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Antiplatelets, Anticoagulants and Its Implications in Dentistry-A Review of Literature

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Authors' contributions

This work was carried out in collaboration between both authors. Author AG designed the study, wrote the protocol and wrote the first draft of the manuscript. Author JV managed the analyses and literature searches of the study. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Oral health care providers must be aware of the impact of bleeding disorders on their patients during any dental procedure and management of such mishaps. Adequate knowledge of the mechanisms underlying hemostasis, and the optimised management of such patients, are therefore very important for these issues. Initial recognition of a bleeding disorder, in such patients with a systemic pathologic process, may occur in dental practice. The dental treatment of these patients might get complicated during the course of the treatment due to the use of anticoagulant and/or antiplatelet drugs raises a challenge in the daily practice of dental professionals. Adequate hemostasis is critical for the success of any invasive dental procedure, because bleeding problems can give rise to complications associated with important morbidity-mortality. Besides, prophylactic, restorative and surgical dental care of patients with any bleeding disorders is handled skilfully by practitioners who are well educated regarding the pathology, complications which could arise and treatment options associated with these conditions. The purpose of this paper is to review common

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bleeding disorders and their effects on the dental aspect. Many authors consider that patient medication indicated for the treatment of background disease should not be altered or suspended unless so indicated by the prescribing physician. Local hemostatic measures have been shown to suffice for controlling possible bleeding problems resulting from dental treatment.

Keywords: Tooth extraction; oral surgery; hemostasis; platelet aggregation inhibitors; antiplatelet drugs; anticoagulants; warfarin.

1. INTRODUCTION

Hemostasis is a defence mechanism composed of a series of independent biological systems that aims to preserve vascular integrity and avoid blood losses, while ensuring optimum fluidity throughout the circulatory system [1,2]. Hemostatic alterations have a broad range of potential causes, including deficiency states, hereditary and metabolic alterations, cancer, etc. However, at present, the most frequent cause of blood coagulation disorders in developed countries is the use of drug substances [3].The most common inherited bleeding disorder in the population is von Willebrand disease with an estimated prevalence of 1–2%. Von Willebrand factor (vWF) is required to adhere platelets to exposed sub endothelium and protects factor VIII from proteolysis in the circulation.The prevalence of vWF rises in studies involving women with menorrhagia, with estimates ranging as high as 10–20% in white women, and 1–2% among African American women. Other bleeding disorders seen in adolescents with menorrhagia are disorders of inherited platelet dysfunction, clotting factor deficiencies, thrombocytopenia, and disorders of the fibrinolytic pathway. [4] Dentists must be familiar with the impact of bleeding disorders on the management of their patients. Proper dental and medical evaluation of patients is therefore necessary before starting any invasive treatment.

2. HISTORY TAKING AND CLINICAL EVALUATION FROM DENTAL ASPECT

Patient evaluation and history taking should be done with standard medical questionnaires regarding patients systemic health conditions. Most of the bleeding disorders, such as hemophilia and von Willebrand's disease, run in genetics; therefore, a family history of bleeding disorders should be carefully listed. Patients should be queried about any previous unusual bleeding episode after surgery or injury, spontaneous bleeding and easy or frequent bruising. A history of nasal or oral bleeding should be noted down in the case sheet. Suppose if the patient is under any such medication then a complete drug history is important. If a patient is taking anticoagulant drugs, it will be important to consult his or her physician before any major surgical procedure. In addition, a number of medications may interfere with hemostasis and prolong bleeding. Other medication drugs of abuse, such as alcohol or heroin, may also cause excess bleeding by causing liver damage resulting in altered production of coagulation factors [5].

Illicit injection drug use carries an increased risk of transmission of viral pathogens that may lead to viral hepatitis and altered liver function.

For the purpose of history-taking, a clinically significant bleeding episode is one that: [6]

- continues beyond 12 hours
- causes the patient to call or return to the dental practitioner or to seek medical treatment or emergency care
- results in the development of hematoma or ecchymosis within the soft tissues or
- requires blood product support.

