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Review

Pathological Background and Clinical Procedures in Oral Surgery Haemostasis Disorders: A Narrative Review

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Abstract: Haemostasis disorders are serious pathologies that could put dental and surgical procedures at risk as they are associated with postoperative bleeding, which in some circumstances could be prolonged and dangerous for the patient. In-depth knowledge of the problems associated with coagulation pathologies and the suitable specific procedures should be implemented in dental practice. A good awareness of the clinical protocols to be used in these circumstances may help reduce operator stress and increase patient compliance. Collaboration with the haematologist is always recommended to establish an adequate treatment plan, both regarding the administration of therapies that promote haemostasis and for assessing the operative risk. Hereby, we summarize the congenital and hereditary pathologies that lead to haemostasis disorders, which can be found in patients undergoing dental procedures. The purpose of this narrative review is to frame the diseases from a clinical, anamnestic, and etiopathological standpoint, as well as to evaluate an operative approach to the pathology under consideration, with particular attention to anaesthesia manoeuvres and post-surgical haemostasis, to avoid hematoma formation and uncontrolled bleeding which can lead procedure failure up and even death. Of note, it is likewise important to educate the patient about prevention, to keep the oral cavity healthy and avoid invasive procedures, limiting the number of operative sessions.

Keywords: haemostasis; haemophilia; haemorrhage; oral surgery; purple; thrombocytopathies; thrombopenia

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1. Introduction

Haemostasis represents a dynamic process able to maintain the equilibrium between thrombotic and bleeding events, in which the main role is played by platelets and the vessel wall. Thus, pathologies of haemostasis present different aetiology, including defects or malfunctioning of platelets, deficiency of one or more coagulation factors, and defects in the vascular components. Genetic and environmental factors can affect platelets and the vessel wall, as well as the coagulation and fibrinolytic systems, compromising the normal haemostatic process and resulting in a thrombotic or haemorrhagic diathesis [1–6]. This article examines the congenital and hereditary pathologies that lead to haemostasis disorders and that can be found in patients undergoing dental surgery. The purpose of this narrative review is to frame the diseases from a clinical, anamnestic, and etiopathological point of view and to consider a therapeutic approach to the pathologies considered. Particular attention must be paid to anaesthesia manoeuvres to avoid the formation of hematomas

in the inoculation area and post-surgical haemostasis, which must often be assisted by substitutes for deficient factors or drugs. It is always necessary to educate the patient from the point of view of prevention to keep the oral cavity healthy, avoid invasive procedures, and limit the number of operative sessions.

2. Materials and Methods

2.1. Focused Questions

What are the pathologies related to haemostasis? What clinical protocols should be implemented in oral surgery to minimize the risk of bleeding?

2.2. Eligibility Criteria

The following inclusion criteria guided the analysis of the studies: (I) study design—narrative reviews, systematic reviews, meta-analysis, (II) participants—patients with haemostasis disorders, (III) interventions—oral surgical procedures in patients with haemostasis disorders, (IV) outcome—pathological presentation, surgery techniques, clinical management indications. We considered including only studies with free full text available. Only studies that met all the inclusion criteria were included. It was also considered to exclude (I) abstracts of articles published in non-English languages, (II) duplicate studies, (III) in vitro or animal clinical studies, (IV), not pertinent studies, and (V) the absence of free full-texts available.

2.3. Search Strategy

The PICO model (Population, Intervention, Comparison, Outcome) was used to perform this review, through a literature search of the PubMed (MEDLINE) and Scopus electronic databases. Abstracts of studies that evaluated the clinical and pathological presentation of haemostasis disorders and proper management in oral surgery were reviewed.

2.4. Research

The medical subject heading (MeSH) terms are haemostasis, haemophilia, haemorrhage, oral surgery, purple, thrombocytopathies, and thrombopenia. An electronic search was carried out with the PubMed (MEDLINE) and Scopus databases. The articles published in the years 1984–2022 were targeted. The duration of data extraction was about 20 weeks. The last search was performed on 10 September 2022. Two calibrated reviewers (F.P. and M.P.) performed the search. Disagreements and discrepancies were resolved by consensus, and two other reviewers were consulted (E.K. and F.S.). All the titles and abstracts were read thoroughly from the articles searched primarily, and nonrelevant studies were excluded. The relevant articles were enlisted and scrutinized for any similar studies that matched our inclusion criteria. For the extraction of pertinent results, we read the full texts of the included studies, and the findings were recorded.

3. Results

The primary search identified 561 articles based on MeSH terms, published from 1984 to 2022. Following those, the research has been restricted to narrative reviews, systematic reviews, and meta-analyses concerning human studies and the English language, so 119 results were found. As a result, it was decided that only articles with full text or free full text should be used, so 45 articles were screened and evaluated for eligibility.

4. Discussion

4.1. Physiology of Haemostasis

The surface of activated platelets is the most important site for the activation of coagulation factors, which results in further platelet activation and the formation of fibrin.

In a healthy organism, the normal platelet count in peripheral blood ranges from 150,000 to 450,000/μL and the half-life of circulating platelets is approximately 7–10 days. The main regulator of platelet production is the thrombopoietin hormone (TPO), whose

synthesis occurs in the liver and is increased during inflammation, specifically induced by Interleukin 6. TPO binds to its receptor present on megakaryocytes and platelets, which are removed from the bloodstream. The reduction in megakaryocyte and platelet mass increases the level of TPO, which in turn stimulates the production of platelets [5–9].

As for the role of the vessel wall, the endothelium is a physiologically active entity that intervenes in the flow of nutrients and biologically active molecules, the control of vascular permeability, the interactions of the figurative elements of the blood with the vascular wall, the inflammatory response, and angiogenesis [10–13]. Under normal conditions, the endothelium represents an antithrombotic surface, but under stimulation, it rapidly turns towards a prothrombotic function capable of promoting coagulation, inhibiting fibrinolysis, and activating platelets [1,2].

The normal vascular endothelium contributes to the prevention of thrombosis by inhibiting platelet function. However, when it is damaged, its inhibitory effects are overcome, and the platelets adhere to the exposed subendothelium surface through the Von Willebrand factor (VWD). Platelet adhesion promotes intracellular signals that lead to a conformational change and activation of the membrane platelet receptor glycoprotein IIb/IIIa, followed by fibrinogen or VWF binding and platelet aggregation [1–4].

