

Bleeding disorders in dental practice: A diagnostic overview

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ABSTRACT

Dental health care workers are increasingly called upon to provide quality dental care to individuals whose bleeding and clotting mechanisms have been altered by inherited or acquired diseases. This provides an opportunity for the dentist who is trained in the recognition of oral and systemic signs of altered hemostasis to assist in the diagnosis of the underlying condition. A number of dental procedures result in the risk of bleeding that can have serious consequences, such as severe hemorrhage or possibly death, for the patient with a bleeding disorder. Oral care providers must be aware of the impact of bleeding disorders on the management of their patients. These disorders must be recognized from history, clinical examinations, and laboratory investigations, if indicated, prior to surgical procedures including those in dental surgery to prevent bleeding related complications. Safe dental care may require consultation with the patient's physician, systemic management, and dental treatment modifications. The purpose of this article is how to identify these patients with bleeding disorders.

Key words: Bleeding disorders, coagulation disorder, diagnosis

Access this article online

Website: www.jicdro.org

DOI: 10.4103/2231-0754.143529

Quick Response Code:



INTRODUCTION

Bleeding disorders are due to altered ability of blood vessels, platelets, and coagulation factors to maintain haemostasis. These may be inherited due to genetic transmission or acquired secondary to diseases affecting vascular wall integrity, platelets, and coagulation factors or due to drugs, radiation or chemotherapy. Most of the bleeding disorders are iatrogenic.

The most common inherited bleeding disorder is von Willebrand disease affecting approximately 1% of the population in the United States while Hemophilia A is the most common inherited coagulation disorders with an overall prevalence of 1 case for every 20000 people in the United States.^[1]

Normal control of bleeding

The three phases of haemostasis for controlling bleeding are *vascular, platelet and coagulation phases*. The coagulation phase is followed by *fibrinolytic phase* that dissolves the clot.

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Vascular phase (In Seconds)^[1,2]

Any injury triggers vascular phase, which consists of:

- Vasoconstriction of arteries and veins in the area of injury.
- Retraction of cut arteries.
- Build-up of extra vascular pressure by blood lost from cut vessels.

Platelet phase (primary hemostasis-in seconds)^[1,2]

- Platelets and vessel walls become sticky.
- Mechanical plugs of platelets seal off openings of cut vessels.

Coagulation phase (secondary haemostasis-in minutes) [Figure 1]^[1,2]

- Blood lost into surrounding areas coagulates through extrinsic and common pathways.
- Blood in vessels in areas of injury coagulates through intrinsic and common pathways.
- Takes place more slowly than other phases.

Fibrinolytic/Metabolic phase [Figure 2]^[1,2]

- It is activated simultaneously with the coagulation and functions to maintain fluidity of blood during coagulation.
- It also serves in clot lysis once tissue repair begins.

- c. Anti-thrombotic agents are released.
- d. Spleen and liver destroy these anti-thrombotic agents.

The coagulation cascade

The fundamental reaction of formation of the blood clot is conversion of the soluble protein fibrinogen into insoluble fibrin under the action of thrombin. The conversion of prothrombin to thrombin involves a series of plasma serine proteases (collectively referred to as clotting factors) that normally exist in inactive, pro enzyme forms, becoming activated in cascade sequence as shown in Figure 1.^[3]

The anticlotting mechanism and fibrinolysis

In vivo, there is a natural tendency for blood to clot. This is balanced by various naturally occurring anticoagulants. The most important of these is antithrombin III, which inhibits the activity of factors IX, X, XII as well as thrombin. This inhibition is greatly facilitated by heparin. Coagulation is also inhibited by thrombomodulin, secreted by intact endothelial cells and binds thrombin. The thrombomodulin-thrombin complex then activates a proenzyme protein C, found in plasma, to its enzymatic form and this, together with co-factor, protein S, in plasma, results in inactivation of activated factors V and VIII.

