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Research Article

Management of Anti-Platelet Agents in Patients Undergoing an Oral Surgery

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Abstract

In oral surgery, bleeding associated with antiplatelet agents is a frightening situation to deal with, from a simple extraction to more complicated surgeries such as implant, periodontal or orthognathic surgeries. For this reason, each dentist needs to balance the risk of interrupting or not the antiplatelet agent. Systemic complications associated with the interruption of the drug outweigh the haemorrhagic complication associated with continuation of the same. Moreover, oral surgeries are considered at low risk of haemorrhage and hemostatic measure are in most of the cases enough to prevent excessive bleeding or platelet transfusion. In these situations, clinicians are in front of a question: Is bleeding worse than dying? Meaning that on one side, bleeding associated with continuation of antiplatelet agent, on the other side the remote but significant chance of lethal cardiovascular event. The decision should be obvious: stopping antiplatelet agent monotherapy or dual antiplatelet therapy is not anymore acceptable. Furthermore, special attention should be given to all those patients on dual antiplatelet therapy or combined anticoagulant/antiplatelet therapy because the risk of bleeding will be always higher compared to antiplatelet monotherapy and the anti-haemorrhagic measures such as gauze compression, collagen sponge, topical thrombin and sutures, are even more indispensable. From this point for a correct management of these drugs and in order to provide the best treatment to the patient, clinical history knowing the risk of thromboembolic event, additional antiplatelet tests, consultation with the cardiologist would be necessary and a teaching session and recommendations for the patient to explain how to manage at home post-operative bleeding is essential.

Keywords: *Anti-Platelets Agents; Oral Surgery; Hemostatic Measures; Thrombosis; Oral Hemorrhages*

Abbreviations

CV: Cardiovascular; TXA2: Thromboxane A2; ADP: Adenosine Diphosphate; NSAID: Non-Steroidal Anti-inflammatory Drugs; COX-1: Cyclooxygenase 1; COX-2: Cyclooxygenase 2; PGI2: Prostacyclin; GI: Gastrointestinal; MI: Myocardial Infarction; ESC: European Society of Cardiology; DAPT: Dual Antiplatelet Therapy; INR: International Normalized Ratio; aPTT: Activated Partial Thromboplastin Time; PT: Prothrombin Time; CHADS: Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke

Introduction

Hemostasis and thrombosis

Excessive bleeding can become one of the most frightening situations a dental health care provider can face; for this reason, it is important to know the physiologic mechanisms of bleeding, those induced by drugs and the anti-hemorrhagic measures that prevent major complications. The series of physiologic events that occur in response to an injury with the aim of arrest bleeding, is called hemostasis [1]. According to this we distinguish between primary he-

mostasis and secondary hemostasis. In primary hemostasis platelets, are essential and have a first-line role in atherothrombosis due to the capacity of releasing vasoactive mediators that provoke platelets adhesion and aggregation and subsequent plug formation [1,2]. The development of these blood components derived from the fragmentation of megakaryocytes coming from bone marrow and regulated by thrombopoietin, which is an hormone produced in the kidneys and the liver [3]. While in secondary hemostasis is a series of processes called coagulation cascade that takes place and the formation of fibrin is essential to stabilize the clot.

Atherosclerosis is defined as the degeneration of the walls of the blood vessels due to the accumulation of atherosclerotic plaque [2]. Thrombosis, instead, is the formation of a clot in a blood vessel that hinder or impede normal blood circulation. The related ischemic cardiovascular diseases are sustained by the progression of atherosclerotic plaque or the disruption of the atherosclerotic plaque by an exposition of thrombogenic substrates that lead to a thrombosis that can occlude partially or completely the blood vessels or the rupture of the plaque that can release atherosclerotic debris into the blood flow producing an embolism.

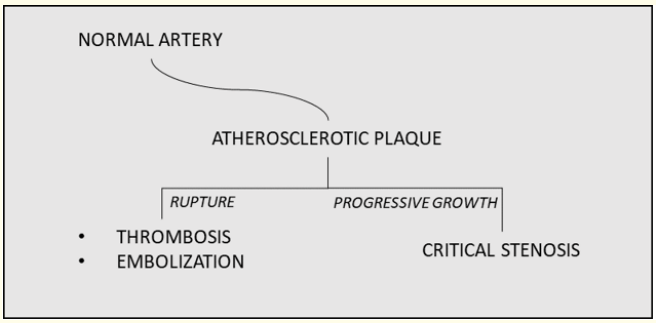

Figure 1: Possible way of progression of atherosclerotic plaque.

