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Bleeding Disorders in Oral and MaxillO-Facial Surgery

A Project Submitted to The College of Dentistry, University of Baghdad, Department of Surgery in Partial Fulfilment for the Bachelor of Dental Surgery

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Certification of the Supervisor

I certify that this project entitled" Bleeding disorders in oral and maxilla-facial surgery" was prepared by Daniah Hameed Mola and Doaa Ali under my supervision at the College of Dentistry/University of Baghdad in partial fulfilment of the graduation requirements for the bachelor's degree in dentistry.

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Supervisor's Dedication

This is to clarify that the organization and the preparation of this graduation project have been made by the under graduated students **Daniah Hameed Mola** and **Doaa Ali** under my supervision in the college of dentistry, University of Baghdad/ Department of oral and maxillofacial surgery.

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Abstract

Oral and maxillofacial surgeons perform a wide variety of surgical procedures. One of the major complications of these various surgical techniques is uncontrolled bleeding. The best management of perioperative haemorrhage is prevention. This includes proper preoperative patient evaluation, knowledge of the various bleeding disorders, and the characterization of the correct methods of management. This project has evaluated the most common causes of bleeding disorders associated with oral and maxillofacial surgeries. In order to safely treat a patient receiving anticoagulant therapy, familiarity with anticoagulants and with the potential for drug–drug interactions is required, in addition to knowledge about the topical hemostatic options available.

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aPTT: activated partial thromboplastin time
BT: bleeding time
CBC: complete blood count
DDAVP: desmopressin
EACA: epsilon aminocarpronic acid
INR: international normalized ratio
NO. nitric oxide
PBS: peripheral blood smear
PLT: platelets counts
POC: point of care
PPT: partial prothrombin time
PT: prothrombin time
TXA: tranexamic acid
VWD: von willbrand disease
WHO: world health organization
$CaCl_2$: calcium chloride

بسم الله الرحمن الرحيم

((قَالَ رَبِّ اشْرَحْ لِي صَدْرِي وَيَسِّرْ لِي
أَمْرِي وَاحْلُلْ عُقْدَةً مِّن لِّسَانِي يفقهوا قولي))

صدق الله العظيم

Capter 1: INTRODUCTION

All surgical procedures, including dental surgery, present risk of complications, which may include pain, nerve injury, swelling, infections, and hemorrhage. Dental surgery is defined as any dental intervention including an incision in the oral mucosa or gingiva, including anything from a simple dental extraction to alveoloplasty **(Wahl, 2018)**. Bleeding control is an important step during dental surgery procedures **(Akolkar et al., 2017)**. Because excessive bleeding complicates surgery and increases the risk of morbidity. Immediately following the removal of a tooth, bleeding or oozing commonly occurs. To avoid such complications when long-lasting bleeding occurs, despite the proper use of traditional techniques for hemorrhage control, a broad range of hemostatic agents are available, as adjunctive measures to enhance hemostasis in the course of dental surgeries **(Chiara et al, 2017).**

This bleeding can be easily controlled in most cases **(Amer et al., 2014)**. And almost completely stops within eight hours of extraction. However, sometimes it may continue, resulting in a life-threatening situation **(Funayama et al., 1994)**. In major oral and maxillofacial surgical procedures, electrocautery and suture ligatures are most used to control bleeding from small and major vessels. However, when generalized oozing is present, and the use of pressure is not effective, useing of electrosurgical instruments could endanger teeth and nerves topical hemostasis agents may be needed **(Ogle et al., 2011)**.

Despite the expressive rise in the amount and types of topical hemostatsis in the past decade, high-level evidence regarding the management of these agents during bleeding in dental surgery is still lacking.

1.1 Bleeding diathesis in dental surgery: acquired, autoimmune, or genetic

Hemorrhage in dental surgery can be categorized as:

1- Primary hemorrhage: bleeding occurs during surgery

2-Reactionary hemorrhage: bleeding occurs 2–3 hours after surgery

3-Secondary hemorrhage: bleeding occurs until 14 days after surgery, probably due to an infection

Hemorrhage can also be categorize according to the area injured: vascular, bone, and soft tissue **(Robinson, 2000)**, **(Mani et al, 2018)** Bleeding diathesis is an unusual

susceptibility to bleeding and may be genetic, autoimmune, or acquired (Table *1-1*) **(Vezeau, 2016), (Triplett, 2000).**

Table 1-1 Hemorrhagic diatheses–adapted from **(Vezeau, 2016)** ; **(Goswami et al, 2014*)*.**

Disorders of Platelets	Thrombocytopenias: immune thrombocytopenia; drug-induced thrombocytopenia (heparin-induced and chemotherapy); hypersplenism; myelodysplasia/aplastic anemia
	Platelet function alterations: adhesion disorders (genetic); von Willebrand disease; therapeutic platelet inhibitors [$P2Y_{12}$ inhibitors (clopidrogel and prasurgel), cyclo-oxygenase inhibitors (aspirin), phosphodiesterase inhibitors (cilostazol), GP IIB/IIIA inhibitors, adenosine reuptake inhibitors (persantine)]; uraemia; cirrhosis
Disorders of coagulation	Hemophilia: factor VII (classic/A), IX (B), and XI (C), and others; factor antibody syndromes; hepatic dysfunction
	Therapeutic anticoagulants: vitamin K antagonists (ex: warfarin, acenocoumarol); low-molecular-weight heparins (tinzaparin, dalteparin, enoxaparin); direct dental anticoagulants [factor II inhibitor (dabigatran); factor X inhibitors (apixaban and rivaroxaban)]
	Diffuse intravascular coagulopathy
	Massive transfusion states
Vascular Disorders	Scurvy Hereditary hemorrhagic telangiectasia Ehlers-Danlos syndrome
Fibrinolytic Defects	Streptokinase therapy Disseminated intravascular coagulation

1.2 Aim of project

The aim is to know the causes of the bleeding that effect the oral cavity and its proper management to prevent complications after bleeding.

Capter 2: Normal hemostasis

The physiological mechanism that prevents and hinders bleeding at the area of an injury while preserving regular blood flow everywhere else in the circulation is called hemostasis **(Gale, 2011)**. The hemostasis process has two major components. Primary hemostasis and secondary hemostasis.

2.1 Primary hemostasis

Is defined as the process of platelet plug formation at the site of injury. It occurs within seconds of injury and is important in stoppage of blood from small arterioles,

venules, and capillaries. There is platelet adhesion, release of granules and platelet aggregation resulting in formation of a primary hemostatic plug **(Mehra et al., 2015)**. Initiates promptly after vascular injury, and it can be divided into four consecutive and superposed stages: (A) vasoconstriction, (B) platelet adhesion, (C) platelet activation, and (D) platelet aggregation **(Revel-Vilk et al., 2017)**.