Fibrinolysis (dissolution of fibrin) occurs mainly through the action of plasmin, which degrades fibrin and fibrinogen into fibrin degradation products [Figure 2]. Plasmin is present

as an inactive precursor, plasminogen. Its conversion to plasmin is brought about primarily by tissue-type plasminogen activator (t-PA), a protein released from endothelium.^[3]

Modern concept of coagulation

The classical separation of coagulation into extrinsic and intrinsic pathways is overly complicated and now not thought to occur *in vivo*. Instead there is a common pathway of initiation [Figure 3]. Tissue factor from damaged vascular beds combines with factor VIIa and activates factors IX and X which leads to generation of small amounts of thrombin (IIa), followed by amplification. This then activates further factors (V and VIII), leading to massive production of thrombin and generation of fibrin from fibrinogen.^[4] Classification of bleeding disorders as detailed in Table 1.^[1,5,8]

IDENTIFYING PATIENTS AT RISK OF BLEEDING

History of:

- Bleeding problems in relatives.
- Bleeding problems after surgery, tooth extraction and trauma.
- Medications: Aspirin, anticoagulants, long term antibiotics.
- Illnesses associated with bleeding problems: Leukemia, congenital heart disease, liver disease, hemophilia
- Spontaneous bleeding

Clinical findings:

- Jaundice, pallor
- Spider angiomas
- Ecchymoses, petechiae
- Oral ulcers
- Hyperplastic gingival tissue
- Hemarthrosis

Screening laboratory tests:

