by delayed post-traumatic bleeding and associated with a deficiency of alpha granule contents including Factor V, possibly secondary to absence of a binding protein termed multimerin.[33] Several dense granule deficiencies have been identified. An isolated autosomal dominant form and a variant form, characterized by a dual deficiency of dense and alpha granules, are both associated with prolonged mucocutaneous bleeding, likely due to the absence of secreted ADP.[34]

In several other situations, dense granule deficiency is a single element in a multi-component syndrome, such as Hermansky-Pudlak syndrome and Chediak-Higashi syndrome, autosomal recessive conditions in which the dense granule deficiency is accompanied by a pigment abnormality or albinism.[34] Bleeding associated with milder platelet granule defects often responds to treatment with desmopressin, but cannot be predicted; a trial of desmopressin is warranted to evaluate response in patients for whom this is being considered as prophylaxis for surgery. For nonresponders, platelet transfusion may be required.

Drug-induced Platelet Defects

A variety of prescribed drugs and over-the-counter preparations are known to have significant adverse effects on platelet number and function (**Table 6**). Of drugs affecting platelet number, heparin-induced thrombocytopenia (HIT), which occurs in an estimated 5% to 40% of patients to whom it is administered,[35] is the most common. Of the others, quinidine, gold and the trimetho-

Table 7 Management of patients with coagulation factor deficiencies, who require dental extraction or complex procedures

Bleeding disorder	Pretreatment for extraction or nerve block	Postextraction treatment for all bleeding disorders
vWD, Type 1	Desmopressin, 0.3 μg/kg (maximum dose 20 μg) IV over 20–30 minutes or subcutaneously	Antifibrinolytic agents (e.g., tranexamic acid, 25 mg/kg t.i.d.) for 3–5 days Soft diet for 7 days Within 24 hours, assess need for repeat treatment
vWD, Types 2A and 2M	Desmopressin, as above, if tested response or Humate-P, 50 IU of vWF:RCoF/kg	
vWD, Types 2B and 3	Humate-P, 50 IU of vWF:RCoF/kg	
Hemophilia A (mild)	Desmopressin, as above, if tested response is adequate	
Hemophilia A (moderate or severe)	Recombinant Factor VIII concentrate, 20–25 IU/kg Re-evaluate postprocedure	
Hemophilia B (mild, moderate or severe)	Recombinant Factor IX concentrate, 40–60 IU/kg Re-evaluate postprocedure	

RCoF = ristocetin cofactor; t.i.d. = 3 times daily; VWF = von Willebrand factor

prim–sulphamethoxazole combination are most frequently associated with the development of thrombocytopenia.[36]

A large number of drugs attenuate platelet activity. The most common is aspirin, which acetylates COX, thereby blocking TxA_2 release from activated platelets. As this is an irreversible effect, the activity of the platelet is compromised for the life of the platelet. This accounts both for the prolonged effect (several days) that a single aspirin can have on bleeding and the antithrombotic action of aspirin. Other nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, ketorolac and indomethacin, also inhibit COX, but in contrast to aspirin, the inhibition is reversible and the antiplatelet effects are present only as long as the NSAID is in contact with the platelet. ADP antagonists, such as ticlopidine and clopidogrel, and phosphodiesterase inhibitors, such as dipyridamole, are clinically used antiplatelet agents and may also increase the risk of clinical bleeding. Several over-the-counter preparations, particularly first-generation histamine H_1 antagonists, can also affect platelet function.

Management for Dental Procedures

Systemic Therapies

The choice of appropriate systemic therapy for dental procedures should be made in consultation with the patient's hematologist. Decisions regarding the need for, and type of, coagulation factor replacement will depend on the specific hemostatic diagnosis, the severity of the bleeding diathesis and the type of dental procedure (major or minor). **Table 7** outlines systemic replacement therapy options for vWD and hemophilia.[37] Some patients may require further laboratory testing before dental surgery, such as a trial of desmopressin to confirm adequate response, or screening for inhibitors. The choice of factor replacement for individuals with rare coagulation disorders should be made in consultation with a hematologist familiar with the replacement products and local availability (as some are unlicensed).

Appropriate prophylaxis for platelet disorders will depend on both the specific defect and the nature of the planned dental surgery (**Table 8**). Mild thrombocytopenia or mild functional disorders may require no specific systemic therapy other than the use of local hemostatic measures and antifibrinolytic agents. More severe disorders will require measures that transiently raise the platelet count or improve function. Choice of the appropriate prophylaxis should be made in consultation with the patient's physician.

