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‘Bleeding Disorders’- Significance in Prosthodontic Treatments

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Bleeding disorders are a group of conditions that affect the way blood clots, leading to excessive bleeding either spontaneously or after an injury. Bleeding disorders are a diverse group of conditions that lead to an increased tendency to bleed due to abnormalities in the hemostatic process.[1] Oral signs and symptoms of bleeding disorders can vary depending on the specific condition, but they generally include increased bleeding and difficulty controlling bleeding within the oral cavity. Bleeding disorders are crucial for dentists to understand because they can significantly impact dental procedures, potentially leading to excessive bleeding or complications.[2] Here are some of the most important bleeding disorders that dentists should be aware of:

1. Hemophilia A and B

Hemophilia A and B are X-linked recessive disorders caused by deficiencies in clotting factor VIII (Hemophilia A) or factor IX (Hemophilia B). Patients with these conditions can experience prolonged bleeding even after minor injuries, including during dental procedures.Dentists must take precautions to prevent excessive bleeding during extractions, periodontal surgery, or other invasive procedures. Consultation with a hematologist is often necessary to manage these patients properly.[3]

2. Von Willebrand Disease (VWD)

VWD is the most common inherited bleeding disorder, resulting from a deficiency or dysfunction of von Willebrand factor, which helps platelets adhere to blood vessel walls and carries factor VIII. Patients may experience mucosal bleeding, making dental procedures like scaling or extractions risky. Pre-treatment with desmopressin (DDAVP) or von Willebrand factor concentrates may be required.[4]

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3. Platelet Disorders

Platelet disorders include thrombocytopenia (low platelet count) and qualitative platelet defects (e.g., Glanzmann's thrombasthenia). These conditions lead to impaired clot formation. Patients may exhibit prolonged bleeding during and after dental procedures. Platelet count and function should be assessed before surgery, and platelet transfusions may be necessary for severe cases.[5]

4. Liver Disease

Chronic liver diseases like cirrhosis can lead to coagulopathy due to impaired synthesis of clotting factors, thrombocytopenia, and increased fibrinolysis. These patients are at increased risk of bleeding during dental procedures. Pre-operative assessment of liver function tests, coagulation profile, and platelet count is essential.[6]

5. Vitamin K Deficiency

Vitamin K is essential for the synthesis of clotting factors II, VII, IX, and X. Deficiency can occur due to malabsorption syndromes, liver disease, or the use of vitamin K antagonists like warfarin. Implications for Dentistry: Dentists need to evaluate the coagulation status of patients with vitamin K deficiency before invasive procedures. Supplementation or adjustment of anticoagulant therapy may be required.[7]

6. Disseminated Intravascular Coagulation (DIC)

DIC is a complex acquired disorder characterized by widespread activation of coagulation, leading to the consumption of platelets and clotting factors, resulting in severe bleeding. Dental treatment in patients with DIC requires immediate medical attention and coordination with a multidisciplinary team to manage the bleeding risk.[8]

Pathophysiology of Bleeding Disorders:

Understanding the pathophysiology of these disorders is crucial for their effective management. Here's an overview of the pathophysiology of some key bleeding disorders:

A. Hemophilia A and B

Pathophysiology:

Hemophilia A is caused by a deficiency in clotting factor VIII, while Hemophilia B (also known as Christmas disease) is due to a deficiency in factor IX. Both factors are essential in the coagulation cascade, particularly in the intrinsic pathway, where they act to amplify the production of thrombin. In the absence or significant reduction of these factors, the coagulation cascade is severely impaired, leading to inadequate thrombin generation and a poor fibrin clot formation. This results in prolonged bleeding, especially in joints, muscles, and soft tissues.[9]

B. Von Willebrand Disease (VWD)

Pathophysiology:

VWD is caused by quantitative or qualitative defects in von Willebrand factor (vWF), a large multimeric glycoprotein crucial for platelet adhesion to subendothelial collagen and for stabilizing factor VIII in the circulation. Deficiency or dysfunction of vWF leads to defective platelet adhesion and secondary reduction in factor VIII levels, which compromises both primary hemostasis (platelet plug formation) and secondary hemostasis (fibrin clot stabilization), causing mucocutaneous bleeding.[10]

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C. Platelet Disorders

Pathophysiology:

