

Bleeding disorders and periodontology

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Delivery of patient care encompasses a wide range and variety of challenges, one of which is unexpected clinical bleeding. Clinical bleeding can be presented in two forms: the first can occur during surgery; and the second can manifest several days after the procedure. In both situations, the clinician will need to take immediate action to control the hemorrhage and stabilize the patient. The present article will review bleeding disorders and their management. The discussion will address the following issues:

- significance of bleeding disorders in the treatment of periodontal disease.
- prevalence of bleeding disorders.
- basic physiology of hemostasis.
- classification and definition.
- medical diagnosis.
- management of periodontal patients with bleeding disorders.
- current concepts and new approaches in treating periodontal patients with bleeding disorders.

Significance of bleeding disorders in the treatment of periodontal disease

The extent and severity of periodontal disease determines the necessity for a surgical or nonsurgical treatment approach in its management. Both of the above share the common goal of debriding the root surfaces. Periodontal cases can be more complicated and treatment may involve tooth extractions and dental implant surgical procedures in order to restore loss of function (14, 52).

Patients undergoing periodontal treatment may be at increased risk for bleeding. Although the incidence of bleeding disorders is low in the general population, a hemorrhagic episode during or after periodontal procedures can lead to detrimental complications and can place the patient's life at risk (60).

An increasing number of medically compromised patients within the aging population manifest signs of periodontal disease. Illnesses, along with pharmacotherapy, may contribute to the tendency for excessive bleeding. Polypharmacia and medical conditions found in an aging population are the main reasons to reconsider treatment approaches in patients with bleeding disorders and periodontal disease (19).

The dental professional must be aware of the possibility that periodontal patients with no previous indication of bleeding can manifest their first bleeding event in the dental office. A detailed knowledge of intra-operative and postoperative hemostatic measures under challenging hemorrhagic situations is considered a priority for the dental care professional. If a patient has been diagnosed with a hematologic deficiency, the dental care provider needs to consult the patient's hematologist. Thus, the dental care provider can modify the treatment to be provided and may refer the patient out to a multidisciplinary comprehensive care center for further care and investigation (29).

Prevalence of bleeding disorders

Coagulation factor abnormalities are the most common inherited bleeding disorders. However, the overall frequency rate of congenital coagulation disorders in the general population is low, at 10–20 per 100,000 individuals (50).

Von Willebrand disease, Hemophilia A and Hemophilia B account for 95–97% of all coagulation deficiencies (40, 42).

Von Willebrand disease is the most frequently inherited bleeding disorder, affecting 0.8–2% of the general population in Europe and America. However, von Willebrand disease often remains undiagnosed and, as a result, statistical prevalence does not indicate the actual prevalence of the disease (55, 68, 69).

For example, how many people within dental care settings who experience bleeding are actually tested for von Willebrand disease?

Hemophilia A is the most common of the inherited coagulopathies, with a prevalence of up to one per 5,000 male births (70). Hemophilia B occurs in one per 50,000 male births. In the U.S.A., 18,000 people are diagnosed with hemophilia (61). How many of these people have experienced bleeding during dental treatment? Further studies in this area would shed more light on the risks of bleeding and periodontal treatment.

Other coagulation factor deficiencies, such as factor I (fibrinogen), factor II (prothrombin), factor VII (proconvertin), factor X (Stuart-Prower) and factor XI (plasma thromboplastin antecedent), are even more rare (1, 41, 48–50). Literature regarding such deficiencies and periodontal treatment is not substantial.

Currently, more than one million people receive anticoagulation therapy each year in the U.S.A. (38). Furthermore, *ca.* 200,000 people have chronic renal failure, which affects clotting (46). Because of the presence of inherited and acquired bleeding disorders in a population that increasingly undergoes periodontal therapy, it is important to review the basics of hemostasis in order to understand the nature of bleeding disorders in greater detail.

Basic physiology of hemostasis

Hemostasis can be viewed as either primary or secondary (27), or as a four-phase process (58). Primary hemostasis entails platelet plug formation and lasts for 2–3 seconds (27). It is considered to be the pre-

dominant mechanism of blood loss stoppage in capillaries and small-diameter vessels (27).

Secondary hemostasis is associated with fibrin synthesis and its deposition, which surrounds and links the platelet aggregate and provides stabilization of the hemostatic clot (27). Localized formation of the fibrin clot in the injury site restores the blood flow of arteries and veins (27). This stage can take up to several minutes to complete (27). Having briefly outlined primary and secondary hemostasis, we will now address the hemostatic process, which consists of four phases: vascular; platelet; coagulation; and fibrinolytic (58) (Fig. 1).

Vascular phase

The vascular phase starts immediately after the disruption of blood vessels. Vascular smooth muscle cells become readily activated and contract to reduce the vascular lumen and thus maintain vascular integrity (58). As a result, the endothelial cells become closely situated and this inhibits blood loss (58). Also, blood concentrated in the extravascular space exerts pressure, which further contributes to diminished blood loss (58).

Platelet phase

Platelets have an anucleated discoid shape, 2–4 μm in diameter. They are derived from megakaryocytes in the bone marrow. Under normal circumstances, they number 150,000–400,000/ μl and circulate in the periphery of the vascular lumen (53). The platelet phase is characterized by platelet adhesion, activation, secretion and aggregation (53).