2.2 Secondary hemostasis

Secondary hemostasis is traditionally broken up into two basic pathways as seen in (Figure 2-1): the intrinsic pathway and the extrinsic pathway. The intrinsic pathway is primarily activated by collagen, which is exposed and binds Factor 12 to initiate this cascade. The extrinsic pathway is stimulated by tissue factor, which is exposed by the tissue injury and through Factor 7 activation initiates this pathway. These two pathways then converge in a common pathway where thrombin converts fibrinogen to fibrin and then the final clot **(Ogle et al., 2011)**.

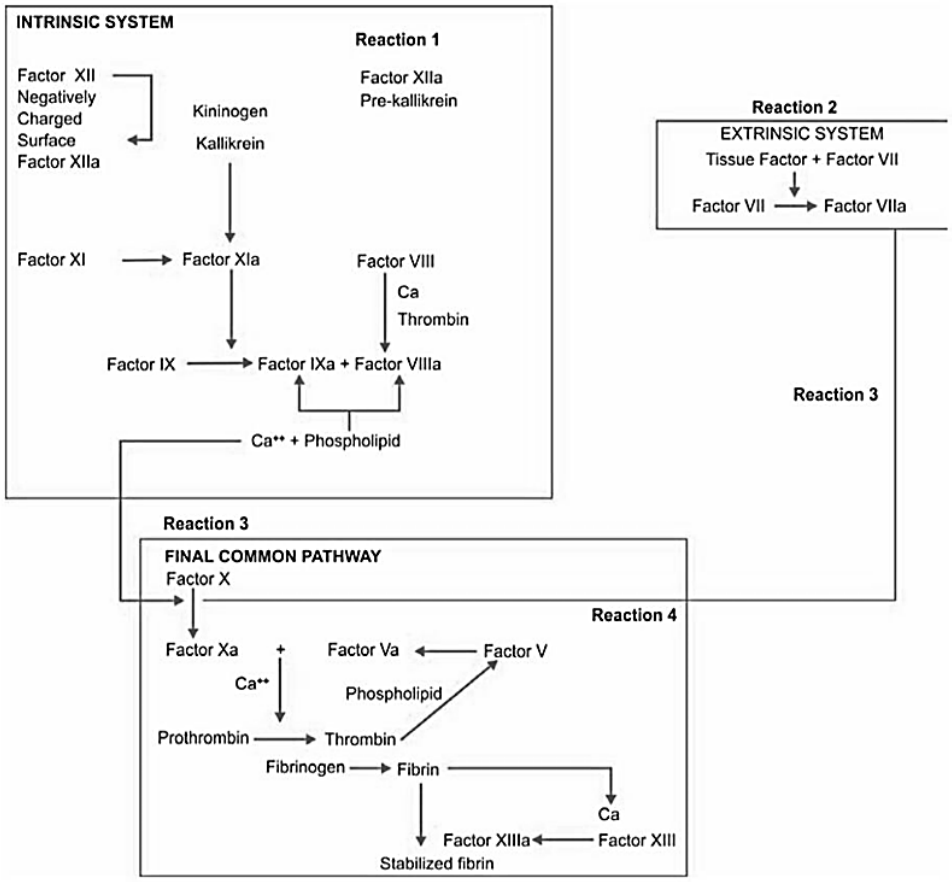

Figure 2-1 Coagulation cascade **(Malik, 2012)**.

2.3 Investigation for bleeding disorders

There are several test and investigation that done to the patient before oral and maxillafacial surgery

2.3.1 Bleeding time (BT)

Is a widely used and popular test to explore primary hemostasis **(Paniccia et al., 2015)**. The most common use of the bleeding time is as preoperative screening of potentially dangerous platelet disorders. The normal range of BT is between 1 and 6 minutes and is considered significantly prolonged when it is grater than 15 minute. Because surgery entails a major challenge to hemostasis, which may be fatal in case of hemostatic defects, it makes sense to search for preoperative screening of potentially dangerous bleeding **(De Caterina et al., 1994)**.

2.3.2 Platelets Counts (PLT)

The platelet count test is a lab test which measures the number of platelets you have in your blood. The normal platelets count 150000 to 450000/mm^3. Platelets, also known as thrombocytes, are tiny, round cell fragments which circulate in your blood and are essential for the formation of blood clots. A blood clot is a mass of blood that the body forms to stop bleeding. **(Shamshad et al., 2021)**.

2.3.3 Prothrombin time PT AND INR

The PT measures the time required for clotting to occur after the addition of a source of tissue factor to recalcified citrated plasma in laboratory instruments and on point of care (POC) devices as seen in (Table 2-1). The normal PT count from 11 to 13 seconds. The PT is measured by adding thromboplastin (a mixture of tissue factor, calcium, and phospholipid) to a patient's citrated plasma sample, and clot formation is determined World Health Organization (WHO) **(Yang and Moosavi, 2021)**. Patients taking oral anticoagulants are required to monitor INR to adjust the VKA doses because these vary between patients. INR value is dimensionless and ranges from a score of 2.0 to 3.0, **(Shikdor et al., 2018)**.

2.3.4 Partial Thromboplastin Time (PTT)

Partial thromboplastin time screens the intrinsic coagulation pathway and tests for the adequacy of factors VIII, IX, X, XI, XII of intrinsic system and factors I, II, V of the common

pathway. It is prolonged in haemophiliacs **(Rountree et al., 2021)**. The normal range of PTT is between 25 to 35.

Table 2-1 summary of conditions may be present based on result of PT and PTT testing **(Levy et al., 2014)**.

PT Result	aPTT Result	Examples of Conditions That May Be Present
Prolonged	Normal	• Liver disease • Vitamin K deficiency • Decreased or defective factor VII • Chronic, low-grade DIC • Vitamin K antagonist (warfarin) therapy
Normal	Prolonged	• Decreased or defective factor VIII, IX XI, XII, prekalikrein, high-molecular-weight kininogen • Type 3 vWD • Presence of lupus anticoagulant
Prolonged	Prolonged	• Decreased or defective fibrinogen, factor II, V, or X • Severe liver disease • Acute DIC
Normal	Normal or slightly prolonged	• May indicate normal hemostasis; however, PT and aPTT can be normal in conditions such as mild deficiencies in other factors and in the mild form of vWD • Further testing may be required to diagnose these conditions

Capter 3: Bleeding disorders

3.1 Types of Bleeding disorders

Bleeding disorders can be classified as coagulation factor deficiencies, platelet disorders, vascular disorders, or fibrinolytic defects as numerated in (Table 3-1)**(Patton, L.L., 2003)**.