Use of Antifibrinolytic Agents

Aminocaproic acid and tranexamic acid are synthetic derivatives of the amino acid lysine. They inhibit fibrinolysis by blocking the binding of plasminogen to fibrin and its subsequent activation to plasmin. The oral mucosa is rich in plasminogen activators, and saliva has significant fibrinolytic activity. These agents are useful in preventing clot lysis following oral surgery or dental extraction. They are used as adjuncts to specific systemic therapy that corrects the coagulation factor or platelet abnormality. In

Table 8 Management of patients with platelet disorders, who require dental procedures

Platelet disorder	Preprocedure	Postprocedure
Thrombocytopenia	If platelet count < 50×10^9/L, consider measures that will raise platelet count transiently (therapy depends on etiology)	Antifibrinolytic agents (e.g., tranexamic acid, 25 mg/kg t.i.d.) for 3–5 days Soft diet for 7 days Within 24 hours, assess need for repeat treatment
Glanzmann thrombasthenia Bernard Soulier syndrome	Platelet transfusion or Recombinant Factor VIIa	
Non-specific aggregation abnormalities	Desmopressin, 0.3 μg/kg (maximum dose 20 μg) IV over 20–30 minutes or subcutaneously	
Granule defects	Desmopressin, as above, if tested response to desmopressin or, if necessary, platelet transfusion	

t.i.d. = 3 times daily

hemophilia, for example, they have been shown to reduce both the risk of delayed bleeding and the amount of clotting factor replacement therapy required.[38,39] Oral dosing starts before the surgery and continues for several days after or until the socket is healed (**Table 7**). These agents can also be used locally as a mouthwash and may make it possible to perform dental procedures in patients on oral anticoagulation therapy without reducing or withholding the anticoagulant.[40]

Patients Receiving Antithrombotic Therapy

Most patients on long-term anticoagulation or antiplatelet therapy do not have to discontinue their medication before surgical procedures. Although common practice has been to discontinue warfarin for at least 2 days before procedures, and in high-risk patients replace this with heparin, a series of studies now demonstrates that, with attention to local hemostatic measures, the risk of serious bleeding is minimal and patients may be at greater risk of thromboembolic events if they are not adequately protected.[41–43] In a review of 950 patients receiving anticoagulation therapy, Wahl[44] showed that fewer than 1.3% required other than local measures for management of bleeding. Proceeding with most dental procedures if INR ≤ 3.5 has been recommended, although 1 study suggests that bleeding risk does not correlate with the INR.[42,45]

Patients receiving prophylactic doses of either unfractionated heparin or LMWH should be able to proceed with dental surgery without discontinuing their prophylaxis. Patients receiving therapeutic LMWH may have to forego the dose before dental surgery and restart following the procedure.

There is less information about the risk of antiplatelet drugs, although 1 small study of patients taking 100 mg of aspirin a day showed no increased risk of bleeding following dental extractions compared with control patients.[46] In all studies, attention to good local hemostatic procedures was the most important measure in preventing hemorrhage.

Treatment Considerations

The dental management of people with bleeding disorders must take into consideration not only the nature and severity of the disorder, but also the type, location and extent of the intervention. Management decisions then depend on a fusion of the local and systemic considerations.

The risk of the intervention will depend on the accessibility of the surgical site for local control of hemostasis. For example, simple exodontia usually allows ready access to the potential sites of postoperative hemorrhage for application of local hemostatic measures, such as pressure or topical agents. In contrast, deep spatial or cavity (e.g., sinus) surgery and some flap surgery may afford little or no access to the bleeding sites postoperatively. The more limited the access to these sites, the more important systemic, rather than local, measures to control postoperative hemorrhage become.

Surgical location is also important with regard to possible postoperative sequence of hemorrhage. Specifically, hemorrhage and hematoma formation that may cause airway obstruction must be controlled by systemic measures.

Not only is the nature and location of the surgical procedure important to the potential for local or systemic management of hemorrhage, but injection of local anesthetic also poses various degrees of risk. Nerve-block injections (inferior alveolar and posterior superior alveolar) can cause airway obstruction. The greater risk is presented in the inferior alveolar nerve block situation, although such risks from mandibular blocks can

be reduced by using the Gow-Gates technique. The need for nerve blocks must be considered preoperatively and, if possible, an alternative technique should be employed (e.g., local infiltration, periodontal ligament injection). If these alternatives cannot provide satisfactory pain control, the need for systemic methods of hemostasis must be considered — even for nonsurgical dental procedures.