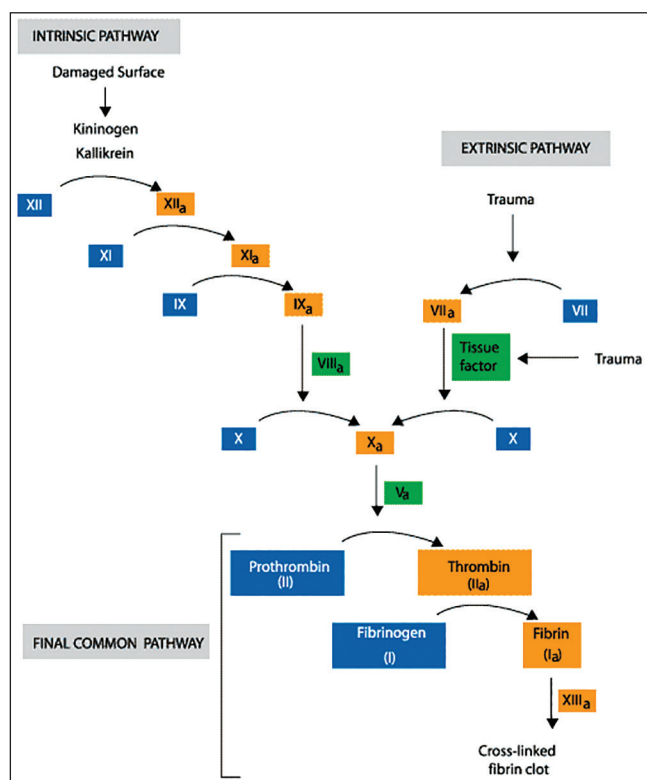


Figure 1: Coagulation cascade

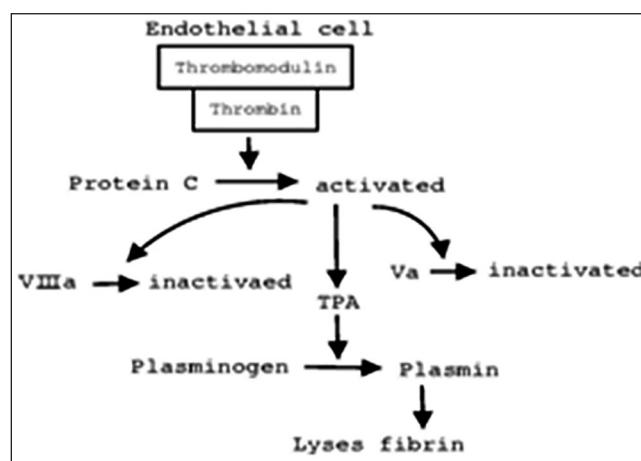


Figure 2: Fibrinolytic system

Table 1: Classification of bleeding disorders

Bleeding disorders	
Platelet related disorders	Quantitative disorders (Thrombocytopenia) Primary/idiopathic Secondary to diseases, chemicals and physical agents, drugs Qualitative disorders (Reduced Platelet Function) Inherited (von Willebrand's disease) Acquired Uraemia Cirrhosis Medications (e.g., Aspirin, Clopidogrel, NSAIDs)
Coagulation Disorders	Genetic Haemorrhagic Disorders Factor VIII deficiency (e.g. Haemophilia A) Factor IX deficiency [Hemophilia B (Christmas disease)] Factor VIII: C deficiency and platelet dysfunction (von Willebrand Disease) Factor XI deficiency (Hemophilia C) Factor II, V, VII, X-deficiency (Common Pathway Proteins) Factor XIII and fibrinogen deficiency Hypercoagulable Diseases Antithrombin III deficiency Protein C and S deficiency Acquired Prohaemorrhagic Liver Diseases Drugs Vitamin K deficiency Warfarin Heparin Hemodilution and massive transfusion Disseminated intravascular coagulation Immunoglobulin-mediated factor deficiency (VIII, V, XIII, X) Hyperfibrinolysis Venom-induced coagulopathy Prothrombotic Heparin-induced thrombocytopenia Antiphospholipid antibody syndrome (Lupus anticoagulant) Microvascular thrombosis Thrombotic microangiopathy Coumarin-Induced skin necrosis
Vascular Disorders	Scurvy Purpura Hereditary hemorrhagic telangiectasia Ehlers-Danlos syndrome
Fibrinolytic Defects	Streptokinase therapy Disseminated intravascular coagulation

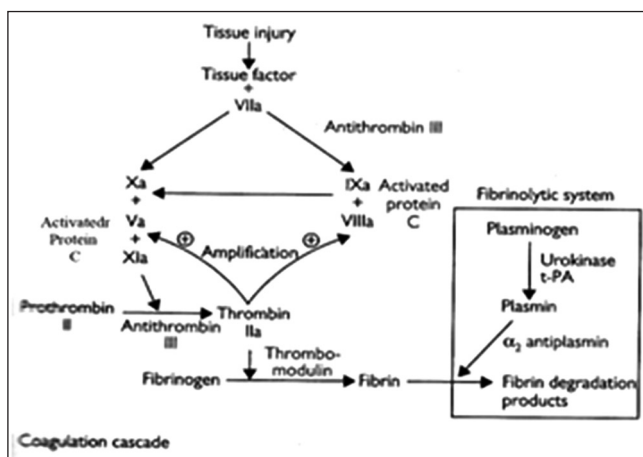


Figure 3: Coagulation cascade (modern concept)

- Platelet count
- Ivy bleeding time (BT)/PFA*
- Prothrombin Time (PT)&INR
- Activated partial thromboplastin time (aPTT)
- Thrombin time (TT)

[*Platelet function analysis may ultimately replace BT]^[1,5,6]

SCREENING LABORATORY TESTS FOR PLATELET ABNORMALITIES

Quantitative (Platelet Count):^[7]

- Normal Platelet Count-150,000~440,000/mm³
- Thrombocytopenia-Platelet < 150,000/mm³
- Severe intraop bleeding-Platelet < 40,000~70,000/ mm³
- Spontaneous bleeding-Platelet < 20,000/mm³

e. Minimal recommended preop platelet $>75,000/\text{mm}^3$

However, qualitative difference makes it unwise to rely solely on platelet count

Qualitative (platelet function):^[1]

- a. Ivy Bleeding Time-Normally 1~6 mins
- b. Closure Time from PFA 100-Normally 60~120 seconds

Ivy bleeding time

In the Ivy method [Figure 4], a blood pressure cuff is placed on the upper arm and inflated to 30 mm of Hg. A lancet or scalpel blade is used to make a stab wound on the underside of the forearm. An automatic, spring-loaded blade device is most commonly used to make a standard-sized cut. The area stabbed is selected so that no superficial or visible veins are cut. As these veins, because of their size, may have longer bleeding times, especially in people with bleeding defects. The time from when the stab wound is made until all bleeding has stopped is measured and is called the bleeding time. Every 30 seconds, filter paper or a paper towel is used to draw off the blood. The test is finished when bleeding has stopped completely.

No two wounds are the same, so the test does not reproduce well.