Source: Gale AJ. Continuing Education Course #2: Current Understanding of Hemostasis. Toxicol Pathol. 2011;39(1):273-80.

On the other hand, regarding the venous system, thrombosis is secondary to conditions that compromise the venous return, produce damage to the vessel and endothelial dysfunction or provoke a state of hypercoagulability [4].

Anticoagulants and antiplatelet agents

All these processes are the underlying causes of acute or chronic artery or venous diseases that are treated acutely and chronically with antithrombotic and/or anticoagulants agents to reduce cardiovascular (CV) risks but exposing the patient to a higher risk of bleeding.

Different situations can individuate risk factors: age that is proven to be a relevant factor that increases the risk of thrombosis, different major surgeries, and tumors, hypertension, atrial fibrillation, diabetes, hypercholesterolemia, obesity, diet, lack of exercise, smoking, intravascular devices (mechanical cardiac valves, artery stents) [5].

It is essential to distinguish and explain these drugs. Firstly, anticoagulant acts in secondary hemostasis and the coagulation cascade. Among the different anticoagulant agents there are: heparins that binds to the enzyme inhibitor antithrombins III inactivating thrombin, vitamin K antagonists preventing the action of factor II,VII, IX, X and new oral anticoagulants that in the last few years have been developed: apixaban, rivaroxaban, and edoxaban which are direct inhibitor of factor Xa in a dose-dependent way. Dabigatran instead, is a direct inhibitor of thrombin [6].

Anticoagulants	
Heparin	Inhibitor of antithrombin III
Warfarin/Acenocoumarin	Vitamin K antagonist
Oral anticoagulants: • Apixaban • Rivaroxaban • Edoxaban • Dabigatran	 Inhibitor of factor Xa Direct inhibitor of thrombin

Table 1: *Different anticoagulant agents and their action.*

Source: Harter K, Levine M, Henderson SO. Anticoagulation drug therapy: A review. West J Emerg Med. 2015;16(1):11–7.

On the other side, antiplatelet agents act modifying or inhibiting adhesion and aggregation processes, acting on thromboxane A2 (TXA2) from arachidonic acid or/and glycoprotein GPIIb/IIIa receptors or on adenosine diphosphate (ADP).

There are different antiplatelet drugs: aspirin, clopidogrel, prasugrel, ticlopidine, ticagrelor, abciximab and tirofiban.

Aspirin is the most studied one, it is classified in the group of NSAIDs (non-steroidal anti-inflammatory drugs), a class of drugs that blocks the synthesis of prostanoids, lipid mediators that regulate numerous physiological and pathological processes in the body. Aspirin itself inhibits irreversibly the *Cyclooxygenase 1 and 2* (COX-1 and COX-2) of the enzyme prostaglandin H-synthase-1/2 which are precursors of TXA2 and prostacyclin (PGI2) in a dose-dependent way [7]. The inhibition of COX-1 occurs with a low dose ranging from 75 - 150 mg while inhibition of COX-2 occurs with a higher dosage [4]. The inhibition of TXA2 prevents vasoconstriction and platelet aggregation making the blood more fluid, it needs 30 min to produce inhibition and the half-life depends on the urine pH [4]. The irreversible inhibition of platelets lasts for their entire life, which is around 10 days. Every 24 hours 10% of platelets are replaced and after five or six days of discontinuation, roughly 50% is replaced. Optimal dosage of aspirin for prevention of CV events depend on each situation but it is evidence seen that it can range from 75 - 325 mg/day, knowing that an elevated dosage is not associated with a higher reduction of the risk of thrombosis but instead, there should be taken into account gastrointestinal (GI) side effect such as GI ulcers or GI bleeding, which are dose-dependent and also make a stratification of the bleeding risk of each patient [8].

Another important aspect of aspirin is in the immediate treatment of suspicious Myocardial infarction because it is seen, that chewing the antiplatelet agent allows the maintenance of blood flow through coronary arteries in a rapid way preventing cell death [4,9]. It does not avoid completely the infarction but at least it is going to reduce it in size [7,9,10].