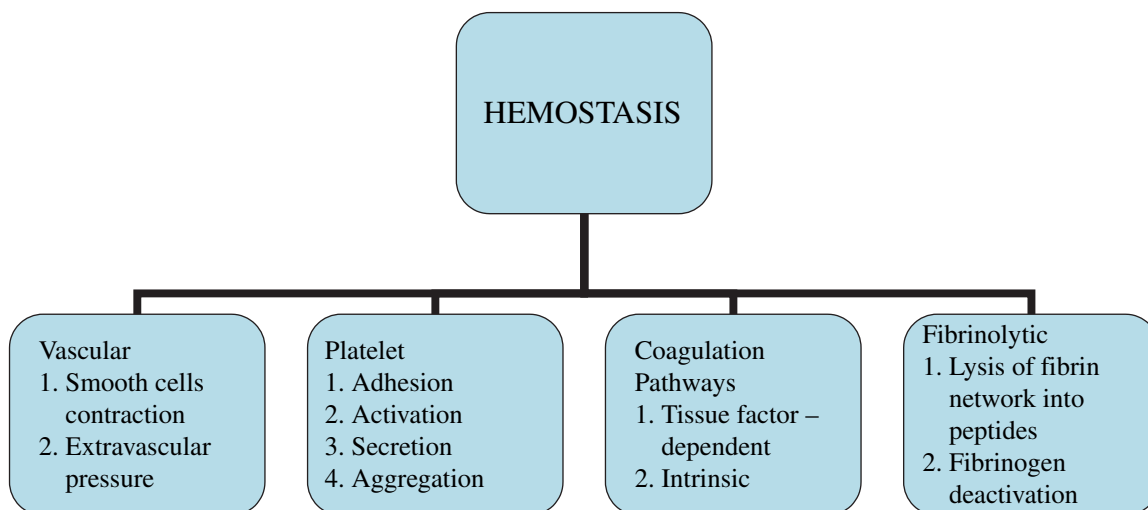


Fig. 1. Hemostasis phases.

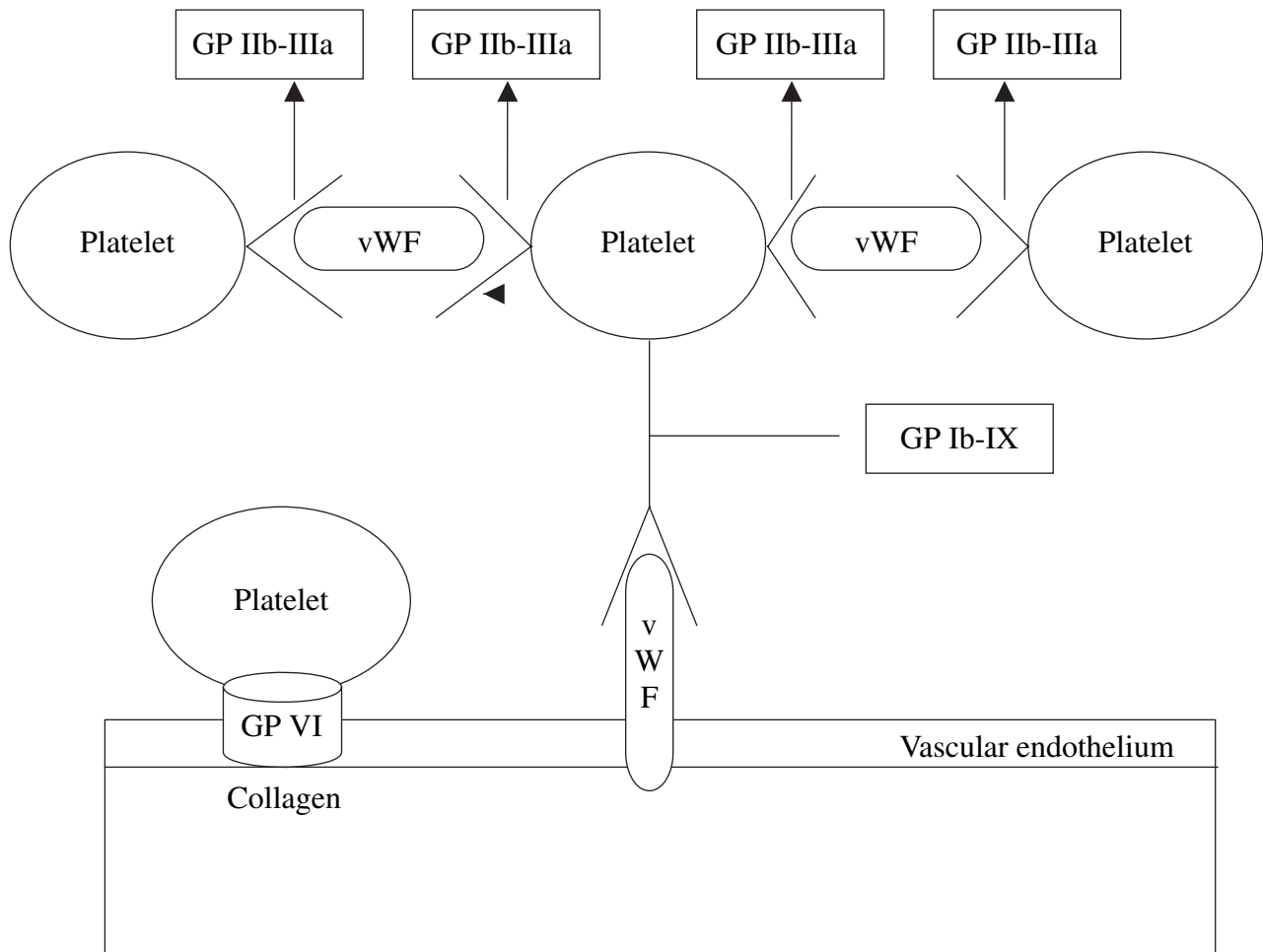


Fig. 2. Platelet adhesion and aggregation. GP, glycoprotein; vWF, von Willebrand factor.