Platelet function analysis

The “Platelet Function Analyzer” [Figure 5] is an *in vitro* system for the detection of platelet dysfunction. It provides a quantitative measures of platelet function in anticoagulated whole blood. The system consists of a microprocessor-controlled instrument and a disposable test cartridge containing a biologically active membrane.^[1]

Generally 2 types of disposable test cartridges are used

- A standard cartridge containing collagen-ADP
- A cartridge containing collagen-epinephrine



Figure 4: Ivy bleeding time: Method

The instrument aspirates blood sample under constant vacuum from the sample reservoir through a capillary and a microscopic aperture cut into the membrane, that has been coated with collagen and with either ADP or epinephrine (EPI). The presence of either ADP or EPI and the high shear rates generated under the standardised flow condition result in platelet attachment, activation, and aggregation which slowly builds to a stable platelet plug of the aperture. The time required to obtain full occlusion of the aperture is reported as “closure time” (CT). An initial screen is done with collagen/EPI. If the CT is normal, it is unlikely that a platelet dysfunction exists. The collagen/ADP test is run to confirm an abnormal collagen/EPI test. If both tests are abnormal, it is likely that the patient has a platelet dysfunction and further testing for inherited or acquired bleeding disorders is indicated. If the collagen/ADP test is normal, then the abnormal collagen/EPI test may be due to aspirin ingestion. This is the most frequently encountered abnormal collagen/EPI result as a single dose of aspirin can affect platelet function for about 10 days.^[1]

SCREENING LABORATORY TESTS FOR COAGULATION DISORDERS

Prothrombin time (PT) and International normalized ratio (INR)

PT-Activated by tissue thromboplastin.

It tests extrinsic and common pathways.

INR: It is a mathematical ‘correction’ of the PT ratio (patient PT/mean normal PT) for differences in the sensitivity of thromboplastin reagents. It relies upon “reference” thromboplastins with known sensitivity to antithrombotic effects of oral anticoagulants (ISI). INR is the PT ratio one would have obtained if the “reference” thromboplastin had been used.

It allows for comparison of results between laboratories that is, T ratio) orrection”d as closure timebuilds to a stable platelet plug of the apperture tachments and standardizes reporting of the prothrombin time.



Figure 5: Platelet function analyzer

Equation for calculation of INR:

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

ISI = International Sensitivity Index, assigned to the test system

Normal values:

PT = 11-15 secs, INR = 1.0-1.2

Activated partial thromboplastin time (aPTT)

Initiated by phospholipid platelet substitute and activated by addition of contact activator (kaolin)

Tests intrinsic and common pathways

- Normal value: 25-35 secs

Thrombin time (TT):

Tests the common pathway, thus the ability to form initial clot from fibrinogen.

- Normal Value: 9-13 secs

[Control should be run for all the above mentioned tests]

- Characteristic changes in Inherited Coagulopathies: [Table 2]
- Characteristic changes in Acquired Coagulopathies: [Table 3]

RECENT ADVANCES IN DIAGNOSING BLEEDING DISORDERS

Thromboelastography (TEG)

Thromboelastograph is an instrument that measures the development of blood clot viscoelastic strength over time. A rotating piston is suspended in a cuvette filled with heated blood. As clot formation proceeds, the rotation of the piston is affected and characteristic curves are generated [Figure 6a and b].

TEG assesses the whole blood clotting system. The measurements are displayed as a graph from the beginning

Table 2: Characteristic changes in Inherited Coagulopathies^[6,7]

Clotting factor deficiency	PT (INR)	aPTT	TT	BT
Factor VIII	N	Increases	N	N
Factor IX	N	Increases	N	N
Von Willebrand Factor	N	Increases	N	Increases
Factor XI	N	Increases	N	N
Fibrinogen	N	N	Increases	Increases

Table 3: Characteristic changes in Acquired Coagulopathies^[6,7]

Disorders	PT (INR)	aPTT	TT	BT	Platelet count	Comments
Liver Disease	Increases	Increases	Increases	N or Increases	N or Decreases	Liver function tests abnormal
Vit K Deficiency	Increases	Increases	N or Increases	N	N	
DIC	Increases	Increases	Increases	Increases	Decreases	Consumable factors
Heparin	N	Increases	N or Increases	N or Increases	N or Decreases	Increases or decreases in Heparin Induced Thrombocytopenia
Warfarin	Increases	N	N	N	N	

of clot formation to fibrinolysis [Figure 7].^[7,8]

TEG provides information about the kinetics, strength and stability of the blood clot. The shape of the graph is determined by the viscoelastic properties of the blood and functional activity of the blood components. Its interpretation requires comprehensive knowledge.