Thienopyridines are those drugs that inhibit ADP-induced platelet aggregation. Among those, we can find ticlopidine, clopidogrel and prasugrel and ticagrelor. Ticlopidine, first-generation, is as effective as aspirin in secondary prevention of cerebrovascular events but it has been replaced by clopidogrel due to bone marrow and hematologic toxicity [4]. Clopidogrel which have rapid absorption, is an irreversible inhibitor of P2Y12 adenosine diphosphate receptor. It is administered orally and it has a half-life of 8 hours and it is recommended for patients at high risk of coronary artery disease and in most of the cases in combination with aspirin [4,11]. Prasugrel works as the previous ones but it is more potent, rapid absorption and well metabolized by the organism. Compared with clopidogrel it produces an increased risk of bleeding and for this reason, is contraindicated in patients with active bleeding or a history of stroke [4,11]. Ticagrelor in contrast to the other thienopyridines acts inhibiting reversibly ADP-induced receptor and prevents the binding of 'G' protein to the ADP binding site [8]. It is shown a better risk reduction over clopidogrel in a patient with myocardial infarction (MI) and relative CV death. Among the side effects of ticagrelor, there has been an increased frequency of dyspnoea (an effect related to the metabolism of adenosine) and ventricular pauses during the first week of therapy, so the drug should be used with caution in patients with severe disorders respiratory or at risk of bradycardic events [8].

The last group consists of those drugs which are glycoprotein IIb/IIIa antagonist: abciximab and tirofiban. They have a rapid onset and renal excretion with a half-life ranging from 30 minutes to 2 hours. They are mainly used in a hyperacute situation with an intravenous injection where an immediate response is needed. They can be added to aspirin to reduce thrombosis in patients undergoing to a percutaneous coronary angioplasty [4]. The most frequent side effect is thrombocytopenia which is withdrawn when the drug is stopped but in some cases platelet transfusion is needed [4].

Dual anti-platelet therapy and drugs combination

There are situations in which aspirin monotherapy is not enough to prevent the cardiovascular event and for this reason, one or more antiplatelet agents can be added to reduce the risk of complications, for example after myocardial infarction or coronary intervention. Analysing the risk of interaction between the different drugs and the cardiovascular diseases, the duration of the

	Inhibition	Metabolism	Half-life	Side effects
Aspirin (ORAL ADM)	Cox-1 (low dose) Cox-2 (high dose)	Hepatic	Depends on urine pH	Bleeding
Ticlopidine (ORAL ADM)	Inhibitor of P2Y12 receptor (irreversible)	Hepatic	12 hours	Hematologic disorders
Clopidogrel (ORAL ADM)	Inhibitor of P2Y12 receptor (irreversible)	Hepatic	8 hours	Bleeding
Prasugrel (ORAL ADM)	Inhibitor of P2Y12 receptor (irreversible)	Hepatic and intestine	7 hours	Bleeding
Ticagrelor (ORAL ADM)	Inhibitor of P2Y12 receptor (reversible)	Hepatic	7 hours	>> Bleeding
Abciximab/Tirofiban (IV ADM)	Glycoprotein IIa/IIIb antagonist	Primarily by proteolytic cleavage	30min-2hours	Thrombocytopenia

Table 2: *Different antiplatelet drugs: inhibition, metabolism, half-life, side effects.*

Source: Eikelboom JW, Hirsh J, Spencer FA, Baglin TP, Weitz JI. Antiplatelet drugs - Antithrombotic therapy and prevention of thrombosis. Am Coll Chest Physicians. 2012;141(2 SUPPL.):e89S-e119S).

treatment and the risks of bleeding in the different interventions, 'The European Society of Cardiology's (ESC)' in 2017 summarised and evaluated the different strategies of dual antiplatelet therapy management (DAPT) even though, still nowadays there are controversies among health physicians [12]. These drugs can be used together since their pattern of action is different regarding primary hemostasis and they do not interfere with each other. However is essential to note that although there is a reduction of CV risk, there is also an increased risk of bleeding in comparison with antiplatelet monotherapy, and the intake should not last for the entire, life but the health care provider should weight the risks of thrombotic or haemorrhagic events against the benefits.

An association can be found also between antiplatelet and anticoagulants, in those patients which are at a high risk of thromboembolic events and low risk of bleeding, and the association should be for a short period of time due to the high risk of major bleeding [13]. Even if the protocols suggest not to prescribe both anticoagulants and antiplatelet at the same time except few situations, according to the 'American college of Chest physicians' there is evidence of prescription up to 39 - 55% of cases [14].

Surgical risk and risk of complications

To later evaluate the risk of bleeding and the correct management of those drugs, we need to classify the different types of oral surgery from low to high risk. The surgical risk of dental interventions it is classified as a low risk (< 1%) of complication, while head and neck are classified as intermediate risk (1 - 5%) [15]. Among them, minor surgical oral procedures are described as all the intervention that can be performed in 30 minutes and have a relative low risk of bleeding and do not alter the general status of the patient [16]. While major oral surgeries are all those procedures performed in more than 30 minutes and have high risk of bleeding, for this reason, most of them are performed by a team in the hospital due to the fact that they should be safely prepared to manage major bleeding [16].