A general examination of the patient might indicate a tendency to bleed. Multiple purpura of the skin, bleeding wounds, evident hematomas or swollen joints may be seen in patients with severe bleeding disorders. Evidence of petechiae, ecchymoses, hematomas or excessive gingival bleeding should be noticed by the practitioner's to understand the possible underlying bleeding disorder [6].

3. SIGNS AND SYMPTOMS

Patients may elicit signs of underlying systemic disease. Patients with liver disease may have jaundice, spider nevi, ascites and other signs of defective hepatic function. A cardiac patient may tend to show tachycardia or hypertension, which may make hemostasis more difficult to achieve [7].

4. CONGENITAL BLEEDING DISORDERS

4.1 Hemophilia A

Hemophilia A, is rare genetic disorder caused by missing or defective factor VIII-a clotting protein. It's also called as factor VIII (FVIII) deficiency or classic hemophilia. About 1/3 of cases are caused by a spontaneous mutation, but sometimes it is also passed down from parents to children.

4.1.1 Symptoms

People with hemophilia A often bleed longer than other people.

- Bleeds can occur internally, into joints and muscles, or externally, from minor cuts,
- dental procedures or trauma.
- a person bleeds and the severity of those bleeds depends on how much FV-III is in the plasma, the straw-coloured fluid portion of blood.

Normal plasma levels of FVIII range from 50% to 150%. Levels below 50%, or half of what is needed to form a clot, determine a person's symptom.

4.1.2 Orofacial manifestation

- Angina bullosa haemorrhagica
- Oral hematoma
- Palatal and tongue purpura
- Ecchymotic lesions on lips,tongue,oral mucosa
- Epistaxis
- Spontaneous and post traumatic gingival hemorrhage
- Poor oral hygiene with cavities and gum disease
- TMJ hemarthrosis and arthropathy [8,9]

4.2 Hemophilia B

Hemophilia B, is a genetic disorder caused by missing or defective factor IX- a clotting protein. Other names for hemophilia B are-factor IX (FIX) deficiency or Christmas disease, Although it is passed down from parents to children, about 1/3 of cases are caused by a spontaneous mutation-a change in a gene.

4.2.1 Symptoms

Bleeds can occur internally, into joints and muscles, or externally, from minor cuts, dental procedures or trauma. How frequently a person bleeds and how serious the bleeds are depends on how much FIX is in the plasma, the straw-coloured fluid portion of blood.

Normal plasma levels of FIX range from 50% to 150%. Levels below 50%, or half of what is needed to form a clot, determine a person's symptoms.

4.2.2 Orofacial manifestation for Hemophilia B

- Angina bullosa haemorrhagica
- Oral hematoma
- Palatal and tongue purpura
- Ecchymotic lesions on lips,tongue,oral mucosa
- Epistaxis
- Spontaneous and post traumatic gingival hemorrhage
- Poor oral hygiene with cavities and gum disease
- TMJ hemarthrosis and arthropathy [9,10]

4.3 Von Willebrand Disease

This condition is named after Finnish physician Erik von Willebrand, who first described it in the 1920. Von Willebrand disease (VWD) is a genetic disorder and most common inherited bleeding disorder caused by missing or defect in both quantity or quality of von Willebrand factor (VWF)-a clotting protein. VWF binds with factor VIII, a key clotting protein and platelets in blood vessel walls, which helps to form a platelet plug during the clotting process.

4.3.1 Symptoms

- People with VWD experience frequent nosebleeds, easy bruising and excessive bleeding during and after invasive procedures, such as tooth extractions and surgery.
- Women often experience heavy menstrual bleeding (heavy menstrual periods that last longer than average), and hemorrhaging after childbirth [11–13].