Thrombocytopenia: A reduced number of platelets can result from bone marrow disorders (e.g., leukemia, aplastic anemia), increased peripheral destruction (e.g., immune thrombocytopenic purpura), or sequestration in the spleen. The reduced platelet count leads to impaired formation of the primary platelet plug, prolonging bleeding time.Conditions like Glanzmann's thrombasthenia (defective platelet aggregation due to integrin αIIbβ3 deficiency) and Bernard-Soulier syndrome (defective platelet adhesion due to glycoprotein Ib deficiency) impair the ability of platelets to form a stable plug, resulting in a bleeding tendency despite a normal platelet count. [11]

D. Liver Disease

Pathophysiology:

The liver is the primary site for the synthesis of most coagulation factors, including fibrinogen, prothrombin, and factors V, VII, IX, X, XI, and XII, as well as natural anticoagulants like protein C and S. Liver disease, such as cirrhosis, leads to impaired production of these factors, contributing to a coagulopathy. Additionally, liver disease often results in portal hypertension, leading to hypersplenism and consequent thrombocytopenia, further exacerbating bleeding risks. Impaired clearance of activated clotting factors and fibrinolysis inhibitors can also contribute to a complex coagulopathy.[12]

E. Vitamin K Deficiency

Pathophysiology:

Vitamin K is essential for the post-translational γ-carboxylation of glutamic acid residues on factors II (prothrombin), VII, IX, and X, which is necessary for their calcium-binding activity in the coagulation cascade. Vitamin K deficiency, whether due to dietary insufficiency, malabsorption, or the use of vitamin K antagonists (e.g., warfarin), leads to the production of inactive forms of these clotting factors, resulting in a bleeding diathesis characterized by prolonged prothrombin time (PT).[13]

F. Disseminated Intravascular Coagulation (DIC)

Pathophysiology:

DIC is an acquired syndrome characterized by systemic activation of the coagulation cascade, leading to the formation of microvascular thrombi throughout the body. This widespread clotting depletes platelets and coagulation factors, causing secondary fibrinolysis and severe bleeding. The underlying triggers of DIC include sepsis, trauma, malignancies, and obstetric complications, all of which can induce the release of procoagulant substances into the circulation, overwhelming the body's regulatory mechanisms.[14]

The oral signs and symptoms of each bleeding disorder: [1,2,15]

Below is a summary of oral signs and symptoms associated with some common bleeding disorders:

Hemophilia

Patients with hemophilia may experience prolonged or excessive bleeding following tooth extractions or other dental surgeries. Spontaneous bleeding: Unprovoked bleeding, especially from the gums, can occur without apparent injury. Hemarthrosis of the temporomandibular joint (TMJ): Bleeding into the TMJ can cause pain and swelling. Formation of blood-filled swellings in the oral mucosa or after minor trauma. Bruising of the oral soft tissues, often without significant trauma.

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2. Von Willebrand Disease (vWD)

Spontaneous or prolonged bleeding from the gums. Prolonged bleeding after dental procedures: Similar to hemophilia, patients may experience excessive bleeding after dental work. Petechiae: Small red or purple spots on the oral mucosa due to minor haemorrhages. Nosebleeds that may be associated with oral bleeding.

3. Platelet Disorders (e.g., Thrombocytopenia)

Spontaneous bleeding of the gums, often without trauma. Small red or purple spots on the mucous membranes, tongue, or palate. Difficulty stopping bleeding following dental procedures or even minor injuries within the mouth.Larger areas of bruising, often on the oral mucosa.

4. Disseminated Intravascular Coagulation (DIC)

Unprovoked bleeding from the gums. Generalized bleeding from various oral sites, including the tongue, cheeks, and floor of the mouth. Extensive bruising and small red or purple spots on the oral mucosa due to widespread clotting abnormalities. Significant and potentially life-threatening bleeding after dental extractions or surgeries.

5. Vitamin K Deficiency

Persistent or spontaneous bleeding from the gums. Bruising in the oral cavity, particularly on the soft tissues. Increased bleeding tendency following dental work due to impaired clotting factor synthesis. Generalized bleeding from the oral mucosa.

6. Liver Disease (e.g., Cirrhosis)

Spontaneous or prolonged bleeding from the gums due to impaired clotting factor production.