The platelets adhere to the exposed subendothelial connective tissue through glycoprotein receptors located in the platelet membrane (27). Glycoprotein receptors GP Ib-IX-V and GP Ia-IIa, as well as GP VI, play a predominant role in the binding of platelets at the site of injury (27). Von Willebrand factor acts as a bridge between GP Ib-IX-V and underlying collagen (27) (Fig. 2) and, as a result, initiates platelet activation. With this 'bridging', the platelet is able to move towards the direction of blood flow until it binds firmly to the vascular wall through the GP Ia-IIa and GP VI receptors.

The activation of platelets leads to the formation of filopodia and, at this time, the platelet cell is prepared for secretion. The first wave of platelet aggregation ends before platelet granule secretion (58), the next step in the platelet phase.

The second wave begins with the granule release (58). Platelets contain a number of storage granules, including alpha granules and dense granules, as well as glycogen particles, mitochondria and lysosomes

(53). Both categories of granules play an important role in hemostasis. Moreover, the second wave of platelet aggregation is associated with hemostatic plug organization through the binding of GP IIb-IIIa platelet adhesive receptor with fibrinogen (58) (Fig. 2).

Coagulation phase

The third phase of hemostasis, known as coagulation, includes a complex series of proteolytic reactions that occur on the phospholipid membrane of the activated platelets (58). During coagulation, a variety of factors, including enzymes, cofactors and contact factors, contribute to thrombin formation and the important conversion of fibrinogen to fibrin (35).

The traditional way of division of the coagulation system into extrinsic and intrinsic pathways has been underscored, and the new model of coagulation is viewed as two inter-related pathways merging into the common pathway, which entails the formation

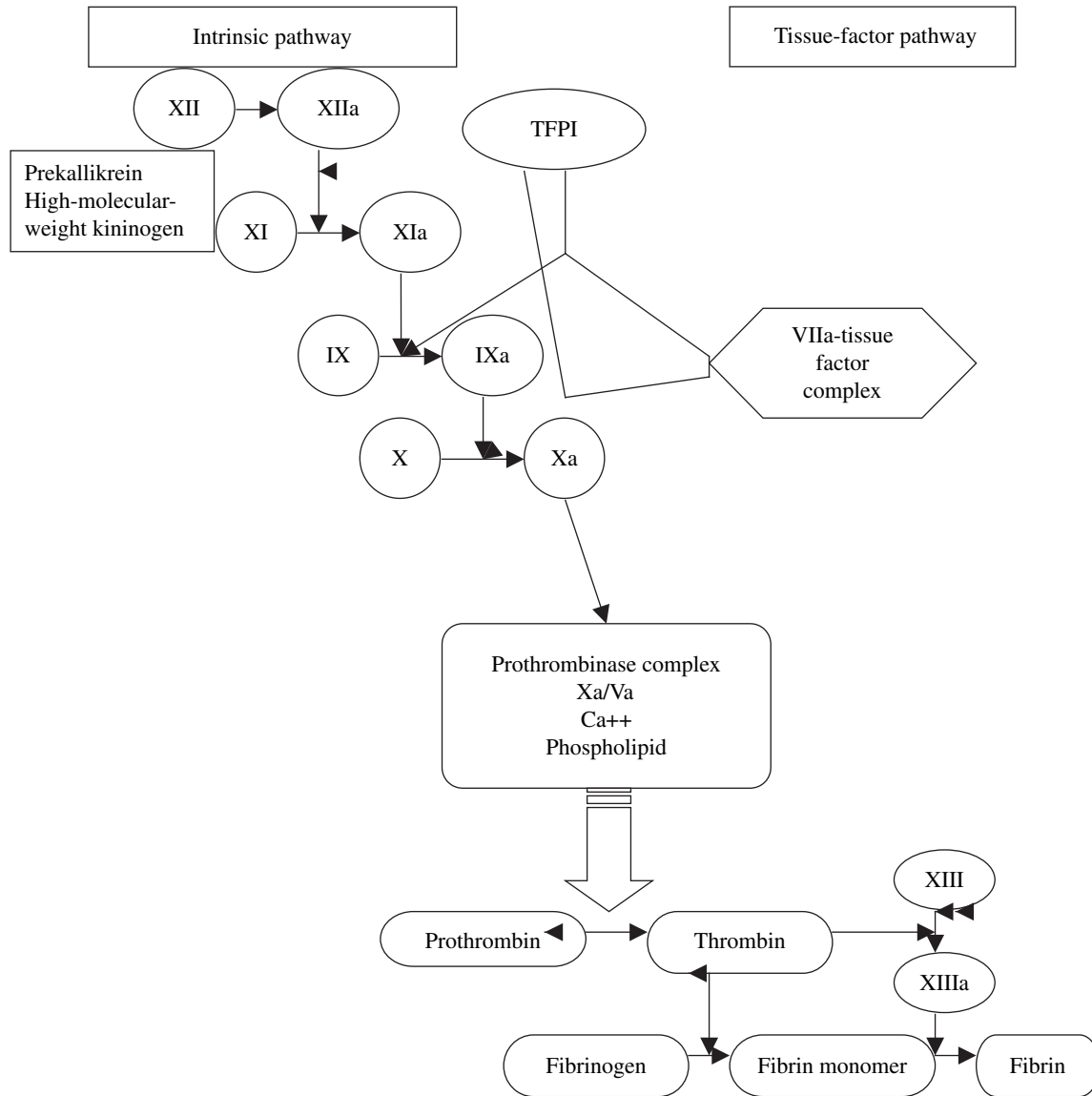


Fig. 3. Coagulation phase. TAFI, thrombin-activatable fibrinolysis inhibitor.

of prothrombinase complex (8). The tissue factor-dependent pathway, also known as the extrinsic pathway, acts rapidly and produces a small quantity of thrombin, triggering the initiation of the intrinsic pathway that is responsible for the main production of thrombin through the prothrombinase complex (7, 58). The prothrombinase complex is composed of activated factor X, activated factor V, phospholipid membrane and calcium ions (58) (Fig. 3).