Local Measures to Limit and Control Hemorrhage

The method of pain control has already been discussed. That is, choosing techniques and injection sites least likely to result in hematoma formation causing airway obstruction. Consideration may be given to alternative or adjunctive means of pain control to limit or avoid injection into vulnerable areas. Examples of this are sedation techniques or even general anesthesia. Hypnosis has been used as an adjunct in pain control in these circumstances.

Surgical techniques may be modified or refined somewhat to minimize both intraoperative and postoperative leeding.

Some suggestions in this regard are:

- minimize trauma (e.g., elective sectioning of difficult extractions, limiting the number of teeth to be removed at a time depending on the severity of the bleeding defect)
- avoid flaps, as they provide a much greater bleeding area that is harder to control with local measures
- choose surgical and closure techniques that permit easy access for packing, suturing, cautery, etc.
- strive to obtain primary surgical closure
- remove all granulation tissue from areas of chronic inflammation.

Depending on the nature and severity of the bleeding disorder, it may be important to consider alternatives to surgery, including treatment decisions that would be unusual under normal circumstances. For example, it might be preferable to perform endodontic treatment on teeth or roots that are not restorable to retain them without symptoms or risk, rather than remove them. In some circumstances, simply opening root canals and leaving them open indefinitely, so that there is no acute infection, may be a reasonable option if surgery is a risk. This technique has been used successfully in circumstances where medical management is not readily available.

Various adjuncts to hemostasis can be employed at the surgical site to enhance hemostasis, aid in vascular closure and prevent clot breakdown.

- Gelfoam (Pfizer, Markham, Ont.) is an absorbable gelatin sponge material that holds many times its weight in blood and provides a stable "scaffold" for clot formation. It is placed in tooth sockets in the form of tapered cones rolled from the sheet material. Gelfoam is absorbed within 4–6 weeks with little or no scar tissue formation. It should not be used under epithelial incisions or flaps because it inhibits healing of the epithelial edges.[47]
- Bleed-X (QAS, Orlando, Fla.) is a hemostatic product containing "microporous polysaccharide hemispheres" (potato starch) that dehydrate blood and accelerate clotting. It can be applied to all types of surgical sites, including tooth sockets. It has been used successfully when Gelfoam cones have been rolled in the dry powder and placed in sockets. There are no known contraindications to its use.[48]
- Tisseel (Baxter, Mississauga, Ont.) is a fibrin sealant that acts both through its adhesive action and by direct contribution of fibrin to clot formation. Tisseel is technique sensitive and requires special preparation just before application. It is expensive and is probably best reserved for particularly complicated or difficult dental situations.[49]
- Cyklokapron (tranexamic acid) (Pfizer) has also been used successfully in the form of a mouthwash after oral surgical procedures to inhibit postoperative bleeding episodes. As outlined above, it is an inhibitor of fibrinolysis that can be administered parenterally. In addition, the intravenous preparation can be diluted to a 4.8% aqueous solution and used as a mouthwash (4 times daily for 7 days). In controlled trials, it markedly decreased postoperative bleeding episodes in patients on anticoagulant therapy.[40]
- Electrocautery is a useful tool to slow intraoperative bleeding and stem postoperative episodes. However, it must be used cautiously to avoid excessive tissue necrosis. Not only will the necrosis delay healing but it may also become a source of postoperative bleeding when the necrotic tissue sloughs.[50]
- Suturing is worthwhile if significant apposition of soft tissue can be achieved or if it retains a pack such as Gelfoam. However, suturing may provide additional traumatic puncture points that contribute to postoperative bleeding episodes and may cause confusion over the nature and source of the hemorrhage.[51]
- Amicar (aminocaproic acid) (Wyeth, Markham, Ont.), a popular antifibrinolytic agent, and Thrombostat (Pfizer), a dry thrombin powder, are no longer available for topical use.

The use of preformed splints to protect and enhance the placement of pressure on sockets is a valuable adjunct in multiple extraction procedures. It is a technique that should be considered for complicated situations where systemic management is required, but is difficult or expensive to deliver. The most popular material is soft, mouthguard type material. The teeth to be extracted are cut from the working model before the splint is fabricated. Great care must be taken to ensure that there are no abrasive or overextended areas on the splint that will traumatize soft tissue. Splints enhance the formation of firm, well-or-

ganized clots and prevent them from being dislodged or traumatized. Splints also shield the clots from saliva and the fibrinolytic substances it contains. They are quick and simple to fabricate. They must be removed and cleaned once a day. After the second day, competent patients may do this themselves. It is recommended that they be worn for 4–7 days.[51]

The most effective — and often underrated — method for achieving hemostasis is pressure. Pressure must be applied at the appropriate location, and gauze should be prewetted to prevent the clot from adhering to it. Patients should be told that the pressure must be maintained for at least 30 minutes, and preferably for an hour, as frequent interruption of pressure will cause bleeding to continue.