Table 3-1 Common bleeding disorders **(Patton, L.L., 2003)**.

Coagulation factor deficiencies	**Congenital** Hemophilia A and B von Willebrand's disease Other factor deficiencies (rare) **Acquired** Liver disease Vitamin K deficiency, warfarin use Disseminated intravascular coagulation
Platelet disorders	**Quantitative disorder (thrombocytopenia)** Immune-mediated Idiopathic Drug-induced Collagen vascular disease Sarcoidosis Non-immune-mediated Disseminated intravascular coagulation Microangiopathic hemolytic anemia Leukemia Myelofibrosis **Qualitative disorder** Congenital Glanzmann thrombasthenia von Willebrand's disease Acquired Drug-induced Liver disease Alcoholism
Vascular disorders	Scurvy Purpura Hereditary hemorrhagic telangiectasia Cushing syndrome Ehlers-Danlos syndrome
Fibrinolytic defects	Streptokinase therapy Disseminated intravascular coagulation

There are several bleeding disorders but the most common are:

3.1.1 von Willebrand disease (VWD)

Is the most common inherited bleeding disorder and is the result of either quantitative (Type 1 and Type 3) or qualitative defects (Type 2) in von Willebrand factor (VWF) as seen in (Table 3-2) **(Sadler et al., 2006)**. von Willebrand's Factor is a carrier protein for Factor VIII and increases its half-life by protecting it from proteolytic degradation. In addition, it

also aids platelet adhesion to damaged vascular endothelium and enhances platelet aggregation **(Rafique et al., 2013)**.

Patients with VWD are at particular risk of hemorrhage in the perioperative setting, given the key role of VWF in both hemostasis (**Leebeek and Eikenboom, 2016)** and wound healing **(Ishihara et al., 2019)**.

This risk depends on the severity of the patient's bleeding phenotype and the type of surgery or procedure being performed. Treatment options for patients with VWD who are undergoing surgery include administration of VWF-containing concentrates (both plasma derived and recombinant), desmopressin to induce release of stored endogenous VWF from the vascular endothelium, and adjunctive antifibrinolytic therapy such as tranexamic acid (TXA) **(Sharma and Flood, 2017)**. The primary structure of von Willebrand factor (vWF) is a large, glycosylated protein which is synthesized in endothelial cells and megakaryocytes (platelet precursors) **(Wilde and Cook, 1998)**.

Difficulties in diagnosis are compounded by the existence of 3 major subtypes of VWD **(Sadler et al., 2006)**.

Table 3-2 Classification of VWD: major types and subtypes **(Sadler et al., 2006)**.

Type	Characteristic
1	Quantitative decrease in VWF with preserved ratios between VWF/Ag, VWF/Act, and FVIII; normal multimer distribution
1C	Quantitative decrease in VWF with preserved ratios between VWF/Ag, VWF/Act, and FVIII; increased VWF/pp compared with VWF/Ag
2A	Decreased platelet-dependent VWF activity with loss of high-molecular-weight multimers
2M	Decreased platelet-dependent VWF activity with preserved multimer pattern
2N	Decreased binding of FVIII
2B	Increased binding to GPIbα, often leading to thrombocytopenia
3	Absence or near absence of VWF
Platelet-type VWD	Functional defect of platelet GPIbα, leading to excessive binding of platelets and VWF and subsequent thrombocytopenia and loss of high-molecular-weight multimers
Acquired von Willebrand syndrome	Decreased VWF and particularly loss of high-molecular-weight multimers as a result of either shearing from mechanical forces (eg, aortic stenosis resulting in Heyde syndrome), adsorption on tumors (eg, Waldenström macroglobulinemia or Wilms' tumors), or autoimmune inhibitor formation

3.1.1.1 Management

In patients who present with a documented diagnosis of vWD, safely delivering dental treatment will be guided by three key elements: reviewing the patient's hematologic history, assessing dental needs and the anticipated procedural risks for bleeding, and communicating and coordinating with the patient's hematologist **(Szumita et al., 2018)**.

Briefly, precision in performing surgical procedures, careful handling of the soft tissues, and suturing helps limit local bleeding in all patients **(Haghighi et al., 2016)**. Additionally, the application of one or more of the following prohemostatic therapies has also shown to be effective in vWD: hemostatic wound dress- ings, tissue adhesives, and use of antifibrinolytic oral rinses are the mainstay of the local treatments **(Berthier et al., 2002)**. As in all cases of wound bleeding, careful assessment of the effectiveness of local measures must be performed **(Szumita et al., 2018)**.

3.1.2 Hemophilia A and B

Hemophilia A, also referred to as classic hemophilia, is caused by a deficiency in factor VIII. Hemophilia A is the most common hereditary disease associated with life-threatening hemorrhage as seen in (Table 3-3)**(Little et al., 2008)**.

Hemophilia B, also known as Christmas disease, is due to a deficiency in factor IX and produces a disorder clinically indistinguishable from hemophilia A **(Little et al., 2008)**.

Both hemophilia A and B are X-linked recessive disorders **(Zimmerman and Valentino, 2013)**. As a result of the X-linked inheritance pattern, hemophilia A and B are more commonly seen in males than females **(Smith, 2016)**.

Depending on the level of factor VIII in the plasma, hemophilia A is categorized into 3 types: mild, moderate, and severe **(Franchini, 2013)**.

Table 3-3 Severity levels of hemophilia A and general recommendations for dental management **(Franchini, 2013)**.

Severity	Plasma level of factor VIII (%)	Dental management
Mild	6%-50%	• Preventive dentistry in the primary care setting should be emphasized. • All dental treatment can be delivered in the primary care setting. However, shared care with prior consultation with a hematologist is recommended.
Moderate	2%-5%	• Dental care providers should consider managing patients with a moderate level of hemophilia A as if they were patients with a severe level who require management in a secondary care setting. • Patients at these levels may require preoperative prophylactic factor replacement therapy. Therefore, consultation with the treating hemophilia center or hematologist is necessary. • Following consultation with the patient's hematologist, preventive dentistry measures, including oral hygiene instructions, diet analysis, pit and fissure sealing, and fluoride applications, are important.
Severe	<1%	

Lab investigation

Using screening tests such as prothrombin time (PT) and activated partial thromboplastin time (APTT) or platelet function tests to identify the potential cause of bleeding in hemophilia **(Srivastava et al., 2020).**

(Table 3-4) Interpretation of screening Tests **(Jennings et al., 2013)**.

Table 3-4 Interpretation of screening tests.