Thromboelastogram- normal parameters

There are five parameters of the TEG tracing^[7]:

1. R: Period of time from the initiation of the test to initial fibrin formation
2. K: Time from the beginning of clot formation until the amplitude of TEG reaches 20 mm, representing the dynamics of clot formation.
3. α angle: Angle between the line in the middle of the TEG tracing and the line tangential to the developing body of the tracing, representing the kinetics of fibrin cross linking.
4. MA (maximum amplitude): Reflexes the strength of the clot, which is dependent on the No. and function of platelets and their interaction with fibrin.
5. A60: Measures the rate of amplitude reduction 60 min after MA, representing the stability of the clot.

The etiology of the coagulopathy may be obtained by analyzing the thromboelastograms [Figure 8].

Portable systems for rapid measurement of PT and INR

Portable systems for rapid measurement of PT and INR [Figure 9]

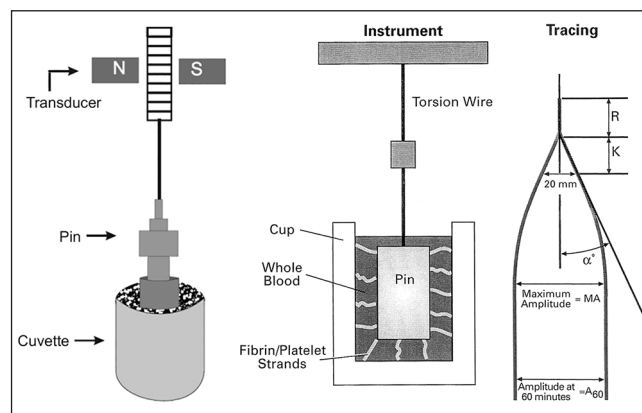


Figure 6: (a) Working principles of TEG (b) Working principles of TEG

have been specifically designed for healthcare professionals and their patients to enable on-the-spot analysis of coagulation levels (PT/INR) during mobile emergency treatment or for routine follow-up in a hospital ward and/or at their general practice. These systems are easy-to-use reflectance photometers, portable and battery-powered devices for rapid measurement of Prothrombin Time (PT) and International Normalized Ratio (INR). It has always been a challenge to health care professionals and to their patients which involves a venous blood sample or the patient themselves being sent to a laboratory. This is time-consuming and patient's compliance can be limited, as it often requires a second appointment with the healthcare professional. These systems provide accurate results from a single drop of capillary blood from the fingertip within one minute improving compliance.

- Systemic diseases which cause bleeding during procedure, their causes and their resulting coagulation defects: [Table 4].^[8]
- Treatment protocols in short: Principal Products for Systemic Management of
- Patients with Bleeding Disorders:^[9] [Table 5].

Patients on dual antiplatelet therapy

The combination of clopidogrel plus aspirin is mainly used in patients with percutaneous coronary stent intervention (coronary stents), in order to prevent thrombotic complications following placement. While the combination of aspirin and clopidogrel has been associated with bleeding risk with coronary artery bypass graft (CABG) surgery, there have been no studies to examine whether an increased risk of bleeding exists in the dental setting following extractions compared to more invasive surgical procedures (such as a CABG). Of significance however, is that a recent Science Advisory from the American Heart Association, American College of Cardiology, American College of Surgeons and the American Dental Association recommended continuing aspirin and clopidogrel therapy for minor dental surgical procedures in patients who have coronary artery stents or delaying treatment until the prescribed antiplatelet regimen is completed and warned of the significant thrombotic risks if therapy was discontinued.^[10]

According to the European school of thought, a literature review and guideline development process conducted by the Oral Medicine and Oral Surgery Francophone Society. They found that, based on agreement among professionals in the field, interruption of aspirin or thienopyridine therapy before dental procedures is unnecessary. Most such procedures carry a low risk of bleeding, and any bleeding that occurs can usually be controlled by local homeostasis. Oral, periodontal, and