Small and large hemorrhages on the oral mucosa due to coagulopathy associated with liver disease. Difficulty controlling bleeding after dental procedures, reflecting the liver's impaired ability to produce clotting factors. Yellow discoloration of the oral mucosa due to elevated bilirubin levels.

Bleeding disorders and their significance in Prosthodontic treatment: [1,2,16,17]

Bleeding disorders pose significant challenges in prosthodontic treatment due to the potential for excessive bleeding during and after procedures. Proper management and understanding of these conditions are crucial for ensuring patient safety and successful treatment outcomes. Here's an overview of how bleeding disorders impact prosthodontic treatment:

Hemophilia

Impact on Prosthodontics: Prosthodontic procedures such as tooth extractions, implant placements, or even minor adjustments involving the gingiva can lead to prolonged bleeding. Wound healing may be impaired due to inadequate clot formation, necessitating careful planning and coordination with a hematologist. Hemostatic agents, antifibrinolytics, and possibly factor replacement therapy should be considered before any invasive procedure. Careful monitoring and non-invasive techniques are essential when fitting dentures or other prostheses to avoid mucosal trauma.

Von Willebrand Disease (vWD)

Impact on Prosthodontics: Similar to hemophilia, vWD patients are at risk for prolonged bleeding during invasive procedures. Desmopressin (DDAVP) may be administered to increase von Willebrand factor levels prior to surgery. Local hemostatic measures are essential. Non-invasive adjustments and careful impression-taking are recommended to minimize trauma and bleeding.

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Platelet Disorders (e.g., Thrombocytopenia)

Impact on Prosthodontics: Reduced platelet count leads to an increased risk of bleeding during even minor prosthodontic interventions. Platelet transfusions may be necessary before procedures. Local hemostatic measures such as sutures, pressure packs, or hemostatic agents should be readily available. Dentures may need to be adjusted frequently to prevent mucosal irritation, which can lead to bleeding.

Disseminated Intravascular Coagulation (DIC)

Impact on Prosthodontics: Patients with DIC have widespread clotting and bleeding tendencies, making any prosthodontic procedure potentially life-threatening. Coordination with medical specialists is critical. Invasive procedures are generally avoided unless absolutely necessary. Intensive monitoring for any signs of bleeding, even with non-invasive procedures.

Vitamin K Deficiency

Impact on Prosthodontics: Vitamin K is essential for clotting factor synthesis, and its deficiency can lead to bleeding during procedures. Vitamin K supplementation may be required before any prosthodontic treatment. Warfarin therapy (if present) should be carefully managed. Maintaining good gingival health is critical to prevent spontaneous bleeding, which can complicate the fitting and wearing of prostheses.

Liver Disease (e.g., Cirrhosis)

Impact on Prosthodontics: Liver disease affects the synthesis of clotting factors, leading to increased bleeding risk during procedures. Invasive procedures should be minimized. Non-invasive techniques are preferred, and careful attention should be paid to post-operative bleeding. Frequent follow-up is necessary to ensure that any prosthesis does not cause mucosal injury, which could lead to bleeding.

General Considerations in Prosthodontics for Patients with Bleeding Disorders

Pre-Treatment Planning:

A thorough medical history and consultation with the patient's physician or hematologist are essential before starting treatment. Consideration of non-invasive alternatives and use of local hemostatic agents.

Intra-Operative Management: Use of atraumatic techniques and minimizing soft tissue injury. Readiness to manage unexpected bleeding with appropriate local and systemic hemostatic measures.

Post-Treatment Care: Careful post-operative monitoring for signs of bleeding or hematoma formation. Instructions for the patient on managing any bleeding at home, such as applying pressure or using prescribed hemostatic agents.

Precautions to be taken during prosthodontic treatments in various bleeding disorders

When managing prosthodontic treatments for patients with bleeding disorders, specific precautions are crucial to minimize the risk of excessive bleeding and ensure patient safety. Below are detailed precautions along with exact references.

1. Hemophilia

Pre-Treatment Precautions:

a).Consultation with Hematologist: Essential to determine the patient's clotting factor levels and to plan for prophylactic administration of clotting factor concentrates before any invasive procedures.

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b).Laboratory Testing: Baseline clotting tests (e.g., APTT) should be reviewed to assess the severity of the disorder.

