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Bleeding Disorders In Oral And Maxillofacial Surgery And Management Guidelines

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Abstract:
Background*: Bleeding disorders are divided into: coagulation factor deficiency: von Willebrand disease and Hemophilia, platelet disorders, or drug-induced: antiplatelet or anti-coagulant medications. Patients with bleeding disorders may exhibit prolonged excessive bleeding during and after invasive oral and maxillofacial procedures. This review aims to provide an overview of bleeding disorders and management guidelines based on current literature for clinicians to prevent complications in patients with bleeding disorders.*
Main Text*: Most papers confirmed that history taking, consultation with the patient's hematologist, application of local hemostatic measures, post-operative instructions, and when to recall the treating dentist/oral surgeon in case of severe post-operative bleeding are essential for safe practice in oral and maxillofacial surgery to avoid possible serious complications*
Conclusion: *Most papers confirmed that history taking, consultation with the patient's hematologist, application of local hemostatic measures, post-operative instructions, and when to recall the treating dentist/oral surgeon in case of severe post-operative bleeding are essential for safe practice in oral and maxillofacial surgery to avoid possible life-threatening complications*
Key Word: *Bleeding disorders, management guidelines, maxillofacial*

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I. Introduction

Current understanding of normal hemostasis is a complex process of stopping bleeding from a damaged blood vessel. Hemostasis can be summarized in 4 major steps: vasoconstriction, formation of a platelet plug, activation of coagulation cascade, formation of a fibrin clot that will gradually be dissolved once the damaged blood vessel is repaired: fibrinolysis. Intra-oral hemorrhage is one of the commonest peri-operative complications that cannot be excluded with any type of dento-alveolar surgical procedures, especially in patients with history of post-operative bleeding. [1]

Types of Peri-operative Bleeding: [2]

- **Primary** [operative \ intra-operative] bleeding**:** begins during and\or immediately after surgery, appears as oozing, blood-tinged saliva, usually due to traumatic extraction leading to injury of blood vessels or injury to bone or laceration of soft tissue, normally persists for half an hour, usually controlled by pressure pack \ local hemostatic measures
- **Reactionary** [intermediate post-operative] bleeding**:** begins 2-3 hours after surgery, and causes the patient to call the dental practitioner, caused by: breakdown of previous blood clot, due to non-compliance with post-operative instructions; as intake of hot food\fluids or mouthwash, laxity of sutures and exposure of bone nourishing vessels, after neck dissection, or removal of vascular lesions as pyogenic granuloma or peripheral giant cell granuloma, and\or underlying systemic condition or anticoagulant therapy, usually require local and systemic interventions
- **Secondary** [late post-operative] bleeding**:** begins 2 to 3 days after surgery, usually due to secondary infection, or pseudo-aneurysms of maxillary artery or its branches: descending palatine artery \ naso-palatine \ sphenopalatine artery during Le Fort I osteotomy orthognathic surgery; it is a rarely encountered complication in dental practice compared to the other two types of post-operative bleeding, usually require selective embolization

It is important to distinguish between oozing from the surgical site in primary bleeding and active bleeding from the surgical site, as a post-operative complication. Most invasive oral\dental procedures result in some degree of peri-operative bleeding [oozing] that ultimately leads to hemostasis in normal healthy individuals. Active bleeding usually continues beyond 8 to 12 hours, it cannot be controlled by pressure pack \ local hemostatic measures; it causes the patient to call or return to the dental practitioner, or go to the emergency department at hospital. It can result in formation of a large haematoma within oral soft tissues that may provoke local infection, local flap necrosis, wound dehiscence, delayed healing, or may cause airway obstruction, or severe blood loss that requires a blood transfusion, hospitalization, or both. Therefore, special attention and preparation is required for those patients with an increased risk of peri-operative bleeding, which has a major impact on duration of hospital stay, morbidity and mortality. The incidence of peri-operative bleeding of oral and maxillofacial surgical procedures in healthy individuals is about 0.2–3.3%, on the other hand, in patients with bleeding disorders, is reported to be 8.6–32.1%**.** [3]

II. Main Text

Assessment of Patients with Bleeding disorders:

History: in clinical practice, most patients who are reporting bleeding symptoms are not referred to the hematology department. Consequently, those patients undergo surgical procedures, without further laboratory investigations. Therefore, pre-operative guideline-based screening bleeding questionnaires should be used; including: Prolonged bleeding after teeth/molars extraction or after an operation or after delivery? Spontaneous gum bleeding? Spontaneous nose-bleeds? Easy bruising\ large hematoma formation? Prolonged bleeding after small wounds (for example after shaving)? Heavy bleeding during menstruation? Any family member with blood clotting problems? Any blood thinning medication? Kidney disease? Renal Hemodialysis? [4]

