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Clinical Pharmacology of Patients with Bleeding Disorders

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Abstract

Bleeding disorders can be developed by the use of anticoagulants, inherited genetic abnormalities, or illnesses such liver disease, autoimmune illness and chronic renal disease. Hemostasis is dependent on interactions between the vascular vessel wall, active platelets, and clotting factors upon blood vessel injury. In one of these stages, bleeding disorders are the result of any obvious deficiency. The amount of severity of bleeding episodes can vary depending on vascular wall flaws, platelet problems, or clotting factor deficiencies Patients. The purpose of this article is to educate dental professionals on how to treat patients with inherited bleeding disorders.

Keywords: dental management, bleeding disorders, oral care

Introduction

When a patient presents with a bleeding disorder, how should dental providers proceed to manage the complexity of the case? Management of such medically-complex patients involves ―an understanding of basic physiology of hemostasis,‖ which can greatly enhance one's comprehension of most bleeding and clotting disorders. In addition to this composite of knowledge, clinical application of recent evidence-based recommendations can contribute to the management of these patients who may potentially require specialized medical and/or dental care**.[1-4]**

The physiological mechanism that prevents and hinders bleeding at the area of an injury while preserving regular blood flow everywhere else in the circulation is called hemostasis [**5,6**]. The hemostasis process has two major components. Primary hemostasis initiates promptly after vascular injury, and it can be divided into four consecutive and superposed stages: (A) vasoconstriction, (B) platelet adhesion, (C) platelet activation, and (D) platelet aggregation **[7–10].** Primary hemostasis results in the formation of a platelet plug **[10].** Secondary hemostasis comprises a sequence of serine protease zymogens and their cofactors, which interact successively on phospholipid surfaces (damaged endothelial cells or platelets), leading to the development of covalently cross-linked fibrin **[10–12].** This cross-linked fibrin mesh is then incorporated into and around the platelet plug. It strengthens and stabilizes the blood clot. These two processes are intertwined and occur at the same time **[6].** These systems are regulated by multiple anticoagulant mechanisms, which are responsible for maintaining blood fluidity in the absence of injury, generating a clot that is consistent with the trauma.

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Hemostasis and the avoidance of bleeding or thrombosis are directly related to the adequate balance between procoagulant and anticoagulant systems. **[6].**

The dental care of individuals receiving therapeutic anticoagulation becomes critical when invasive procedures are needed. At this time, the clinician must decide either to maintain the anticoagulation therapy and risk bleeding complications or withdraw the anticoagulation medication and risk developing systemic thrombosis **[1].** After decades of controversial data, there is currently a nearly unanimous consensus that anticoagulation therapy, for most dental surgeries, should not be discontinued. The higher risk of bleeding complications is compensated by the elevated risk of developing thromboembolic complications.**[1-7].**

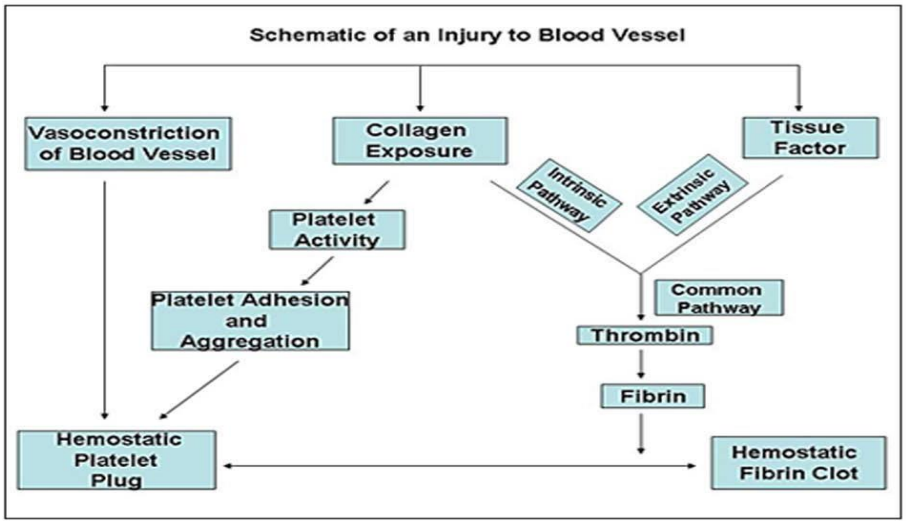

Fig. 1. Schematic of an Injury to Blood Vessel,

Vascular phase : Immediately, when blood vessels are injured, vasoconstriction of the arteries and veins begins. Within the injured vessel wall, exposure of subendothelial tissues, collagen, and basement membrane contribute to prothrombotic activites. Clotting activities include platelet aggregation and adhesion via release of adenosine diphosphate (ADP) and von Willebrand factor (vWF). **[6]**

Additionally, the release of a tissue factor (formerly known as tissue thromboplastin) during this phase initiates coagulation via the extrinsic pathway. At this point, the initial layer of the platelet plug is established at the site of the injury. **[7]**

Platelet phase ; —Platelets are cellular fragments from the cytoplasm of megakaryocytes‖ that survive in the vascular system for 8–12 days. They are essential for the clotting process in the blood. Primary hemostatic functions of platelets include: maintaining the health of the inner lining of the vascular wall; formation of a platelet plug during vessel wall injury; and initiation of the coagulation phase, which leads to the stabilization of the platelet plug. **[1-6]**

During the platelet phase, platelets become sticky and adhere to one another and to the site of injury after contact with exposed collagen and subendothelial tissue component vWF

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glycoprotein Ib. Additionally, Adenosine Di-phosphate (ADP) is released by exposed subendothelial tissues that cause platelets to aggregate, change shape, release dense and a-granule contents and synthesize thromboxane A2 that can further act as a feedback activator potentiating platelet responses by binding to thromboxane receptor (TP). A product of platelets, thromboxane, causes another surge of platelet aggregation. **[6-12]**

In summary, platelets adhere to the damaged subepithelial surface, change shape, become sticky, and aggregate to form a hemostatic platelet plug at the injured blood vessel site. Under these normal conditions, adequate numbers and function of platelets are required, resulting in the primary cessation of the bleed by the hemostatic platelet plug formation. **[6-11]**

Coagulation phase : Virtually simultaneously with the vascular and platelet phases, the extrinsic, intrinsic and common pathways, containing 12 circulating plasma proteins, (also termed plasma coagulation factors) are initiated. (Table 1). These plasma proteins are produced in the liver. More specifically, of the 12 plasma proteins, factors II, VII, IX and X are Vitamin-K dependent for synthesis. The coagulation factors (F) are activated in a cascade-like manner within their respective pathways. The ―faster‖ extrinsic pathway is initiated by F-VII when exposed to a tissue factor (or a membrane protein) within the injured vessel; and the intrinsic pathway is initiated when F-XII contacts with injury-exposed subendothelial tissues. Subsequently, coagulation factors in the intrinsic pathway activate one another: F-XII activates F- XI; F-XI activates-IX; and F-IX activates F-VIII. Both pathways merge and F-X is activated, yielding the activation of the common pathway. Subsequently, prothrombin is converted to thrombin; thrombin acts as a catalyst for the conversion of fibrinogen; fibrinogen is the precursor to fibrin. **[6-14]**

List of .1; Circulating Coagulation Factors		Intrinsic Pathway	Extrinsic Pathway	Common Pathway
Factor I	Fibrinogen			P
Factor II	Prothrombin	P		
Factor III	Tissue Factor	P		
Factor IV	Calcium			P
Factor V	Proaccelerin			P
*				
Factor VII	Proconvertin		P	
Factor VIII	Antihemophilic factor	P		
Factor IX	Plasma thromboplastin	P		
Factor X	Stuart-Power factor			P

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Factor XI	Plasma thromboplastin antecedent	P		
Factor XII	Hageman factor	P		
Factor XIII	Fibrin-stabilizer factor			P

*** Factor VI is non–existent.**

Table 2. Coagulation Phase

Fibrin is thus converted to a stringy, insoluble protein that forms an intricate network of minute delicate structures called fibrils. At this point, blood cells and plasma are enmeshed in the network of fibrils to form the clot. Therefore, fibrils are responsible for tightly binding the platelet plug, stabilizing the plug, and affixing it to the site of injury. Resulting in a semi-solid, gelatinous mass, it is termed the hemostatic clot or thrombus. This definitive clot prevents blood from leaking out of blood vessels after injury. Within approximately 9 to 18 minutes, the fibrin clot is produced. (Fig. 2). Under these physiological conditions, it is important to note that too few platelets, abnormal platelets, platelets that do not function normally, or deficiencies of clotting factors may not form normal clots; thus, disorders of the hemostatic system can result. **[12-15]**

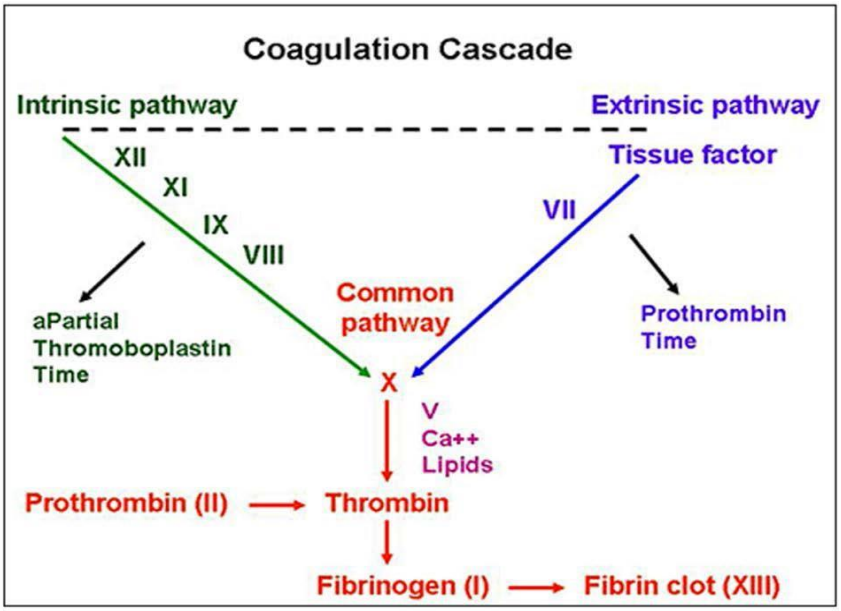

Table 2. Coagulation Cascade,

Finally, anticlotting mechanisms (broadly termed fibrin degradation products) in the fibrinolynic pathway are activated to prevent the formation of more clots and to allow for the dissolution of the definitive clot. The expected outcome is accomplished: repair of the injured blood vessel wall results and bleeding ceases. **[6]**