Once activated, platelets release the contents of their granules, including nucleotides, adhesion proteins, growth factors, and procoagulant factors, promoting platelet aggregation and clot formation, as well as modifying the environment in which the clot itself forms [1–3]. During the aggregation phase, more platelets are recruited to the site of damage, resulting in the formation of the occlusive platelet thrombus. Thus, the platelet plug is then stabilized by a fibrin network, which forms simultaneously as a product of the coagulation cascade [1].

The haemostatic process can therefore be summarized in two main phases: primary haemostasis and secondary haemostasis.

Primary haemostasis is the formation of the primary platelet thrombus, which depends on vascular integrity and platelet function and the following two physiological mechanisms: (1) vasoconstriction, which reduces blood extravasation and initiates the next phase, favouring platelet adhesion, through the exposure of the collagen fibres of the damaged vessel; (2) exchange of electrical potential [1], assisted by intrinsic factors of the vascular endothelium. In platelet activation, platelets are recruited on the damaged site, adhere to it, and subsequently, with the secretion of platelet factors, aggregation occurs with the formation of the thrombotic plug [2,3].

In primary haemostasis, in response to a vessel injury, the vessel itself contracts and increases its permeability in response to the release of endothelin. The extracellular matrix exposed by vascular damage attracts circulating platelets, which undergo conformational changes and degranulate, releasing factors such as fibronectin, ADP, and thromboxane. This increases the aggregation capability between one platelet and another and between platelets and the endothelium, leading to the formation of the "white thrombus" first (temporary "plug") and, eventually, the secondary haemostatic plug [7].

Thereafter, secondary haemostasis, also called the plasma phase, takes place, consisting of the processes of coagulation and fibrinolysis. Furthermore, the plasma phase of haemostasis includes anticoagulant systems mediated at the injury site by protein S, protein C, and thrombomodulin, which the body uses to limit vascular blockage or constriction and maintain proper tissue perfusion [4,5].

Secondary haemostasis, in turn, can be divided into three ways:

- Extrinsic pathway: the fastest cascade of reactions, activated when a venous vessel is injured.
- Intrinsic pathway: the slowest cascade of reactions, activated when the arterial vessel lesion causes contact between the blood and the extracellular matrix, with consequent activation of Hageman's factor XII.
- Common pathway: activated by the two previous pathways, it begins with the formation of a complex between factors Xa and Va that cuts prothrombin (factor II), activating it into thrombin; the latter converts fibrinogen (factor I) into fibrin monomers [1–4].

In addition, fibrinolysis has the function of limiting the formation of the haemostatic plug in the sites of vascular damage, breaking down the soluble fibrin complexes, and then removing them at the end of the repair of the vessel. Specifically, fibrin is degraded and transformed into soluble elements called D-dimers during fibrinolysis.

4.2. Oral Surgery Procedures and Bleeding Risk

The dental procedures most at risk of bleeding are extractions, implant surgery, scaling and root planning, and surgical interventions aimed at the excision of oral lesions present on soft and hard tissues [5–7].

Bleeding during oral surgery can become a major problem if it becomes significant, as it leads to decreased operator vision, prolonged post-operative bleeding, or hematoma formation, which can lead to bacterial infections. Although the risk of complications from hypovolaemia is generally associated with technical errors or preoperative evaluations, an accurate preventive anamnesis is always required to rule out the presence of congenital or acquired haemostatic disorders [5–7].

Primary haemorrhage in dental surgery occurs during surgery and may be caused by traumatic procedures resulting in laceration of soft tissues and blood vessels, or due to infection or bone injury; post-operative haemorrhage, or reactionary bleeding, occurs 2–3 h after surgery and is common in patients with coagulation disorders or secondary haemorrhage. Finally, if bleeding occurs within 14 days after surgery, it is likely secondary bleeding caused by an infection. It is also possible to classify haemorrhage according to the area of origin: vascular, bone, and soft tissue [5,6].

Congenital haemostasis disorders are not uncommon: the deficiency leads to recurrent joint, mucosal and soft tissue bleeds, and intracranial and intraperitoneal haemorrhages can occur. The bleeding frequency and severity are proportional to the deficiency [5,6]. Medical and dental management may differ depending on the bleeding disorder and the intervention expected.

Even in the perioperative stage, the surgeon must be careful with some procedures such as the administration of local anaesthesia, due to the risk of bleeding. In fact, anaesthetic injections (both intramucose or truncular) can cause prolonged bleeding that can be uncontrollable with local measures and can have serious consequences: haemorrhage with anaemia until hypovolaemic shock [4,5], conspicuous haematoma up to respiratory tract obstruction and an additional risk is bacterial superinfection of a haematoma formed as a result of oral surgery [4,5].

In cases of bleeding, the surgeon can act both locally and systemically. The systemic intervention involves the administration of fresh frozen plasma, platelets, or both; factor replacement therapy, intranasal desmopressin, oral or intravenous tranexamic acid or amino-d-caproic acid. Systemic therapy is generally reserved for patients who have systemic disorders affecting haemostasis [5–7].

Local interventions include surgical procedures such as suturing the bleeding site or using haemostatic agents, including oxidized cellulose, gel foam, collagen fleeces, cyanoacrylate glue, and collagen or gelatin sponges [5].

4.3. Pathology and Disorders of Haemostasis

Excessive bleeding can result from increased fragility of the vessels, platelet deficiency, dysfunction, and impaired coagulation.

These predisposing factors can occur singly or in combination, causing hereditary or acquired haemostasis diseases [1–6].

4.4. Pathologies Caused by Defects of the Vascular Wall

The diseases included in this category, called non-thrombocytopenic purpura, are quite frequent but do not usually cause severe bleeding problems. Most of the time, they induce small haemorrhages (petechiae and purpura) of the skin and mucous membranes, particularly of the gums.

Sometimes, however, major bleeding may occur, affecting the joints, muscles, or subperiosteal areas, or may manifest as epistaxis, gastrointestinal bleeding, menorrhagia, or haematuria. Laboratoristically, the number of platelets, bleeding time, and clotting tests (PT and PTT) usually give normal results [7,8].

Clinical diseases and situations that may cause vascular wall changes and bleeding include [9–14]: meningococcal sepsis and other forms of sepsis, infective endocarditis, rickettsia infections, reactions to drugs (sometimes they cause the formation of petechiae and purpura without inducing thrombocytopenia), scurvy, Ehlers-Danlos syndrome, Henoch-Schönlein purpura, Weber-Osler-Rendu syndrome, and amyloidosis [15–21].