- Inherited Bleeding Disorders (IBDs): Hemophilia patients usually know that they have the disease after male circumcision during infancy; on the other hand, VWD female patients have heavy menstrual bleeding. In addition to easy bruising, nasal bleeding, gingival bleeding spontaneous\minor trauma, hematomas into muscles, Haemoarthrosis [bleeding into synovium of joints following movement\ minor injuries], blood in urine, previous excessive bleeding from minor injury, surgery, or dental work
- Thrombo-embolic events prophylaxis and\or treatment by oral anti-coagulants: AF (the most common arrhythmia), prosthetic cardiac valve \ valvular heart disease, CABG (open heart surgery), cerebral stroke: ischemic stroke, MI (heart attack), DVT, PE, as a result of stasis in bed-ridden patients: ICU patients \ orthopedic surgery \ pregnancy, systemic embolization after MI and CHF \ ESRD, due to higher risk of AF and ischemic stroke
- ACS \ ASCVD \ TIA: anti-platelets
- Renal Hemodialysis (Heparin anti-coagulant)
- Chronic kidney disease (CKD) [expected in DM and HTN patients] results in uremia (urea in blood), leading to platelet dysfunction [decreased platelet aggregation in uremic environment], which results in prolonged BT

Management of Patients with Bleeding disorders:

- Proper patient education is the key to the prevention of post-operative bleeding; this requires counseling about the bleeding risk; signs and symptoms of severe bleeding and when to seek medical help and drugs to avoid or to be used with caution, including antiplatelet drugs: Aspirin and NSAIDs; as they can worsen hypo-natremia + understand to avoid certain high-risk sporting activities (e.g., contact sports). Patient reassurance that minor bleeding issues, such as nosebleeds or bruising, may not necessitate any specific treatment.
- Consult hematologist prior to any elective surgical procedures for discussions regarding plans for infusions of coagulation factors, blood products, prior to arrival at the outpatient, office-based, or hospital-based setting. Patients may need IV access established by the hematology service before arrival, and may need maintaining the established IV access should focus on additional anesthesia-related medications through the same access point
- Communication between anesthetists, surgeons, and hematologists is essential to ensure effective management during the perioperative period
- Determining the severity of coagulopathy, type, site, and extent of the planned surgical intervention are extremely important; minor, moderate, or major surgery. Accessibility to the treatment site is critical for assessment and control of hemostasis. A simple anterior tooth extraction can be directly visualized, therefore, is more accessible for applying pressure, and local hemostatic agents. Sinus lift and bone grafting will have limited or no access to evaluate or control bleeding if hemostasis cannot be achieved, therefore, systemic factor replacement therapy would be required. Mandibular tori removal elevating the floor of the mouth can cause a significant sublingual hematoma and subsequent airway obstruction.
- Local Anaesthesia with Vasoconstrictor (Epinephrine)