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A complete drug history is important. If a patient is taking anticoagulant drugs, it will be important to consult his or her physician before any major surgical procedure. In addition, a number of medications may interfere with hemostasis and prolong bleeding. Drugs of abuse, such as alcohol or heroin, may also cause excess bleeding by causing liver damage resulting in altered production of coagulation factors. Illicit injection drug use carries an increased risk of transmission of viral pathogens that may lead to viral hepatitis and altered liver function. **[9]**

A general examination of the patient might indicate a tendency to bleed. Multiple purpurae of the skin, bleeding wounds, evident hematomas or swollen joints may be evident in patients with severe bleeding defects. In addition, patients may show signs of underlying systemic disease. Patients with liver disease may have jaundice, spider nevi, ascites and other signs of impaired hepatic function. A cardiac patient can show tachycardia or hypertension, which may make hemostasis more difficult to achieve. Evidence of petechiae, ecchymoses, hematomas or excessive gingival bleeding should direct the practitioner's attention toward a possible underlying bleeding disorder. When a bleeding disorder is suspected, laboratory investigations, including blood counts and clotting studies, should be carried out. Preoperative laboratory tests of the hemostatic system are:

• bleeding time to determine platelet function (normal range: 2–7 minutes)

• activated partial thromboplastin time to evaluate the intrinsic coagulation pathway (normal range: 25 ± 10 seconds)

• international normalized ratio to measure the extrinsic pathway (normal range: 1.0)

• platelet count to quantify platelet function (normal range: 150,000–450,000/μL).

The purpose of this article is to educate dental professionals on how to treat patients with inherited bleeding disorders.

Laboratory Assessment of Hemostasis

Many of the bleeding disorders can be diagnosed and monitored by way of laboratory testing. When a significant coagulation disorder occurs in the vascular or platelet phase a clinical bleeding problem is observed immediately after injury, or during invasive medical or dental procedures. Conversely, when a significant disorder affects the coagulation phase (clotting factors), the clinical bleed will most likely not be observed until several hours or longer after the injury or invasive procedure.

Various laboratory screening tests can be ordered by the dentist when the patient reports a bleeding disorder, when the patient responds positively to a family history of a bleeding disorder; or when the clinician observes a sign/symptom of a bleeding problem during the clinical exam. Patients with unknown bleeding problems should be referred to their physician or to a hematologist for further evaluation. Laboratory tests provide an assessment of adequate numbers of platelets, proper functioning of platelets, sufficient levels of plasma

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coagulation factors, and proper functioning of the fibrinolytic pathway. When evaluating defects in the hemostatic system prior to invasive dental treatment, dental professionals should become familiar with the following common blood laboratory tests.

Several tests are available to screen patients for bleeding disorders and to help pinpoint the specific deficiency. Three tests are recommended for use in initial screening for possible bleeding disorders: activated partial thromboplastin time (aPTT), prothrombin time (PT), and platelet count.

If no clues are evident two additional tests can be added to the initial screen: platelet function analyzer (PFA-100) and thrombin time (TT).

A hematologist orders these tests, establishes a diagnosis that is based on the additional testing, and makes recommendations for treatment of the patient who is found to have a significant bleeding problem.

Partial thromboplastin time (PTT); is used to check the intrinsic system (factors VIII, IX, XI, and XII) and the common pathways (factors V and X, prothrombin, and fibrinogen). It also is the best single screening test for coagulation disorders.

When a contact activator is added, the test is referred to as activated PTT (aPTT). In general, aPTT ranges from 25 to 35 seconds, and results in excess of 35 seconds are considered abnormal or prolonged in cases of mild to severe deficiency of factor VIII or IX.

Prothrombin Time;

The prothrombin time (PT) is used to check the extrinsic pathway (factor VII) and the common pathway (factors V and X, prothrombin, and fibrinogen). When the test is used to evaluate the level of anticoagulation with coumarin-like drugs the INR format is recommended.

Platelet Count. Platelet count is used to screen for possible bleeding problems due to thrombocytopenia. Normal platelet count is 140,000 to 400,000/μL of blood. Patients with a platelet count of between 50,000 and 100,000/μL manifest excessive bleeding only with severe trauma.

Patients with counts below 50,000/μL demonstrate skin and mucosal purpura and bleed excessively with minor trauma. Patients with platelet counts below 20,000/μL may experience spontaneous bleeding. **[1-6]**

Thrombin Time. In this test, thrombin is added to the patient's blood sample as the activating agent. It converts fibrinogen in the blood to insoluble fibrin which makes up the essential portion of a blood clot. This test bypasses the intrinsic, extrinsic, and most of the common pathway. For example, patients with hemophilia A or factor V deficiency have a normal TT. Generally, the normal range for the TT test is 9 to 13 seconds, and results in excess of 16 to 18 seconds are considered abnormal or prolonged. Abnormal test results usually are caused by excessive plasmin or fibrin split products. **[1-6]**

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a.Common blood laboratory tests

Platelet Count is a routine blood laboratory test that provides a quantitative assessment of circulating platelets in the vascular system. A normal platelet count should be within the range of 150,000 to 450,000 cells/mm3 of blood. When the platelet count is less than 100,000 cells/mm3, thrombocytopenia is diagnosed. Patients presenting with a platelet count between 50,000 and 100,000 cells/mm3 will predictably bleed mildly with severe trauma or with dental surgical procedures. When the platelet count is less than 20,000 cells/mm3 an excessive and prolonged bleed is predictable; thus, this high-risk condition will [require medical attention prior to dental invasive procedures. Ultimately, thrombocytopenia can prevent the formation of a hemostatic plug, resulting in hemorrhage. **[11-22]**

The following major conclusions were drawn regarding this test :

1. Given the normal results of a standard bleeding time test one cannot exclude the possibility of a significant clinical bleed with invasive dental procedures.

2. Without a positive medical history finding related to a bleeding disorder/platelet disorder, the bleeding time test is not a ―useful predictor‖ of an excessive bleed when performing invasive dental procedures; and**[17-23]**

3. The results of a prolonged bleeding time cannot reliably identify patients who are taking anti-platelet therapy; thus, a prolonged bleeding time cannot be linked to the ingestion of aspirin or NSAIDs. Therefore, the bleeding time test is merely a tool to screen for platelet disorders; it is not an effective clinical testing method for predicting the quantity of a bleed associated with an increased bleeding time in such patients. **[17-24]**

4. Platelet Function Analyzer (PFA-100) is a sophisticated laboratory screening testing devise that is currently being used in place of the Ivy Bleeding Time test. Platelet function tests or platelet function assay (PFA) evaluate the qualitative function of platelets. **[23- 25]**

5. These tests provide an assessment of platelet adhesion, platelet activation and platelet aggregation during the development of a platelet plug, or primary hemostasis. [12] Generally, these tests measure the time it takes for a clot to form (platelets to clump together) to prevent blood loss as the closure time. The PFA test (and other platelet function tests) has not been shown to predict the likelihood that a patient will bleed excessively during invasive procedures; although, it's full clinical utility has yet to be established. **[26]**

Prothrombin Time (PT), measures the patient's ability to form a definitive clot by monitoring the proper functioning of the extrinsic coagulation pathway (Factor VII) and the common pathway (Factors V, X, prothrombin and fibrinogen). Factors VII, X and prothrombin are Vitamin K-dependent for their synthesis and become unstable when coumarin-like drugs are prescribed.

1. **A** normal coagulation profile indicates adequate levels or percentages of clotting factors in the extrinsic and common pathways. Generally, the laboratory testing range is

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between 11–15 seconds.Testing results beyond 15 seconds indicate an abnormal or prolonged PT. This outcome is indicative of deficient coagulation factors needed to form a fibrin clot, resulting in a prolonged bleed in the body. An active bleed caused by anticoagulation therapy, coumarin-like drugs, is most commonly monitored by the international normalized ratio (INR) laboratory test. **[27]**

1. International Normalized Ratio (INR):In 1983, the World Health Organization Committee on Biological Standards established a more precise laboratory testing method, the INR, to monitor patients taking anticoagulation drugs (warfarin therapy). [12] Consequently, laboratory materials (thromboplastin reagents) and laboratory techniques were internationally instituted for the purpose of standardizing the assigned values. Patients with a normal coagulation profile result in an INR value of 1.0.The ―low intensity‖ INR range is between 2.0 and 3.0; and the ―high-intensity‖ INR range is between 2.5 and 3.5. What governs the intensity of anticoagulation therapy? The intensity is determined by the patient's predisposition to abnormal clotting. Patients diagnosed at high risk clot formation, will require higher intensity of anticoagulation. From a pharmacological standpoint, anticoagulant drugs inactivate Factor VII within the extrinsic pathway by inhibiting Vitamin K action; Vitamin K is required by the liver to synthesize Factor VII. **[28-30]**

6. Activated Partial Thromboplastin Time (aPTT) also measures the patient's ability to effectively form a definitive clot by evaluating the effectiveness of the intrinsic and common pathways of the coagulation cascade. It tests for deficiencies in the intrinsic pathway, specifically factors VIII, IX, XI, XIII; and deficiencies in the common pathway, specifically factors V and X, prothrombin and fibrinogen. A normal aPTT is usually 25 to 40 seconds. A aPTT is the laboratory test most often used by physicians to monitor heparin therapyand to diagnose the hemophilias, which result in a prolonged or increased aPTT time. **[28-31]**

Thrombin Time laboratory test assesses the conversion of fibrinogen to insoluble fibrin by adding thrombin to the patient's blood sample. Specifically, this test bypasses the extrinsic, intrinsic and common pathways to determine the stability of the clot. Normally, the range of this test is between 9 and 13 seconds. A prolonged time, in excess of 16 to 18 seconds, is considered abnormal. (Table 8).