5. ACQUIRED DISORDER

5.1 Liver Disease

5.1.1 Orofacial manifestation

- Facial petechiae
- Conjunctival haemorrhage

- Angina bullosa haemorrhagica
- Oral hematoma
- Palatal and tongue purpura
- Ecchymotic lesions on lips,tongue,oral mucosa
- Epistaxis
- Spontaneous and post traumatic gingival haemorrhage [10]

5.2 laboratory Investigations

Blood counts and clotting studies, should be carried out. Preoperative laboratory tests of the hemostatic system [1,2] are:

- bleeding time to determine platelet function (normal range: 2–7 minutes)
- activated partial thromboplastin time to evaluate the intrinsic coagulation pathway (normal range: 25 ± 10 seconds)
- international normalized ratio to measure the extrinsic pathway (normal range: 1.0)
- platelet count to quantify platelet function (normal range: 150,000–450,000/μL).

With a rich case bank established over 3 decades we have been able to publish extensively in our domain [14–24].

Based on this inspiration we aim to study the present antiplatelet drugs and anticoagulant drugs used for the treatment of these illnesses and also to establish guidelines for the approach of patients treated with antiplatelet drugs and anticoagulant drugs who are going to be treated with oral surgery procedures.

5.3 Role of Blood Thinners in Dental Aspect

Patients are administered with blood thinner for various reasons such as for the treatment or prevention of formation of potentially harmful blood clots which leads to stroke, heart attack, deep vein thrombosis (DVT) or pulmonary embolism (PE). However, these medications interfere with the body's normal clotting mechanism to stop blood flow at a site of tissue injury, which needs to be taken under consideration by the dentist [25].

5.4 Mechanism of Clot Formation

The two major factors which cause the blood clot normally in our body [26]

- platelets which clump together at the wound to form a plug which slows the flow of blood through the vessel and forms a matrix
- Fig. 1. Mechanism of clot formation
- Fig. 2. Mechanism of coagulation
- Coagulation where proteins in the blood interact with each other to fill in the spaces between the platelets, stabilize the clot, and make it more solid until bleeding stops.

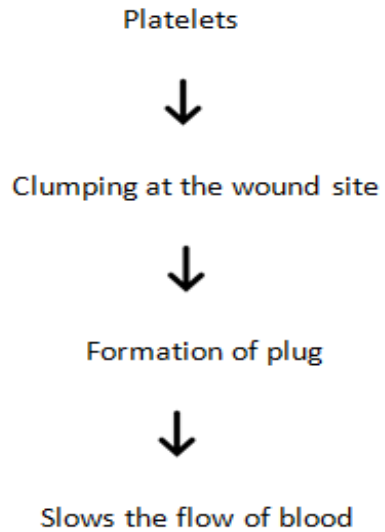

Fig. 1. Mechanism of clot formation

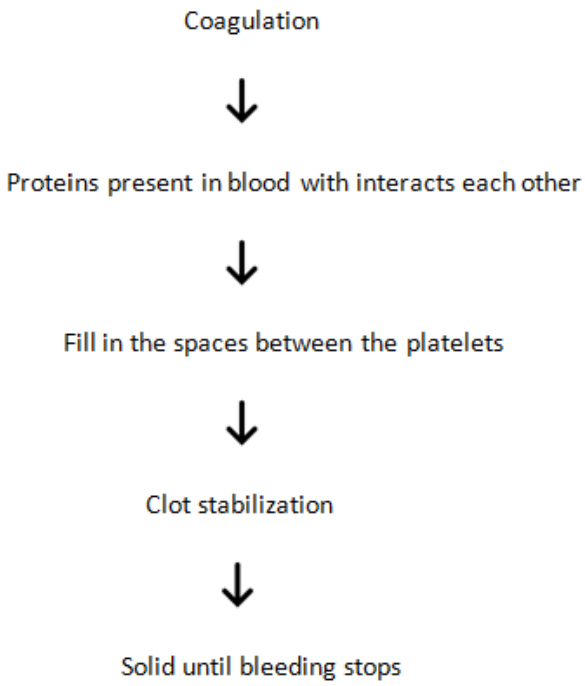

Fig. 2. Mechanism of coagulation

5.5 Mechanism of Action of Vasoconstriction

Tissue damage is generally associated with vascular injury resulting in more or less profuse bleeding [2]. Vascular endothelial rupture exposes different proteins of the subendothelial tissue layer to the blood stream, triggering three different hemostatic mechanisms.