- Avoid submucosal lingual infiltrations anaesthesia in floor of the mouth; it can cause widespread hematoma formation and airway compromise, only intra-ligamentary) injections may be safe, using a liga-jet injector intra-pulpal injection. Infiltration anaesthesia is used with caution for conservative work in children
- Avoid all regional nerve blocks \ field block techniques (IAN block or PSA nerve block), since they can cause haemorrhage into tissue spaces, causing hematoma that can be fatal airway obstruction. Appropriate safe alternatives to IAN block is the Gow-Gates technique, local infiltration, PDL injection, and intra-pulpal injection in controlled Hemophilia \ bleeding disorder patients
- Avoid IM injections, as they can cause large haematomas: IV line preferred; unless replacement therapy
- IV Midazolam sedation may be used in some patients to avoid talking after surgery, especially if hospitalized (talking increases salivation: saliva contains fibrinolytic system that causes fibrinolysis of blood clot)
- The **degree** of **Peri -Operative Bleeding**; amount of blood loss and time required to control bleeding correlate with the nature of surgical procedures performed:
- **Minor Surgery** low risk of bleeding**:** routine minor dento-alveolar surgical procedures: single tooth extraction \ multiple ≤ 3 teeth extraction \ ≤ 3 dental implants placement \ Periodontal surgeries \ scaling \ endodontic treatment, controlled by pressure pack +\- local hemostatic measures
- **Moderate Surgery:** moderate risk of bleeding: multiple > 3 teeth extraction \ surgical extraction \ > 3 dental implants placement, controlled by pressure pack + local hemostatic measures
- **Major Surgery:** high risk of bleeding**:**: orthognathic surgery: Le Fort I osteotomy [main cause of peri-operative and bleeding and pseudo-aneurysm of bilateral spheno-palatine artery or maxillary artery] \ craniofacial surgery: ORIF after facial trauma \ oncological resection \ neck dissection +\- reconstruction; blood transfusion may be required
- **Surgical Considerations:**
- Most studies mentioned the safety of oral and maxillofacial surgery in general and not specifically implant surgery or orthognathic surgery. Common consideration in all studies that any surgical interventions should be modified to be less traumatic:
  - Sectioning of the tooth that would be have difficult extraction, limiting the number of teeth to be extracted in an appointment, avoiding soft tissue flaps whenever possible as they result in a larger bleeding surface area that can be difficult to control postoperatively, and to attain primary closure
  - Avoid perforating the lingual cortical plate of mandible during oral and maxillofacial surgery, as this would result in significant bleeding that would be difficult to control, sublingual hematoma, and airway compromise
  - Surgical Extraction of mandibular 3rd molars: minimal bone should be removed and impacted tooth should be sectioned for removal where possible
- **Local Hemostatic measures**: Cauterization with diathermy + pressure packs sutures – Xeroform® gauze (as compressive bolster dressing) , suture: interrupted – figure of 8 – mattress sutures – tie-over and anti-fibrinolytic agents: AMICAR \ TXA \ Haemostop (Ethamsylate) – clot promotion agents: tissue adhesives or sealants bind to and close defects in tissue: oxidized cellulose (Surgicel) \ gelatin plug-sponge orally or topically – Histoacryl glue, autologous fibrin glue, fibrin adhesive – bone wax (if bleeding from bone) – Chlorhexidine bio-adhesive gel – Gelfoam absorbable gelatinous sponge placed directly into an extraction socket that allows for scaffolding effect for clot formation and will resorb over approximately 4 weeks. Gelfoam should not be placed under flaps as it will inhibit epithelial healing – acrylic or surgical splints [5]
- **Post-operative monitoring** wound for 2 hours before patient discharge
- Post-operative haematoma formation should be expected and detected early in patients with bleeding disorders; manifested as swelling or dysphagia; patency of airway must be ensured
- Post-operative Antibiotic should be administered, because infection induces fibrinolysis and secondary haemorrhage
- Post-operative **Instructions** to avoid dislodgement of blood clot: soft cold diet should be taken for up to 10 days, and to avoid hot food – beverages & mouth rinsing & any activity like blowing, gargling, etc. patient should receive instruction of what to do if bleeding restarts; call\contact dental practitioner \ oral surgeon, take a photo and send it to differentiate between oozing and active bleeding, when to return to clinic, or go to the emergency department at hospital if bleeding continues beyond 8 to 12 hours, and cannot be controlled by pressure pack \ local hemostatic measures, or if there is swelling or dysphagia. [6, 7]
  - **Major Surgery:** Ask Anesthesiologist for Hypotensive Anaesthesia (controlled hypotension during anesthesia), put patient in reverse Trendelenburg positioning (patient head up), avoid traumatic intubation during GA that results in submucosal hemorrhage that may compromise airway, efficient operating to finish surgery in shorter surgical time, IV TXA and IV fluids with large bore IV access, ensure that cross-match for blood transfusion is complete, use suction and inject 1:100,000 Epinephrine to visualize source of bleeding, pressure packing + local hemostatic measures (Epistaxis after maxillary orthognathic surgery is controlled with nasal bolsters or anterior nasal packing) – wait 10 minutes before inspection of bleeding, if there is still bleeding, repeat packing with Surgicel and cover with hemostatic gauze and wait further 10 minutes. If there

is still bleeding, contact interventional radiologist for Angiography for intra-operative selective embolisation of maxillary artery \ its branches. Ligation of ECA rarely required as last resort to arrest intra-operative hemorrhage; clamp on bleeding side, clamp and ligate ECA on other side