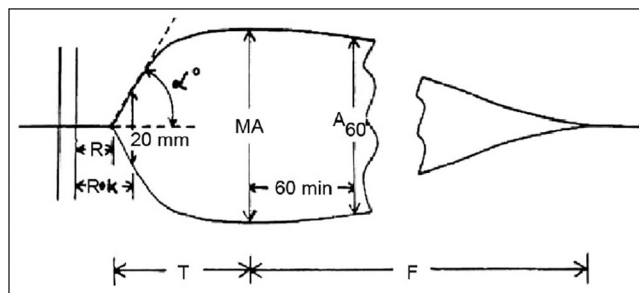


Figure 7: Thromboelastogram, normal parameters

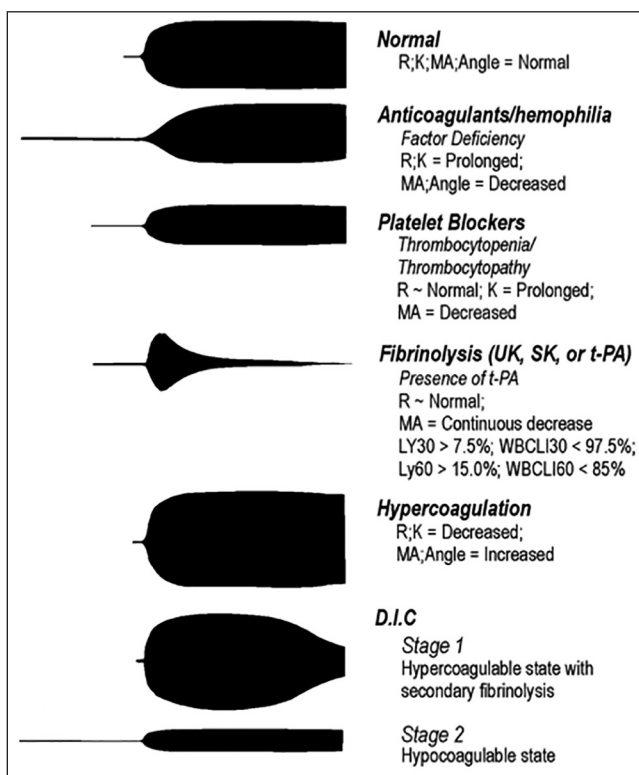


Figure 8: TEG patterns in some coagulation disorders



Figure 9: Portable systems for rapid measurement of PT and INR

implant dental surgery are not associated with high rates of bleeding. Any bleeding that occurs can usually be controlled

Table 4: Systemic diseases which cause bleeding during procedure, their causes and their resulting coagulation defects

Diseases	Common causes	Resulting coagulation defects
Renal failure and uremia	Diabetes mellitus Glomerulonephritis Pyelonephritis Hypertension	Inhibition of adhesion and primary aggregation of platelets from glycoprotein IIb-IIIa deficit
Hepatic failure	Alcohol abuse Hepatitis B and C Cancer (e.g., hepatocellular Carcinoma)	Obstructive jaundice: Deficiency of vitamin K-dependent factors II, VII, IX and X Loss of liver tissue and all clotting factors except VIII and von Willebrand's factor
Bone marrow failure	Alcohol abuse Cancer (e.g., leukemia) Myelosuppressive medications (e.g., chemotherapy for cancer) Uremia from renal failure	Reduced number of functioning platelets Anemia from bone marrow suppression

In all these above mentioned scenarios the patient has to be referred back to the concerned physician for management of the systemic disorders

Table 5: Principal products for systemic management of patients with bleeding disorders