Laboratory Tests	Measures Normal Function	*Normal Values/Ranges	Importance in Diagnosing Bleeding Disorders	*Abnormal Values/Ranges
Platelet Count	Adequate platelet numbers	150,000 to 450,000/mm3	Assess thrombocytopenia or inadequate numbers of platelets	100,000 cells/mm3
Ivy Bleeding Time	Adequate platelet function	2-10	Screening test for thrombocytopathy;	Prolonged time:

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		minutes		>9-10 minutes
			von Willebrand's disease	
Platelet Function Tests	Assess function of platelets: attachment, activation, and aggregation		Discriminates between normal and abnormal function of platelets	
Prothrombin Time (PT)	Assess the time it takes to form a fibrin clot when calcium and tissue factor are added to the plasma (extrinsic pathway: coagulation function of factor VII; common pathway: factors V, X, prothrombin and fibrinogen)	11 to 15 seconds	Assess defects in the extrinsic pathway of the coagulation system: anticoagulant therapy (warfarin); Prothrombin deficiency, vitamin K deficiency; liver disease; antiplatelet drugs	Prolonged time: >30 seconds
International Normalized Ratio (INR)	Coagulation function of the extrinsic pathway: Factors V, VII, X, prothrombin and fibrinogen	1.0	Monitors oral anticoagulation therapy: warfarin	INR greater than 1.2 in patients not on anticoagulation therapy. In patients on anticoagulants, therapeutic range is between 2.0 and 3.5

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Partial Thromboplastin Time (activated aPTT)	Assess the time it takes to form a fibrin clot when calcium and partial thromboplastin containing phospholipids are added to the plasma (intrinsic pathway: coagulation function of factors VIII, IX, XI and XII	25 to 40 seconds	Assess defects in the intrinsic pathway of the coagulation system: anticoagulant therapy (heparin); von Willebrand's disease; hemophilia A and B	Prolonged time: 45 to 50 seconds
Thrombin Time	Thrombin is added to blood to convert fibrinogen to fibrin	24 to 35 seconds	Assess defects in the conversion of fibrinogen to fibrin	Prolonged or beyond normal

***Normal values or ranges may vary among different laboratories.**

Table 3. Blood Laboratory Tests that Evaluate Hemostasis and Bleeding Disorders

a. Common bleeding disorders

Excessive or prolonged bleeding may result from (According to **D'Amato-Palumbo S.** [12]):

1. Extremely fragile blood vessels;
2. Decreased number of platelets or impaired platelet function;
3. Abnormalities in the blood clotting coagulation factors;
4. Defects in the fibrinolytic pathway; or
5. A combination of these.

The following information provides an overview of the various abnormalities in the hemostatic system.

7. **Blood vessel wall abnormalities:** S. blood vessel wall abnormalities, or increased fragility of the blood vessels, are relatively common but do not usually cause a serious bleed. [12] When evaluating the laboratory tests for this condition, one can expect a normal platelet count, bleeding time and coagulation times (PT and aPTT). Pathophysiologically, this condition manifests itself by observable extraoral and intraoral signs of hemorrhage: petechiae and ecchymosis are found in the skin or on the mucous membranes, particularly on the gingiva. Very rarely, significant hemorrhage may occur, particularly in the joints, muscles,

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and subperiosteal locations. Excessive bleeding may also take the form of menorrhagia (abnormal long and heavy menstrual periods), nosebleeds, gastrointestinal bleeding, or hematuria (abnormal presence of blood in the urine). **[2-17]**

b. Causes of Blood Vessel Wall Abnormalities;

-Infections (i.e., septicemia, infective endocarditis, several forms of rickettsioses)

-Drug reactions (i.e., hypersensitivity vasculitis)

-Scurvy, Henoch-Schönlein purpura

-Hereditary hemorrhagic conditions.

c. **Thrombocytopenia:**The important role of platelets in hemostasis is to form the temporary hemostatic plug, primarily requiring a sufficient number of platelets. [12] When a quantitative reduction of platelets exists, it can result in a significant cause of generalized bleeding. Patients presenting with a platelet count of less than 100,000 cells/mm3 are

8. diagnosed with thrombocytopenia. When the platelet count is under 50,000 cells/mm3, bleeding will be excessive postoperatively; thus, a platelet transfusion may be necessary prior to invasive treatment. Moderate to severe thrombocytopenia (less than 50,000 cells/mm3) is usually manifested by petechiae in the skin or on the mucous membranes; purpura or ecchymoses on the skin; spontaneous mucosal bleeding; or intracranial hemorrhage. In the oral cavity, bleeding gingiva is a common sign, spontaneous bleeding associated with brushing or flossing may be observable, and bleeding from teeth extractions is possible. This condition is diagnosed by a platelet count laboratory test, or by a complete blood count (CBC). Depending on the cause, thrombocytopenia can be a consequence of increased platelet destruction, decreased platelet production, decreased platelet survival, or increased splenic sequestration. **[32-37]**

Thrombocytopenia is the leading cause of bleeding disorders, as presented in the following major categories :

1. Causes of Decreased Production of Platelets;
2. Generalized diseases of the bone marrow; Aplastic anemia;
3. Drug-induced thrombocytopenia: Cytotoxic drugs, Alcohol, Thiazide diuretics;
4. Infections: measles, HIV;
5. Ineffective megakaryopoiesis;
6. Causes of Platelet Destruction or Decreased Platelet Survival;
7. Immunologic destruction: Immune thrombocytopenic purpura (ITP);
8. Infections: HIV, infectious mononucleosis, cytomegalovirus (CMV);
9. Drug-associated: Quinine or quinidine, Methyldopa, Sulfonamides, Heparin,

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Gold, D- penicillamine, Þ-aminosalicylic acid;

10. Nonimmunologic destruction: Thrombotic thrombocytopenic purpura, Giant hemangiomas, Hemolytic anemias.

9. **Thrombocytopathy** : Thrombocytopathy is characterized by impairment in platelet function, but adequate numbers of platelets are normally present. [12] Thrombocytopathy may be congenital or acquired. The PFA-100 test (or other platelet function tests) provides an assessment of the adequacy of platelet function, **[38-41]** and contributes to the diagnosis of the following disorders:

Causes of Platelet Destruction or Decreased Platelet Survival

a.Inherited disorders: von Willebrand's disease: consists of a platelet dysfunction and a Factor VIII deficiency (Refer to inherited coagulation disorders)

b.Acquired disorders: Drug-induced defects:

*Aspirin (antiplatelet),

**Nonsteroidal anti- inflammatory drugs (NSAIDS),

***Other antiplatelet drugs; Alcohol in combination with aspirin or NSAIDS; Uremia; Myloproliferative disorders

*Aspirin and aspirin-containing drugs are by far the most common reason for platelet dysfunction, frequently resulting in a prolonged bleeding time. Aspirin, a nonsteroidal salicylate, acts as an inhibitor of cyclooxengenase; thus, inhibits the synthesis of prostaglandins and interferes with the production of thromboxane A2.The net result of aspirin therapy is to inhibit platelet aggregation, hence, the formation of a platelet plug. (Fig. 4).

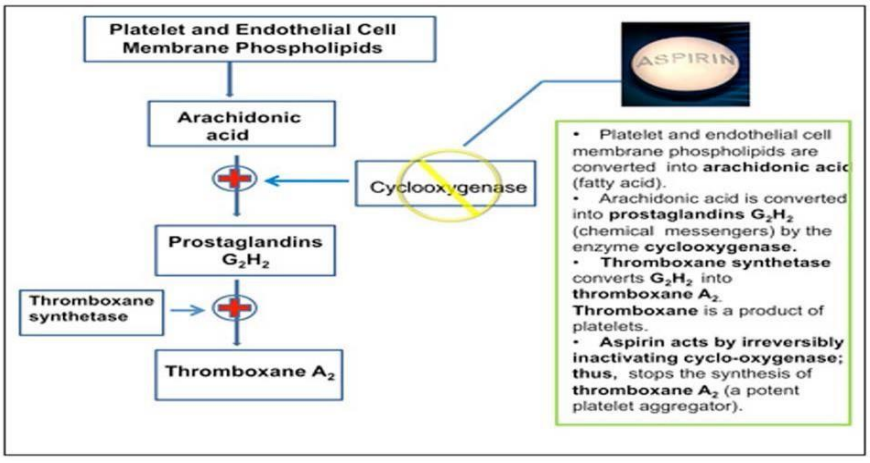

Table 4. The effect of aspirin on platelets, Source: D'Amato-Palumbo S. [12]

Aspirin therapy, prescribed or self-administered, is a leading drug widely used by millions of people in the U.S. for its cardioprotective properties. (Table 5). Its anti-platelet action

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prevents thrombus formation by impairing platelet function and by interfering with their ability to form an intact platelet plug. As a result, aspirin causes irreversibility of platelet function for the duration of their lifetime, approximately 7–10 days. Use of aspirin therapy is indicated for primary and

secondary prevention of thromboembolism, myocardial infarction and cerebrovascular accident.

Medication	Indication for Use	Effects on Dental Treatment	Strategies to Address Perioperative and
			Postoperative Bleed (For more information on Drug Products and Dental Procedures Used as Local Measures to Limit and Control Bleeding During Invasive Dental Procedures see Table 3.)
Aspirin	Treatment of mild-to-moderate pain, inflammation, and fever; prevention and treatment of acute coronary syndromes, acute ischemic stroke, and transient ischemic episodes; management of rheumatoid arthritis, rheumatic fever, osteoarthritis; adjunctive therapy in revascularization procedures (coronary artery bypass graft, percutaneous transluminal coronary angioplasty, carotid endarterectomy), stent implantation.	Key adverse event(s) related to dental treatment: As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity. See	• No specific remedy • Consider platelet transfusion ± DDAVP • Normal platelet function returns within 7 to 10 days after discontinuation

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		clopidogrel.	
Cilostazol (Pletal)	Used for symptomatic management of peripheral vascular disease, primarily intermittent claudication.	No significant effects or complications reported.	• No specific remedy • Normal platelet function returns within 4 days after discontinuation
Clopidogrel(Plavix)	To decrease the rate of a combined end point of cardiovascular death, MI, or stroke.	Aspirin in combination with clopidogrel (Plavix®), prasugrel (Effient®), or ticagrelor (Brilinta™) is the primary prevention strategy against stent thrombosis after	• No specific remedy • Consider platelet transfusion ± DDAVP • Normal platelet function returns within 7 to 10 days after discontinuation
		placement of drug-eluting metal stents in coronary patients. Any elective surgery should be postponed for 1 year after stent implantation, and if surgery must be performed, consideration should be given to continuing the antiplatelet therapy during the perioperative period in high-risk patients with drug-eluting stents.	