Possible diagnosis	PT	APTT	Platelet count
Normal	Normal	Normal	Normal
Hemophilia A or B	Normal	Prolonged[a]	Normal
VWD	Normal	Normal or prolonged[a]	Normal or reduced
Platelet defect	Normal	Normal	Normal or reduced

3.1.2.1 Management

Patients with mild hemophilia and no inhibitors can usually be managed on an outpatient basis without the need for factor replacement **(little et al., 2008)**. Patient with moderate hemophilia and no inhibitors may require factor replacement for less invasive procedures and will require factor replacement for more invasive oral surgical procedures **(little et al., 2008)**. Patients with moderate hemophilia can also be treated with DDAVP (desmopressin) and EACA (epsilon-aminocaproic acid) or tranexamic acid **(little et al., 2008)**. Patients with severe hemophilia will require hospitalization and treatment with factor replacement, DDAVP, EACA, or tranexamic acid **(Smith, 2016)**. surgical management of patients with hemophilia can be concerning for both the patient and provider. However, thorough preoperative assessment, coordination with the patient's hematologist, and careful preoperative planning allow safe and effective surgical management of patients with hemophilia. **(Szumita et al., 2018)**.

Surgical treatment, including a simple dental extraction, must be planned to minimize the risk of bleeding, excessive bruising, or hematoma formation.

Emergency surgical intervention in dentistry is rarely required as pain can often be controlled without resorting to an unplanned treatment. All treatment plans must be discussed with the hemophilia unit if they involve the use of prophylactic cover. **(Brewer and Correa, 2005)**

3.1.3 Vitamin k deficiency

Newborns are given vitamin K at birth to prevent vitamin K–deficient bleeding, which can otherwise occur because vitamin K does not cross the placenta **(Puckett and Offringa, 2000)**. Beyond the neonatal period, vitamin K deficiency is rare. A recent analysis of the 2011–2012 NHANES indicated that vitamin K intakes have overall declined in the last 2 decades and, indeed, over half of adults >70 y old do not meet vitamin K dietary recommendations **(Harshman et al., 2017)**. Although this does not manifest as overt vitamin K deficiency, low vitamin K intakes and status have been linked to increased risk of certain age-related

comorbidities, such as cardiovascular disease. However, results of vitamin K supplementation trials have been equivocal **(Shea et al., 2021)**.

Patient bruises easily, gets small blood clots underneath their nails, bleeds in mucous membranes that line areas inside the body, produces stool that looks dark black (almost like tar) and contains some blood **(Committee on Fetus and Newborn, 2003).**

Lab investigations

Most likely your doctor will perform coagulation test called the prothrombin time (PT) test to see if a vitamin K deficiency is causing your symptoms. This is a blood test that measures how long it takes for your blood to clot **(Sahni et al., 2014)**.

3.1.3.1 Managements

In the case of postoperative haemorrhage, surgical intervention is necessary. After local anaesthesia, the wound should be reopened and verified, and procedures of local haemostasis should be recapitulated **(Wahl, 1998)**.

Postoperative guidelines should also be emphasised, the investigation of haemostasis should include measures of INR and platelet counting, in cases where, despite recapitulation of haemostasis, bleeding continues, the patient should be hospitalized **(DE MELLO et al., 2005)**. Biological status sheet with amongst others the value of INR should be achieved in the 24 hours that precede the surgery **(DE MELLO et al., 2005).**

3.2 Liver disease

Liver cirrhosis is characterized by replacement of the hepatic parenchyma by fibrous tissue and formation of nodules, Physiological damage to the liver results in several cirrhotic complications and impairment of other organs and systems (e.g. kidneys, lungs, cardiovascular s ystem, etc.) (**Di Profio et al., 2018)** .

Hemorrhagic processes are of particular interest as it can increase the morbidity and mortality rates of patients. The mechanisms involved in bleeding events include insufficient production of clotting factors, dilatation, and relaxation of vessel walls due to accumulation of nitrogen compounds (particularly nitric oxide, NO), decrease of circulating platelets (as a result of hypersplenic sequestration and decrease in the liver production of thrombopoietin) **(Amitrano et al., 2002)** and change of platelet function (adhesion) related to the action of NO and ammonia **(Emerson et al., 1999)**. Moreover, there is also the possibility that bacterial infections can trigger the release of endogenous heparinoids **(Kujovich, 2015)**.

Recommendations for predicting bleeding events in dental surgeries are that prothrombin time (PT), international normalized ratio (INR) and platelet count should be ordered. The published studies recommend that patients with platelet count less than 40,000 or 50,000 and/or INR greater than 3 should not be operated, instead they should be submitted to prophylactic transfusions to avoid intra or postoperative bleeding **(Efeoğlu et al., 2019)**.

3.3 Scurvy

When vitamin C is absent from the diet, collagen synthesis is disrupted resulting in malformation and absence of mature collagen. In early disease states, approximately 3 to 6 months after the dietary intake falls below 10 mg/day, nonspecific symptoms, such as fatigue, weakness, irritability, weight loss, vague myalgia, and arthralgia, predominate, making the diagnosis of scurvy difficult **(Hodgeset al., 1971)**.

The most distinguishing feature of scurvy is tissue bleeding with nonpalpable purpura**. (Stephen and Utecht, 2001)**.

More classic manifestations, such as petechiae, purpura, hemarthroses, dystrophic hair lesions, delayed wound healing, and bone fragility, occur sometime later **(Halligan et al., 2005)**.

The patient presented with significant gingival hyperplastic lesions as seen in Figure 3-1