In the extrinsic (or tissue factor-dependent) pathway, factor VII is activated from the tissue factor and provokes the activation of factor X and formation of the prothrombinase complex. The tissue factor pathway inhibitor regulates the extrinsic pathway, inhibiting the factor VII-tissue factor complex (58) (Fig. 3).

In the intrinsic pathway, the contact factors prekallikrein and high-molecular-weight kininogen and factor XII form a complex that activates factor IX and XI, resulting in the formation of prothrombinase complex (27) (Fig. 3).

Thrombin is associated with acceleration of the clotting process through the activation of factors V, VII, VIII, XI and XIII, as well as through platelet aggregation, in addition to its role in fibrin formation (Fig. 4).

The platelet clot is transformed to the fibrin clot under the influence of the activated fibrin stabilization factor XIII, which crosslinks the fibrin monomers (27) (Fig. 3).

In addition, thrombin stimulates the thrombin-activatable fibrinolysis inhibitor to protect the fibrin clot from premature dissolution (8).

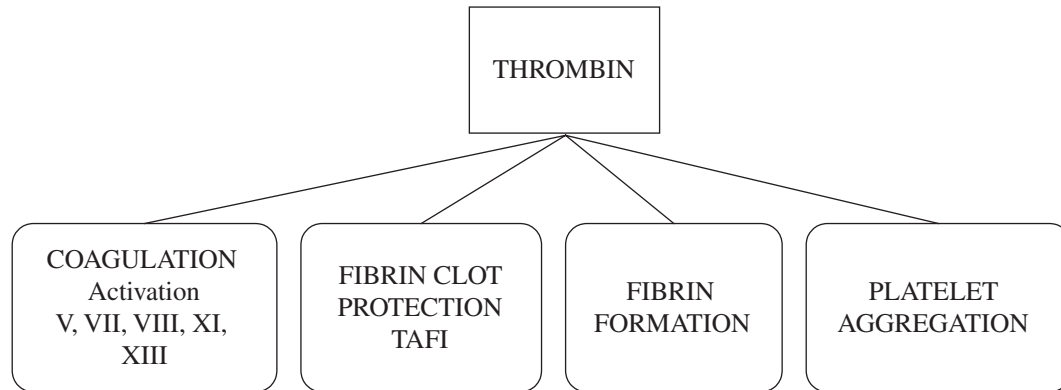


Fig. 4. Thrombin functions. TAFI, thrombin-activatable fibrinolysis inhibitor.

Fibrinolytic phase

Fibrinolysis is the last stage of hemostasis and initiates disintegration of the hemostatic plug and the tissue repair process. Two plasminogen activators – tissue plasminogen activator and urinary plasminogen activator – have the task of transforming plasminogen to plasmin, which breaks down the fibrin network to fibrin peptides and, to a lesser extent, deactivates fibrinogen (58). The fibrinolytic action is limited at the site of the hemostatic clot and is regulated by specific plasminogen activator inhibitors and by α -2-antiplasmin that acts directly on plasmin (8) (Fig. 5).

Classification and definition

Bleeding disorders are hematological conditions characterized by a functional impairment in the hemostatic process.

The bleeding disorders are classified in two broad categories: inherited or hereditary; and acquired.

We will highlight the most common hematologic disorders in relation to each of the hemostatic phases.

Inherited bleeding disorders

Vascular disorders

Hereditary vascular defects are associated with syndromes and are characterized by blood vessel developmental abnormalities. Hereditary hemorrhagic telangiectasia, or Osler–Weber–Rendu syndrome and Ehlers–Danlos syndrome, are classic examples that manifest bleeding diathesis because of malformed blood vessels and defects in the subendothelial and perivascular connective tissue respectively (27, 58).

Platelet disorders

Platelet disorders are classified into quantitative and qualitative disorders. An example of a quantitative disorder is congenital thrombocytopenia, which is characterized by a low number of platelets, specifically if the platelet count is $<150,000/\mu\text{l}$ (30).

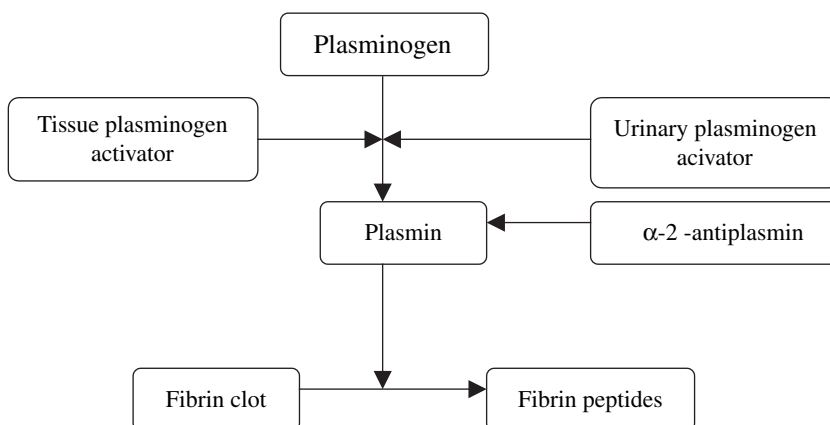


Fig. 5. Fibrinolytic phase.