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Prasugrel(Effient)	To reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients who are to be managed with percutaneous coronary intervention for unstable angina, non-ST-segment elevation MI, or ST- elevation MI.	See clopidogrel.	• No specific remedy • Consider platelet transfusion ± DDAVP • Normal platelet function returns within 5 to 9 days after discontinuation
Ticagrelor(Brilinta)	Used in conjunction with aspirin for secondary prevention of thrombotic events in patients with unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction managed medically or with percutaneous coronary intervention and/or coronary artery bypass graft.	See clopidogrel.	• No specific remedy • Consider aminocaproic acid, tranexamic acid, recombinant factor VIIa • Normal platelet function returns within 3 to 5 days after discontinuation
Ticlopidine	Use platelet aggregation inhibitor that reduces the risk of thrombotic stroke in patients who have had a stroke or	No significant effects or complications reported; if a patient is to undergo elective surgery and an	• No specific remedy • Consider platelet transfusion ± DDAVP

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	stroke precursors (**Note:** Due to its association with life-threatening hematologic disorders, ticlopidine should be reserved for patients who are intolerant to aspirin, or who have failed aspirin therapy); adjunctive therapy (with aspirin) following successful coronary stent implantation to reduce the incidence of subacute stent thrombosis.	antiplatelet effect is not desired, ticlopidine should be discontinued at least 7 days prior to surgery.	• Normal platelet function returns within 5 to 10 days after discontinuation

Table 5. Oral Antiplatelet Comparison

Although the blood thinning properties of aspirin cause an increased risk of a clinical bleed, proper management usually includes maintaining patients on —low-dose‖ aspirin therapy (75 to 100 mg) to prevent the risk of a clot-threatening event. (Table 6).

Brand Name	Chemical Name	Mechanism of Action	Contradictions	Disadvantages
Gauze		2‖ x 2‖ sterile gauze pads; place pressure on wound to close or apply finger pressure		
Gelfoam		Absorbable gelatin sponge material; provides stable 'scaffold' for clot formation	Should not be used under epithelial incisions or flaps, inhibits healing	
Surgical		Oxidized regenerated cellulose; exerts physical effect rather than		

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		physiological		
Bleed X		Hemostatic	No known	
		product containing microporus poly-saccharide hemispheres (potato starch); dehydrates blood and accelerates clotting	contraindications	
Tisseel		Fibrin sealant; adhesive action that binds fibrin to the clot		Technique sensitive: requires special attention to preparation; reserved for complex procedures
Cykloapron	Tranexamic acid	Used in the form of a mouthwash after surgical procedures to inhibit postoperative bleeding; can be administered parenterally or as an 4.8% aqueous solution (4 times daily for 1 week)		
Suturing		Apposition of soft tissue		
Amicar	Aminocaproic acid	Antifibrinolytic agent		No longer available for topical use

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Electrocautery		Tool to slow intraoperative bleeding and interfere with postoperative episodes		Use cautiously to avoid excessive tissue necrosis

Every drug or dental product is not without side effects/adverse events or drug interactions; dental provider must use dental drug reference prior to their use and/or consult with the patient's supervising physician.**[37-44]**

Table 6. Drug Products and Dental Procedures Used as Local Measures to Limit and Control Bleeding During Invasive Dental Procedures,

In conclusion, it is recommended that a clinical bleed caused by routine dental extractions, can be managed by standard local hemostatic measures (with direct packing of gauge, from suturing to hemostatic agents). Additionally, it is recommended dental professionals adhere to the expert opinion that the benefits of continuing antiplatelet therapy deceases the risk of a cardiovascular episode. This strategy, therefore, outweighs the benefits of a decreased risk of bleeding

complications with surgery following cessation of aspirin . **[37-44]**

Non steroidal anti–inflammatory drugs (NSAIDs) cause abnormal platelet function; thus, bleeding tendencies can be expected. Once the drug is discontinued thrombocytopathy is reversed within 1–5 half–life's of the drug. And, when considering aspirin and NSAIDs as pain relievers after dental procedures, dental professionals should not prescribe these analgesics when optimum blood clotting/hemostasis is desired. **[44-48]

***Other antiplatelet drugs irreversibly inhibit platelet aggregation, causing platelet dysfunction (Table 5). Normal platelet aggregation/function returns when the antiplatelet drug is discontinued and only when new platelets are produced, usually within a range of 3 to 10 days. It is recommended that prescription antiplatelet drugs, when prescribed with or without aspirin, not be discontinued for minor dental surgical procedures. However, more studies are needed to examine the quantity of the bleed during major or complicated surgical dental procedures.Thus, prudent treatment planning takes into account the use of hemostatic agents and dental procedures used as local measures to control bleeding during and/or after the invasive dental procedure. (Table 6).

In the event these antiplatelet drugs are to be discontinued, it is prudent to consult with the patient's supervising physician or cardiologist, especially when patients present with coronary artery stents: the American Heart Association strongly advises against the discontinuation of dual antiplatelet therapy in patients with coronary artery stents within 12 months after

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placement. If antiplatelet therapy (i.e., aspirin and clopidogrel) is suddenly discontinued it may increase the risk of a fatal event in these patients. **[44-50]**

Coagulation Factor Disorders. Anticoagulation

Warfarin Sodium is a coumadin derivative listed in the drug class as an oral anticoagulant. It 9interferes with the liver's synthesis of Vitamin K-dependent clotting factors; resulting in depletion of blood clotting factors II, VII, IX, and X. Its therapeutic effect is to prevent further development of the hemostatic plug; and it prevents new thromboembolic clot formation. Thrombosis is the formation of abnormal blood clots (termed thrombi) that develop within the vascular system. Thrombi are carried through the bloodstream (termed emboli) which can potentially occlude the lumen of an artery or a vein and shut down a vital organ. The following conditions increase the risk of a thromboembolic event: deep venous thrombophlebitis (inflammation of a vein); atrial fibrillation (rapid, random contractions of the atria); myocardial infarction (heart attack); mechanical heart valves (artificial heart valves); carotid artery disease; or peripheral vascular disease. Additionally, clots form because there is an existing hypercoaguable condition where by the blood has a tendency to clot more rapidly than normal, caused by either a blood vessel defect, clotting factor abnormality or an immunologic abnormality. **[51-56]**

When patients are taking warfarin therapy to prevent thromboembolic events, they are monitored by the International Normalized Ratio (INR) laboratory test. The recommended INR therapeutic range for patents on ;

—low-intensity‖ warfarin therapy is between **2.0 to 3.0,** with a target goal of 2.5 INR. When patients are on

—high-intensity‖ warfarin therapy, the INR range is between **2.5 to 3.5,** with a target goal of 3.0 INR.

Indications for placing patients in these ranges are determined by the severity of the thromboembolic condition. (Table7).

—Low Intensity" Warfarin Therapy INR of 2.0 to 3.0, with a target of 2.5 (5-7mg/day for 3-6 months)	—High Intensity" Warfarin Therapy INR of 2.5 to 3.5, with a target of 3.0 (7-10mg/day, long term)

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Prophylaxis of venous thrombosis (high risk surgery) -Treatment of pulmonary embolism -Prevention of systemic embolism Tissue heart valves in aortic or mitral position for the first 3 months - Tissue valves with history of pulmonary embolism - Tissue heart valves with atrial	-Mechanical prosthetic heart values - Prevention of recurrent MI - Treatment of thrombosis associated with antiphospholipid antibodies
fibrillation Acute MI Atrial fibrillation Valvular heart disease Mitral valve prolapse with history of atrial fibrillation or embolism	

Table 7. Recommended Therapeutic Range for Warfarin Therapy

Historically, anticoagulation profiles for patients were much higher.Thus, it was necessary to discontinue or alter the warfarin therapy to avoid the risk of an excessive bleed (hemorrhage) during and post invasive surgical and non-surgical procedures. Rationale for this practice: Since Coumadin has a slow onset of action and a half-life of 36 hours it requires complete withdrawal of the drug two to three days prior to the invasive procedure. **[37-44]**

Consequently, patients' coagulation profiles resulted in suboptimal therapeutic levels, and possibly, placed patients at risk for a thromboembolic event. More specifically, the following clinical guidelines summarize dental management strategies for patients on Coumadin therapy who are

anticoagulated in the ―low intensity‖ and ―high intensity‖ therapeutic ranges, and who are scheduled for various simple and complex surgical and non-surgical procedures:

Low intensity INR 2.0-3.0

-Consult with the patient's physician and obtain recent INR laboratory results prior to the invasive dental procedure. It is important to obtain an INR lab result within 24 hours of highly

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invasive procedures.

-If the INR is between the range of 2.0-3.0:

-When performing highly invasive non-surgical or simple surgical procedures, one can proceed if the INR is within therapeutic range 2.0-3.0. (Non-surgical invasive procedures can include subgingival debridement with slight to moderate inflammation.) Proceed with attention to control bleeding with standard local hemostatic measures. **[57-64]**

-If the INR is greater than 2.5:

-When performing complex surgical procedures or subgingival debridement with severe

inflammation, consult with the patient's physician to allow the INR to drift down to a safe INR

range between 2-2.5. Proceed with attention to control bleeding with standard local hemostatic measures.

-Considerations for transiently interrupting the anticoagulation therapy must be discussed with the patient's physician.

High intensity INR 2.5-3.5;

-Consult with the patient's physician and obtain recent INR laboratory results prior to the invasive dental procedure.