Vascular or vasoconstriction phase:- Vasoconstriction of the damaged blood vessel occurs immediately after vascular injury, mediated by the vascular smooth muscle and reduces blood loss from the damaged vessel. Such vasoconstriction lasts about 20 minutes. The vasoconstrictive response alone is not sufficient to stop bleeding, but it does have two important effects: it reduces blood loss and triggers the second phase, facilitating platelet adhesion secondary to exposure of the sub endothelial collagen fibres and basal membrane of the damaged blood vessel wall [2,3,27,28].

6. ANTIPLATELETS

An antiplatelet agent is an agent whose main function is to inhibit the aggregation of thrombocytes and, therefore, the formation of a thrombus or clot inside the arteriovenous system. Any invasive or surgical procedure in the oral cavity involves intra and postoperative haemorrhage, being one of the most frequent emergencies for a dentist. This way, patients undergoing antithrombotic therapy have a higher haemorrhage risk. One treatment option is the interruption of the antithrombotic therapy eliminating this way the haemorrhage risk, nevertheless, the interruption implies an increased risk of cerebrovascular or cardiac thromboembolism. For this reason, it is necessary to manage patients undergoing these types of pharmacological treatments in order to minimize haemorrhagic as well as thromboembolism risks [29,30].

6.1 Mode of Action of Drug

These medications target the first phase of clot formation by preventing platelets from sticking to each other and to the blood vessel walls. Aspirin does this by creating permanent changes in the platelets which last throughout the lifetime of the platelet (7-10 days) which can only be reversed as the body produces new platelets that have not been exposed to the medication [29].

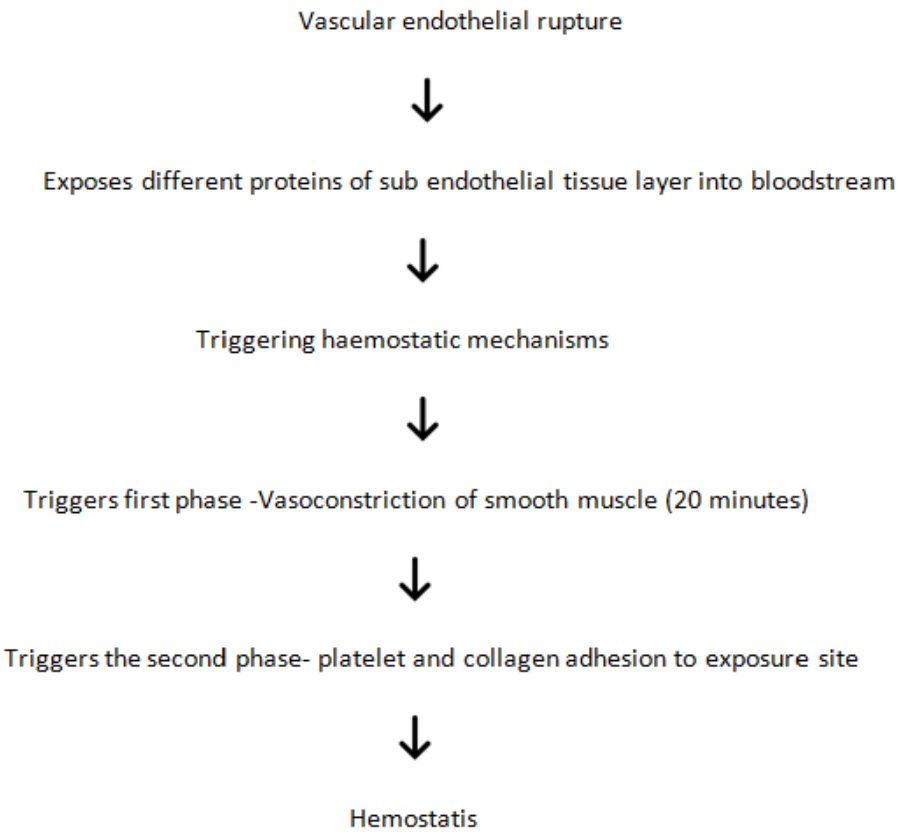

Fig. 3. Mechanism of action of vasoconstriction

Table 1. Different antiplatelet agents drugs [31]