On the other hand, qualitative platelet disorders are divided into platelet receptor and platelet secretion defects (8). The platelet receptor defects include a number of syndromes, such as Bernard–Soulier syndrome and Glanzmann’s thrombasthenia (53, 54). Platelet secretion defects, known as storage pool defects, can be caused by absent or deficient granules. These disorders are the most common of the congenital platelet disorders, which include Gray platelet syndrome, dense granule deficiency and Wiscott–Aldrich syndrome (8, 53).

Coagulation disorders

Von Willebrand disease is described as a qualitative or quantitative deficiency of von Willebrand factor, leading to a hematologic disorder (28). The von Willebrand factor is composed of a series of plasma protein multimers originally presented in the form of a propeptide in the endothelial and megakaryocyte cells (68). The von Willebrand factor acts as a connecting link between the injured subendothelial collagen and the platelet receptor GP Ib, providing an aggregate of platelets at the bleeding site (39). The subsequent binding reinforcement provided by the large multimers enhances the formation of fibrin and the conversion to a stable hemostatic clot. von Willebrand factor binds, in a complimentary manner, to coagulation factor VIII and makes it more resistant to the degradation process (16).

Sadler (56) classified von Willebrand disease into three types. Types I and III are associated with partial and total deficiency of von Willebrand factor, respectively. Type II represents a qualitative disorder. All the forms are inherited in an autosomal-dominant manner, except for subtype IIN, which has an autosomal-recessive pattern (20).

Hemophilia A is defined as a recessive X chromosome-linked coagulation factor VIII disorder (9). Carrier mothers transmit the hemophilia gene to sons. Hemophilia A, known also as classic hemophilia, accounts for 80–85% of all hemophilia and is grouped into three types, according to the level and activity of coagulation factor VIII (14). In the severe form, coagulation factor activity is <1%, compared with the normal and moderate ranges (1–5%) and the mild range (5–49%) (15).

Hemophilia B, or Christmas disease, is 10 times less frequent than hemophilia A and is inherited in the same manner (15). The deficiency in factor IX may have different pathogenic mechanisms, characterized by inefficient activation, insufficient binding and decreased half life of factor IX (15). Other coa-

gulopathies have been reported in the literature, with very low incidence rates (8, 41, 50).

Fibrinolytic disorders

There have been few cases published in which a plasminogen activator deficiency has been detected, as well as α -2-antiplasmin deficiency, leading to hemorrhagic episodes (8). The limited number of specialized laboratory centers, and the inability of current tests to identify these abnormalities, have contributed to the underdiagnosis of congenital fibrinolytic disorders (8).

Acquired bleeding disorders

Vascular disorders

Acquired vascular defects are associated with diseases affecting the epithelium and connective tissue of blood vessels. Scurvy (as a vitamin C deficiency) affects the formation of connective tissue and thus the perivascular connective tissue network. The weakened capillaries are prone to hemorrhage and create a series of challenging bleeding episodes (27, 58).

Platelet disorders

Acquired platelet disorders can be categorized as quantitative and qualitative disorders (30).

A number of conditions lead to acquired thrombocytopenia, including decreased platelet production, increased platelet destruction, and increased sequestration. The disease entities associated with decreased platelet production involve primarily anemia, leukemia and medication-induced infection. In regard to platelet destruction, the cause can be immunologic or nonimmunologic in nature, such as immune thrombocytopenic and nonimmune thrombocytopenic purpura. Moreover, hypersplenism, as a secondary feature of portal hypertension and splenic neoplastic conditions, can remove a large portion of platelets from plasma (30).

Furthermore, acquired qualitative platelet disorders are present in chronic renal failure. A defect in platelet receptor glycoprotein IIb–IIIa, and the associated hyperviscosity of this disease, contribute to the impairment of platelet function (38).

Coagulation disorders

Patients with hepatic failure as a result of hepatitis B and C, cirrhosis or alcohol abuse, present decreased synthesis of coagulation factors (38, 47).

Patients on long-term anticoagulation therapy develop acquired coagulopathies (37). The orally

administered anticoagulant, coumarin (36, 59), intravenously administered unfractionated heparin (36, 59), and subcutaneously administered low-molecular-weight heparin (33), are commonly used medications that inhibit the coagulation system and are of particular importance to periodontal patients. Specifically, coumarin interferes with the vitamin K-dependent factors II, VII, IX, and X. Meanwhile, fractionated and unfractionated heparin enhances the action of antithrombin III, resulting in the deactivation of activated prothrombin and activated factors IX, X, XI, and plasmin. Moreover, and to a lesser degree, it inhibits the transformation of fibrinogen to fibrin (33).

Patients taking aspirin or aspirin-containing compounds are candidates for excessive bleeding. Aspirin affects the transition of arachidonic acid to thromboxane A by blocking the enzyme cyclooxygenase. The enzymatic inhibition is irreversible and interferes with the homeostatic ability of existing circulating platelets. The duration of its effect is equal to the life span of platelets: *c.* 7–10 days (17, 36, 59).

Other antiplatelet medications, administered as a part of anticoagulation therapy, are ADP receptor inhibitors and fibrinogen receptor (GP IIb–IIIa) inhibitors. ADP receptor inhibitors, such as clopidogrel bisulfate and ticlopidine hydrochloride, and GP IIb–IIIa inhibitors, such as tirofiban, abciximab and eptifibatide, result in the irreversible inhibition of platelet aggregation (17, 36, 59). Dipyridamole inhibits reversibly the phosphodiesterase enzyme, which reduces cAMP. cAMP inhibits platelet activation and aggregation. The duration of the antiplatelet effect is estimated to be up to 24 hours.

Nonsteroidal anti-inflammatory medications act reversibly on the cyclooxygenase enzyme, which interferes with platelet hemostatic function. Hemostatic dysfunction is limited to the presence of the medication in the circulation (59). Patients with malabsorption syndromes placed on long-term antibiotic therapy, and others lacking vitamin K, may manifest coagulation disorders because of synthetic impairment of vitamin K-dependent factors (38).