Intraoperative Precautions:

a).Atraumatic Techniques: Minimize soft tissue trauma during procedures such as impression-taking, denture fitting, or crown placement.

b).Local Hemostasis: Use of hemostatic agents like fibrin glue or absorbable gelatin sponges.

Post-Treatment Precautions:

a).Pressure Dressings: Apply pressure with gauze or hemostatic materials to prevent post-operative bleeding.

b).Follow-Up: Close monitoring post-procedure, with the patient advised to avoid vigorous activities that could trigger bleeding.[19]

2. Von Willebrand Disease (vWD)

Pre-Treatment Precautions:

a).Desmopressin (DDAVP): This medication may be administered prior to procedures to increase von Willebrand factor and factor VIII levels.

b).Hematology Consultation: To determine the need for von Willebrand factor concentrates or other prophylactic treatments.

Intraoperative Precautions:

a).Gentle Tissue Handling: Avoidance of procedures that may cause excessive trauma to the mucosa or gingiva.

b).Hemostatic Measures: Local application of tranexamic acid or aminocaproic acid may be beneficial.

Post-Treatment Precautions:

a).Prolonged Observation: Longer observation period after procedures to monitor for delayed bleeding.

b).Patient Instructions: Provide detailed instructions on managing bleeding at home and when to seek medical help.[1]

3. Platelet Disorders (e.g., Thrombocytopenia)

Pre-Treatment Precautions:

a).Platelet Count Assessment: Ensure platelet count is adequate (usually >50,000/μL) for minor procedures; consider platelet transfusion if necessary.

b).Hematology Involvement: Coordinate with the patient's hematologist to optimize platelet levels before treatment.

Intraoperative Precautions:

a).Minimize Trauma: Use sharp instruments and avoid excessive pressure to reduce tissue trauma.

b).Topical Hemostatics: Application of platelet-rich plasma (PRP) or other topical agents can help control bleeding.

Post-Treatment Precautions:

a).Extended Monitoring: Monitor the patient for longer periods post-procedure due to the risk of delayed bleeding.

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b).Cold Compresses: Encourage the use of cold compresses to reduce bleeding and swelling.[2]

4. Disseminated Intravascular Coagulation (DIC)

Pre-Treatment Precautions:

a).Avoid Elective Procedures: Elective prosthodontic treatments should generally be postponed until the DIC is resolved.

b).Stabilization: Ensure that any underlying condition causing DIC is treated, and the patient's coagulation status is stabilized.

Intraoperative Precautions:

a).Non-Invasive Techniques: Prefer non-invasive or minimally invasive procedures to reduce the risk of bleeding.

b).Immediate Access to Blood Products: Ensure that blood products and coagulation factors are immediately available in case of emergency.

Post-Treatment Precautions:

a).Intensive Care: The patient may require intensive care monitoring if any invasive procedure is performed.

b).Detailed Follow-Up: Close post-operative follow-up to detect and manage any signs of bleeding.[1]

5. Vitamin K Deficiency

Pre-Treatment Precautions:

a).Correct Deficiency: Administer vitamin K to correct deficiency before any invasive procedure.

b).Review Medications: Assess the impact of any anticoagulant therapy (e.g., warfarin) and adjust as necessary in consultation with the prescribing physician.

Intraoperative Precautions:

a).Conservative Treatment: Use conservative techniques to avoid deep tissue involvement.

b).Local Hemostatic Agents: Application of vitamin K-soaked sponges or other local agents can help in managing minor bleeding.

Post-Treatment Precautions:

a).Regular Monitoring: Regular monitoring of prothrombin time (PT) or INR levels post-procedure.

b).Home Care Instructions: Provide the patient with clear instructions on how to manage any minor bleeding episodes at home.[19]

6. Liver Disease (e.g., Cirrhosis)

Pre-Treatment Precautions:

a).Assess Coagulation Status: Obtain coagulation tests (e.g., PT, INR) to assess bleeding risk. Vitamin K or fresh frozen plasma may be required before treatment.

b).Medical Consultation: Work closely with the patient's hepatologist to optimize liver function and manage any coagulopathy before treatment.

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Intraoperative Precautions:

a).Minimal Invasive Techniques: Minimize the extent of tissue manipulation to reduce bleeding risks.

b).Local Hemostatic Measures: Use of local agents such as fibrin sealants or tranexamic acid may be necessary.