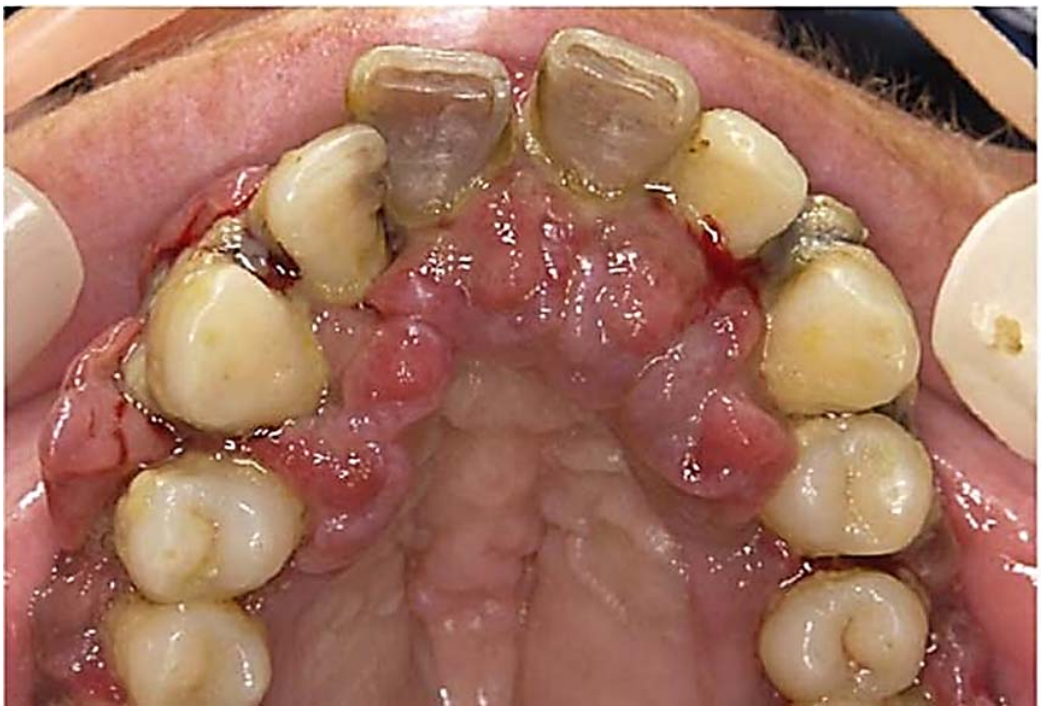

Figure 3-1gingival hyperplastic lesion from palatal view**. (AAP, 1999).**

Vitamin C is needed for the synthesis of collagen, which is essential for firmness of the blood vessels. In patients with scurvy, the vessels become weak, leak and abnormal bleeding. The presentation of scurvy is often malaise, fatigue, stiff joints, and bruising, mostly on the upper thighs and legs. Frequently, easy bleeding of spongy gums is encountered. The next stage consists of open wounds, jaundice, fever, loss of teeth and finally death **(Omeldo et al., 2006)**.

3.4 Thrombocytopenia

Defined as platelet counts <150x1000000000, thrombocytopenia may be caused by a decrease in platelet production, increased sequestration, or peripheral platelet destruction. A low platelet count may be associated with life-threatening hemorrhage and therefore profoundly affects dental management of these medically compromised patients **(Israels et al., 2006)**. The use of careful surgical technique is imperative when managing patient at risk for postoperative bleeding. Releasing incisions and extensive flaps should be realistically avoided to minimize soft tissue injury. Conservative bony removal and tooth sectioning are advised to reduce hard tissue bleeding. **(Szumita et al., 2018)**. Granulation tissue should be carefully curetted and removed as it may be responsible for postoperative bleeding. **(Fillmore et al., 2013)**. Many of the drugs shown in multiple studies to be capable of causing drug-induced thrombocytopenia are seen in Table 3-5 .

Lab investigations

A first line of bloodwork includes a complete blood count (CBC), Thromboelastography (TEG), bleeding time (BT), and coagulation studies such as prothrombin time (PT) and platelet function analysis (PFA)-100 **(Stasi, 2012)**.

3.4.1 Management

Procedures at low risk for bleeding in patients with platelet count above 30,000/μL can safely be performed in a dental office **(Fillmore et al., 2013)**. Patients requiring platelet prophylactic transfusions or undergoing invasive procedures such as dental extractions are ideally managed in a hospital outpatient setting which facilitates the coordination of care and gives the dentist greater resources to manage surgical complications **(Szumita et al., 2014)** .

Table 3-5 Drugs commonly implicated as triggers of drug-induced thrombocytopenia **(Aster and Bougie, 2007).**

Drug Category	Drugs Implicated in Five or More Reports	Other Drugs
Heparins	Unfractionated heparin, low-molecular-weight heparin	
Cinchona alkaloids	Quinine, quinidine	
Platelet inhibitors	Abciximab, eptifibatide, tirofiban	
Antirheumatic agents	Gold salts	D-penicillamine
Antimicrobial agents	Linezolid, rifampin, sulfonamides, vancomycin	
Sedatives and anticonvulsant agents	Carbamazepine, phenytoin, valproic acid	Diazepam
Histamine-receptor antagonists	Cimetidine	Ranitidine
Analgesic agents	Acetaminophen, diclofenac, naproxen	Ibuprofen
Diuretic agents	Chlorothiazide	Hydrochlorothiazide
Chemotherapeutic and immunosuppressant agents	Fludarabine, oxaliplatin	Cyclosporine, rituximab

Capter 4: Common hemostasis-altering medications

The most common acquired bleeding diathesis is the one related to hemostasis-altering medications. Anticoagulant agents are among the most prescribed medications in the USA **(Kaplovitch et al, 2019)**. For decades, anticoagulants have been prescribed to prevent arterial and venous thromboembolism **(Wahl ,2018)**. Prolonged bleeding and bruising are some of the adverse events related with these medications. The most frequently used drugs are therapeutic platelet inhibitors, vitamin K antagonists, or direct oral anticoagulants. Patients susceptible to hemorrhage may present severe bleeding resulting from dental surgery procedures. The use of biosurgical hemostatic agents to decrease or control bleeding may be beneficial for patients at risk for bleeding diathesis **(Wahl ,2018)**.

4.1 Biosurgical topical hemostatic agents in dental surgery

Bleeding complications can occur either in healthy or systemically compromised patients. Some patients tend to bleed excessively during or after dental surgery, due to different factors, such as anticoagulant therapy, inherited bleeding disorders, uncontrolled hypertension, extreme trauma to soft tissues, and non-compliance to postoperative recommendations. In these cases, the use of an effective hemostatic agent enhances hemostasis, providing a wide spectrum of benefits, such as superior management of the anticoagulated patient, shorter operation time, as well as smaller wound exposure and shorter recovery time.

The ideal topical hemostatic agent should be biocompatible, affordable, and effective **(Mani et al, 2018)**, **(Kamoh et al, 2012)**, **(Kumar, 2016)**. In recent years, the number of different topical hemostatic agents has increased significantly (Table *4-1*). Knowledge and familiarity with the wide range of topical hemostaticagents available are essential for dental practitioners, including their effectiveness, mode of action, and adverse effects. A well-informed professional will be able to opt for the most effective and practical agent for each situation. In relation to the use of local hemostatic in dental procedures, available scientific data is not homogenous. Most publications use one or more local hemostatic agents to compensate for the anticoagulant effect and prevent postoperative bleeding **(Svensson et al, 2013)**. The most common local biosurgical hemostatic agents used in dentistry and approved by the Food and Drug Administration (FDA) are listed in (Table *4-1*).

