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Review Article

Hemophilia: What a dental surgeon needs to know?

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Abstract:

Hemophilia is a medical condition that can cause medical emergency for dentist. Hemophilia patients have high risk of bleeding during various dental procedures. A dentist must know the impact of blood dyscrasias in the management of their patients. A good history taking in these patients is required to prevent any unwanted incident in the operatory, & more so if any invasive treatment is planned. So management of bleeding in these patients during & after surgery is the biggest challenge for the dental surgeons. Here we present a review on management of hemophilic patient in different dental procedure for which literature obtained from published articles, books & manual.

Key words: Hemophilia, Factor VIII, Oral health, Dental management.

Introduction

Bleeding disorders are the group of disorders in which blood does not clot properly. An affected individual may bleed spontaneously or for longer than a healthy person may.[1] Dentists may encounter patients with various types of bleeding disorders in their day to day practice. Initial recognition of such bleeding disorders & their possible systemic causes play a significant role in reducing potential complications. Bleeding disorders can be classified as coagulation factor deficiencies, platelet disorders, vascular disorders & fibrinolytic defects.[2] Among these, hemophilias are the most frequently occurring congenital plasmatic hemorrhagic diathesis. It is the commonest X-linked hereditary bleeding disorders affecting more than 400,000 people worldwide, which occurs due to absence or deficiency of plasma clotting factors, resulting in prolong & uncontrolled bleeding either spontaneously or following trauma.[3] Two commonest forms of hemophilia are Hemophila A & Hemophilia B, both are inherited as X linked recessive pattern, but incidence is different. Hemophlia A is related to factor VIII deficiency & occurs in 80-85% of patients & has an incidence of 1:5000 in male population. Hemophilia B (Christmas disease) is a deficiency of factor IX & is diagnosed 10 times less frequently than hemophilia A. It accounts 10-15% of hemophilia cases with incidence of 1:15000.[4,5] Uncommon types are, Hemophilia C or Rosenthal syndrome that result in deficiency of factor IX, parahemophilia or Owren's syndrome (deficiency of factor V) & acquired hemophilia.[1,6] Hemophilia is one of the pervasive bleeding disorders in the world that entail attention. It challenges the skills of dental specialists by inducing bleeding during treatment, which can even be life threatening in certain cases. The aim of this article is to review Hemophilia with an emphasis on its management in different dental procedure.

Epidemiology

Hemophilia is prevalent worldwide & occurs in all racial & socioeconomic groups.[4] According to the report of the annual global survey (AGS) 2020, published by the World federation of Hemophilia(WFH) with participating 144 countries, total number of hemophilia A or B & types of unknown is 241, 535 of which 24.6/100,000 males for all hemophilia A where 9.5/100,000 males for severe Hemophilia A & 5.0/100,000 males for all hemophilia B where 1.5/100,000 males for severe Hemophilia B. Number of Hemophilia A & Hemophila B patients with clinically identified inhibitors was 5013 & 363. However, these figures are an underestimate than actual ones. So majority of the patients remain under diagnosed & it is true that most of them are living in the developing countries. In Bangladesh (population 160 millions)would have 10800 hemophilics. But reported cases are only 424(367 Hemophila A & 57 Hemophila B) & there is no inhibitors. Among the reported cases, only 9 cases are under 5years of age.[7] The severity of hemophilia has been classified into the following three forms by the Scientific & Standarization committee of the International Society on Thrombosis & Hemostasis.[Table-I][8]

Table-I: Relationship of factor level to the severity of Hemophilia

Severity	Clotting factor level
Severe	<1 IU dl - 1 (<0.01 IU ml - 1) Or <1% of normal
Moderate	1-5 IU dl - 1 (0.01-0.05 IU ml - 1) Or 1-5% of normal
Mild	5-40 IU dl - 1 (0.05-0.40 IU ml -1) Or >5-40% of normal