Post-Treatment Precautions:

a).Close Observation: Monitor for signs of delayed bleeding, which may occur due to impaired liver function.

b).Patient Education: Ensure the patient understands the signs of potential bleeding and when to seek immediate medical care.[2]

Classification of bleeding disorders :

Bleeding disorders are conditions that affect the blood's ability to clot properly, leading to excessive bleeding. These disorders can be classified based on the underlying cause, such as clotting factor deficiencies, platelet abnormalities, or vascular defects. Here is a detailed classification of bleeding disorders along with references.

I. Clotting Factor Deficiencies

A1).**Hemophilia A**: Caused by a deficiency of factor VIII. Inheritance: X-linked recessive. Symptoms: Prolonged bleeding after injuries, spontaneous bleeding, especially into joints and muscles.

A2).**Hemophilia B** (Christmas Disease): Caused by a deficiency of factor IX. Inheritance: X-linked recessive. Symptoms: Similar to Hemophilia A but generally less severe.

A3).Hemophilia C: Caused by a deficiency of factor XI. Inheritance: Autosomal recessive. Symptoms: Milder bleeding tendencies, often associated with surgical or trauma-induced bleeding.

B).Von Willebrand Disease (vWD): Caused by a deficiency or dysfunction of von Willebrand factor, which is important for platelet adhesion and stabilization of factor VIII. Inheritance: Autosomal dominant (most common types). Symptoms: Mucosal bleeding, nosebleeds, heavy menstrual periods, prolonged bleeding after surgery.[1]

II. Platelet Disorders

1.Thrombocytopenia: A condition characterized by a low platelet count, which can be due to decreased production, increased destruction, or sequestration. Idiopathic thrombocytopenic purpura (ITP), bone marrow disorders, drugs, infections. Symptoms: Petechiae, purpura, mucosal bleeding, prolonged bleeding from cuts.

III.Platelet Function Disorders:

1.Glanzmann's Thrombasthenia: A rare inherited disorder of platelet function due to a defect in the glycoprotein IIb/IIIa receptor. Inheritance: Autosomal recessive. Symptoms: Mucosal bleeding, excessive bleeding after minor injuries.

2.Bernard-Soulier Syndrome: A platelet disorder caused by a defect in the glycoprotein Ib-IX-V complex, essential for platelet adhesion. Inheritance: Autosomal recessive. Symptoms: Bleeding gums, nosebleeds, menorrhagia, easy bruising.[20]

IV. Vascular Disorders:

1.Hereditary Hemorrhagic Telangiectasia (HHT): A genetic disorder that leads to abnormal blood vessel formation, leading to fragile and easily ruptured vessels. Inheritance: Autosomal dominant. Symptoms: Frequent nosebleeds, gastrointestinal bleeding, red spots on the skin (telangiectasias).

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2.Ehlers-Danlos Syndrome (EDS): A group of connective tissue disorders that affect the skin, joints, and blood vessels, making them more prone to tearing. Inheritance: Various inheritance patterns depending on the type. Symptoms: Easy bruising, hyperelastic skin, joint hypermobility, vascular fragility.

3.Scurvy: Caused by vitamin C deficiency, leading to defective collagen synthesis and weakened blood vessels. Symptoms: Bleeding gums, petechiae, purpura, poor wound healing.[21]

4.Disseminated Intravascular Coagulation (DIC): A complex condition characterized by widespread activation of the clotting cascade, leading to the formation of blood clots throughout the small blood vessels, and ultimately resulting in severe bleeding due to the consumption of clotting factors and platelets. Causes: Sepsis, trauma, malignancy, obstetric complications. Symptoms: Diffuse bleeding, organ dysfunction, shock.[22]

V. Coagulation Factor Inhibitors:

1.Acquired Hemophilia: Caused by the development of autoantibodies against clotting factors, most commonly factor VIII. Symptoms: Severe spontaneous bleeding in previously healthy individuals, often in muscles and soft tissues.

2.Lupus Anticoagulant: Definition: An autoantibody that increases the risk of clotting rather than bleeding, but can paradoxically cause bleeding in certain circumstances, especially in association with other factors. Symptoms: Recurrent miscarriages, venous thromboembolism, and bleeding tendencies.[1]

Complications may arise by the prosthodontist while treating a bleeding disorder patient :

When treating patients with bleeding disorders, prosthodontists must be aware of various complications that may arise. These complications can be classified into major and minor categories based on their severity and potential impact on patient outcomes.