Management of Postoperative Hemorrhage

One of the fallacies surrounding patients with bleeding disorders is that they will have uncontrollable hemorrhage. However, when the diagnosis is clear, appropriate precautions are taken and preoperative preparations are carried out, this is highly unlikely. Nevertheless, postoperative bleeding episodes should be anticipated and managed appropriately.[43]

An important aspect of treating any patient with the potential for excessive bleeding is to inform him or her of the risk and describe plans for intervention should excessive bleeding occur. Too often, patients assume that any amount of bleeding is abnormal.[52] They are reassured when they are given a 24-hour a day contact and next-day reassessment is prearranged. The frequency and duration of reassessment is determined by the significance of the bleeding problem and by the extent and nature of the surgery.

Techniques for managing postoperative bleeding episodes are:

- Reapplication of pressure packs. Often patients do not do this properly. The technique must be demonstrated to the patient to ensure that this simple technique is effective. Pressure packs must be kept in place at least 30 minutes without checking them before the need for other intervention is determined.
- Packing or repacking sockets with Gelfoam is usually the second step, with pressure packs replaced over the fresh Gelfoam.[47]
- Reinjection of local anesthetic with epinephrine can help slow hemorrhage and allow vessel constriction, platelet plug formation and stable clot formation. However, after epinephrine rebound, vasodilation can occur, which may lead to significant hemorrhage.
- Any large, exophytic clots should be removed down to the level of the socket as they may provide a pathway for continued bleeding and prevent application of adequate pressure to the site.
- The use of astringents may be considered, especially on incisions and raw areas. The "old tea-bag trick" refers to the practice of using a tea bag as a pressure pack. The tea contains the astringent tannic acid. Commercial preparations containing aluminum chloride produce a similar result.[53]
- Patients should be instructed to limit physical exertion, to sit or sleep in a semi-sitting position and to avoid smoking and alcohol consumption.[54]

Choosing the Best Course

The dentist must be prepared to provide the physician with a clear picture of the treatment proposed and the local measures that the dentist can employ to control hemorrhage. The physician must be made aware of the degree of risk associated with serious sequelae, such as airway compromise.[55] Together, the dentist and physician should choose the least traumatic course of management affording the minimum amount of risk.[44] Then the patient should be carefully informed of the options. The patient must understand what role he or she has and agree to and be able to fulfill those obligations.[56] Finally, the circumstances must be carefully controlled and the procedure carried out in the least traumatic way possible.[53]

A patient may have a diagnosed bleeding disorder, but is not currently being followed by a hematologist. Dentists can obtain expert advice and consultation through bleeding disorders programs across Canada. A list of these programs is available on the Canadian Hemophilia Society website (www.hemophilia.ca).

Postoperatively, monitoring by the dentist and the ability of the patient to contact him or her for help or reassurance are essential. Even patients without bleeding disorders frequently turn up in emergency departments believing they are having a serious problem because they were not well informed and because they cannot contact their dentist. Being prepared to deal with bleeding episodes in a calm, competent manner will result in minimal morbidity for the patient.[51]

Conclusions

In the last decade, studies have shown a remarkable degree of complexity associated with the hemostatic process. Cellular and soluble components act in a highly orchestrated manner to stop blood loss rapidly at the site of injury. Dentists are facing an ever-increasing number of conditions — inherited, acquired and drug-related — associated with abnormal hemostatic function. These raise the possibility of excessive blood loss, poor wound healing and infection. In this review, we have described many of these conditions and discussed both systemic and local management of bleeding. Further information on a variety of bleeding disorders, for both dentists and patients, is available on the Canadian Hemophilia Society website (www.hemophilia.ca).

The dentist must maintain clear and open communication, not only with the patient, but also with his or her

physician or hematologist. This will ensure that the dentist obtains complete and, most important, contemporary information on the severity and control of the patient's condition and advice on management of the patient before and after surgery. The dentist must be prepared to deal with intraoperative hemorrhage, should it occur, in a calm and efficient manner.

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