Clinical feature in Hemophilics

Severe cases may manifest with massive intrauterine hemorrhage leading to still birth & neonatal intracranial hemorrhage. Tendency towards easy bruising, massive hemorrhage after trauma or minor surgical procedures are commonly encountered. Spontaneous hemorrhage from the middle ear ,epistaxis, hemarthrosis (70-80%) & bleeding into soft tissues (10-20%) may occur. Bleeding from central nervous system (CNS) constitutes less than 5%. Complications in hemophiliacs include musculoskeletal complications such as chronic hemophilic arthropathy, synovitis, constractures, pseudotumor formation, development of inhibitors against factor VIII & most importantly transfusion related infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis A virus.[9,10]

Prevalence of oral diseases in Hemophilics

The main oral diseases affecting patients with hemophilia are bleeding from multiple sites in the mouth from gingiva & extraction sockets. Patients may have history of multiple bleeding events over their lifetime. Poor oral hygiene & iatrogenic factors can also induce the oral bleeding. In toddlers, oral ulcerations & ecchymosis involving lips & tongue are common. A study by Sonis & Musselman found an average of 29.1% bleeding events per year in hemophilia patients out of which 9% involved oral structures(labial frenum 60%;tongue 23%; buccal mucosa 17%;gingiva& palate 0.5%).[11] Hemarthrosis of temporomandibular joints is unusual. Therefore,for dental consideration through history taking is mandatory for proper diagnosis & management of hemophilia.[12]

Investigation & Evaluation

Diagnosis of hemophilia: At birth hemophilia is diagnosed either due to known family history or after presenting with clinical history of exaggerated bleeding response to minor trauma.

Prenatal testing: A gene test can be performed during pregnancy. For this, a sample of placenta is removed from the uterus & chorionic villus sampling (CVS) test perform.[13]

Two different approaches of the genetic evaluation of bleeding disorders now are used: tracking the defective chromosome in the family (linkage analysis) or identification of the disease-causing mutation in the patient's coagulation factor gene(direct mutation detection).[14,15]

Blood testing: If a doctor suspects a child may have hemophilia a blood test can determine whether the patient has hemophilia A or B. Blood tests can be performed from the time of birth onwards.[13]

Laboratory evaluation: Laboratory test related to the differentiation of hemophilia types. It demonstrates normal platelet count, normal bleeding time (BT),prolonged activated partial thromboplastin time (APTT), normal prothrombin time (PT).Screening tests show a prolonged activated partial thromboplastin time in severe & moderate cases but may not show prolongation in mild hemophilia. APTT is considered normal if the control APTT & the test are within 10s of each other. Control APTT is usually 25+10s. It is determined by adding an activator to plasma (e.g. kaolin) along with extract of phospholipid. Normal bleeding time assesses the vascular & platelet phases of blood clotting but is of limited sensitivity.PT test evaluates the extrinsic system & measures the presence or absence of clotting factor I,II,VII,X. In order to standardize PT in1983,the World Health Organization (WHO) introduced the international normalized ratio (INR).It is the ratio between the PT of a patient in seconds & control PT standardized by means of International Sensitivity Index (ISI).For a PT value within the normal range, INR=1.[2,16,17] Definitive diagnosis is established by quantification of the procoagulant activity of factor VIII, which is found to be reduced in hemophilia A & factor IX ,which is found to be reduced in hemophila B. For specific study, correction study with deficient plasma might identify the types of hemophilia &with normal plasma might suggest presence of inhibitors. Quantitative assay of FVIII, FIX helps in identify the types of hemophilia & its severity.