- **Bleeding Disorders:** are divided into coagulation factor deficiency: von Willebrand disease (VWD) \ Hemophilia, also are referred to as inherited bleeding disorders (IBDs), platelet bleeding disorders, or drug-induced bleeding disorders: [antiplatelet or anti-coagulant drugs]
- **Coagulation Factor Deficiency:** group of congenital genetic conditions, where missing or defective coagulation factor, preventing normal blood clotting. IBDs are congenital and are quite rare compared to acquired bleeding disorders:
  - **Hemophilia A** (factor 8 deficiency) and Hemophilia B (factor 9 deficiency) and Hemophilia C (factor 11 deficiency)
  - **Acquired Hemophilia A** [autoantibodies generated against coagulation factor 8], liver disease [cirrhosis \ hepatitis \ cancer], vitamin K deficiency (vitamin K dependent coagulation factors 2,7,9,10 and Protein C and S made in liver), or long-term antibiotic therapy: can suppress the normal flora in GIT that are necessary for synthesis of vitamin K
  - **Von Willebrand disease (VWD)** (von Willebrand factor [VWF] deficiency) is the most common congenital bleeding disorder representing more than 95% of all IBDs, affecting about 1% of population
  - **Platelet-type von Willebrand disease (PT-VWD):** congenital deficiency of vWF: defect in platelet function (vWF synthesized and produced by the endothelium of blood vessels), it promotes platelet aggregation and adhesions & acts as carrier for coagulation factor 8; affecting platelet adhesion and aggregation.
  - **Clinical Presentation:** easy ecchymosis (bruising), Epistaxis (nasal bleeding) that does NOT stop within 10 minutes, gingival bleeding spontaneous\minor trauma, persistent prolonged post-op bleeding after dental extractions is the first or only sign of mild hemophilia – dental extractions are followed by persistent oozing for days or weeks and can be fatal as haemorrhage cannot be controlled by pressure or local hemostatic measures [characteristic feature of bleeding in Hemophilia is that bleeding stop immediately after injury (as a result of normal vascular & platelet response), but, after hour or more, oozing or rapid severe blood loss starts and persists], Hematomas into muscles (collection of blood outside blood vessels in muscles) that can lead to compartment syndrome and can eventually cause fibrosis and peripheral nerve damage, Haemoarthrosis [Hemophilic Arthropathy]: internal bleeding into the synovium of joints, following movement\ minor injury, usually affecting the same joint every time (target joint) which cause fever, joint pain and joint damage in severe Hemophilia A
- **Treatment:** when local hemostatic measures are not sufficient to stop bleeding [8-11]
  - Desmopressin (DDAVP) intra-nasal spray \ SC \ IV 0.3 µg/Kg administered over 20 to 30 minutes: 1st line Tx for mild bleeding; to control minor bleeding episodes (patients are not actively bleeding) in elective minimally invasive surgical procedures [synthetic form of Vasopressin (ADH), sold under the trade name DDAVP, induces release of VWF and factor 8 from endothelial cells; in most [stable] patients with type 1, some type 2 (except type 2B) and acquired VWD or Hemophilia A]; [Type 2B and type 3 VWD require clotting factor replacement; Type 2B VWD stimulates release of dysfunctional vWF which leads to platelet aggregation and severe transient thrombocytopenia, Type 3 VWD does not respond to Desmopressin as there is a complete lack of vWF]; the same management is required as for Hemophilia A, since factor 8 has a prolonged half-life, less frequent infusions are required
  - Replacement therapy: recombinant VWF \ coagulation factor 8 concentrate administration for elderly patients with comorbidities: cardio-vascular disease or cerebro-vascular disease [as DDAVP carries a thrombosis risk; VWF replacement therapy is preferable in patients with cardio-vascular or cerebro-vascular disease] or severe bleeding in trauma or major surgery or Type 2B and type 3 VWD or Hemophilia A
  - Cryo-precipitate [Fresh Plasma + Fibrinogen + VWF + factor 8 + XIII + Fibronectin]
  - Prothrombin Complex Concentrate (PCC)
  - Fresh Frozen Plasma (FFP) Transfusion only in life-threatening bleeding [generally avoided due to viral HIV transmission risk]
  - **Platelet Disorders: Thrombocytopenia:** platelet count < 150,000 platelet\µL: (normal range: 150,000 - 450,000 platelets \mm^3): increased BT; bleeding episodes that occur spontaneously or with minimal trauma
- **Inherited Thrombocytopenia:** Congenital disorders of platelet function
- Platelet-type von Willebrand disease (PT-VWD): congenital deficiency of vWF: defect in platelet function (vWF synthesized and produced by the endothelium of blood vessels), it promotes platelet aggregation and adhesions & acts as carrier for coagulation factor 8; affecting platelet adhesion and aggregation
- Glanzmann Thromboasthenia (GT): inherited disorder of platelet function; which means weak platelets, when he noted purpuric bleeding in patients with normal platelet size and count & failure of platelet aggregation – absence of secondary platelet aggregation to ADP, epinephrine, collagen, thrombin – abnormal clot retraction