4.4.1. Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) comprises a group of clinically and genetically heterogeneous inherited diseases of the connective tissue [22]. Various defects in collagen synthesis led to greater elasticity within different types of connective tissue (joints, muscles, tendons, blood vessels, skin, and visceral organs). The current Villefranche classification recognizes six main genetic subtypes: classical (type I and II according to the old "Berlin classification"), hypermobility (type III), vascular (type IV), kyphoscoliotic (type VI A), arthrochalase (type VII A and B), and dermatosparaxis (type VII C). Most are linked to mutations in one of the genes that code for fibrillar collagen proteins or enzymes involved in the post-translational modification of these proteins). Depending on the specific subtype and individual aspects, the defects are mild to life-threatening. Each subtype has typical symptoms, although individual symptoms and severity depend on each specific patient. The classic type (type I and II) presents with severe hyperextensibility and fragility of the skin, delayed wound healing, easy bruising, and generalized hypermobility of the joints, while the type of hypermobility (Type III) presents with generalized joint hypermobility, recurrent dislocations, and chronic musculoskeletal pain, but less severe skin fragility [22–25].

The most severe subtype is the vascular subtype (type IV), characterized by extremely fragile blood vessels and internal organs, such as the gastrointestinal tract, spleen, and liver, which are subject to laceration, but also the fragility of the pregnant uterus [24–26].

From an operative, anaesthetic, and surgical standpoint, most of the subtypes share the same problems and complications.

Therefore, accurate patient classification should be planned before any invasive procedure.

Regarding anaesthetic procedures, local anaesthetics may have little or no effect in some patients [24,25], due to tissue scarring that determines a reduced diffusion of local anaesthetics and the failure of nerve conduction block. This includes the use of EMLA cream as a topical anaesthetic. In dental surgery, reports of analgesia failure are mainly related to local anaesthesia and peripheral nerve blocks [25].

The risk of postoperative bleeding in these patients must be carefully evaluated through a detailed medical history. Tests of coagulation usually give results in the normal range, but the clotting time may be prolonged, particularly in patients who have already had bleeding episodes in their medical history [25].

Patients with EDS require special care during mobilisation because they are prone to easy skin lesions and hematoma formation. Moreover, during oral surgery manoeuvres, the ease of dislocation of the joints should also be remembered, with specific regard to the temporomandibular joint. Additionally, surgical cutting procedures should be reduced as much as possible, as wound healing and bone remodelling are impaired in severe EDS subtypes [24–26].

4.4.2. Weber-Osler-Rendu Syndrome (Hereditary Haemorrhagic Telangiectasia)

Hereditary haemorrhagic telangiectasia (Rendu-Osler disease) is a hereditary disease that leads to altered angiogenesis without coagulation disorders. The result is a dilation of the capillaries of the arteriovenous junction, with peripheral vascular manifestations,

responsible for mucosal-cutaneous telangiectasias and visceral arteriovenous fistulas. The signs and symptoms that allow the diagnosis are:

spontaneous, recurrent, chronic epistaxis, and anaemia (90% of patients), due to the presence of nasal telangiectasias; telangiectasias in the skin (fingers, lips, face) and mucous membranes (lips, tongue, oral cavity, nose), the latter contributing to the state of anaemia; arteriovenous malformations (AVMs) affecting some organs (lung, brain, liver, and gastrointestinal tract) with possible complications and comorbidities, which can be life-threatening, especially when the diagnosis has not yet been made [27–29]; familiarity with the disease, with an autosomal dominant inheritance [29].

Vascular abnormalities form when arteries and veins directly anastomose, bypassing the local capillary system. Large AVMs can occur in the lungs, liver, and brain, increasing the risk of morbidity and mortality. Smaller AVMs, known as telangiectasias, are prevalent in the skin and mucous membranes of the nose, mouth, and gastrointestinal tract and are prone to bleeding [27–30].

The presence of pulmonary AVM exposes patients to the risk of introducing bacteria into the bloodstream, especially during some invasive medical, surgical, or dental procedures. These bacteria can then form an infectious focus to reduce this risk and take preventive antibiotic treatment to decrease the risk of bacterial endocarditis [28]. In cases of bleeding from telangiectasias present on the skin, or if requested by the patient for an aesthetic evaluation, it is possible to perform laser therapy [28,29].

No precautions are required regarding local anaesthesia, instead, it is necessary to pay particular attention to general anaesthesia procedures, since nasal-tracheal intubation and nasal aspiration are contraindicated, because they favour rupture of telangiectasias of the nasal mucosa, and cause bleeding. In addition, in the case of pulmonary AVM, positive pressure ventilation aggravates the shunt and increases hypoxia [29].

There are no formal contraindications to the use of drugs [29,30].

4.5. Pathologies Caused by a Reduction in the Number of Platelets

The reduction in the number of platelets is an important cause of generalized bleeding. A value below 100,000/μL is generally considered to be a sign of thrombocytopenia. However, spontaneous bleeding does not occur if the count does not fall below 20,000/μL. A platelet count between 20,000 and 50,000/μL can aggravate post-traumatic bleeding. If the bleeding disorder depends only on thrombocytopenia, it is associated with normal PT and PTT [31].

Spontaneous bleeding associated with thrombocytopenia occurs very often in the small vessels. Typical sites are the skin and mucous membranes of the gastrointestinal and genitourinary tracts. However, intracranial haemorrhage is a danger for all patients who present a marked reduction in platelet count [31].

The causes of thrombocytopenia can be reduced production of platelets, decreased platelet survival, sequestration (dysfunction of the spleen, splenomegaly), or dilution (caused by massive transfusions) [31].

Idiopathic Thrombocytopenic Purpura (ITP)

Immune thrombocytopenia, formerly known as idiopathic thrombocytopenic purpura (ITP), is an autoimmune disease related to the production of antiplatelet immunoglobulin (IgG). The production of IgG autoantibodies by B cells is critically dependent on cellular immune mechanisms, where T cells play a fundamental role in pathophysiology. T cell-mediated cytotoxicity is an alternative mechanism for platelet destruction in ITP [31–33]. Other causes include genetic factors (immune genes-FcR, immune syndromes, platelet antigens) and susceptibility to the initial event (infection, inflammation) [33]. Immune thrombocytopenia is characterized by an increased risk of mucocutaneous bleeding with a low platelet count [34–38].