All these situations have a certain bleeding risk which increases with the intake of antiplatelet agents, mono or dual therapy. For this reason along the years, dentist tried to figure out a correct management of antiplatelet drugs, being aware of the risk of continuation of the medication or the interruption [17]. The continuation of the medication increases the bleeding risk while the interruption puts the patient at risk of suffering a thrombotic event (even if is low).

Regarding minor oral surgeries, most of the studies concern the fact that there is a relatively low risk of bleeding pre-operative, peri-operative and post-operative and among them, there is a distinction between low-risk intervention such as simple extrac-

Minor oral surgeries		Major oral surgeries	
I.	Complicated surgical extraction	I.	Big lesion in the floor of the mouth
II.	Mucoperiosteal flap elevation	II.	Salivary glands surgery
III.	Bone removal	III.	Tumors and cancer
IV.	Elimination of small lesions	IV.	In block or marginal bone resection
V.	Biopsy (incisional)	V.	Hemi-mandibulectomy or Hemi-maxillectomy
VI.	Implant surgery	VI.	Orthognathic surgery
VII.	Sinus lift for implant placing		

Table 3: *Main minor and major oral surgeries.*

Source: Wahl MJ. Dental surgery and antiplatelet agents: Bleed or die. Am J Med [Internet]. 2014;127(4):260–7. Available from: http://dx.doi.org/10.1016/j.amjmed.2013.11.013. Lee JK. Dental management of patients on anti-thrombotic agents. J Korean Assoc Oral Maxillofac Surg. 2018;44(4):143–50. Harris M. Textbook of oral and maxillo-facial surgery. Vol. 18, British Journal of Oral Surgery. 1980. 90 p.

tion, incision, and drainage, periodontal examination, subgingival scaling, restoration with subgingival margin [18]. High-risk intervention in oral surgery are: complex extraction, flap raising periodontal surgery, pre-prosthetic surgery, peri-radicular surgery, crown-lengthening, dental implant surgery [18].

Minor surgery (Low bleeding risk)			
Lower risk		Higher risk	
I.	Simple extractions	I.	Complex extractions
II.	Incision and drainage	II.	Flap raising
III.	Periodontal examination	III.	Periodontal surgery
IV.	Subgingival scaling	IV.	Pre-Prothetic surgery
V.	Restoration with subgingival margins	V.	Peri-Radicural surgery
		VI.	Crown lengthening
		VII.	Dental implant surgery
		VIII.	Biopsies

Table 5: *List of low risk and high-risk surgeries in minor surgeries.*

Source: Lee JK. Dental management of patients on anti-thrombotic agents. J Korean Assoc Oral Maxillofac Surg. 2018;44(4):143–50.

The risk of each patient depends on the CV disease, the presence of not of risk factors of the patient such as heart failure, hypertension, diabetes, stroke, age. The presence of any prosthetic mechanical valve, atrial fibrillation or venous thromboembolism.

Low risk of thromboembolic event (< 5%)	High risk of thromboembolic events (>5%)
I. Atrial fibrillation with CHADS between 0-2	I. Atrial fibrillation with CHADS between 3-6
II. Atrial fibrillation with CHADS between 0-4	II. Atrial fibrillation with CHADS between 5-9
III. Prosthetic heart valve	III. Venous thromboembolism within 3 months
IV. Venous thromboembolism after 3 months under antithrombotic agent	IV. Coronary stent placement within the past year
V. Coronary stent after 1 year of antiplatelet	
CHADS: Congestive Heart Failure, Hypertension, Age > 75, Diabetes, Stroke/Ischemic Attack	

Table 5: *Table for the evaluation of the risk of thromboembolic events.*

Source: Lee JK. Dental management of patients on anti-thrombotic agents. J Korean Assoc Oral Maxillofac Surg. 2018;44(4):143–50.

Anti-Hemorrhagic measures

At the moment of the surgery, dentists should be prepared to manage bleeding. First of all the intervention, should be minimally invasive to reduce the hemorrhagic risk but if necessary, different hemostatic measures can be used: oxidized cellulose in the socket

fixed with sutures, if necessary the use of electrocautery and surgical splint are recommended, gauzes alone or impregnated with tranexamic acid for the inhibition of fibrinolysis, microporous polysaccharide hemi-spheres, fibrin glue used to create a fibrin clot and topical thrombin, gelfoam [19].