Management Strategies:

Hemophilia is managed through a combination of education, clotting factor replacement & comprehensive care. A number of dental procedures do not require augmentation of coagulation factor levels. There may be four therapeutic management options depending on the type of haemphilia:

1. Coagulation factor replacement therapy;
2. Release of endogenous factor stores using desmopressin(DDAVP);
3. Improving clot stability by antifibrinolytic drugs, for example, tranexamic acid;
4. Local haemostatic measures.[18]

Providing dental treatment to Hemophilic patients: The management of patients with hemophilia depends on the severity of the condition (mild,moderate,severe) & the invasiveness of the planned dental procedure.[19] If the procedure has limited invasiveness & the patient has a mild bleeding disorder, only slight or no modification will be required. In patients with severe bleeding disorders, the goal is to minimize the challenge to the patient by restoring the hemostatic system to acceptable levels & maintaining hemostasis by local adjunctive methods.[20] Avoidance of brusque maneuvers during dental management & local hemostatic measures are recommended. It is also essential to prevent accidental damage to the oral mucosa when carrying out any dental procedure by the cautions use of saliva ejectors, protection of soft tissues during restorations, taking care in the placement of X-ray films. Aspirin & its derivatives must be avoided. Restorable sutures are recommended if needed.[19]

Surgical treatment

Hemophilia patients are at high risk of secondary bleeding following oral surgery. International guidelines advise the use of clotting factor replacement therapy for all invasive surgical interventions in patients with hemophilia.[21] The World Federation of Hemophilia (WFH) recommends the use of factor concentrates to cryoprecipitate or fresh frozen plasma for replacement therapy in the patients with hemophilia. Surgical treatment must be planned to minimize the risk of bleeding or hematoma formation. Patients's hematologist must be consulted before treatment initiation regarding the factors levels, factor replacements, type of surgery & the need for systemic hemostatics. If necessary, replacement therapy comprising coagulation factor VIII or desmopressin (DDAVP) [Table-III].[22] is administered. Allthe measures to reduce the risk of infection (administration of antibiotics,topical antiseptic mouthwash) must be instituted. Aspirin, aspirin containing medication, NSAIDs should be avoided which may prolong bleeding. For the patients taking warfarin, their INR should be measured before the surgical procedure. The normal therapeutic range is 2.0-3.0.According to current recommendations, most surgical procedures can be performed without altering the warfarin dose if the INR is less than 3.0.[23] In pre-operative management, Factor VIII is given 1hour before procedure, Dose in units= weight in kg x25.Tranexamic acid 1g(30mg/kg) by i/v or orally 1hour before surgery.

Pain control by local anesthesia

Although there are no restrictions with respects to the type of local anesthetics, but Local anaesthesia injection technique should be avoided in the absence of factor VIII replacement. Nerve block anaesthsia (inferior alveolar or posterior superior alveolar nerve)are contraindicated unless there is no better alternative & prophylaxis is provided as the anesthetic solution is deposited in a highly vascularized area, which carries a risk of hematoma formation. The commonly used blocks require minimum clotting factor levels of 20% to 30%.Infiltration anesthesia may be used with caution but lingual infiltration must be avoided. An anesthetic with vasoconstrictor should be used when possible. Alternative techniques, including sedations with diazepam or nitrous oxide-oxygen analgesia, can be employed to reduce or eliminate the need of anesthesia. Patients undergoing extensive treatment requiring factor replacement may be treated under general anesthesia in a hospital operating room.[20]

Table-II: Dental anaesthetic procedure

No hemostatic cover Required	Hemostatic cover Required
Buccal infiltration	Inferior dental block
Intra-papillary injection	Lingual infiltration
Intraligamentary injection	

Oral Surgery

Surgery must be performed with caution to reduce trauma to soft tissues. Proper suture placement may help to prevent clot formation postoperatively & surgical stent should be fabricated to protect the surgical site during healing. Post extraction bleeding should initially be managed with pressure & other local hemostatic agents such as fibrin glue, oxidized cellulose. Anti fibrinolytic agents such as tranexamic acid (1g 4 times daily) for 7 days. Epsilon aminocaproic acid (50mg/kg 4times daily) continued for 7days.[24,25] Persistent oozing & bleeding following the procedure requires hematologist consultation.[26]