Fibrinolytic disorders

Liver disease can reduce the metabolism of certain fibrinolytic activators, thus impacting the fibrinolytic stage and subsequently dissolution of the hemostatic plug. On the other hand, certain medications, such as streptokinase, administered to destroy the formed clot in thromboembolic disorders, create the potential for fibrinolysis. Prostate carcinoma cases are also associated with increased plasmin levels and fibrinolysis (43, 47).

Medical diagnosis and bleeding

Medical diagnosis of a patient with a bleeding disorder is based on the medical history, physical examination and laboratory evaluation. Taking a patient's medical history is of paramount importance in determining the nature of hemorrhagic disease, whether inherited or acquired. Physical examination, revealing multiple and small-in-size mucocutaneous hemorrhagic lesions in the form of petechiae and ecchymoses, is indicative of vascular or platelet disorders. Moreover, superficial cuts, with persistent and often profuse bleeding, may indicate the presence of a vascular or a platelet bleeding disorder (53).

The characteristics of severe inherited coagulation bleeding disorders include enlarged, solitary, or deep dissecting hematomas, as well as haemarthrosis, intramuscular and intracranial hemorrhage (53). Laboratory evaluation contributes adjunctively in establishing the diagnosis. Screening tests for bleeding disorders include partial thromboplastin time, prothrombin time and platelet count. Partial thromboplastin time evaluates the intrinsic and common pathways, with normal values ranging from 25 to 35 seconds, depending on the laboratory, and always require a control sample. Prothrombin time evaluates the extrinsic and common pathways, and averages between 11 and 15 seconds, based on the laboratory. Running a control sample is mandatory. The platelet count depicts the number of platelets in the circulation, with the normal range being 150,000–400,000/ μ l. Other specialized tests can be performed by the hematologist to identify specific defects causing the bleeding disorder (47, 57).

Management of periodontal patients with bleeding disorders

Pre-operative precautions

Pre-operative management of patients starts with a medical history focusing on the previous bleeding history of the patient and medical conditions associated with bleeding.

A detailed medical history must include the following.

- Previous hemorrhagic episodes after trauma or surgery, or even spontaneous bleeding.
- Family history regarding hereditary bleeding disorders.

- Current illnesses, such as hepatic and renal failure, and a list of medications interfering with hemostasis, such as nonsteroidal anti-inflammatory drugs and antibiotics.
- Anticoagulation medications, such as coumarin, heparin, aspirin, clopidogrel, and ticlodipine.

Patients with a family history of bleeding or past hemorrhagic episodes should be encouraged to seek medical advice to find the cause of bleeding. Consultation with the primary care physician and a hematologist is deemed necessary, and proper recommendations will be proposed by the medical health providers concerning the dental management of these patients. The nature and severity of an acquired bleeding disorder, and the degree of invasive dental procedures, determine the need for treatment to be provided in a specialized treatment center setting. In such cases, the hematologist will suggest the proper pharmacological regimen to be administered prophylactically in order to achieve hemostasis (43).

Patients presenting with certain illnesses, such as hepatic failure or renal failure, or those taking anticoagulant medications, aspirin, antiplatelet medications and/or nonsteroidal anti-inflammatory drugs, are prone to bleeding during delivery of dental treatment. The treatment protocol may have to be modified to minimize the risk of intra-operative and postoperative bleeding. First, patients diagnosed with chronic renal failure should be managed the day after dialysis when heparin has been cleared from the system and the patient regains his/her strength after the dialysis process (71). Second, patients lacking vitamin K, because of malabsorption syndrome, should receive vitamin K supplement before the dental appointment to restore liver function and the synthesis of coagulation factors. If the patient has liver failure, the dental management of the patient should involve platelet transfusion in a hospital setting (38). Third, the management of patients on anticoagulant therapy has been controversial. Anticoagulant treatment is indicated in the following medical conditions: deep-vein thrombosis, pulmonary embolism, atrial fibrillation, mechanical prosthetic heart valve, valvular heart disease, cerebrovascular accident, transient ischemic attacks, and myocardial infarction (4, 36, 37). Anticoagulant medications reduce the risk of embolism and increase the probability of bleeding during and after the dental procedure. There is considerable evidence supporting the safety of dental procedures performed on anticoagulated patients (31). There are a number of case reports concerning serious thromboembolic events developing after the interruption of

anticoagulation treatment (65, 67). In some instances, the likelihood of a thromboembolic episode in patients who discontinued taking the anticoagulant medications is three times higher than that of a bleeding event in patients who remained on the anticoagulant regimen (66). Detailed risk assessment has to be performed on each patient, and the possibility of life-threatening situations has to be taken into serious consideration before the dental practitioner suggests discontinuation of anticoagulation therapy. Pre-operative care of patients on anticoagulant therapy with coumarin involves the continuation, reduction or withdrawal of the medication (10, 31, 36, 59). The decision should be based on the international normalized ratio value, the invasiveness and extent of dental procedure, current illnesses and medications (59). The international normalized ratio is a key component in the dental treatment of these patients. When the international normalized ratio is ≤ 3.5 , periodontal surgical procedures can be carried out on these patients in a dental office (36, 37, 59). When the international normalized ratio is > 3.5 , the anticoagulation regimen has to be adjusted. The dental care provider should consult with the medical care provider and describe, in detail, the periodontal procedure and risk for bleeding (66, 67). The dental professional may decide if modification of the anticoagulant regimen will place the patient at risk for a thromboembolic event (65). A safe approach entails reduction of the coumarin dose 2–3 days before the procedure and repetition of international normalized ratio testing the morning of the procedure to ensure that the value is < 4 (36, 37, 59). The international normalized ratio can also be measured at home using a portable device (36, 43, 59). International normalized ratio therapeutic levels for most medical conditions range between 2.5 and 3.5 (4). International normalized ratio values may be increased because of the use of medications enhancing the effect of coumarin, a diet rich in vitamin K and/or compliance reasons (59). International normalized ratio values can be normalized to 3.5 by making minor adjustments involving the reduction, but not the discontinuation, of coumarin. Entire withdrawal of coumarin is not recommended because of the rebound thrombotic effect noticed especially in patients with prosthetic cardiac valves when coumarin intake reinitiated (59, 65, 66). It takes up to 4 days for the international normalized ratio values to return to normal (59). Therefore, reducing the international normalized ratio value may increase the risk for thrombosis in patients with other concomitant illnesses such as liver and renal disease, and patients