-When performing non-surgical (subgingival debridement with sight to moderate inflammation) and simple surgical procedures maintain INR in the 2.5-3.5 range; proceed with attention to standard local hemostatic measures to limit and control bleeding.

When performing complex surgical procedures or subgingival debridement with severe inflammation consult with the patient's physician; it may be safe to proceed in the lower ranges of INR 2.5-3.0 with attention to local hemostatic measures. Considerations for transiently interrupting the anticoagulation therapy must be discussed with the patient's physician.

Consider use of low molecular weight heparin preparations to bridge the patient through the invasive procedure as a substitute anticoagulant. **[37-44]**

It can be concluded that most simple and routine invasive dental procedures can be safely performed when the INR is ≤ 3.0/3.5; and it is advised not to proceed when the INR value is out of range or when complex, surgical and non-surgical procedures are planned. When allowing for higher normal therapeutic ranges of INR during invasive dental procedures, consider operator experience. Under these conditions, it is prudent to consult with the patient's supervising physician; obtain results of an INR laboratory test within 24 hours of the invasive dental procedure; and be prepared to use hemostatic measures to manage the expected clinical bleed for all planned dental procedures. **[64-69]**

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While the current recommendations should be tailored towards the patients' individual needs, dental professionals must consider the following dental implications when treating anticoagulated patients:

-Identify the fundamental cause of the bleeding disorder for which anticoagulation therapy is indicated.

Consider operator experience with complex invasive dental procedures.

--Consider preexisting infection and/or the degree of inflammation of the soft tissues.

-Consider the extensiveness of the invasive procedure, especially significant soft tissue and bone trauma.

-Consider bleeding management strategies and the availability of local hemostatic measures when the risk of a bleed is expected.

-Consider the probable risk of inducing a thromboembolic event when discontinuing or altering the anticoagulant drug; thus, resulting in coagulation profiles that are in the suboptimal therapeutic range. **[67-74]**

-Implement a heightened awareness when treatment planning: consider the complexity of the invasive dental procedure; seek medical advice from the patient's physician; and retrieve the results of the most recent INR test.

Heparin: Managing dental patients on standard heparin and low molecular weight heparin (LMWH) is important when providers need to control bleeding during and following invasive dental procedures. [12] Standard heparin itself is not considered an anticoagulant but serves as the catalyst that inhibits plasma thrombin as well as coagulation factors IX, X, XI, XII and plasmin; thus, preventing the conversion of fibrinogen to fibrin. LMWHs exert their potentiating anticoagulant effects more so on factor Xa. **[35-44]**

These drugs are used as a prophylaxis antithrombic agent and in the treatment of thromboembolic disorders. Treatment with standard heparin usually consists of IV infusions in a hospital setting which requires monitoring with the aPTT laboratory test. LMWH preparations are administered subcutaneously on an out-patient basis. Their dosage is calculated based on the patient's body weight and is given on an every 12-hour basis. **[33-44]**

When considering substituting LMWH preparations, dalteparin (Fragmin), for Coumadin when a dental surgical or nonsurgical procedure is planned, one must consult with the patient's physician to strictly and safely manage the medication schedules. The following short-term heparinization schedule is recommended: Coumadin is discontinued 4 days prior to the invasive dental procedure and Fragmin is started. During this 4-day period Fragmin is administered every 12 hours. An evening dose of Fragmin is administered on day 4; the invasive dental procedure is scheduled 12 hours after the evening dose of Fragmin. On the morning of the dental procedure Fragmin is held back. During the evening of the surgical procedure both Fragmin and Coumadin are resumed and continued until the INR is within the

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therapeutic range of 2.0-3.5. At this point, Coumadin is continued and Fragmin is discontinued. **[3-14]**

a. Inherited coagulation disorders

A number of congenital blood clotting factor deficiencies exist; but three diseases account for more than 90% of all inherited coagulant deficiencies. Deficiencies for discussion include: Hemophilia A, Hemophilia B, and von Willebrand's disease. These diseases can present with mild to severe forms, which parallels the degree of deficiency of the blood coagulation factor.

Hemophilia A , also known as classic hemophilia, is caused by a defect or a deficiency in the activity or the amount of factor VIII, respectively. This hemophilia is a hereditary blood disorder that is transmitted as an X-linked recessive trait, thus, predominately affecting males over females. Its incidence rate is about 1 in 5,000 male births. The

severity of this condition is related to the degree of the deficiency of factor VIII; therefore, the greater the deficiency of the blood level factor the greater the bleed. Regarding hemostasis, minimally 30% of factor VIII is required for normal activity. Approximately 60% of individuals with hemophilia A possess a severe degree of deficiency, which is less than 1% of factor VIII. (Table 12). It is diagnosed by a positive family history, a history of bleeding episodes and a prolonged aPTT test with a normal PT test, along with inadequate levels of factor VIII. These series of laboratory tests indicate a defective intrinsic coagulation pathway. When considering the treatment planning for these patients, the dental professional should consult with the patient's hematologist. Usually, treatment for a minor bleed includes hemostatic dental products, local pressure, and/or cold compresses; treatment for an expected major bleed includes administration of factor concentrates termed purified factor VIII products.

Classifications of Hemophilia A and B	Degree of Deficiency	Risk of a Bleed After Trauma or Surgery
Mild	5% to 30%	Delayed onset of a bleed with trauma or surgery or dental extractions
Moderate	1% to 5%	Excessive bleeding with surgery
Severe		Excessive bleeding with trauma or surgery

Table 8. Classifications of Hemophilia A and B., Source: D'Amato-Palumbo S. [12]

Clinical characteristics of Hemophilia A include: bleeding into joints (hemarthrosis), commonly affecting knees, elbows and ankles; bleeding into soft tissues exhibiting extensive ecchymoses; bleeding into a closed space such as muscle can lead to life-threatening blood loss; intracranial bleeding; and bleeding into other sites such as gastrointestinal and urinary tracts.

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Hemophilia B , also known as Christmas disease or plasma thromboplastin component deficiency, is transmitted in a sex-linked recessive fashion similar to Hemophilia A. It is a bleeding disorder caused by a deficiency or defective factor IX within the intrinsic pathway of the coagulation system. (Table 8). Not as prevalent as Hemophilia A, Hemophilia B accounts for 10–15% of all hemophiliacs. It is diagnosed by a positive family history, a history of bleeding episodes and a prolonged aPTT test with a normal PT test, along with inadequate levels of factor IX. Replacement therapy for factor IX is more variable because factor IX is distributed within and outside of the blood system, intravascular and extravascular respectively.

Although, both purified and recombinant factor IX products (or high-purity FIX [factor IX] products) are recommended for the prevention or treatment of bleeding in patients with hemophilia

B. Clinical features of hemophilia B are similar to hemophilia A: they include: deep tissue hemorrhage in joints, brain, and muscles.

Pre-treatment of invasive procedure:	Management recommendations:
Consult with hematologist	**Hemophilia A:**Factor VIII replacement, desmopressin (increases factor level)
Confirm diagnosis and severity of hemophilia	e-aminocaproci acid (stablizes the clot)
Patients with mild to moderate hemophilia are usually treated in the dental office	**Hemophilia B:** Purified Factor IX products
Patients with severe hemophilia are usually treated in a dental-based hospital setting	**von Willebrand's:** Factor VIII replacement; vWF in some cases; and Hemophilia A management recommendation

Table 9. Dental Management of Patients with Hemophilia

Management during invasive procedure:	Management after the procedure: Monitor bleeding:
Use good surgical technique	Hospitalize the pt if bleeding is not controlled
Use hemostatic agents	Examine pt 24-48 hrs post procedure: treat infection and/or bleeding issues
Hematologist will monitor hospitalized patient	Avoid aspirin, use acetaminophen with or without codeine

Table 10. Dental Management of Patients with Hemophilia

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Treatment Planning Considerations ;

Appropriate management for patients with bleeding disorders who require routine invasive dental procedures, including subgingival debridement (scaling and root planing), restorative procedures or simple surgical procedures, consists of the following:

Step 1: Take accurate, comprehensive histories: personal, medical, dental and pharmacological. Perform a thorough extra and intraoral examination to identify lesions indicative of a bleeding disorder. When a known bleeding disorder is evident, understand the pathophysiology and its related impact on dental treatment. When an unknown bleeding disorder is suspected, refer the patient to his physician or a hematologist to establish a diagnosis. Definitive diagnosis of the bleeding/clotting disorder can be established by the physician or hematologist by ordering the

―Prolonged Clotting Time Profile‖ laboratory tests.

Step 2: Consult with the supervising physician to obtain additional information about the patient's disorder or bleeding history. Continue to investigate and/or to obtain medical clearance to treat. Secondly, retrieve and evaluate the blood laboratory test results while scheduling the appointment within 24 hours of the results.

Step 3: Develop an appropriate treatment plan: establish whether or not the invasive dental procedure will be carried out in the dental office or in a hospital-based dental facility. Possibly, prior to invasive treatment, consider blood and/or clotting factor replacement therapy for patients with hemophilia; and patients with platelet disorders may require platelet transfusion therapy. In addition, other medical interventions may be required beyond infusion therapies for the respective disorders; for example, fibrinolytic defects, vascular defects or modification of anticoagulant therapy may require specialized medical care. When performing the invasive dental procedure recommendations include: minimize tissue trauma; consider hemostatic systems for predictable extensive bleeding during and after complex surgical procedures; consider alternative pain control techniques other than nerve-block anesthesia, especially for patients with coagulopathies; emphasize periodontal health to minimize gingival inflammation which can result in increased bleeding; and/or consider using a combination of local hemostatic systems to manage bleeding episodes. Specialty dental procedures (restorative, endodontic or surgical) can adhere to these fundamental guidelines in their approach to manage bleeding episodes, but most importantly, various invasive oral procedures carry a range of bleeding risk.

When considering the management of a clinical bleed during various invasive dental procedures, hemostatic measures can include the following systemic or local applications: hemostatic irrigant; absorbable gelatin sponge containing a thrombin solution; gauze-soaked squares and/or mouthrinses with fibrin or tranexamic acid (TXA); aminocaproic acid (EACA); vasoconstrictors in local anesthetics; surgical techniques and sutures; ice packs; and/or a combination of these measures. (Table 11).