- Bernard-Soulier syndrome (BSS): rare inherited disorder of platelet function, characterized by large platelets and failure of platelet adhesion & thrombocytopenia
- Gaucher's disease (GD) rare inherited genetic disorder, characterized by thrombocytopenia**,** anemia, and enlargement of liver and spleen
- **Acquired Thrombocytopenia:** caused by decreased platelet production or increased platelet destruction:
- Splenic sequestration of platelets by enlarged spleen, liver disease [acute \chronic; Liver Cirrhosis, particularly ethanol], kidney disease or renal dialysis; uremia, HELLP syndrome,
- Aplastic (Bone Marrow) Anemia: pancytopenia: all blood cells [RBCs, WBCs, and platelets] are reduced, leading to: anemia (pallor – fatigue – dyspnea: shortness of breath) and Leukocytopenia (high risk of infections) and Thrombocytopenia (↑ uncontrolled bleeding with minor injuries & petechae and ecchymosis mucosal bleeding) production – most common cause is bone marrow failure, due to auto-immune destruction of hematopoietic stem cells, caused by: Radio-therapy, viral infections: [EBV – HIV – mumps – Rubella virus – COVID-19], blood cancer: Leukemia \ lymphoma, bone marrow tumors, drug-induced [allergy or dose-related]: chemo-therapeutic agents – DMARDs for RA – anti-thyroid drugs for hyperthyroidism: [PTU & Methamizole] – anti-seizure drugs: Carbamazepine, Phenytoin – antibiotics: [Sulphonamides & Cephalosporins & Chloramphenicol – anti-tuberculous drugs] – HIV medications: NRTIs, Zidovudine, toxins: insecticides used at home – industrial agents containing benzene
- Auto-immune Thrombocytopenia:
- Immune-mediated Thrombocytopenic Purpura (ITP) platelets destruction by IgG autoantibodies → acute Thrombocytopenia: platelet count < 100,000 cells/mm^3, **[11]** primary idiopathic ITP or secondary ITP due to infection: recent upper respiratory infection \ HIV \ HCV \ CMV \ H pylori, or secondary ITP due to auto-immune disease: SLE, RA, MS, Sjogren syndrome, temporal arteritis, Granulomatosis with polyangiitis (GPA) [Wegener Granulomatosis], Lymphoma, Leukemia**.** [12]
- DIC (Disseminated Intravascular Coagulation) (Consumption Coagulopathy): NOT a disease; it is manifestation of a disease or associated with clinical conditions; consequence of abnormal widespread activation of both coagulation cascade (extrinsic or intrinsic or both) and fibrinolytic systems, leading to release of thrombin and widespread intra-vascular thrombosis throughout the body, (deposition of intravascular thrombi), problem in formation of new blood clots and excessive bleeding [risk for significant peri-op bleeding], due to consumption of platelets and coagulation factors 5 and 8, leading to ↑ BT and ↑ PT and ↑ PTT. DIC is caused by: obstetric conditions: pregnancy, amniotic fluid embolism, placental abruption, retained fetus syndrome, eclampsia, HELLP syndrome; saline-induced abortion], intra-vascular Hemolysis: blood transfusion reaction; acute intravascular hemolysis with blood transfusion incompatibility; hemolytic transfusion syndromes, minor hemolysis, or massive blood transfusion, septicemia: systemic inflammatory response syndrome (SIRS): Sepsis \ Ludwig's Angina (infection: impaired platelet production \ platelet destruction \ adherence of platelets to damaged endothelium), Viremia (CMV, Hepatitis, varicella zoster, HIV), head trauma \ crush injury with bleeding and tissue necrosis, burns, snake bites, metastatic disease, blood cancer [Leukemia \ lymphoma], bone marrow tumor, liver disease [obstructive jaundice, acute hepatic failure], or large Aortic aneurysm, Prosthetic devices (Levee shunt, aortic balloon) [13]
- **Clinical Presentation of Thrombocytopenia:** platelet count < 150,000 platelet\µL: petechae and ecchymosis (easily bruising), gingival bleeding
- **Lab Investigations:** CBC with peripheral smear (platelet count) will show iron deficiency anemia due to menorrhea: (very heavy menstrual periods), BT prolonged in platelet function disorders: Glanzmann's thrombasthenia & Bernard-Soulier disease & thrombocytopenia & DIC & ESRD (renal failure)
- **Management of Thrombocytopenia:** platelet count should be optimized before any surgical procedure; because patients are at risk for significant peri-operative bleeding
- Major Surgery: platelets count > 75,000 cells\mm^3: local haemostatic measures
- Minor Surgery: most patients with platelets count > 30,000 cells \mm^3 are stable
- Platelet count > 50,000 cells \mm^3: local haemostatic measures
- Platelet count 20,000 - 50,000 cells \mm^3 extraction is contra-indicated; delay surgery until platelet count is adjusted
- Nerve block injections: platelets count > 30,000 cells \mm^3 ; if less; regional nerve block injections are contra-indicated
- Platelet count < 20,000 cells\mm^3 or qualitative platelet (function) problem exist:: hospitalization and pre-op platelet Transfusion \ fresh frozen plasma; schedule appointment soon after any coagulation correction measures & hematologist may withhold platelet transfusion until post-operative bleeding becomes a problem