The diagnosis of immune thrombocytopenia is made by excluding other factors that cause thrombocytopenia. The annual incidence of ITP in adults is 1.6–6.6 per

100,000 people [31–34], more prevalent in women in the middle age group (30–60 years), and approximately equal for the sexes in all ages [35,36]. The hypothesized initial cause of ITP has increased destruction of platelets at a rate that exceeds the production by the bone marrow. Recently, new evidence has called this model into question, since platelet production is decreased in many ITP patients [36]. There is no "gold standard" test that reliably establishes the diagnosis. However, a positive response to specific ITP therapy, such as intravenous immunoglobulins and/or steroids, supports the diagnosis.

The phases of the disease have been redefined:

(a) Newly diagnosed ITP: within 3 months after diagnosis;
(b) Persistent ITP between 3 and 12 months after diagnosis;
(c) Chronic ITP lasting more than 12 months.

The primary goal of treating ITP is the prevention of major bleeding events by achieving a safe platelet count, without returning the platelet count to normal. A level of $50 \times 10^9/\mu L$ may be sufficient in ITP patients with well-functioning platelets. Adults with platelet counts below $30 \times 10^9/\mu L$ are usually treated. Several large cohort studies have reported that patients with platelet counts above this level have been observed safely without treatment [37].

The incidence of bleeding diathesis increases with age, and the effect of this condition on quality of life, mortality, and morbidity should be considered. Studies of comorbidities and risk factors in a large series of ITP patients with long follow-ups are rare [37]. Surgical complication and mortality studies were only conducted for splenectomy procedures. The overall characteristics of adverse postoperative outcomes for ITP patients undergoing all types of surgical procedures have not been studied in a population-based cohort [38].

The risk of fatal bleeding is generally very low. Risk factors for serious bleeding include elderly age, bleeding diseases (>65 years with a previous history of bleeding, gastrointestinal problems, liver cirrhosis, controlled hypertension), and specific drugs (aspirin, Coumadin, NSAIDs, etc.) [38].

In the case of dental procedures, transfusions of platelet concentrates should be considered when the platelet count falls under [38]:

- $20–30 \times 10^9/\mu L$ Dentistry (calculus removal, root planning)
- $30 \times 10^9/\mu L$ during simple extractions
- $50 \times 10^9/\mu L$ during complex extractions
- $30 \times 10^9/\mu L$ during locoregional (troncular) anaesthesia
- $50 \times 10^9/\mu L$ during small dental surgery
- $80 \times 10^9/\mu L$ during major dental surgery (complex interventions)

Outpatient anaesthesia can be performed in ITP patients with normal preoperative examinations without further haemostasis issues [37,38]. Outpatient anaesthesia can be performed in ITP patients with normal preoperative examinations without further haemostasis issues [37,38].

An anticoagulant strategy is not needed in patients with ITP, except in the case of other comorbidities, such as thrombosis, stenting, or heart valve disease [37,38].

Preoperative planning of surgery in an ITP patient that takes anticoagulants should include the regulation of the anticoagulant drug and/or low molecular weight heparin, in relation to the patient's health state and the characteristics of the planned intervention.

Antifibrinolytic agents, such as oral or IV tranexamic acid and epsilon-aminocaproic acid, may be useful in the prevention of recurrent bleeding in patients with severe thrombocytopenia. It has been observed that tranexamic acid (1 g, 3 times a day, orally) and epsilon-aminocaproic acid (1–4 g every 4–6 h, maximum dose, 24 g/day) can be particularly useful during dental surgery interventions [38].

4.6. Haemorrhagic Diseases from Defects in Platelet Function

Qualitative deficits in platelet function can be inherited or acquired. Numerous inherited diseases with normal platelet counts but abnormal platelet function have been described and classified into three groups based on pathogenesis [39–41]:

- adhesion deficit (Bernard-Soulier syndrome)
- aggregation anomalies (Glanzmann's thrombasthenia)
- platelet secretion disorders (release reaction).

Glantzmann's Thrombasthenia

Glanzmann's thrombasthenia (GT) is a rare haemorrhagic syndrome, that affects the megakaryocytic line and is characterized by the loss of platelet aggregation [42–46]. The clinical picture is variable: some patients have only minimal bleeding, while others show frequent, severe, and life-threatening bleeding [42–46]. The sites of the haemorrhage are well-defined: purpura, epistaxis, gingival haemorrhage, and menorrhagia are almost constant, whereas gastrointestinal bleeding and hematuria are less common. In most cases, bleeding symptoms appear soon after birth, however, GT is occasionally diagnosed later [42–46].

The syndrome is transmitted as an autosomal recessive trait. The molecular defect consists of a quantitative and/or qualitative anomaly of the integrin αIIbβ3. This receptor mediates the binding of adhesion proteins, which ensures the formation of platelet aggregates and the formation of thrombi in damaged sites of blood vessels. The diagnosis is based on the presence of mucocutaneous haemorrhages, and the absence of platelet aggregation in response to physiological stimuli, despite normal platelet count and morphology [42–46].

Platelet deficiency in integrin αIIbβ3 or its failure should be confirmed, for example, by flow cytometry. To avoid platelet alloimmunization, therapeutic management should include, if possible, local haemostatic treatments and/or the administration of desmopressin [42–46]. When these methods are ineffective, or in anticipation of surgery, management is based on the transfusion of HLA-compatible platelet concentrates. The administration of recombinant factor VIIa is a new therapeutic alternative that needs to be considered [45].

In case of loss of deciduous dentition, GT patients may experience haemorrhage. In this case, prolonged wound compression is required, as well as the application of haemostatic biological adhesive (tranexamic acid), either locally or systemically (20 mg/kg/day in 3–4 doses). When patients undergo surgery, it is necessary to avoid the administration of drugs that aggravate haemostatic disorders (non-steroidal anti-inflammatory drugs, aspirin) and intramuscular injections [42–46].

As regards the administration of anaesthetics, locoregional anaesthesia is discouraged, and prolonged local pressure is recommended after subcutaneous injection to avoid the risk of hematomas [42–46].

4.7. Bleeding Diathesis from Disorders of Coagulation Factors

Hereditary or acquired deficits in virtually every coagulation factor have been reported as causes of bleeding diathesis. All deficiencies in these factors cause haemorrhages, except factor XII deficiency, as it is assumed that the extrinsic pathway and thrombin-mediated activation of factors IX and XI in vivo compensate for the absence of factor XII [47]. Unlike thrombocytopenia petechial haemorrhages, bleeding due to isolated coagulation factor deficiency usually manifest as large bruising or post-traumatic hematomas, or as prolonged bleeding after an injury or surgical intervention. The typical picture is that of a subject who complains of oozing lasting days after the extraction of a tooth or who develops hemarthrosis after a modest stimulus to the knee joint [48–50].