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Brand Name	Chemical Name	Mechanism of Action	Contradictions	Disadvantages
Gauze		2‖ x 2‖ sterile gauze pads; place pressure on wound to close or apply finger pressure		
Gelfoam		Absorbable gelatin sponge material; provides stable 'scaffold' for clot formation	Should not be used under epithelial incisions or flaps, inhibits healing	
Surgical		Oxidized regenerated cellulose; exerts physical effect rather than physiological		
Bleed X		Hemostatic product containing microporus poly-saccharide	No known contraindications	
		hemispheres (potato starch); dehydrates blood and accelerates clotting		
Tisseel		Fibrin sealant; adhesive action that binds fibrin to the clot		Technique sensitive: requires special attention to preparation; reserved for complex procedures

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Cykloapron	Tranexamic acid	Used in the form of a mouthwash after surgical procedures to inhibit postoperative bleeding; can be administered parenterally or as an 4.8% aqueous solution (4 times daily for 1 week)		
Suturing		Apposition of soft tissue		
Amicar	Aminocaproic acid	Antifibrinolytic agent		No longer available for topical use
Electrocautery		Tool to slow intraoperative bleeding and interfere with postoperative episodes		Use cautiously to avoid excessive tissue necrosis

Table 11. Drug Products and Dental Procedures Used as Local Measures to Limit and Control Bleeding During Invasive Dental Procedures

Every drug or dental product is not without side effects/adverse events or drug interactions; dental provider must use dental drug reference prior to their use and/or consult with the patient's supervising physician. More importantly, when selecting a hemostatic therapy that achieves adequate hemostasis when performing invasive dental procedures on patients with bleeding disorders one must consider the following elements:

-The specific bleeding disorder.

-The need for a hemostatic agent and/or intervention.

-The type of local and/or systemic hemostatic agent.

-The need for a consultation with the patient's supervising physician to determine the need for coagulation factor replacement as indicated.

-The severity of the bleeding disorder.

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-The specific invasive dental procedure that will induce a bleed intraoperatively and postoperatively.

Knowledge of these essentials is important for proper treatment planning and dental management of such patients. Additionally, complex cases of clotting and bleeding disorders most likely require physician consultation, interpretation of laboratory testing, and prudent decision making when selecting a dental or hospital treatment site. Generally, comprehensive assessment of data, including laboratory tests; diagnosis of the condition;

individualized treatment planning with regards to controlling the bleed; and careful manipulation of tissues during implementation is tantamount to successful management of dental patients with bleeding disorders . **[1-18]**

Drugs and haemostasis;

Coagulation initiates with tissue factor (TF), a cell membrane protein that binds activated factor VII .Although there is a small fraction of circulating factor VII in the activated state, it has little or no enzymatic activity until it is bound to TF. Most nonvascular cells express TF in a constitutive1 fashion, whereas de novo TF synthesis can be induced in monocytes and damaged endothelial cells. Injury to the arterial or venous wall exposes extravascular TF-expressing cells to blood. Lipid-laden macrophages in the core of atherosclerotic plaques are particularly rich in TF, thereby explaining the propensity for thrombus formation at sites of plaque disruption. Once bound to TF, factor VIIa activates factor IX and factor X (to IXa and Xa, respectively), leading to thrombin generation and clot formation.

Drugs that prevent fibrinolysis;

Antifibrinolytics are useful in a number of bleeding disorders.

Tranexamic acid competitively inhibits the binding of plasminogen and tPA to fibrin and effectively blocks conversion of plasminogen to plasmin; fibrinolysis is thus retarded An intravenous bolus passes largely unchanged in the urine with a t1/2 of 1.5 h. Oral and topical formulations are available.

Tranexamic acid is used principally to prevent the hyperplasminaemic bleeding state that results from damage to tissues rich in plasminogen activator, e.g. after prostatic surgery, tonsillectomy, uterine cervical cone biopsy and menorrhagia, whether primary or induced by an intrauterine contraceptive device. Tranexamic acid may also reduce bleeding after ocular trauma, and in von Willebrand disease and haemophilia after dental extraction. It is frequently given as an adjunct to desmopressin therapy. Some patients with hereditary angioedema may benefit, presumably by prevention of plasmin-induced activation of the complement system. Tranexamic acid may be of value in thrombocytopenia (idiopathic or following cytotoxic chemotherapy). The natural fibrinolytic destabilisation of small platelet plugs is inhibited, reducing the risk of haemorrhage and requirement for platelet transfusion. Adverse effects are rare but include nausea, diarrhoea and sometimes orthostatic hypotension. Tranexamic acid is contraindicated for patients with haematuria because clot lysis in the urinary tract is prevented

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and clot colic results.

Aprotinin is a naturally occurring inhibitor of plasmin and other proteolytic enzymes that has been used to limit perioperative bleeding during cardiac bypass and liver transplantation surgery. In 2008, aprotonin was withdrawn from the market after studies suggested it may be associated with an increased mortality following cardiopulmonary bypass. However in 2012, a review of these data concluded that they were unreliable and the ban was lifted so that its use was approved for patients 'undergoing isolated heart bypass surgery who are at high risk of major blood loss'. **[34-45]**

Platelet function;

Platelets have a key role in maintaining vascular integrity. They aggregate at and adhere to exposed collagen to form a physical barrier at the site of vessel injury; they accelerate the activation of coagulation proteins; they release stored granules that promote vasoconstriction and wound healing. Platelets have rightly been termed 'pharmacological packages'. To deliver the above functions, they must first undergo a process of activation that involves multiple agonists through numerous intracellular second-messenger pathways and complex networks . These pathways converge on and activate the fibrinogen receptor, glycoprotein IIbIIIa (integrin αIIbβ3), inducing a conformational change that results in fibrinogen/fibrin binding. When fibrinogen occupies the receptor, outside-in signalling consolidates platelet activation by up-regulating second-messenger pathways, so providing a positive feedback loop. **[1-4]**

In the coagulation process, platelets provide an anionic phospholipid surface for assembly of the macromolecular enzymatic complexes required for thrombin generation. Phospholipids in the bilayer membrane of resting platelets are distributed asymmetrically, with anionic phospholipid held in the internal leaflet. Full platelet activation results in scrambling of the membrane with exposure of negatively charged phospholipid on the external leaflet. This lipid cooperates in the assembly of the thrombin-generating enzymatic complexes. **[34-45]**

Receptors on the platelet membrane that are known to result in platelet activation through intracellular second messengers include those for thrombin, adenosine diphosphate (ADP), collagen, thromboxane and adrenaline/epinephrine. Activation is enhanced by occupancy of glycoprotein IIbIIIa (the fibrinogen receptor) and glycoprotein Ib (a component of the Ib/IX/V receptor for von Willebrand protein). The process is mediated primarily through G-coupled second messengers in response to occupancy of the thrombin, ADP and collagen receptors (at high collagen concentration), and through phospholipases and consequent thromboxane generation in response to occupancy of the thromboxane, adrenaline/epinephrine and collagen receptors (at low collagen concentration). Both thromboxane and ADP are produced in response to platelet activation, and recruit further platelets to activation sites, so providing a positive feedback loop to their respective receptors. There are several ADP receptors on the platelet membrane. Multiple second-messenger pathways are probably involved in their mechanism of activation, not just G-protein–coupled systems. Collagen-induced platelet

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activation involves at least three receptors with both thromboxane-dependent and thromboxane-independent second-messenger pathways. High 'shear forces' also activate platelets, but the mechanisms are unclear: fibrinogen and its receptor, GPIIbIIIa, are required at low shear rates, and von Willebrand factor and its receptor, GPIb, at high shear rates. ADP and adrenaline/epinephrine are synergistic at high shear and result in larger thrombi for a given rate of shear. **[45-56]**

Drugs that inhibit platelet activity (antiplatelet drugs);

Aspirin (acetylsalicylic acid) acetylates and thus inactivates COX, the enzyme responsible for the first step in the formation of prostaglandins, the conversion of arachidonic acid to prostaglandin H2. As acetylation of COX is irreversible and the platelet is unable to synthesise new enzyme, COX activity is lost for the platelet lifetime (8–10 days). **[34-45]**

Aspirin prevents formation of both thromboxane A2 (TXA2) and prostacyclin (PGI2) . Therapeutic interest in the antithrombotic effect of aspirin has centred on separating these actions by using a low dose. In general, 75–100 mg/day by mouth will abolish synthesis of TXA2 without significant impairment of prostacyclin formation, i.e. amounts substantially below the 2.4 g/day used to control pain and inflammation. Laboratory testing of TXA2 production or TXA2-dependent platelet function can provide an assessment of the adequacy of aspirin dose. Among several causes of reduced response to aspirin are genetic polymorphisms of COX-1 and other genes involved in thromboxane biosynthesis.

Low-dose aspirin is not without risk: a proportion of peptic ulcer bleeds in people older than 60 years of age occur from prophylactic low-dose aspirin. **[45-61]**

Dipyridamole reversibly inhibits platelet phosphodiesterase, and consequently cyclic AMP concentration is increased and platelet activity reduced. Dipyridamole also inhibits the reuptake of adenosine by platelets resulting in elevated extracellular adenosine concentration. It is bound extensively to plasma proteins and has a t1/2 of 12 h.

Clopidogrel is a thienopyridine derivative that irreversibly inhibits ADP-dependent platelet aggregation by covalently binding to the ADP P2Y12 receptor. The t1/2 of the parent drug is 40 h, and metabolism by the liver converts it to its active form. Clopidogrel reduces the risk of the combined outcome of stroke, myocardial infarction (MI) or vascular death in patients with thromboembolic stroke. It decreases vascular death and MI in patients with unstable angina, reduces acute occlusion of coronary bypass grafts, and improves walking distance and decreases vascular complications in patients with peripheral vascular disease. Clopidogrel also finds use in the prevention of stroke in patients who are intolerant of aspirin. An initial dose of 300 mg is followed by a daily dose of 75 mg. **[44-61]**

Prasugrel is a thienopyridine derivative like clopidogrel. It inhibits ADP-induced platelet aggregation more rapidly, more consistently, and to a greater extent than standard-dose clopidogrel. A 60-mg loading dose results in at least 50% inhibition of platelet aggregation by 1 h in 90% of patients. The subsequent daily dose is 10 mg.