Table 4-1Types and trade name of some biosurgical agents–adapted from (Pereira et al, 2018)

Topical hemostatic		Commercial name
Passive or Mechanical Agents	Gelatins	Surgifoam®, Gelfoam®, Gelfilm®, Gelita-spon®, Geli putty®
	Collagen	Instat®, Helitene®, Helistat®
	Cellulose-based products: oxidized regenerated cellulose	Surgicel Original®, Surgicel Nu-Knit®, Oxycel®, Surgicel Fibrillar®, Interceed®, Gelitacel®
	Cellulose-based products: oxidized cellulose	ActCel®, Gelitacel®
	Polyssacharide hemospheres	Arista™AH
	Adhesives	BioGlue®
Active Agents	Topical thrombin	Thrombin-JMI®, Evithrom®, Recothrom®
	Fibrin sealants	Tisseel®, Evicel®, Crosseal™
Flowable agents	Porcine gelatin + thrombin Bovine collagen + thrombin	Surgiflo®, Floseal®

*Local biosurgical hemostatic agents can be classified into (A) passive or mechanical, (B) active, and (C) flowables (Vyas et al, 2013).

4.2 Passive or mechanical agents

Considered as the most effective agents for small amounts of bleeding, passive or mechanical agents provide platelet activation and aggregation. This results in a matrix formation in the bleeding area that works as a barrier to stop bleeding, by activating the extrinsic clotting pathway and providing a surface that will allow coagulation to occur faster (Vyas et al, 2013). As these agents are biologically inactive, they rely on the individual's own fibrin production to attain hemostasis. Passive hemostats are only indicated for individuals with an unscathed coagulation cascade (Kumar, 2016). They are generally applied as frontline agents, since they are readily available, do not require special storage or handling, and are relatively affordable (Mani et al, 2018), (Kumar, 2016), (Brodbel et al, 2002).

4.3 Active agents

Active hemostatic agents are biologically active, as they play a direct role in the coagulation cascade, inducing the formation of a fibrin clot (Kamoh et al, 2012)
(Kumar, 2016).

4.4 Flowables (Surgiflo, Floseal)

There are two main categories of flowable biosurgicals: products containing porcine gelatin, which can be combined with thrombins (bovine, human-pooled plasma thrombin, or rhThrombin), and bovine collagen-based agents, packed with human-pooled plasma thrombin. The flowable agents are deemed the most effective of all the local hemostatic agents **(Spotnitz, 2012),** (**Vyas et al, 2013)**.

4.4.1 Surgiflo

Is an absorbable, sterile, hemostatic porcine gelatin matrix, combined with Thrombin-JMI, a topical bovine-derived thrombin. It should be placed directly to the bleeding areas to activate the hemostatic process (Vyas et al, 2013). A compression period is required for polymerization of the sealant components (Pereira et al, 2018).

4.4.2 Floseal

Consists of a bovine gelatin matrix, plasma-extracted human thrombin, and $CaCl_2$. Its gelatin granules expand (10–20%), as it comes in contact with blood, producing a seal when the product is applied to a bleeding area **(Kumar, 2016)**, **(Vyas et al, 2013)**. The thrombin fraction of the product triggers the regular pathway of the coagulation cascade, converting fibrinogen to a fibrin polymer and creating a clot around the firm matrix **(Kumar, 2016)**, which is reabsorbed within the expected period of standard wound healing (6–8 weeks) **(Mani et al, 2018)**, **(Kumar, 2016)**, **(Spotnitz et al, 2008)**, **(Schreiber et al, 2011)**, **(Spotnitz et al, 2010).** A distinctive feature of Floseal is the need for the presence of blood for activation **(Vyas et al, 2013)**, **(Galanakis et al, 2011)**. Neither compression, nor a dry surgical field is required for its application **(Pereira et al, 2018).**

Because of this biosurgical flowability, they can easily adapt to irregular wounds. Flowables have been utilized as frontline topical hemostats in major dental surgeries, in patients where conventional procedures are ineffective. They can be utilized as an adjunct to

hemostasis in practically all dental surgical interventions. Flowables are effective on both hard and soft tissues **(Kumar, 2016), (Vyas et al, 2013)**. They have a risk of transmitting infectious agents and are contraindicated in patients who are allergic to materials of bovine origin **(Kumar, 2016)**.

4.5 Some pictures of topical hemostatic agents:

Figure 4-1 (Picture 1: show surgifoam type of passive agents) https://www.jnjmedtech.com/en-US/product/ethicon-surgifoam-absorbable-gelatin-sponge

Figure 4-2 (Picture 2: Show fibrin sealants type of active agents) https://images.app.goo.gl/2kQcjU6qwzSgcGwn7 , 2019

Figure 4-3 (Picture 3: show surgiflo from (Zhang, 2011)

4.6 Effectiveness of different biosurgical hemostatic agents' dentistry

Although traditional methods, such as ligature and manual pressure, can promote hemostasis, they are not an effective approach of bleeding control in less accessible sites and complex injuries. Furthermore, bleeding control is especially challenging in patients presenting acquired or congenital coagulation disorders.

Topical biosurgical hemostatic agents comprise a wide range of products aiming at minimizing the risk of bleeding. In recent years, several clinical trials have analyzed the effectiveness, advantages, and limitations of biosurgicals, as well as performed comparisons among the different types of biosurgicals and other non-biologic agents. Despite the beneficial effect of these local hemostatic agents in preventing bleeding in dental surgery, available data comparing their effectiveness and efficiency is still scarce and inconclusive. Methodological heterogeneities, such as the lack of a standard therapy and comparable treatment regimens, are noticeable among studies, as well as the reduced number of randomized controlled trials **(Lewis et al, 2013)**, **(Bajkin et al, 2014)**, **(Soares et al, 2015)**, **(Wagenhäuser et al, 2016)**, **(Akolkar et al, 2017)**.

In summary, local hemostatic agents are very distinct products with diverse indications. Presently, there is no definite evidence-based approach to guide the dental practitioner when selecting a local hemostatic agent. They must be aware of the characteristics of each single hemostatic agent, to elect the most suitable product for every particular clinical situation. In addition, current available data shows that no topical agent can

be regarded as superior or more effective than the others **(Akolkar et al, 2017)**. Further experimental research and controlled clinical trials are warranted to define the most cost-effective biosurgical hemostatic agents in dentistry.

4.7 Preoperative assessment and risk of bleeding

The dental practitioner should assess the bleeding risk of the patient, as well as the bleeding risk of the surgical intervention, preoperatively. After assessing both bleeding risks, the professional can then conceive an intraoperative and postoperative plan. The international normalized ratio (INR) must be evaluated in patients reporting an elevated risk of bleeding. While a standard parameter of coagulation has an INR of 1 **(Hirsh et al, 1988), the** therapeutic range runs from 2.0 to 3.5. In this case, it is recommended to use local hemostatic measures independently or in combination with conventional methods. These agents can be used before, during, and after dental surgeries.