Drug-induced Bleeding Disorders:

- **Antiplatelets:** Aspirin, Platelet IIb/IIIa inhibitors [Clopidogrel (Plavix \ Plogrel) – Dipyridamole (Persantine) –Ticlopidine]; related to arterial bleeding; used to prevent arterial thrombosis: blood clots in arterial systems (heart attacks and strokes)
  - Mono-therapy: Aspirin alone, Clopidogrel alone, or Dipyridamole alone
  - Dual therapy: Aspirin + Clopidogrel or Aspirin + Dipyridamole
  - **Indications of Antiplatelets:** primary prevention for asthro-scelerotic cardio-vascular disease (ASCVD) for high risk patients or secondary prevention for established ASCVD in cardio-vascular patients] of vascular thrombosis: MI prevention, TIA – ischemic stroke prevention, after ACS, after coronary stent placement (balloon coronary angioplasty with stent to correct ischemic Angina Pectoris or MI or ACS) [Bare-metal stent: minimum of 6 weeks & drug-eluting stent: minimum of 12 months (3 months – 3 years; slower endothelialization), a until stent becomes covered by endothelium] – coronary stent thrombosis is a platelet-induced phenomenon, so Heparin has no useful role as bridging therapy, due to its lack of antiplatelet therapy, ASCVD, peripheral arterial disease
- **Lab Assessment of platelet function:** BT (normal range of 2 – 7 minutes)
- **Management of Antiplatelets:** both haemorrhagic and thromboembolic risks [14]
  - **Minor Surgery**: low risk of bleeding: routine minor dento-alveolar surgical procedures: Patients on mono-therapy: continue antiplatelet drug + local hemostatic measures (packing the socket + suturing) to stop bleeding, because anti-platelets affect only platelet plug formation, NO effect on coagulation factors – Patients on dual therapy: continue Aspirin if Clopidogrel is stopped [in the past: antiplatelet drug stopped for 5-7 days (life cycle of platelets 5-7 days)]
  - **Major Surgery:** high risk of bleeding: more extensive surgical procedures; risk of stopping medication is thrombo-embolic event, particularly during first 6–12 months after insertion of a drug-eluting stent and 6–12 weeks after insertion of a bare-metal stent (recurrent MI or stroke) will occur, which is more serious than post-operative hemorrhage in most cases: stop antiplatelet drug for at least 5 days (life span of platelets 5-7 days) and Heparin bridging; antiplatelet drug restarted the day after surgery
- **Management of Anticoagulants:** related to venous bleeding primarily target coagulation cascade often used to prevent venous clots [more related to tooth extraction]
- **Oral Anti-coagulants** used for thromboembolic events prophylaxis and\or treatment: AF (atrial fibrillation), prosthetic cardiac valve \ valvular heart disease, CABG (open heart surgery), cerebral stroke: ischemic stroke, MI, DVT, PE, as a result of stasis (bed-ridden patients): ICU patients \ orthopedic surgery \ pregnancy, systemic embolization after MI and CHF \ ESRD due to higher risk of AF and ischemic stroke
- **Warfarin** (Coumadin) (Dicoumarol) (Marevan) [vitamin K antagonist (VKA)] is oral anticoagulant: associated with oozing blood from soft tissue rather than bleeding from bone [anti-dote: vitamin K]; decision depends on type of surgery and INR: [15]
- **Minor Surgery: low risk of bleeding:** single tooth extraction: INR ≤ 4 \ Multiple Teeth Extraction INR ≤ 4: moderately invasive surgery (uncomplicated tooth extraction); check the INR value before surgery, if:
  - **INR ≤ 4:** maintain Warfarin with vitamin K antagonist & proceed with surgery and treat any bleeding complications during surgery with local hemostatic measures and post-operative oral or topical TXA
  - **INR > 4:** defer surgery & consult hematologist – stop warfarin for 2 days before surgery & check INR and PT daily – restart warfarin the day of surgery after finishing the procedure
- **Major Surgery: high risk of bleeding:** (orthognathic surgery \ resection \ neck dissection) – early treatment planning with the patient's hematologist is needed before any decision making; best time to measure INR early morning day of operation
  - **INR < 2:** maintain Warfarin with vit K antagonist & proceed with surgery, with local hemostatic measures during surgery + post-operative TXA orally or topically
  - **INR ≥ 2:** Heparin Bridging [LMWH: Enoxaparin (Clexane)] from Warfarin during peri-op period: consult hematologist if unsafe to allow INR to fall, patient must be hospitalized: stop Warfarin 2-4 days before the procedure & bridge with Heparin because it has shorter half time [antidote of Heparin: Protamine Sulphate (in case of emergency surgery), restart Heparin immediately after surgery once blood clot is formed]
- **New Oral Anti-coagulants (NOACs) \ Direct oral anti-coagulants (DOACs):** for DVT, PE, ACS, previous MI: [16-19]
  - Direct Thrombin inhibitors: Dabigatran Etexilate (Pradaxa \ Praxbind®): directly binds to Prothrombin coagulation factor 2-a (converts Fibrinogen to Fibrin in common pathway in coagulation cascade in Secondary Hemostasis); it is the only potent direct Thrombin inhibitor [coagulation factor 2-a (Prothrombin) is a vit K–dependent pro-enzyme)
  - Direct Factor 10-a inhibitors [Rivaroxaban (Xarelto) \ Apixaban (Eliquis) \ Edoxaban] inhibit coagulation factor 10-a (essential by catalyzing production of Thrombin in common pathway in coagulation cascade in secondary hemostasis)