The most common and important hereditary clotting factor deficiencies affect factors VIII (haemophilia A), IX (haemophilia B), and VWD (von Willebrand's disease) [50].

4.7.1. Haemophilia

The most common type of haemophilia is haemophilia A, which is characterized by spontaneous or prolonged bleeding caused by coagulation factor VIII deficiency. The prevalence is estimated to be 1:6000 males [50,51].

The severity of the clinical signs depends on the extent of the factor VIII deficiency. If factor VIII biological activity is less than 1%, the haemophilia is severe with frequent spontaneous and abnormal bleeding, originating as a result of minor trauma, secondary to surgery, or an extraction dental [50,51].

If factor VIII biological activity is between 1% and 5%, haemophilia is moderately severe with abnormal bleeding secondary to minor trauma, surgery, or tooth extractions, although spontaneous bleeding is rare.

If the biological activity of factor VIII is between 5% and 40%, haemophilia is mild with abnormal bleeding secondary to minor trauma, surgery, or tooth extractions, with the possibility of spontaneous bleeding [50–52].

Haemorrhages are often localized in the periarticular regions (hemarthrosis) and the muscles (haematomas), but any anatomical site can be involved as a result of trauma or injury. Spontaneous haematuria is quite frequent and is a strongly suggestive sign of the disease [51,52].

Orally, the most frequent sign of haemophilia is prolonged gingival bleeding episodes, both spontaneous and following trauma, while hemarthrosis of the temporomandibular joint is rare [52]. Dental management must focus on prevention to reduce the need for invasive treatments.

In patients with mild or moderate haemophilia, non-invasive dental treatments can be performed under antifibrinolytic treatment, while the ablation of calculus and some forms of minor surgery can be performed with the combined administration of antifibrinolytics and desmopressin. In severe haemophilia, replacement of the deficient coagulation factor is necessary, with consideration of hospitalization [52]. Moreover, local anaesthesia is considered one of the riskiest procedures, due to the risk of hematoma formation that can lead to airway obstruction and exitus.

In addition, Zanon et al. also suggests administering a combination of tranexamic acid (20 mg/kg) and a single infusion of factor VIII or IX to achieve a peak level of about 30% of factor VIII or IX in vivo prior to dental extraction [53].

Locoregional anaesthesia or intramuscular injection must not be performed with values lower than 50% of factor VIII compared to the normal value and, in any case, must be preceded by replacement therapy. Intraligamentous and intraosseous anaesthesia should be preferred [52].

Haemophilia B is a form of haemophilia characterized by spontaneous and prolonged bleeding from coagulation factor IX deficiency. The prevalence is approximately estimated at 1:30,000 males [51] and recommendations are the same as for type A.

4.7.2. Von Willebrand Factor Deficiency Disease

Von Willebrand's disease (VWD) is an inherited bleeding disorder caused by a genetic defect resulting in a quantitative, structural, and/or functional abnormality of VWF.

The disease is classified into three main groups, based on the VWF deficiency: the form with a partial quantitative defect (type 1); the form with a qualitative defect (type 2), which in turn is subdivided into different subtypes 2A, 2B, 2M, 2N; and the form with a total quantitative defect (type 3) [54].

The overall prevalence of VWD is estimated between 0.1% and 1%, but the prevalence of symptomatic VWD, which requires specific treatment, is estimated to be between 1 per 50,000 and 1 per 8500. The disease onset is variable, being earlier in the most severe forms.

Clinical symptoms include bleeding of varying degrees, which may arise spontaneously or during the use of invasive techniques. Mucocutaneous haemorrhages (epistaxis, menorrhagia, etc.) are the most common type of bleeding abnormality are usually characterized by but haematomas and hemarthrosis can also occur in the most severe cases [54].

VWD is caused by mutations in the *VWF* gene (12p13.3), which encodes for the multimeric protein VWF. The VWF protein has an intra-platelet, endothelial, and plasmatic localization and plays an essential role both in the adhesion of platelets to the endothelium of the injured vessel and in the transport and stabilization of FVIII [54].

VWD is mainly transmitted in an autosomal dominant manner; however, some subtypes of forms 2 and 3 have an autosomal recessive inheritance. The diagnosis is based on laboratory tests based on VWF and FVIII assays, using functional and immunoassays. The subclassification of VWD requires very specific tests, such as studying the distribution of VWF multimers. The VWF assay usually distinguishes VWD from haemophilia A. However, this test does not distinguish VWD type 2N, necessitating further investigation. More problematic is the differential diagnosis of acquired Von Willebrand syndrome, which is associated with other diseases, and hereditary VWD [55]. Notably, people with blood type 0 may have slightly lower VWF levels. Genetic counselling is recommended to inform patients of disease risks and to offer clinical and genetic screening to identify other affected family members. For couples at risk of having a child with type 3 form, genetic counselling should be performed at a specialized multidisciplinary centre [55]. Treatment depends on the VWD type. Specifically, desmopressin is usually effective in preventing or treating abnormal bleeding in type 1 VWD, but in patients with type 2 disease, replacement therapy with purified VWF is often required since the response to desmopressin is variable. On the other hand, desmopressin is ineffective in treating patients with type 3 VWD, who therefore necessitate replacement therapy with purified human VWF associated with FVIII, at least on the first administration. The patients managed in hospitals that have centres specialized in haemostasis and thrombosis have a favourable prognosis, even in the presence of the most severe forms of the disease [55,56].

Prolonged bleeding is frequently observed following tooth extractions or associated with professional oral hygiene procedures. Treatments should be carefully considered in relation to the patient's state of health and the severity of the disease, in coordination with the haematologist [55,57].

In patients responsive to therapy, desmopressin is administered as a preventive measure for interventions at risk, while replacement therapy of the deficient factor is carried out to reduce postoperative bleeding in refractory patients [57,58].

4.8. Acquired Coagulopathies

4.8.1. Antiplatelet Agents

Antiplatelet agents reduce the ability of blood to clot or coagulate by reversibly or irreversibly inhibiting platelet activation and aggregation, which are necessary for the initial platelet plug in primary haemostasis. Platelet function is quantified using the cutaneous bleeding time which has an abnormal range of 2–10 min, although there is no reliable correlation between bleeding time and the rate of surgical bleeding complications [48,49].

The most common drugs used for this purpose are low-dose aspirin, clopidogrel, or both in dual therapy. It is particularly hazardous to stop the therapy in the perioperative stage, due to increased platelet aggregation. Many studies and reviews recommend not stopping the use of these drugs, but Clopidrogrel could be stopped seven days before surgery in patients with a low risk of cardiac events and restarted the day after the surgery. The cessation of dual therapy is associated with an increase in cardiovascular events, so it is not recommended to be suspended [48,49].