Antiplatelet agents	• clopidogrel (Plavix®75 mg) • ticlopidine (Ticlid® 250 mg) • prasugrel (Effient® 10 mg) • ticagrelor (Brilinta® 90 mg) • Aspirin (75 mg,81 mg,100 mg)

6.2 Antiplatelets and Its Implications in Dentistry

There is general agreement that treatment regimens with these older antiplatelet agents should not be altered before dental procedures [32–42].In a article published in the year 2007, the American Heart Association, the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, the American College of Surgeons, and the American Dental Association published their consensus opinion about drug-eluting stents and antiplatelet therapy (e.g., aspirin, clopidogrel, ticlopidine).The consensus opinion states that healthcare providers who perform invasive or surgical procedures and are concerned about periprocedural and postprocedural bleeding should contact the patient's cardiologist regarding the patient's antiplatelet regimen and discuss optimal patient management, before discontinuing the antiplatelet medications. Given the importance of antiplatelet medications post-stent implantation in minimizing the risk of stent thrombosis, the medications should not be discontinued prematurely [43,44]. In a 2009 systematic review and meta-analysis found that there is no increased risk of bleeding associated with continuing regular doses of warfarin in comparison with discontinuing or modifying the dose for patients undergoing single and multiple tooth extraction [36]. A 2013 systematic review found no clinically significant increased risk of postoperative bleeding complications from invasive dental procedures in patients on either single or dual antiplatelet therapy [33]. In a 2013 statement, the American Academy of Neurology recommended that patients taking aspirin or warfarin for stroke prevention and undergoing dental procedures continue taking their medications [38]. A 2015

systematic review of management of dental extractions in patients receiving warfarin determined that patients whose International Normalized Ratio (INR; a measure of warfarin's therapeutic index) was in therapeutic range (i.e., 3.0 or less) could continue their regular warfarin regimen prior to the procedure [42].Some of the recent drugs used are Cilostazol on top of aspirin and clopidogrel appears to be safe, although of questionable clinical benefit. In conclusion, combination antiplatelet therapy should be reserved only for selected cases and following thoughtful consideration of the associated risk/benefit ratio [45].

7. ANTICOAGULANTS

Anticoagulation therapy is required by a lot of patients to prevent, treat or reduce the risk of thromboembolism in atrial fibrillation, treatment of venous thromboembolism, cerebrovascular accidents, ischaemic heart disease, myocardial infarction, pulmonary embolism and in prevention of thromboembolism after hip and knee replacement or stent placement, bypass surgery and prosthetic heart valve placement [46–48]. Historically, vitamin K antagonists such as warfarin and acenocoumarol, have been the oral anticoagulants of choice [49]. However they have some disadvantages such as low therapeutic index, delayed onset of action, many drug and food interactions and difficult pharmacological management since they require a regular monitoring and adjustment [50,51]. In the recent years, Direct Oral Anticoagulants (DOACs) have been introduced in order to eliminate some of these disadvantages. The first four DOACs are: dabigatran, rivaroxaban, apixaban and edoxaban. This novel agents target specific proteins or proteases of the coagulation cascade such as thrombin or activated factor Xa [47,50]. They have an immediate onset of action, more predictable pharmacokinetics, less drug interactions than warfarin and a short half-life [52] Enoxaparin has got more advantages when compared over heparin, because of its bioavailability. Ninety percent of the drug is available when given in the subcutaneous form. Enoxaparin can also be administered in intravenous formulations. The intravenous formulation should not be mixed or co-administered with other medications.In recent times a few novel drugs have been released in the market namely dabigatran, rivaroxaban, apixaban, edoxaban, betrixaban for management of thrombosis. These drugs are popularly known as non-vitamin K antagonist oral anticoagulants (NOAC) [53].