4.8 Preoperative assessment

1- Comprehensive medical history, including all medications in the patient's regimen, to identify potential bleeding issues prior to the surgery **(Kamoh et al, 2012)**

2- In order to decrease surgical bleeding, patients receiving anticoagulant therapy may need to break up exodontia into multiple appointments **(Kamoh et al, 2012)**, **(Brennan et al,2007)**

3- Laboratory values such as platelet count, INR, and prothrombin time are of critical value in medically compromised patients **(Kamoh et al, 2012)**

4- Demographic risk factors (female sex and older age) **(Verma et al, 2014)**

5- Supplemental patient-related risk determinants: diabetes mellitus, hypertension, obesity, hemostatic disorders, renal impairment, and other major organ system failures (**Verma et al, 2014)**, **(Collet et al, 2006)**, **(Eikelboom et al, 2006)**.

6- Timing of the appointment: early morning visits allowing patients to return to the dental office in case of postsurgical hemorrhage **(Kamoh et al, 2012)**.

4.9 Identifying patients at risk of bleeding

Patients at a higher bleeding risk are those reporting family history of bleeding and previous bleeding problems after dental surgery or trauma and individuals using medications,

such as aspirin, anticoagulants, and/or long-term antibiotics. Any illnesses associated with bleeding problems, such as leukemia, congenital heart disease, liver disease, or hemophilia, present a higher risk of bleeding. The dental professional needs to be aware and prepared for any intercurrence, during or after a surgical procedure. Individuals presenting advanced periodontal disease are also considered as having a higher risk of perioperative bleeding. In such cases, the surgical plan should include a preoperative phase, consisting of scaling and root planning and a proper chlorhexidine gluconate mouth rinse regimen, 2 weeks before an elective procedure **(Kamoh et al, 2012)**

The risk of bleeding of a dental intervention may be ranked as high, moderate, and low **(Kaplovitch et al, 2019)**, **(Douketis et al, 2012)**, **(Spyropoulos et al, 2016)**. In most patients, antithrombotic therapy is not interrupted before dental interventions with low bleeding risk, due to the disastrous complications of thrombosis (**Error! Reference source not found.**), **(Kaplovitch et al, 2019)**, **(Douketis et al, 2012)**, **(Spyropoulos et al, 2016)**. Moderate and high bleeding potential interventions might need the temporary discontinuation of the antithrombotic therapy, **(Kaplovitch et al, 2019)**, **(Douketis et al, 2012)**, **(Spyropoulos et al, 2016)**.

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Dental interventions that are unlikely to cause bleeding	Dental interventions that are likely to cause bleeding (low risk)
Local anesthesia	Ordinary extractions
Basic periodontal clinical examination	Incision and drainage of intradental abscess
Supragingival cleaning	Periodontal probing
Supragingival indirect or direct restorations	Subgingival scaling
Endodontics	Subgingival margins of direct or indirect restorations
Impressions and other prosthetic procedures	Implant surgery
Fitting and adjustment of orthodontic appliances	Soft-tissue biopsies

*For vitamin K antagonist therapy (INR values should always be within the therapeutic range when possible)

4.10 Bleeding in dental surgery: clinical implications

Dental surgical interventions are considered by most recommendations, as minor procedures presenting self-limited blood loss and low bleeding risk. Bleeding, in most cases, can be managed with local hemostatic agents, **(Dézsi et al, 2017).**

4.11 Should anticoagulants, antiplatelets, or direct oral anticoagulants be discontinued for minor dental surgeries?

The dental care of individuals receiving therapeutic anticoagulation becomes critical when invasive procedures are needed. At this time, the clinician must decide either to maintain the anticoagulation therapy and risk bleeding complications or withdraw the anticoagulation medication and risk developing systemic thrombosis **(Wahl ,2018)**. After decades of controversial data, there is currently a nearly unanimous consensus that

anticoagulation therapy, for most dental surgeries, should not be discontinued. The higher risk of bleeding complications is compensated by the elevated risk of developing thromboembolic complications **(Little et al, 2002)**, **(Wahl et al, 2015)**, **(Wahl ,2018)**, (**Lusk et al, 2018)**.

National dental and medical group statements and multiple evidence-based clinical guidelines have considered the issue independently and support the maintenance, for most dental patients, of anticoagulation therapy (American Dental Association; American Academy of Dental Sleep Medicine; American Heart Association; American College of Cardiology; American Academy of Neurology; American Society of Anesthesiologists; Society for Neuroscience in Anesthesiology and Critical Care; American College of Chest Physicians (ACCP)) **(Wahl ,2018)**. In a 2012 statement **(Douketis et al, 2012)**, the ACCP recommended continuing anticoagulation therapy with warfarin, with the additional utilization of a local hemostatic. The ACCP advised a 2–3-day anticoagulation therapy suspension, in order to lower the INR levels to a range of 1.6 and 1.9 **(Douketis et al, 2012)**, **(Kunz et al, 2013)**.

Lately, the dental care of patients receiving anticoagulant treatment has been the focus of expressive scientific interest, in both dental and medical fields. A recent literature review showed that only 31 (0.6%) of more than 5400 patients receiving over 11,300 dental surgical interventions while continuing to take vitamin K antagonist anticoagulants (warfarin in most cases) demanded more than local maneuvers for hemostasis. No cases of fatal hemorrhage were reported. In over 2600 individuals whose anticoagulation was discontinued for dental interventions, 22 thromboembolic complications (0.8% of medication withheld), including 6 fatal events (0.2% of medication withheld), were observed **(Wahl et al, 2015)**. Similar results have been shown in a literature review of dental surgery and antiplatelet medications. Of more than 1200 patients receiving over 2300 dental surgical procedures while continuing their antiplatelet medications (aspirin in most cases), only 2 (0.2%) needed more than local measures for hemostasis. Conversely, in over 320 individuals undergoing 370 antiplatelet interruptions for dental procedures, 17 (5.3%) suffered thromboembolic complications **(Wahl, 2014)**

Available data shows that the majority of dental interventions can be safely conducted in patients receiving anticoagulation treatment, when considering older medications. However, there are fewer studies reporting the provision of dental care in individuals using newer direct oral anticoagulants. The clinical implications of these newer anticoagulant and antiplatelet therapies have only been recently investigated **(Dézsi et al, 2017)**, **(Constantinides et al, 2016).** The protocol followed by the dental practitioner when managing these patients varies

significantly and shows inconsistencies reflecting the lack of large-scale studies and evidence-based clinical guidelines (**Johnston et al, 2015)**, **(Sivolella et al, 2015),(Dézsi et al, 2017)**. The risk of postoperative bleeding after invasive periodontal treatment in individuals using different anticoagulation therapies was assessed, retrospectively, in 456 individuals receiving an antiplatelet and/or anticoagulant therapy **(Rubino et al, 2019)**. Data was collected after 484 invasive periodontal interventions, with 99.6% of patients continuing their medications during the procedures. Postoperative bleeding was reported only following three interventions (0.35%), and it was controlled with local hemostatic maneuvers. Although the authors did not specify which type of local hemostatic procedure was used, this retrospective study showed a very low risk of bleeding in patients receiving an invasive periodontal intervention while using an anticoagulant or antiplatelet medication **(Rubino et al, 2019)**. These results support the recommendation that such medications do not need to be discontinued in anticipation to invasive periodontal interventions.