with increased alcohol consumption (59). Extensive and invasive periodontal surgical procedures in such patients should be performed in a hospital setting, and intravenous unfractionated heparin should be given as a substitute for coumarin (59). Unfractionated heparin can be interrupted 4–6 hours before the surgical procedure, thus substantially minimizing the time the patient is under a suboptimal level of anticoagulation and subsequently reducing the risk for a thromboembolic event (31). Anticoagulation treatment is resumed 12–18 hours after the dental procedure (31). Fractionated or low-molecular-weight heparin may provide an alternative substitute for coumarin, without the need for the patient to be admitted to hospital (33, 36). Subcutaneous administration of low-molecular-weight heparin provides the benefit of conveniently adjusting the anticoagulation regimen at the point of care (33, 36).

Patients taking aspirin should discontinue the medication at least 3 days, and up to 7 days, before the surgical procedure (17, 36, 37, 59). However, consultation with the physician is mandatory. In regard to other anti-platelet medications, such as ADP inhibitors and GP IIb–IIIa inhibitors, discontinuation of the medication 7 days before the procedure gives adequate time for the level of circulating functional platelets to be restored (17, 59). Patients taking other antiplatelet medications, such as dipyridamole or nonsteroidal anti-inflammatory drugs, and presenting a bleeding potential, should consult their physician. The physician should recommend the proper regimen according to the half life of the administered medication. In most cases, three half lives of this medication provide sufficient time for the medication to be removed from the circulation (17, 59).

In addition, the care of patients with bleeding disorders must be placed into new perspective. Preventive dental care for patients with known bleeding disorders has to be intensive and should include regular dental visits, frequent professional tooth cleanings, oral hygiene reinforcement, fluoride supplements and mouthrinses, a low-sugar diet and annual radiographic examination. Continued efforts to prevent dental diseases, and arresting dental diseases at the initial stage, eliminate the need for invasive dental procedures and reduce the risk of associated prolonged bleeding (7).

Patients with diagnosed congenital bleeding disorders should consult their hematologist before any treatment is rendered. Dental management protocols proposed for these patients are individualized and based on a very specific design plan by the dental care professional and the hematologist. Key compo-

nents taken into consideration are the severity of the bleeding disorder and the type of dental procedure and associated potential for bleeding. To minimize the risk to the patient, a dental care professional must be familiar with the pathology of inherited bleeding disorders, and recommended dental procedures to be performed on a high-risk patient should be carried out in a facility in which all necessary equipment and biological products are available (7, 32).

Intra-operative actions

Intra-operative measures include a number of systemic and local measures administered prior to, or during, the procedure to prevent unlikely bleeding diathesis. Patients with inherited bleeding disorders require specific systemic hematologic coverage in order for the dental professional to provide the necessary dental care (23, 24). Every case is unique, and the severity of the bleeding disorder determines the need for systemic prophylactic coverage in conjunction with the local hemostatic measures (23). The hemostatic deficiency in these patients can be corrected by systemic and local measures (22). Thus, coverage should be determined after consultation with a hematologist. Inherited platelet disorders, leading to bleeding or increased risk for bleeding, are managed systemically with platelet transfusions (30). Patients with moderate and severe thrombocytopenia, in which the platelet counts range from 50,000 to 100,000/ μl and from 25,000 to 50,000/ μl , respectively, are candidates for extensive and prolonged bleeding and definitely require platelet transfusion (30). However, minor surgery, involving soft tissues, can be performed with platelet counts as low as 30,000/ μl (30). Moreover, inherited coagulopathies are managed systemically with replacement of coagulation factors (9). Intravenous infusion of deficient, or missing, coagulation factor starts 1 hour before the procedure in order to achieve a level that is 30% above the normal plasma concentration of this particular factor (22). The level has to be higher and to reach 50% of the normal amount when regional block anesthesia is administered (22). Proper treatment planning addresses the half life of coagulation factors, and treatment sessions are programmed accordingly. For instance, factor VIII has a half life of 10–12 hours, and prophylactic coverage with factor VIII is sufficient for dental treatment performed in only one appointment (24, 25, 32, 44). In mild and moderate inherited coagulopathies, desmopressin or 1-desamino-8-D arginine vasopressin can be useful. Desmopressin induces the release of factor VIII/von

Willebrand Factor from platelets and endothelial cells. Prior testing is required to determine the degree of response to 1-desamino-8-D arginine vasopressin (13, 21, 44, 51).