Table-III: Clotting factor administration in hemophilia patients prior to surgery

Condition	Dose of Factor VIII
Mild Bleeding	Dose: 15U/kg factor VIII every 8-12h for 1-2days Target: 30% of normal level.
Major bleeding	Dose: 50U/kg factor VIII every 8-12h for 7-14 days Target: 80-100% of normal level
Adjuvant Therapy	Desmopressin, tranexamic acid or epsilon Aminocaproic acid (for mild disease)

Elective treatment

Scaling & Periodontal Procedures: Periodontal health is of critical importance in patients with bleeding disorders.[2] as inflamed & hyperemic gingival tissue are at increased risk of bleeding. Patients with coagulopathies may neglect their oral health due to fear of bleeding during tooth brushing & flossing which leads to increase gingivitis, periodontitis & caries.[20] Routine periodontal probing, supragingival scaling & polishing (ultrasonic scaling)is unlikely to cause prolonged bleeding for patients., especially those with mild conditons.[27] Factor replacement therapy is seldom needed for subgingival scaling & root planning if those procedures are done carefully. For severely inflamed tissues, initial treatment with chlorhexidine mouthwashes & gross debridement is recommended to reduce tissue inflammation before deep scaling.[28] Periodontal surgery is regarded as a high risk procedure with significant risk of blood loss & poses greater challenge to hemostasis than a simple extraction.[25]

Prosthodontic procedure

These procedures do not usually involve a considerable risk of bleeding. Trauma should be minimized by careful post insertion of removable prosthesis. Oral tissue should be handled delicately during the various clinical stages of prosthesis fabrication to reduce risk of ecchymosis.[20]

Endodontic treatment

Endodontic therapy is preferred over extraction whenever possible, as endodontic treatment generally has low risk of bleeding in patients with hemophilia. However, if vital pulp tissue is present at the apical foramen this may bleed for some time & can cause pain. the use of 4% sodium hypochlorite for irrigation & calcium hydroxide paste appears to minimize this problem.Reaming through the apex should be avoided. Endodontic surgical procedures may require factor replacement therapy upto 50-75%.[29]

Restorative procedure

General restorative procedures do not pose a significant risk of bleeding. Care should be considered to avoid injuring the gingiva while placing rubber dam clamps, matrices, wedges & soft tissue trauma. A rubber dam should be used to prevent soft tissue lacerations. High-speed suction can injure the mucosa in the floor of the mouth & cause hematoma & ecchymosis, thus they should be used carefully[20].

The latest treatment procedure-Gene therapy

Through the introduction of a functional gene into a target cell, gene therapy aims to restore, modify or enhance cellular functions.[30] In 1984 the current recombinant treatment of hemophilia was the isolation & cloning of the genes that produce clotting factor VIII & clotting factor IX. Hemophilia is an ideal disease to target for gene therapy since it is caused by mutations in a single identified gene. So recombinant technology made it possible to prepare replacement factor from mammalian & human cells rather than human plasma. A slight increase in factor activity can make a severe hemophilic to be mild. Main issue remains: finding of a gene delivery system which is nonimmunogenic so as to allow for long term expression. More than 25 patients with hemophilia have now been treated in phase I gene-therapy protocols.[4] However, hemophilia is no longer a life-threatening disease with current therapy that is both safe & effective.[31]

Conclusion

Hemophilic patients form privilege group for dental professionals because of uncontrolled bleeding during dental procedure which may be life threatening. Moreover, maintenance of oral hygiene & prevention of oral disease is of great significance to improve the quality of life & avoid the dangers of surgery. Improvement in communication among hematologist, general physician, oral physician & surgeon & those in general dental practices is necessary for effective dental management of hemophilic patients. So proper medical history & consult with hematologist always be helpful to prevent bleeding complications & successful dental practice management.

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