4.8.2. Oral Anticoagulants

Oral anticoagulant therapy is intended for patients with venous or cardiac pathologies, such as valve carriers, heart disease in the decompensation phase, or atrial fibrillation, who are at risk of both arterial and venous acute thromboembolisms [48,49]. Patients on continuous treatment with vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) are at increased risk of bleeding complications. As recommended for therapies with antiplatelet drugs, anticoagulant treatment is preferably continued at the same dose,

since dose reduction or discontinuation of treatment is associated with an increased risk of thromboembolism and should not be suspended. The use of haemostatic measures during or after the procedure could enable the continuation of oral anticoagulant treatment [48,49].

Table 1 summarizes the main characteristics of haemostasis disorders and the risk of bleeding.

Table 1. Haemostasis disorders and risk of bleeding.

Causes	Pathology	Congenital/Acquired	Characteristics
Defect of vascular wall	Ehlers-Danlos syndrome	Congenital	Type I–II: hyperextensibility and fragility of the skin, delayed wound healing, easy bruising, and generalized hypermobility of the joints. Type III: less severe skin fragility. Type IV: extremely fragile blood vessels and internal organs, such as the gastrointestinal tract, spleen, and liver, which are subject to laceration
	Weber-Osler-Rendu syndrome	Congenital	Altered angiogenesis, without coagulation disorders. Vascular abnormalities (AVM) when arteries and veins directly anastomose bypass the capillary system. Small AVMs can occur in the oral cavity, and they are prone to bleeding.
Defect in number of platelets	Idiopathic thrombocytopenic purpura	Congenital	Increased risk of mucocutaneous bleeding when the platelet count is low. Fatal bleeding is very low but increases in elderly patients with comorbidities and the use of drugs.
Haemorrhagic diseases from defects in platelet function	Glantzmann's thrombasthenia	Congenital	The risk of bleeding is variable, gingival haemorrhage is almost constant and mucocutaneous haemorrhage. Bleeding occurs even in the loss of deciduous dentition. Risk of hematomas during injection.
Bleeding diathesis from disorders of coagulation factors	Haemophilia A	Congenital	Spontaneous or prolonged bleeding caused by coagulation factor VIII deficiency. Factor VIII less than 1%: severe haemophilia presents spontaneous and abnormal bleeding with minor trauma or surgery. Factor VIII 1–5%: moderately severe haemophilia, bleeding due to secondary minor trauma, surgery but spontaneous bleeding is rare. Factor VIII 5–40%: haemophilia is mild, abnormal bleeding due to secondary minor trauma, surgery, and the possibility of spontaneous bleeding.
	Haemophilia B	Congenital	Factor IX is between 1% and 5%, haemophilia is moderately severe with pathological bleeding secondary to minor trauma, surgery, or tooth extractions, while spontaneous haemorrhage is rare. If the biological activity of factor IX is between 5% and 40%, haemophilia is mild with bleeding secondary to minor trauma, surgery, or dental extractions, but spontaneous bleeding is also possible.
	Von Willebrand Disease	Congenital	Prolonged bleeding is frequently observed following tooth extractions or associated with professional oral hygiene procedures.
Drug-induced coagulopathies	Antiplatelet agents	Acquired	Bleeding risk is increased, but therapy should not be suspended.
	Vitamin K antagonists—DOAC	Acquired	Bleeding risk is increased, but therapy should not be suspended.

Table 2 shows the operational suggestions for haemostasis pathologies in oral surgery.

Table 2. Operational suggestions for hemostasis pathologies in oral surgery.

Authors and Year of Publication	Haemostasis Pathologies	Operational Suggestions in Oral Surgery
Hakim et al., 2005 [24]	Ehlers-Danlos syndrome	- Local anaesthetics may have little or no effect in some patients, due to tissue scarring that determines a reduced diffusion of local anaesthetics. This includes the use of EMLA cream as a topical anaesthetic. - Tests of coagulation usually give results in the normal range, but the clotting time may be prolonged, particularly in patients who have already had bleeding episodes in their medical history - Attention is needed in the mobilization of patients with EDS, as they are prone to easy skin lesions and hematoma formation. Ease of dislocation of the joints should also be remembered with specific regard to the temporomandibular joint - Wound and bone remodelling are impaired
Sharathkumar et al., 2008 [29]	Weber-Osler-Rendu syndrome	- The presence of pulmonary AVM exposes patients to the risk of introducing bacteria into the bloodstream, especially during some invasive medical, surgical, or dental procedures. Antibiotical prophylaxis is required - Small AVMs can be treated with laser therapy - No precautions are required regarding local anaesthesia, and no formal contraindications to the use of drugs
Zhou et al., 2005 [38]	Idiopathic thrombocytopenic purpura (ITP)	- Transfusions of platelet concentrate should be considered when the platelet count falls under 20–30 $\times$ 10^9/μL during dentistry (calculus removal, root planing), 30 $\times$ 10^9/μL during simple extractions, 50 $\times$ 10^9/μL during complex extractions 30 $\times$ 10^9/μL during locoregional (troncular) anaesthesia, 50 $\times$ 10^9/μL during small oral surgery, 80 $\times$ 10^9/μL during major oral surgery (complex interventions) - An anticoagulant strategy is not needed, except in the case of other comorbidities, such as thrombosis, stenting, or heart valve disease - Preoperative planning of surgery in patients that takes anticoagulants should include the regulation of the anticoagulant drug and/or low molecular weight heparin, in relation to the patient's health state - Antifibrinolytic agents, such as oral or IV tranexamic acid and epsilon-aminocaproic acid, may be useful in the prevention of recurrent bleeding in patients with severe thrombocytopenia
Franchini et al., 2010 [46]	Glantzmann's thrombasthenia	- To avoid platelet alloimmunization, therapeutic management should include, if possible, local haemostatic treatments and/or the administration of desmopressin. When these methods are ineffective, or in anticipation of surgery, management is based on the transfusion of HLA-compatible platelet concentrates. The administration of recombinant factor VIIa is a new therapeutic alternative that needs to be considered - GT patients may experience haemorrhage in case of loss of deciduous dentition. In this event, it is necessary to proceed with prolonged compression of the wound and, possibly, the application of haemostatic biological adhesive—use of antifibrinolytic agents (tranexamic acid), locally or systemically - It is necessary to avoid the administration of drugs that aggravate haemostatic disorders and intramuscular injections - Locoregional anaesthesia is discouraged, and prolonged local pressure is recommended after subcutaneous injection to avoid the risk of hematomas