7.1 Anticoagulants and Its Implications in Dentistry

Anticoagulant medications inhibit the second phase of clotting by blocking production or the function of proteins that stabilise the clot.For example *warfarin,* it takes several days after the starting of medication to reach full anticoagulation effect, and several days after the medication is stopped for the anticoagulation to stop. In addition many foods and other medications can affect warfarin by either increasing or decreasing activity, therefore the physician needs to frequently monitor the patients.when an anti coagulated patient presents for a dental procedure, the dentist has three main options:

- Continue the same dose of oral anticoagulation with local hemostatic agents
- Diminish the dose
- Interrupt it altogether a few days before [55]

Our review has shown that the first option is the best in most of the dental procedures, with none of the 10 studies recommending the remaining two options since no statistically significant difference in postoperative bleeding existed between most groups continuing and interrupting oral anticoagulation.

Table 2. Anticoagulent drugs [31,54]

Anticoagulant	Drugs
Direct-acting oral anticoagulants**	● warfarin (Coumadin®1-10 mg) ● dabigatran(Pradaxa®75 mg,110 mg,150 mg) ● rivaroxaban(Xarelto®2.5 mg,15 mg,20 mg) ● apixaban (Eliquis® 2.5 mg,5 mg) ● edoxaban(Savaysa® 30 mg,60 mg[Lixiana® 60 mg in Europe, Japan, elsewhere]

Other studies have also come to the same conclusion: if INR is acceptable and local hemostatic measures adopted properly during the procedure, then there will be no adverse outcome for continuing oral anticoagulation in dental procedures [56–60], provided according to recent literature normal INR values should be 1.1 or less for normal individuals, and patients on anticoagulant therapy should be within 2.0 to 3.0 to carry out surgical dental procedures. It was recommended that vitamin K antagonists must be continued in all surgical procedures if INR is within the therapeutic range. As for novel oral anticoagulants, they must also be maintained in most procedures. Local hemostatic agents are mostly needed in both cases.

Special measures were taken in most studies to handle the risk of bleeding, like reducing soft tissue and bone injuries and minimizing the need to raise a mucoperiosteal flap during the procedures. However, it must be noted that whether a mucoperiosteal flap raise was needed or not in dental extractions [61–66], the outcome remained in favour of maintaining oral anticoagulation. Also, in implant surgery, bleeding risk was not associated with the invasiveness of the surgery [67].

It was also found in a study that there is no association between the number of teeth extracted and postoperative bleeding status [62,68,69], except in one study [64]. In contrast to previous studies [65,66] and in line with others [61,67], a short interruption of oral anticoagulation did not seem to increase the risk of thromboembolic events in the 10 trials. However, the follow-up period, extending from one day to one month, was relatively small, and the thromboembolic risk could not be fully assessed based on these trials.

Some patients who are taking one or multiple anticoagulant medications may have additional medical conditions that can increase the risk of prolonged bleeding after dental treatment, including liver impairment or alcoholism; kidney failure; thrombocytopenia, hemophilia, or other hematologic disorders; or may be currently receiving a course of cytotoxic medication (e.g., cancer chemotherapy). In these situations, dental practitioners has to consult the patient's physician [68,69]. Any suggested modification to the medication regimen prior to dental surgery should be done in consultation with and on advice of the patient's physician [70–72] .In brief, there is an immense need for cooperation between physicians and dental surgeons [39,73]. Although they both admit lacking full knowledge regarding oral anticoagulation in dental surgeries, dentists and physicians tend to mutually criticize [40,74–76].