Extended inter- or postoperative bleeding following dental surgery is infrequent, seldom demanding anything more than the use of local hemostatic biosurgicals. The judgment of whether or not to interrupt anticoagulation treatment can be both intricate and dynamic, and it should be based on the indication for pharmacological therapy, as well as previous thromboembolic history. The discontinuation of anticoagulant therapy may be required in dental interventions with moderate and high bleeding risk **(Douketis et al, 2012)**, **(Spyropoulos et al, 2016), (Kaplovitch et al, 2019)**. Currently, most clinicians dealing with anticoagulant management tend to personalize the periprocedural management of the bleeding potential, according to the individual risk of each procedure—low, moderate, or high—following the current clinical practice recommendations based on best evidence and maintaining the anticoagulant therapy. Thereby, the patient anticoagulant regimen should be continued in specific low-risk dental procedures, without consultation or fear of disproportionate bleeding demanding additional intervention (**Error! Reference source not found.**), **(Kaplovitch et al, 2019).**

4.12 Common anticoagulants and potential interactions with dental medications

Undoubtedly, anticoagulant agents are effective in preventing thromboembolism. Nevertheless, their potential for critical adverse effects cannot be ignored. The use of antithrombotic medications is the most frequent cause of an adverse drug event requiring

individuals to seek out emergency care **(Shehab et al, 2016)**, **(Kaplovitch et al, 2019)**. The majority of drug interactions with anticoagulants lead to elevated risk of bleeding. The nature of the interactions cannot be predicted, as they are expressed through both pharmacodynamic mechanisms and pharmacokinetic properties **(Kaplovitch et al, 2019).**

Regarding patient safety, potential risk for interaction, as well as knowledge of appropriate prescribing and monitoring, is crucial. Equally decisive is selecting the appropriate anticoagulant agent and monitoring the potential for drug–drug interaction **(Robinson, 2000)**, **(Triplett, 2000)**, **(Goodnight et al, 2001)**, **(Lippi et al, 2009)**, **(Kumar et al,2013)**, **(Vezeau, 2016)**, (**Mani et al, 2018)**, (**Kaplovitch et al, 2019)**.

Common anticoagulants and their interaction with the most common medications prescribed for dental patients are described in (

Table *4-2*), **(Kaplovitch et al, 2019).**

Table 4-2 Common anticoagulants and potential interactions with dental medications–adapted from Kaplovitch and Dounaevskaia **(Kaplovitch et al, 2019)**.

Vitamin K Antagonists Warfarin Acenocoumarol	Antibiotics[a]: Clindamycin; Amoxicillin; Amoxicillin Clavulanate; Cephalexin; Doxycycline; Macrolides; Metronidazole Azole antifungals Analgesics Carbamazepine Oxcarbazepine Nonsteroidal anti-inflammatory drug
Direct Dental Anticoagulants Apixaban Rivaroxaban Dabigatran Edoxaban	Antibiotics Clarithromycin; Erythromycin[b] Azole antifungals Analgesics Carbamazepine Nonsteroidal anti-inflammatory drug
Low-Molecular-Weight Heparins Tinzaparin Dalteparin Enoxaparin	Analgesics Nonsteroidal anti-inflammatory drug

Anticoagulant medication	Drug interaction with anticoagulants

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

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

As an example, a controlled clinical trial compared the occurrence of bleeding following dental extractions in individuals receiving oral anticoagulants (experimental group) versus patients that had never received oral anticoagulant therapy (control group). Tooth extractions were performed, and a piece of oxidized cellulose was placed only into the sockets in the experimental group. The wound borders were sutured, and a gauze saturated with tranexamic for 30–60 minutes was applied with pressure in the wound. Both groups presented similar bleeding complications **(Zanon et al, 2003)**. In a similar clinical trial **(Morimoto et al, 2008)** 161 tooth extractions were performed in patients undertaking warfarin. After tooth extraction, an oxidized cellulose gauze was placed in the socket, and the wound was sutured. Patients were assigned to four groups, according to their INR range (INR was 1.5–1.99 in group 1; 2.0–2.49 in group 2; 2.5–2.99 in group 3; and 3.0–3.7 in group 4). No significant differences were found in the postoperative bleeding among groups.

Capter 5: Conclusion

Patients with vascular inherited disorders can usually be managed in primary care using local post–operative measures. Some patients with inherited bleeding disorders may not be diagnosed until they have received invasive dental treatment. Therefore, clinicians need to be aware of identifying those people at risk so that their treatment can be better managed. Clinicians may need to make a decision on whether some people can be treated on a shared care basis, alternating between specialist services and primary care, where appropriate.

Based on the latest evidence and clinical practice recommendations on the perioperative management of dental patients receiving direct oral anticoagulants, on single or dual antiplatelet therapy or vitamin K antagonists, as well as on the current scientific knowledge on biosurgical hemostatic agents, the following conclusions can be made:

The majority of dental procedures can be securely executed without the withholding of anticoagulants, using only local hemostatic therapy. In fact, current recommendations and consensus support the continuation of antiplatelet or anticoagulant therapy. Discontinuing these drugs can increase the risk of thromboembolism, at the cost of minor bleeding, which can be restrained without difficulty. The appropriate use of local hemostatic measures, such as topical biosurgical hemostatic agents, should always be considered whenever indicated.

In order to safely treat a patient receiving anticoagulant therapy, familiarity with anticoagulants and with the potential for drug–drug interactions is required, in addition to knowledge about the topical hemostatic options available.

Topical biosurgical hemostatic agents are diverse agents with distinct indications. The dental practitioner must be aware of the properties of each single agent, in order to properly select the product needed in each different clinical condition.

Based on current available data, no topical hemostatic agent can be regarded as superior or more effective than the others. Further experimental research and controlled clinical trials are warranted to define the most cost-effective biosurgical hemostatic agents in dentistry.

A definite protocol for excessive bleeding is still required for dental surgery in patients with hemorrhagic diathesis. The most effective local hemostatic agent with lesser complications should be determined in future research, considering their availability and cost-effectiveness.

Capter 6: References

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