Table 2. *Cont.*

Authors and Year of Publication	Haemostasis Pathologies	Operational Suggestions in Oral Surgery
Zanon et al., 2000 [53] Rodriguez-Merchan et al., 2019 [56]	Haemophilia	- In patients with mild or moderate haemophilia, non-invasive dental treatments can be performed under antifibrinolytic treatment, while the ablation of calculus and some forms of minor surgery can be performed with the combined administration of antifibrinolytics and desmopressin. In severe haemophilia, replacement of the deficient coagulation factor is necessary, with consideration of hospitalization. - Local anaesthesia must be carefully administrated due to the risk of haematomas. - A combination of tranexamic acid (20 mg/kg) and a single infusion of factor VIII or IX to achieve a peak level of about 30% of factor VIII or IX in vivo can be used prior to dental extraction.
van Galen et al., 2019 [57]	Von Willebrand factor deficiency disease	- desmopressin is usually effective in preventing or treating abnormal bleeding in type 1 VWD, but in patients with type 2 disease, replacement therapy with purified VWF is often required since the response to desmopressin is variable. On the other hand, desmopressin is not effective in the treatment of patients with type 3 VWD, who therefore necessitate replacement therapy with purified human VWF associated with FVIII at least on the first administration - Prolonged bleeding is frequently observed following tooth extractions or associated with professional oral hygiene procedures. Treatments should be carefully considered in relation to the patient's state of health and the severity of the disease, in coordination with the haematologist.

4.9. Considerations for Dental Treatment

4.9.1. Laboratory Tests

American Board of Internal Medicine laboratory test reference ranges [59] are shown in Table 3.

Table 3. American Board of Internal Medicine—Laboratory test reference ranges January 2023 [59].

Laboratory Tests	Reference Ranges
Factor I	200–400 mg/dL
Factor II	60–130% of normal
Factor IX	60–130% of normal
Factor XII	60–130% of normal
INR (International Normalized Ratio)	Therapeutic range: 2.0–3.0 Therapeutic range in high-risk patients: 2.5–3.5 Therapeutic range in patients with lupus anticoagulant: 3.0–3.5
Platelet count	150–450 $\times$ 10^3/mcL
Protein S Plasma Activity	57–131%
Plasma thrombin time	17–23 s

- Platelet count: Used to quantify the number of platelets [59–63]
- Platelet aggregation: Evaluates the adequacy of platelet reactivity to physiological stimuli that activate platelets. It is used to identify abnormal pictures in functional, hereditary, and acquired platelet disorders [59–63]
- VWF Antigen: Measures the total plasma VWF concentration [59–63]
- Ristocetin Agglutination: Detects the presence of large VWF multimers. It is a routine test in the diagnostics of VWD [59–63]

- Prothrombin Time (PT): evaluates the factors of the extrinsic and common coagulation pathways (VII, X, V, Prothrombin II, and fibrinogen) [59–63]
- Partial thromboplastin time (PTT): Evaluates the factors of the intrinsic and common coagulation pathways (Precallicrein, high molecular weight kininogen, factors XII, XI, IX, VIII, X and V, prothrombin II and fibrinogen) [59–63]
- Thrombin time: Evaluates the last stage of coagulation. It is prolonged if there is antithrombin activation caused by heparin or by qualitative changes in fibrinogen or hypofibrinogenemia [59–63]
- Fibrinogen dosage: The fibrinogen dosage allows for the measurement of the concentration of circulating fibrinogen. A lower value indicates a reduced ability to clot, and vice versa [59–63]
- Antithrombin III (AT-III): AT-III is a hepatic synthesized glycoprotein capable of inhibiting the action of various coagulation factors. Its action is particularly efficient against activated factor II (thrombin), but it also inhibits factors IX, X, XI, and XII, plasmin, and many other factors involved in the coagulation cascade, in addition to being a cofactor for heparin anticoagulants. The plasma values of AT-III increase during the use of dicumarol anticoagulants, in situations of hypergammaglobulinemia and the presence of inflammatory states with increased erythrocyte sedimentation rate and C reactive protein. On the other hand, its values decrease during therapy with oral contraceptives, following serious hepatic diseases, as well as following thromboembolic phenomena, such as pulmonary embolism, acute myocardial infarction, disseminated intravascular coagulation, and thrombophlebitis [59–63]
- Protein S: Protein S is a blood factor that limits clotting through the degradation of factors V and VIII and, in doing so, acts together with another protein called coagulation C. Protein S is only effective if it is free, not bound to another protein called C4b. A low percentage of free S is one of the predisposing factors for thrombophilia. In this regard, three conditions are described: an insufficient overall amount of protein S, low activity of the protein, and an excess of the bound component to the detriment of the free one. These conditions can be genetic, albeit quite rare, or acquired, as in the case of liver disease, nephrotic syndrome, excessive use of protein S for clotting episodes, or, more commonly, low levels of vitamin K or oestrogen-progestogen therapies [59–63]
- Factor V Leiden: Factor V determines, once activated, the conversion of factor II into thrombin; this phenomenon is hindered by the coagulation of protein C, in competition with protein S, through the degradation of factor V, which is separated into two inactive fragments called Vi9. There is a genetic variant, linked to chromosome 1, in which arginine is replaced by glutamine, variant G1691A, which prevents the lysis of factor V by protein C, causing the condition of resistance to activate protein C (APC resistance) [59–63]. This condition, called "Factor V of Leiden" after the name of the Dutch locality where it was first described, can be present in the form of either heterozygosity or, more rarely, homozygosity. In these subjects, the risk of thrombotic events and polyabortivity increases [59–63]
- Clot Stability: Assessed in patients with slow wound healing or a history of frequent miscarriages. The lysis of clots occurs if the fibrinolytic activity is excessive or if factor XIII is deficient [59–63]
- Alpha2-antiplasmin: Measures the fibrinolysis inhibitor in plasma, which is reduced in patients with excessive bleeding and increased fibrinolysis [59–63].

4.9.2. Drugs and Factors Promoting Haemostasis

During oral surgery, the control of postoperative bleeding is of fundamental importance in patients suffering from haemostasis disorders since the resulting bleeding can be very prolonged over time and be a danger to the patient's health [62].

For optimal control, it is possible to administer drugs and substitutes for coagulation factors [61].