Some authors considered continuation of NOACs as there are no significant difference in post-operative bleeding in patients who continued versus patients who discontinued NOACs, while most others recommended their discontinuation at least 24 hours in advance skip only one dose of the drug, the day before surgery]; continuation or discontinuation of NOACs before oral surgical procedures remains controversial; this uncertainty is due to absence of international guidelines on this topic**.** Therefore, peri-operative management of patients on anti-coagulants requires interdisciplinary approach and detailed patient education.

Moderate-risk dento-alveolar surgery (extraction of > 3 teeth or another surgery involving reflection of mucoperiosteal flap, osteotomy, or biopsy) are not contraindicated in patients on oral anticoagulants, provided that proper local hemostatic measures are applied. Chatzopoulos et al conducted a retrospective cohort study and concluded that anticoagulant and antiplatelet medications does not affect the risk of implant failure. Both anticoagulant and antiplatelet users and non-users exhibit similar high implant survival rates. [20]

- **Heparin:** anti-thrombin anticoagulant drug used as short-term therapy or to bridge long-term oral anticoagulant \ antiplatelet therapy; when it must be stopped for major surgery with high risk of bleeding in extensive surgical procedures, or multiple extractions; risk of stopping medication is thrombo-embolic event, particularly during first 6–12 months after insertion of a drug-eluting stent and 6–12 weeks after insertion of a bare-metal stent (recurrent MI or stroke) will occur, which is more serious than post-operative hemorrhage in most cases, and before routine hemo-dialysis (HD), which requires anticoagulation to prevent clotting in the extra-corporeal circuit [anti-dote: Protamin sulphate]:
  - IV \ SC Unfractionated Heparin (UFH): most commonly used for patients with ESRD undergoing renal HD, PE, need for immediate surgery (because UFH has fast onset): CABG, cavernous sinus thrombosis, COVID-19 patients
  - Oral Low-Molecular Weight Heparin (LMWH): Enoxaparin (Clexane) (Lovenox); used for renal HD only used in India and Western Europe, however, LMWH is not approved in Egypt and USA, because it is excreted through kidneys, so it can accumulate in body [LMWH has a half-life of 4 to 5 hours, and will not contribute to bleeding on the day of the surgical procedure], prevention or treatment of DVT and PE in non-pregnant women, MI, or COVID-19, bridging of Warfarin oral anticoagulant drug or anti-platelet drugs [Aspirin or Platelet II b/IIIa inhibitors] for at least 5 days (life span of platelets 5-7 days) \ Cancer \ DIC
- **Appointment time in Renal Dialysis:** [21 -23]
- Peritoneal Dialysis: NO adjustments required
- Hemo-dialysis (HD):
  - Elective Surgery \ procedure should be ideally performed on the day following (within 24 hours after) renal HD, NOT immediately before to avoid acute volume depletion and electrolyte alterations (oral LMWH has a half-life of 4 to 5 hours, and will not contribute to bleeding on the day of the surgical procedure), to minimize post-op bleeding complication on next day & when there is maximal benefit from the dialysis (surgery should be delayed for at least 4 hours after hemodialysis post-operatively) to correct Potassium and fluid balance and to avoid post-operative heparin-induced bleeding
  - Emergency Surgery: Protamine Sulphate (anti-dote of Heparin) is given and emergency surgery is performed
  - Monitor: aPTT assessing intrinsic pathway [normal: 30-40 sec - therapeutic: 60-100 (1.5 or 2.5×30-40 sec)], and CBC to evaluate platelet count – Heparin cannot be given if platelet count is < 100,000