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Ticagrelor. Ticagrelor is another orally active inhibitor of the platelet ADP receptor. Unlike other members of this group, it is not a prodrug and is an allosteric, reversible inhibitor of the P2Y12 receptor. It is licensed for secondary prevention of MI and for acute coronary syndromes, usually in combination with aspirin. **[41-61]**

Epoprostenol (prostacyclin) may be given as an anticoagulant during renal dialysis, with or without heparin; it is infused intravenously and subcutaneously (t1/2 3 min). It is a potent vasodilator.

Uses of antiplatelet drugs;

Antiplatelet therapy protects at-risk patients against stroke, myocardial infarction or death. A meta-analysis of 145 clinical trials of prolonged (>1 month) antiplatelet therapy versus control, and trials between antiplatelet regimens, found that the chance of non-fatal myocardial infarction and non-fatal stroke fell by one-third, and that there was a one-sixth reduction in the risk of death from any vascular cause.13 Expressed in another way, in the first month after an acute myocardial infarction (a vulnerable period), aspirin prevents death, stroke or a further heart attack in about 4 of every 100 patients treated. Continuing treatment from the end of year 1 to year 3 conferred further benefit.

Aspirin is by far the most commonly used anti-platelet agent. The optimal dose is not certain, but one not exceeding aspirin 325 mg/day is acceptable, and 75–100 mg/day may be as effective and preferred where there is gastric intolerance. Aspirin alone (mainly) or aspirin plus dipyridamole greatly reduced the risk of occlusion where vascular grafts or arterial patency were studied systematically.

Many patients who take aspirin for vascular disease may also require an NSAID, e.g. for joint disease. Given their common mode of action by inhibiting prostaglandin synthesis, this raises the issue that NSAIDs may block access of aspirin to active sites on platelets, with loss of cardioprotection. Retrospective cohort15 and case-control16 studies suggest no adverse interaction with ibuprofen, but the issue remains unresolved, and in the meantime it seems prudent to take aspirin 2 h before an NSAID, e.g. at bedtime. **[45-65]**

Moderate to severe forms of disease

Before dental extractions, patients with moderate to severe disease require replacement therapy with either factor concentrate (patients with either disease) or recombinant factor VIII (patients

with hemophilia A); there is no recombinant therapy available for vWF. However, factor concentrate is expensive and may result in the development of autoantibodies or inhibitors that impair

clotting, which is why unnecessary dental procedures should be avoided. This will help to decrease the repetition of replacement therapy and reduce the chance of inhibitor formation.

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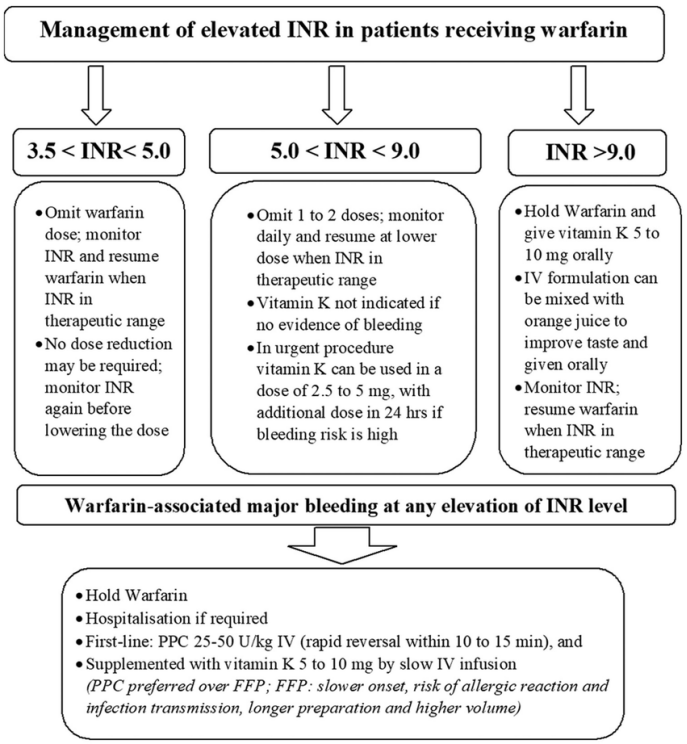
Replacement therapy can be administered by the healthcare provider, the patient's caregiver, or the patient as a prophylactic option and/or as emergency treatment in case of prolonged bleeding. It is recommended to deliver the intended dental treatment within 30-60 minutes following the administration of factor concentrate. Recombinant factor VIII can be given in patients with the moderate to severe forms of hemophilia A, which helps reduce the possibility of blood-borne infection that could result from transfusion of infected blood. **[61-72]**

It is necessary to measure the level of factor VIII in patients with hemophilia A prior to any invasive dental procedures. Hematologists recommend that the patient's level of factor VIII should be between 50% and 75% prior to minor oral and periodontal surgery.However, the factor VIII level should be between 75% and 100% before maxillofacial surgery.

Tranexamic acid (in the form of mouthwash with a concentration of 15-25 mg/kg 4 times a day for 7-10 days; or oral administration of tablets, 1 g, 3 times a day for 7-10 days) may add stability to the clot.48 It has been reported that postoperative bleeding tendency was reduced from 5.4% in a group of patients using other local hemostatic measures, without tranexamic acid, to 3.6% in a group of people using tranexamic acid alone. It is recommended that the patient start use of the mouthwash

2 hours before the dental procedure and continue 4 times daily for 7 to 10 days. Additional local hemostatic measures, including suturing and resorbable hemostatic dressing, will help

stabilize the bleeding clot. Close postextraction monitoring of the patient is necessary, because patients with hemophilia A or vWD may have delayed bleeding episodes. **[61-72]**



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Scaling in patients with hemophilia A and vWD depends on the severity of the probing depths and the patient's level of oral hygiene. Supragingival scaling with local hemostatic measures (eg, tranexamic acid) is considered safe in patients with the mild form. Consultation with the hematologist to obtain replacement therapy is recommended for patients with the moderate to severe forms. Any periodontal surgery or deep root surface debridement requires that the patient have a factor VIII level of at least 50%-75% preoperatively. **[72-77]**

It is safe to deliver orthodontic treatment to patients with bleeding disorders, but any need for tooth extraction should be discussed with the oral surgeon or special care dentist and hematologist. Sharp edges or extruded wire that might cause bleeding should be trimmed from appliances. Maintenance of good oral hygiene during orthodontic treatment is essential.

Dental care providers must attempt to minimize trauma to the soft tissues during placement of rubber dams, clamps, interdental wedges, and matrix bands. Although it is preferable to use a supragingival margin over a subgingival one, crowns and fixed partial dentures are associated with a low risk of bleeding and can be performed in a primary care setting.Moreover, full and partial removable prostheses are considered safe treatments.

Rafique et al suggested the use of nonmetallic trays during impression procedures to avoid soft tissue trauma. Covering the suction tip with gauze also might help reduce trauma to theoral mucosa. Dentists also should consider managing these patients with noninvasive dental procedures, such as atraumatic restorative treatment, air abrasion, and chemomechanical caries removal agents.

Root canal treatment is considered safe. Bleeding from thevital pulp might prolong pain, which can be eliminated by irrigation with 4% sodium hypochlorite and the administ. **[72-80]**

Methods to control bleeding;

A.Mechanical method to control bleeding:

Application of pressure counteracts the hydrostatic pressure within the blood vessel. Applying pressure is usually able to control most of the hemorrhages. It shouldbe applied directly over the bleeding site firmly over agauze pack for at least five minutes. Hemostats are also called a hemostatic clamp, arterial forceps etc. Hemostat (mosquito, artery) forces are specially designed to catch bleeding points in the surgical area. Also, prefabricatedstents can be used after surgery to trauma to the surgical

site also gives it adequate protection. **[61-72]**

Embolization of the vessel: With the help of,angiography, the exact bleeding point can be localized.

Agents that can be used for embolization include steel coils, polyvinyl alcohol foam, gel foam, silicon spheres,and methyl methacrylate. These particles are placedprecisely into the bleeding vessel via a catheter.It has shown significant results in implant surgery to control

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bleeding immediately after the tear in the lingualartery1. Thus, it can be considered as a reliable methodfor hemostasis. **[71-82]**

B.Thermal method to control bleeding:

Cautery: Hemostasis by using cautery is based on the principle of denaturation of proteins by heat. This proteins undergo precipitation and to coagulation of large areas of tissues. The heat produced by the cautery leads to protein denaturationwhich ultimately culminates into the coagulation of large areas in the tissue. In cauterization, heat is conducted directly into the target area (tissue) via the instrument. **[61-70]**

Electrocautery: The fundamental of electrosurgery is based on the principle of using electrical energy which is directly transmitted to the tissue for inducing histological effects. Current range is 1.5 -7.5million per second or megahertz. Using two electrodes, an alternating current may be conducted through the body with almost no effects other than producing heat. The heat produced is solely the result of the resistance created by tissues to the current pathway. This results in a concentration of current at the smaller electrode and the effects are de,hydration, warming of the area, coagulation or tissue destruction by heat depending on the type, the size and the frequency of the active electrode and the duration of application. **[61-72]**

The argon beam coagulator (ABC): It provides radio frequency electrical energy (coagulator monopolar current) to tissue by using a heavy stream of argon gas. It delivers noncontact, monopolar, electrothermal hemostasis. In cases of bleeding from small diameter vessels(size $\leq$ 3mm) where bleeding cannot be stopped using other hemostatic agents or ligatures, an argon coagulator is always a good option for these scenarios. This coagulator has also shown improved results in control of presacral bleeding. **[69-72]**

Lasers: Lasers to perform surgeries with less or almost no blood, as these effectively coagulate the small blood vessels while tissue cutting or sectioning. It provides a clean, dry surgical field with improved visualization3. It was seen that it has enhanced the bactericidal effect when used in implant sites without extreme heat production4. An in vitro thromboelastographic study showed that after three and six seconds there is a decrease in coagulation time while using 10 W of continuous-wave laser irradiation of 10 ml,of blood and resulted in increased clot formation rate.