8. GUIDELINES FOR DENTAL TREATMENT OF PATIENTS WITH INHERITED BLEEDING DISORDERS

8.1 Pre-operative Period

The dentist must ensure that the oral cavity of the patient is as healthy as possible before any surgical procedure. This can be achieved by deep scaling to remove as much calculus and plaque. The regular use of an antibacterial mouthwash, for example chlorhexidine, is also advised .Consider using an antifibrinolytic agent. It may be helpful to start the treatment the day before the surgery. Tranexamic acid (usual adult dose 1 g three times a day) and epsilon aminocaproic acid (EACA) (50 mg/kg four times a day), are the most commonly used drugs. They should be continued for a total of 7 days.

8.2 Perioperative Period

Patient is advised to rinse the mouth with chlorhexidine mouthwash for 2 minutes before the administration of the local anesthetic.The extraction is carried out as atraumatically as possible. Suturing the socket if the gingival margins do not oppose well. Brewer [77] reports a small series where sutures were not used routinely and there was no significant increase in post-extraction hemorrhage. Resorbable and non-resorbable sutures may be used at the operator's discretion. The only problem with non-resorbable sutures is the need for a postoperative visit and the possibility of bleeding during the suture removal. Use local hemostatic measures if indicated. These include the use of oxidized cellulose or fibrin glue.Use a soft vacuum formed splint to protect the socket if needed.

8.3 Post-operative Period

The patient must be given detailed postoperative instructions such as

- No mouth rinsing for 24 hours;
- No smoking for 24 hours;
- Soft diet for 24 hours;
- No strenuous activities for 24 hours;
- Prescribed medication must be taken as instructed;

- Analgesia should be prescribed for use if required;
- Salt-water mouthwashes (1 teaspoon of salt in a glass of warm water) should be used four times a day starting the day after the extraction for 7 days;
- Antibacterial mouthwash may be used;
- Emergency contact details must be given to the patient in case of problems.

8.4 Post-extraction Haemorrhage

Careful pre-operative planning and the use of antifibrinolytic agents will prevent many postoperative problems [78]. However, post extraction bleeding will occur on occasion. If post-extraction haemorrhage occurs: Contact the hemophilia unit and consider using additional factor concentrate, inspect the site of the bleed. If there is any evidence of a tear in the gingiva or other obvious bleeding point this should be treated using local measures as previously described. Instruct the patient to sit up and bite on a damp gauze swab for at least 10 minutes. Use a 10% solution of tranexamic acid or epsilon aminocaproic acid (EACA) to dampen the swab or as a mouthwash if the bleeding is difficult to stop. Monitor the patient's blood pressure as it may increase due to worry and pain. If the patient has pain, a suitable analgesic should be prescribed whilst if there is no pain a small dose of a benzodiazepine or similar will help to reduce the worry and reduce the blood pressure [79]

8.5 Hemostatic Agents

Some of passive hemostatic agents are Collagen-based products: Microfibillar collagen (Avitene), Absorbable collagen hemostat sponge (Helistat), Colla-Cote, Colla-Tape, Colla-Plug, Cellulose-based products: Oxidized regenerated cellulose (Surgicel) ActCel and Gelitacel, Gelatin-based products: Gelfoam, Polysaccharide hemospheres. Active hemostatic agents are Thrombin, FloSeal (flowable hemostatic agent), Fibrin sealant (tisseel), Albumin Derived hemostat(bioglue). Newer Hemostatic Agents Chitosan-based products Polysaccharide-based hemostats Poly-N-acetyl glucosamine-based materials QuikClot (inorganic hemostat). Hemostatic Solutions Styptics Tannic acid Lysine analogs Tranexamic acid [80,81]

9. CONCLUSION

From this review, it gives a clear picture regarding the bleeding disorder and knowledge of anticoagulants and antiplatelets for dentists. Multiple measures are proposed for better cooperation, like having common classes in dental schools and establishing guidelines together. If a physician referral is necessary prior to a dental procedure, the dental surgeon should inform the physician that major bleeding is less likely in most procedures and that most guidelines recommend the continuation of anticoagulation, since physicians tend to overestimate the risk of bleeding.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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