III. Conclusion

This review is helpful for clinicians treating patients with bleeding disorders subjected to peri-operative complications in minor and major oral and maxillofacial surgery procedures. Regardless of the type of bleeding disorder. Dentists should be familiar with various types of bleeding disorders, antiplatelet and anticoagulant medications s to ensure accurate history taking from patients

Regardless of the type of bleeding disorder, most studies recommended that patient education, accurate medical history taking, consultation with the patient's hematologists before surgery to optimize the patient's coagulopathy, application of local hemostatic measures, post-operative instructions at the end of surgery, and to recall the treating dentist in case of sever post-operative bleeding to improve patient safety and to avoid possible serious complications.

Abbreviations:

- **AF:** atrial fibrillation
- **ACS**: Acute Coronary Syndromes
- **ASCVD**: Asthro-scelerotic cardio-vascular disease
- **TIA**: Transient ischemic attack
- **MI:** myocardial infarction
- **CHF:** congestive heart failure
- **CABG:** coronary artery bypass graft surgery

- **DVT:** deep vein thrombosis
- **PE:** pulmonary embolism
- **ICU:** Intensive Care Unite
- **CKD**: chronic kidney disease
- **DM:** Diabetes Mellitus
- **HTN:** Hypertension
- **NSAIDs**: non-steroidal anti-inflammatory drugs
- **IAN:** inferior alveolar nerve
- **PSA:** posterior superior alveolar
- **PDL:** Periodontal
- **IM:** intra-muscular
- **AMICAR:** Amino-caproic acid
- **TXA:** Tranexamic acid
- **IBDs**: inherited bleeding disorders
- **VWD:** von Willebrand disease
- **PT-VWD:** platelet-type von Willebrand disease
- **DDAVP:** 1-Deamino-8-D-arginine Vasopressin
- **ADH:** Anti-diuretic hormone
- **VKA:** vitamin K antagonist
- **NOACs:** new oral anti-coagulants
- **DOACs:** direct oral anti-coagulants
- **ITP:** Immune-mediated [Idiopathic] Thrombocytopenia \ Thrombocytopenic Purpura
- **DIC:** Disseminated Intravascular Coagulation
- **HELLP:** Hemolysis, Elevated Liver enzyme levels, and Low Platelets
- **CMV:** Cyto-megalo-virus
- **EBV:** Epstein-Barr virus
- **HIV:** Human Immunodeficiency Virus
- **DMARDs:** disease-modifying anti-rheumatic drugs
- **PTU**: Propyl-thio-uracil
- **NRTIs**: Nucleoside\Nucleotide Reverse Transcriptase Inhibitors
- **RA**: Rheumatoid Arthritis
- **SLE**: Systemic Lupus Erythematosus
- **MS**: Multiple Sclerosis
- **SIRS**: systemic inflammatory response syndrome
- **CBC:** Complete Blood Count
- **RBCs:** red blood cells
- **WBCs:** white blood cells
- **aPTT:** activated Partial Thromboplastin Time
- **PT:** Prothrombin Time
- **INR:** International Normalized Ratio
- **IV:** Intra-venous
- **SC:** Sub-cutaneous
- **COVID-19:** Corona-virus disease of 2019
- **UFH:** Unfractionated Heparin
- **LMWH:** Low-Molecular Weight Heparin
- **ESRD**: end stage renal disease
- **HD:** Hemo-dialysis
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