- Tranexamic acid is an antifibrinolytic agent. It can be used as a systemic treatment with a dose of 20 mg/kg or as a rinse, being a good adjuvant in the control of bleeding [62–65].
- Desmopressin is a synthetic analogue of the vasopressin hormone, but without vasopressor properties, which increases plasma concentrations of VWF and FVIII. It can be administered by intravenous infusion, subcutaneous injection, or intranasal spray.
- Fresh frozen plasma: in patients with VF deficiency, the infusion of 450 mL of fresh plasma increases the factor level from 1% to 11%, and after 24 h, a level of 6% is maintained.
- Platelet transfusions: indicated when the disorder is severe (less than 30,000 platelets) and when other therapeutic measures have not been effective [62–65].

4.9.3. Antifibrinolytic Therapy Considerations

A Cochrane systematic review was performed in 2019 by Van Galen et al. where the beneficial effect of antifibrinolytic agents (tranexamic acid or epsilon aminocaproic acid) in preventing bleeding was inquired to establish the effectiveness of the agent to treat patients affected by haemophilia or Von Willebrand disease [57]. The review found that, when compared to the placebo group, the two antifibrinolytic agents were effective in reducing the number of bleeds after dental extraction, the amount of blood loss, and the need for a clotting factor. There were rare side effects reported. However, there were no trials of antifibrinolytic medicine to prevent bleeding in patients with Von Willebrand disease and even if it is currently used in dental practice, there is no clear scientific evidence in the literature [57].

4.9.4. Replacement Therapy Considerations

The replacement therapy, together with local haemostasis control manoeuvres significantly reduces the risk of bleeding, while the use of recombinant factors in place of blood products eliminates the risk of viral infections [58]. It is a prophylaxis that aims to keep the amount of the factor constant and is administered on a cyclical basis. This therapy is based on plasma-derived products or synthesis products, called recombinants. [58–65].

The intravenous administration of these products makes it possible to stop or prevent bleeding in the event of trauma or surgery. The high cost and the limited availability of production set the limits of substitution therapy. To overcome the limitations, factor VIII lacking the B domain was made available to haemophilia A patients and is efficiently expressed in cultured cells by modification with genetic engineering techniques, leading to a longer half-life and lower immunogenicity. It was noted that, in some haemophilic patients, the replacement therapy with the deficient factor over time causes the production of antibodies against the inserted factor, which makes the therapy ineffective [64,65]. For this reason, products synthesized with recombinant DNA technology have been studied. These agents are mimetic antibodies, like emicizumab (ACE910) or antibodies that inhibit the tissue factor pathway inhibitor (TPF1). Emicizumab, a humanized bispecific monoclonal antibody that binds and bridges FX and FIXa, was developed to restore the function of FVIIIa. It carries the additional advantages of a subcutaneous mode of administration and a long half-life (∼30 days) [57]. PK modelling showed that, after a weekly loading dose, subjects could be maintained at a steady-state plasma level with weekly, biweekly, or monthly dosing that would be sufficient to maintain the majority of subjects bleed-free, as tested in the clinical trial program [57].

Theoretically, inhibition of TFP1 could ensure adequate thrombin generation by tissue factor, factor VIIa, and factor Xa in the early stages of the coagulation cascade. In this category of antibodies, we find Concizumab, for which a pro-coagulant dose-dependent effect has been noted, which lays the foundation for future studies on the use of the product in the treatment of haemophilia [64,65]. In the management of these therapies collaboration with the haematologist is important to establish which is the best therapy for the patient who needs to undergo surgery is important in the management of these therapies.

4.9.5. Desmopressin Considerations

Desmopressin is one of several non-transfusional pharmacological agents used to treat bleeding episodes, including anti-fibrinolytic agents, such as tranexamic acid, ε-aminocaproic acid, and aprotinin; recombinant human factor VIIa [64]; and conjugated oestrogens. It is used systemically in patients with type-1-vWD, with an available residual concentration of factor VIII and vWF-concentrations of >10 IE/dL. Patients who are not responding to desmopressin, as well as patients with other types of vWD can be treated with vWF-containing factor VIII concentrates [64].

However, desmopressin is not a drug without side effects. The major adverse effect of desmopressin is dilutional hyponatremia, as it increases renal water retention and urine electrolyte concentration. As a result, it can lead to systemic hyponatremia with physiology similar to the syndrome of inappropriate antidiuretic hormone [66]. In rare instances, the hyponatremia caused by this drug manifests as altered mental status or precipitates seizures. For this reason, this drug should be avoided in young patients under the age of 2, because restricting water and fluids in these patients is difficult. It is also not recommended in patients with compromised renal function or suffering from thrombocytopenic purpura, as it can precipitate a thrombotic event [66]. Lastly, desmopressin is contraindicated in patients with known hypersensitivity to desmopressin acetate.

The minor adverse effects that may affect individual patients are headaches, tachycardia, and facial flushing. In exceptional cases, patients receiving desmopressin have suffered strokes or myocardial infarctions; however, the direct role of desmopressin in these cases is not established [66].

4.9.6. Dental Procedures

The most important goal in the treatment of patients suffering from haemostatic disorders is to prevent surgical complications and reduce the risk of bleeding.

For this reason, the following flow chart is suggested [62–65,67]:

- Careful medical history: it is necessary to frame the patient's systemic health, through an accurate medical history and the collection of the necessary diagnostic test data.
- Patient motivation to maintain oral health to prevent invasive dental procedures.
- Collaboration with the haematologist and the attending physician to determine the best therapy for the patient based on his clinical condition; establish any suspensions of ongoing therapies or additions of supportive replacement therapies.
- Avoid sudden manoeuvres during surgery to avoid traumatizing the soft tissues and promoting bleeding.
- Avoid the administration of drugs that can compromise haemostasis, such as aspirin and non-steroidal anti-inflammatory drugs.
- Use of absorbable sutures to avoid the risk of bleeding during removal.
- All local haemostasis manoeuvres are recommended, such as compression, suturing, and the use of local haemostats [61–65].

5. Conclusions

Haemostasis disorders are pathologies of different aetiology and severity; the clinician needs to know the clinical manifestations to be able to set up an adequate operative protocol to minimize the intra- and postoperative bleeding risk. Good clinical practice involves planning dental surgery to use the fewest number of procedural steps, applying adequate local and loco-regional anaesthesia, and ensuring the correct management of intra- and post-operative bleeding through both surgical and pharmacological methods. Finally, it is necessary to know the blood chemistry tests and the physiological ranges necessary to evaluate the health state of the patient and plan future treatments.

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