In the present scenario, LASER is widely used because it aids in pain relief, improved healing and speeds up the tissue repair. **[61-79]**

C.Chemical method to control bleeding:

Astringent and stryptics: When astringent comes in touch with the injured tissue surface, a thin film is formed upon the surface and the superficial membranes and blood vessels are contracted to cause shrinkage of the tissue and thus resulting in protein precipitation6.

Monsel's solution which is quite effective in controlling capillary bleeding contains Ferric sulfate and it acts by precipitating proteins. Tannic acid also has the same mechanism of

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action. A study showed that messaging astringent gels in the edentulous areas showed improved keratinization in the denture wearers.

Adrenaline: Adrenaline or epinephrine, applied topically induces vasoconstriction and thus helps in achieving hemostasis. However, adrenaline has a dualaction called a vasomotor reversal, at low doses it causes vasoconstriction but later it leads to vasodilation. Thus, extensive application or undiluted preparation can cause systemic effects therefore, care should be exercised while using adrenaline. It can also be injected with L.A in a concentration of 1: 80,000 to 1:2,00,000. **[75-82]**

Bone wax: The material is a combination of beeswax, salicylic acid, and almond oil. The mechanism

of action of bone wax is mostly mechanical. It can be applied directly to a particular bleeding point in bone. It is normally non-absorbable in blood or saliva. It results in the formation of a soft and malleable mass when heated and manipulated. Commonly supplied in sterile sticks. **[71-82]**

Another product BoneSeal® which is a composite of biodegradable polylactic acid with hydroxyapatite

and having wax-like handling properties7. BoneSeal is designed to promote hemostasis and deliver improved bone regeneration when compared to bone wax.

Thrombin: Thrombin agents are produced from either human or bovine plasma. It can also be derived

from recombinant DNA techniques. The topical use of thrombin acts by converting fibrinogen into a fibrin clot8. It shouldn't be injected in the bloodstream or open, large blood vessels which can cause intravascular clotting. **[73-82]**

It was found in a study that a thrombin Arg-Gly-Asp complex helps in cell adhesion9.

Gelfoam: It is an absorbable gelatin sponge containing fine, dry, heat-sterilized powder prepared by milling absorbable gelatin. It is insoluble in water, porous and pliable in nature. The mechanism it uses for hemostasis is more physical and it does not affect the blood clotting pathways. Gelfoam is absorbed completely, with little tissue reaction when used in less amount. Normally it is absorbed inside the wound area within 4-6 weeks. It doesn't in abundant scar tissue

formation. It was reported that it can produce better results in clot formation than collagen10. It is contra indicated for skin closure because it might interfere with the healing of the incision lines. **[75-82]**

Oxycel or surgicel (ORC): It is also known as Surgicel or Oxycel for commercial use. It is derived from plant-based alpha-cellulose. It is an absorbable hemostatic agent that has been used to control bleeding safely, simply and effectively. It soaks up the blood and transforms

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into a gel at the target area. It results in lowering the pH and also caused localized vasoconstriction. ORC also acts as a scaffold or matrix for platelet adhesion and also supports the newly formed platelet plug. It was used in the treatment of intrabony defects and it has shown a significant reduction of CAL and PPD11.

Fibrin glue: Fibrin glue or Fibrin sealant is comprised of fibrinogen and thrombin that is used in the damaged tissue sites with the purpose of tissue adhesion. Some fibrin sealants also contain aprotinin, fibronectin and plasminogen. The thrombin(enzyme) leads to the conversion of fibrinogen into fibrin monomers incorporated 3-D gel-like structure within the period of 10-60 seconds. Each fibrin sealant system is made up of two parts. The first part consists of: It is available as a two-component system: the first component contains fibrinogen, factor XIII, fibronectin, and traces of other plasma proteins.

The second part contains thrombin, calcium chloride, and antifibrinolytic agents such as aprotinin. Combining the two parts initiates blood clotting mechanism along with the formation of fibrin.

Fibrin glue can be used in various surgical procedures like implant placement in the anterior tooth region. In a comparative study done in 2008 stated that the use of fibrin sealants is superior to using regular suture material because it is easy to handle, helps in induce hemostasis, proper adhesion of tissues and aids in wound healing. Sealants must be used carefully because an excessive amount of sealant can to tissue necrosis.

Co-seal: It is made up of polyethylene glycols (PEGs) mixed with hydrogen chloride and sodium phosphate. It is a non-toxic, FDA approved material that is biocompatible and can be easily delivered1. When the solution is mixed, it transformed into a hydrogel which attaches itself to the damaged tissues. It is synthetic in nature and doesn't contain Glutaraldehyde. The mechanism of action is mostly physical as the gel swells up in volume (almost 4 times) and can undergo further swelling as it undergoes resorption. **[80-82]**

Platelet-rich plasma gel: Platelets contain severalgrowth factors such as platelet-derived growth factor, transforming growth factor, insulin-like growth factors I and II, and epithelial growth factor. Because of this property, autologous platelet concentrate(APC) is widely used to boost postoperative healing. The platelet concentrate can be prepared via centrifugation by using patients own blood. The thrombocyte count of PRP was 1,035,000/L (mean). It also bears mucosa-adhesive properties thus widely used in the field of dentistry.

Ethamsylate: The hemostatic mechanism of ethamsylate is due to the activation of thromboplastin formation on damaged vessel walls. It also decreases prostacyclin 2 synthesis and facilitates platelet aggregation. It acts by correcting abnormal platelet adhesion. It exerts antihyaluronidase action, improves capillary wall stability not (not an antifibrinolytic).

Tranexamic acid: Tranexamic acid 4.8% is commonly used as a mouthwash because it helps in clot stabilization. It also helps in down regulating plasminogen. Because of its antifibrinolytic activities, it can be used as a prophylactic in patients who are taking

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anticoagulant drugs. A study showed that the efficacy of tranexamic acid when combined with cetylpyridinium chloride, is significantly increased for treating periodontal diseases. **[74-82]**

Botroclot: It is a form of concentrated enzyme sources extracted from the venom of South American viper, Bothropsatorox. Botroclot (Jaggat pharmaceuticals) is a topical preparation that contains extracted hemocoagulase. It aids in healing and also having procoagulant property. Botroxobin, a WHOapproved product, has been introduced to treat the site of injury. It has shown improved healing property when used in extraction sockets. **[75-82]**

Protamine: A proteolytic enzyme from the venom of South American viper, Bothropsatorox. It also functions as a plasma clotting agent for fibrinogen. It is a protein molecule having a positive charge and it attaches with heparin which is negatively charged. The ultimate complex formed inside the body is removed by the reticuloendothelial system. It was found that a combination of heparin and protamine has shown decreased postoperative bleeding. **[75-82]**

Desmopressin: It is a synthetically manufactured vasopressin analogue which was actually originated for treating diabetes insipidus18. Nevertheless, it was used as a hemostatic agent when its ability to release of VWF and factor VIII from the endothelial cells was discovered. It also aids in primary hemostasis.

Vitamin K: Vitamin K plays a massive role in the coagulation process. It also helps in the production of fibrinogen and prothrombin in the liver, thus it can be considered as a vital factor for bleeding control. It can even prevent the chances of bleeding in patients taking high doses of anticoagulant drugs.**[72-82]**

Newer hemostatic agents:

Chitosan-based dressings: Chitosan is abiocompatible, complex carbohydrate acquired from chitin (a natural compound derived from zeolites): when the deacetylation of chitin is above 70% it is called chitosan. It is a type of acid salt which has mucoadhesive property. It has a positive charge and it attracts RBCs and Platelets which have a negative charge. It also offers sealing action and antibacterial property.QuikClot (inorganic hemostat) is a chitosan-based product currently available**[75-82]**

Polysaccharide-based hemostats: Polysaccharide hemostats, like complications (mostly seen after using bone wax) can be considered as additional.

What is the difference in the risk of bleeding between patients ongoing anticoagulant therapy and patients not treated?

Most studies evaluating the occurrence of peri- and postoperative bleeding show anticoagulation therapy can be maintained when adequate local hemostatic maneuvers are used.

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As an example, a controlled clinical trial compared the occurrence of bleeding following dental extractions in individuals receiving oral anticoagulants (experimental group) versus patients that had never received oral anticoagulant therapy (control group). Tooth extractions were performed, and a piece of oxidized cellulose was placed only into the sockets in the experimental group. The wound

borders were sutured, and a gauze saturated with tranexamic for 30–60 minutes was applied with pressure in the wound. Both groups presented similar bleeding complications [81]. In a similar clinical trial , 161 tooth extractions wereperformed in patients undertaking warfarin. After tooth extraction, an oxidizedcellulose gauze was placed in the socket, and the wound was sutured. Patients were

assigned to four groups, according to their INR range (INR was 1.5–1.99 in group 1;2.0–2.49 in group 2; 2.5–2.99 in group 3; and 3.0–3.7 in group 4). No significantdifferences were found in the postoperative bleeding among groups. **[72-82]**

Conclusion

Hemostasis can always be considered as the main pillar for the success of any surgical treatment. Even

with the judicious application of local hemostatic agents, minor to moderate invasive surgeries can be safely performed. Several other factors like the application of local pressure during surgery, post-operative mouth rinses also aids in bleeding control. After consulting with a haematologist, patients with mild bleeding disorders can receive treatment in a primary care setting, but those with moderate to severe bleeding disorders must see a specialist. The best way to address dental problems that need invasive operations is in a hospital. Prior to any dental procedure, a haematologist consultation is advised to determine whether the patient requires prophylactic replacement medication. Prior to inferior alveolar nerve block, lingual infiltration, or floor of the mouth injection, factor replacement treatment is necessary. In most individuals with bleeding problems, restorative, prosthodontic, endodontic, and orthodontic procedures are thought to be safe unless more involved dental procedures are required. Patients with bleeding issues ought to refrain from taking aspirin and other nonsteroidal anti-inflammatory medicines (such ibuprofen and naproxen sodium).

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