Management of patients with acquired bleeding disorders is focused mainly on local hemostatic measures that apply also to inherited bleeding disorders. Professional cleaning, and scaling and root planing, can be safely performed with the use of local antifibrinolytic mouthwash, such as tranexamic acid or epsilon aminocaproic acid (34). Intra-operative local measures for periodontal surgical procedures are very effective and control the bleeding tendency in these patients. The type of periodontal surgical procedure and potential for bleeding are important aspects that must be taken into consideration. Regional block anesthesia must be avoided. Local infiltration anesthesia with the use of vasoconstrictive agent is desirable. Lidocaine 2% with 1:100,000 epinephrine is adequate. Articaine 4% with 1:100,000 epinephrine provides sufficient anesthesia for surgery in the mandible. Another way to prevent excessive bleeding is the meticulous handling of soft tissues. Creating a conservative flap design and minimizing flap elevation are key points. For surgical extractions, tooth sectioning is helpful for preserving bone and minimizing the involvement of anatomic spaces around the surgical site. Mandibular molars should be approached with a buccal flap and no reflection of a lingual flap. To prevent secondary infection and postoperative bleeding, there should be thorough curettage of the extraction sockets and removal of all granulation tissue. Extraction sockets of periodontally involved teeth appear to have more potential for bleeding after a procedure because of the increased local infection in the area. In periodontal surgery, primary closure of the flap is accomplished with nonresorbable or resorbable sutures. Application of pressure for 10 minutes with moistened gauze on the flap has been suggested (59).

There are a number of commercially available local hemostatic agents that enhance clot stabilization (36). These include: absorbable gelatin (5, 21); absorbable collagen (36); microfibrillar collagen (36) and collagen dressings (36); oxidized regenerated cellulose (26), thrombin (36), tranexamic acid (11, 12, 62) and epsilon-aminocaproic acid (45); fibrin glue (6, 12, 17, 18, 26, 63); and platelet-rich plasma (64). Collagen, gelatin and cellulose products provide the scaffold for platelets to adhere to one another and form the platelet plug. Thrombin converts fibrinogen to fibrin and this contributes to the formation of the fibrin clot. Tranexamic acid, along with epsilon

aminocaproic acid, inhibits plasminogen action and reduces the fibrinolytic activity of the early formed hemostatic clot. Fibrin glue consists of thrombin, fibrinogen, fibronectin and aprotinin. Fibronectin acts as a binding protein for the blood clot, and aprotinin delays the degradation of the hemostatic clot. Platelet-rich plasma contains growth factors released by the platelets that accelerate the healing process and thus enhance hemostasis.

Dental extractions and associated bleeding are effectively managed with the insertion of a sponge into the site (5). The sponge can be presoaked with an antifibrinolytic agent, such as tranexamic acid or epsilon aminocaproic acid. An absorbable gelatin sponge should only be used in conjunction with thrombin for this purpose (36). Fabrication of a surgical splint for additional pressure and protection of the site is recommended (2, 63). Another material that has been used in the past to seal the extraction site is cyanoacrylate (3).

At the end of surgery, patients susceptible to bleeding are instructed to bite on a moistened gauze, or gauze soaked with the hemostatic agent, for 30 minutes. After 30 minutes, the gauze is removed and the surgical area is observed for oozing. If bleeding occurs, additional measures are initiated. The surgical area is re-entered and the bleeding source is identified. Electrocautery and laser are used to control bleeding in the soft tissues. When oozing arises from hard tissues, bone burnishing and bone wax are the treatments of choice. Once the bleeding is under control, the patient may leave the site, but not without biting on a gauze moistened with saline, a teabag or gauze soaked in tranexamic acid (59).

Postoperative measures

Postoperative management is crucial for preventing bleeding. General recommendations emphasize the importance of good care of the surgical area. Rinsing is prohibited on the day of surgery and the healing site must be left undisturbed. Specific attention should be given to tongue movements interfering with healing and food intake. Liquids and a high-protein diet are strongly recommended. The use of antifibrinolytic mouthwash is highly recommended the day after periodontal treatment. The regimen may comprise rinsing with 10 ml of 4.8–5% tranexamic acid solution, four times a day, for 2 minutes (22). The rinsing can be carried out over a period of 2–5 days and may be extended up to 8 days (22). The dental professional should exercise caution in prescribing antibiotics and pain medications. Antibiotics, such as penicillin,

erythromycin, tetracycline, metronidazole, cephalosporins, ampicillin and amoxicillin + clavulanic acid, potentiate the coumarin action (31, 37, 59). Acetaminophen can also interact with coumarin and its use must be limited to fewer than six tablets per week (59). Clindamycin should be the antibiotic of choice in these patients, and a lower dose of acetaminophen for a short period of time is the regimen recommended for postoperative pain control (59). When other medications are administered that affect coumarin bioavailability or metabolism, supplemental international normalized ratio tests are performed to evaluate the anticoagulation effect (37).

Current concepts and new approaches

Current concepts emphasize that the management of patients with bleeding disorders can be carried out safely in a dental office. Specific criteria must be met. Dental professionals must be aware of the possible development of bleeding complications and, as such, management protocols should be implemented. Communication and close co-operation with the medical care professional and, particularly, with the hematologist, is essential. The dental care provider should give a detailed description of the dental procedure in order for the medical care professional to obtain a good understanding of the planned procedures and provide proper medical advice (67).

Minor and moderate invasive procedures can be safely performed, even with an international normalized ratio of 3.5, assuming that local hemostatic measures are implemented (4). Low-molecular-weight heparin may be viewed as a less expensive and easier alternative for managing patients on anticoagulation therapy who require alteration of the anticoagulation regimen (33). Antifibrinolytic mouthwashes after scaling and root planing, localized pressure applied to surgical flaps, and a collagen sponge placed into extraction sockets, can be the sole treatment in single coagulopathies (37). Taking a detailed medical history, following the principles of hemostasis and exercising rational clinical judgment, contribute to the effective dental treatment of patients with bleeding disorders.

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