Product	Description	Source	Common indications
Platelets	"One pack" = 50 mL; raises count by 6,000	Blood bank	<10,000 in nonbleeding individuals <50,000 presurgical <50,000 in actively bleeding individuals Nondestructive thrombocytopenia
Fresh frozen plasma	Unit = 150–250 mL 1 hour to thaw Contains Fs II, VII, IX, X, XI, XII, XIII and heat labile V and VII	Blood bank	Undiagnosed bleeding disorder with active bleeding Severe liver disease When transfusing >10 units blood
Cryoprecipitate	Unit = 10–15 mL Contains Fs VIII, XIII, vWF and fibrinogen	Blood bank	Immune globulin deficiency Hemophilia A, von Willebrand's disease, when factor concentrates/DDAVP are unavailable Fibrinogen deficiency
F VIII concentrate (purified antihemophilic factor)	Unit raises F VIII level by 2% Heat treated contains vWF Recombinant and monoclonal technologies are pure F VIII	Pharmacy	Hemophilia A, with active bleeding or presurgical; some cases of von Willebrand's disease
F IX concentrate (PCC)	Unit raises F IX level by 1–1.5% Contains Fs II, VII, IX, and X Monoclonal F IX is only F IX	Pharmacy	Hemophilia B, with active bleeding or presurgical PCC used for hemophilia A with inhibitor
DDAVP	Synthetic analogue of antidiuretic hormone 0.3 µg/kg IV or SQ Intranasal application	Pharmacy	Active bleeding or presurgical for some patients with von Willebrand's disease, uremic bleeding, or liver disease
E-Aminocaproic acid	Antifibrinolytic 25% oral solution (250 mg/mL) Systemic: 75 mg/kg q6h	Pharmacy	Adjunct to support clot formation for any bleeding disorder
Tranexamic acid	Antifibrinolytic 4.8% mouth rinse – not available in US Systemic: 25 mg/kg q8h	Pharmacy	Adjunct to support clot formation for any bleeding disorder

F = Factor; DDAVP = Desmopressin acetate; PCC = Prothrombin complex concentrate

locally, so discontinuation of anti-platelet therapy is not recommended.^[11-13]

According to the recently published POISE-2 study on aspirin in patients undergoing noncardiac elective surgery; "Administration of aspirin before surgery and throughout the early postsurgical period had no significant effect on the rate of a composite of death or nonfatal myocardial infarction but increased the risk of major bleeding."^[14]

CONCLUSION

- A number of surgical procedures including those performed in dentistry may cause bleeding. Normally these procedures carry very little risk; however, this is compounded in the presence of

bleeding disorders.

- Once the patient with bleeding problem has been identified from history, clinical examination, and laboratory diagnostic tests; steps can be taken, to greatly reduce the risk associated with these procedures.

REFERENCES

- Little JW, Falace DA, Miller CS, Rhodus NL, editors. Dental Management of the Medically Compromised Patient. 8th ed.; 2012.
- Morgan GE Jr, Mikhail MS, Murray MJ, editors: Clinical Anaesthesiology. 5th ed. Lange; 2013.
- Minors DS. Haemostasis, blood platelets and coagulation. Anaesth Intensive Care Med 2004;1:11-3.
- Allman KG, Wilson IH, editors. Oxford Handbook of Anaesthesia. 3rd ed. Oxford: Oxford University Press; 2010.

5. Brown V. Clinical aspects of coagulation. *Anaesth Intensive Care Med* 2004;1:14-7.
6. Gupta A, Epstein JB, Cabay RJ. Bleeding disorders of importance in dental care and related patient management. *J Can Dent Assoc* 2007;73:77-83.
7. In: Duke J, editor. *Anesthesia Secrets*. 4th ed. Elsevier; 2010.
8. Yao FF, editor. *Anaesthesiaiology Problem-Oriented Patient Management*. 7th ed. Lippincott-Raven; 2011.
9. Greenberg Martin S. Glick Michael: *Burket's Oral Medicine*. 11th ed. McGraw-Hill Medical; 2011.
10. Henry RG. Dental management of patients taking antiplatelet medications. *Tex Dent J* 2009;126:608-16.
11. Oral Medicine and Oral Surgery Francophone Society. Management of patients under anti-platelet agents' treatment in odontostomatology.
12. Verma G. Dental extraction can be performed safely in patients on aspirin therapy: A timely reminder. *ISRN Dent* 2014;2014:463684.
13. Bertrand ME. When and how to discontinue antiplatelet therapy. *Eur Heart J Suppl* 2008;10 (Supplement A):A35-41.
14. Aspirin in Patients Undergoing Noncardiac Surgery: POISE-2 clinical trial (Perioperative ischemic evaluation study). Gov number, NCT01082874. Published online on March 31, 2014, at NEJM.org.

Cite this article as: Goswami A, Bora A, Kundu GK, Ghosh S, Goswami A. Bleeding disorders in dental practice: A diagnostic overview. *J Int Clin Dent Res Organ* 2014;6:143-50.

Source of Support: Nil. **Conflict of Interest:** None declared.