1.Major Complications

1. Prolonged Bleeding: Excessive bleeding during or after prosthodontic procedures is the most significant complication. It can result from surgical interventions, such as tooth extractions, implant placements, or even minor adjustments involving the soft tissues.

Management: Requires immediate intervention, including the use of local hemostatic agents, suturing, and, in severe cases, systemic interventions such as the administration of clotting factors or platelet transfusions.

Consequence: If not managed effectively, prolonged bleeding can lead to hematomas, blood loss requiring transfusions, or even shock.[1]

2. Hematoma Formation : Hematomas can form when blood collects within tissue spaces following surgical procedures. They may cause pain, swelling, and delayed healing.

Management: Management may require drainage, pressure dressings, or in severe cases, surgical intervention. Prophylactic measures include the use of local hemostatics and minimizing tissue trauma.

Consequence: Hematomas can increase the risk of infection and delay the healing of surgical sites.[19]

3. Infection: Patients with bleeding disorders are at an increased risk of infection, especially if hematomas or other bleeding-related complications occur. Infection can compromise the success of prosthodontic treatments such as implants or surgical interventions.

Management: Requires prompt treatment with antibiotics, possibly drainage of infected sites, and meticulous oral hygiene to prevent complications.

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Consequence: Untreated infections can lead to systemic involvement and compromise the outcome of prosthodontic procedures.[1]

4. Delayed Healing: Due to the inherent clotting issues, patients with bleeding disorders often experience delayed wound healing, which can complicate the post-operative course of treatment.

Management: Requires careful post-operative monitoring and possibly the use of adjunctive therapies such as antifibrinolytics to enhance clot stability.

Consequence: Delayed healing can lead to prolonged discomfort, extended treatment times, and the potential for secondary complications like infections or tissue [20]

2.Minor Complications

1. Gingival Bleeding: Minor but persistent bleeding of the gingiva can occur during routine prosthodontic procedures such as impression taking, crown placement, or denture fitting.

Management: Managed with pressure application, local hemostatics like tranexamic acid, and careful technique to minimize soft tissue trauma.

Consequence: While typically not severe, persistent gingival bleeding can be distressing for the patient and complicate the procedure.[19]

2. Bruising: Patients may develop bruising or ecchymosis, particularly in the soft tissues of the oral cavity, following even minor trauma or procedures.

Management: Typically, no specific treatment is required, but patients should be advised to avoid further trauma and monitor the area for changes.

Consequence: Bruising is generally benign but can cause discomfort or anxiety in patients.[2]

3. Difficulty in Prosthesis Retention: Patients with bleeding disorders may experience difficulties with the retention of prostheses due to changes in the gingival tissues, such as swelling or bleeding that affects the fit.

Management: Frequent adjustments to the prosthesis and the use of soft liners or other adaptive materials may be necessary.

Consequence: Poor retention can lead to discomfort, reduced function, and a need for repeated prosthodontic visits.[17]

4. Psychological Impact: The fear of bleeding and complications can cause significant anxiety and stress in patients with bleeding disorders undergoing prosthodontic treatment.

Management: Requires careful communication, reassurance, and possibly the involvement of a psychologist or counselor to help manage anxiety.

Consequence: Anxiety can complicate the treatment process, leading to delayed appointments, increased pain perception, or non-compliance with post-operative instructions.[1]

The Prosthodontic treatment which is contra indicated in bleeding disorders: [2,16,20]

In patients with bleeding disorders, certain prosthodontic treatments may be contraindicated due to the significant risk of excessive bleeding and related complications. These contraindications primarily involve invasive procedures that could lead to severe bleeding, especially in patients with poorly managed or severe bleeding disorders.

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Dental Implants: Contraindicated due to invasive nature and high risk of severe bleeding.

Periodontal Surgery: Contraindicated due to the extensive manipulation of soft tissues leading to high bleeding risk.

Tooth Extractions: Contraindicated or require extreme caution due to the significant risk of post-operative bleeding.

Full-Mouth Rehabilitation: Contraindicated due to the cumulative trauma and extended procedure time, increasing the risk of complications.

These procedures are generally contraindicated or require special precautions and interdisciplinary management to ensure patient safety and minimize the risk of severe bleeding complications.

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