Tranexamic acid	Gel that prevents fibrinolysis
Microporous polysaccharide hemispheres	Topical use
Fibrin glue	Topical use that creates the fibrin clot
Topical thrombin	Topical use
Gelfoam	Topical use
Surgical splint	Used usually with collagen sponge
Surgical Diathermy	Electrocautery

Table 6: *Hemostatic measures in dental surgery.*

Source: Morimoto Y, Niwa H, Minematsu K. Hemostatic Management of Tooth Extractions in Patients on Oral Antithrombotic Therapy. J Oral Maxillofac Surg. 2008;66(1):51–7.

Post-operative bleeding is a complication that many patients can suffer within 2 - 7 days from the intervention especially in patients under chronic antiaggregant therapy. It is seen that hemorrhage is more likely to occur in more complicated dental surgeries [20].

Postoperative bleeding can be controlled with local hemostatic measures such as compression with gauzes, sutures which are removed after 7 days from the intervention and mouthwashes with tranexamic acid [21]. If the blood loss is excessive and it cannot be controlled, the patient should be referred to the hospital for platelet transfusion.

Is essential to take into account, that a prescription of non-steroidal anti-inflammatory drugs to relieve inflammation and pain should be discussed with the health care provider because of the great interaction of antiplatelet agent and NSAID with a subsequent increased risk of bleeding and gastrointestinal problems especially with those that are selective COX-2 inhibitors that have known kidney and cardiac risk.

Objectives of the Study

Although each situation should be discussed between the dentist and the health care provider of the patient, the aim of this study is:

- To find a clear guideline for the management of antiplatelet drugs in a patient undergoing oral surgery.

Looking for different secondary objectives to enhance the validity of the research:

- Evaluate if there is an increased risk of hemorrhage pre-operative, perioperative and post-operative in the different oral surgeries among the different patients: antiplatelet monotherapy, dual antiplatelet therapy, and combined antiplatelet-anticoagulant therapy.
- Find useful anti-haemorrhagic measures in order to provide less risk of complications and safety.
- All dentists have to decide in front of these patients: Is bleeding worse than dying?

Methods

A review of the literature with systematic research collecting articles, journals and books were made selecting only those related in the last 10 - 12 years. The language selected was limited to English, Italian and Spanish and all the studies were from all over the world.

The database of research were: The PubMed, Cochrane Library, SciELO and Medline using as keywords: 'antiplatelet agents', 'oral surgery', 'dental intervention', 'antiplatelet management in oral surgery', 'antihemorrhagic measures', 'complications', 'bleeding', 'thrombosis'. All the studies selected, consider all the different aspects of minor and major's oral surgeries in patients on antithrombotic agents.

For **inclusion criteria** the research should be focused on specific tools:

- Articles from scientific journals into the JCR.
- Papers about Patients at risk of thrombosis with Antithrombotic therapy and comparison between them.

- Articles that include Management protocols of antiplatelet in Oral Surgery and different antihemorrhagic measures.
- Papers and Textbooks published in the last 10 years.

In each case taking into account:

- Papers that include in its research age of patients, CV pathologies associated, anaesthesia, pre-operative, perioperative, postoperative risks of hemorrhage and treatments.
- Papers that contain research in antiplatelet monotherapy, dual antiplatelet therapy combined antiplatelet.

For **exclusion criteria**:

- Articles before 2008.
- Articles where patients were only anticoagulated.
- Articles that, due to various types of impediments, could not be accessed.
- Articles in other languages not previously specified.
- Studies in animals or *in vitro*.

A total number of 21 papers were obtained matching in each one the criteria described former, obtaining three main sections: antiplatelet monotherapy, dual antiplatelet therapy, and combined therapy. For the methodology in each section the variables analysed were:

- Age and CV associated
- Treatment
- Preoperative, perioperative and postoperative bleeding risk
- Protocol followed
- Anaesthetic used
- Hemostatic measures.

Results

In total, a number of 21 studies were taken for the research. The first thing to be evaluated was the risk of bleeding between patients who discontinued the medication and those that did not. The general guideline proposed by the 'American College of chest physician' and the 'European Society of Cardiology' suggest that each situation need to be discussed with the cardiologist if there is the suspicion of complication to clearly balance the risk of life-threatening surgical bleeding on antiplatelet therapy, and the life-threatening thrombosis especially in patients under multiple antiplatelet therapy [15]. In general, the oral surgery guideline suggest not to stop the medication and that bleeding can be controlled by local hemostatic measures. Despite this, a lot of studies have found a negative result: many dentists discontinue the medication exposing the patient to a possible thromboembolic event [23].

Table 7 summarises the main differences in the percentage of bleeding between those groups of patients. The treatments performed were in most of the cases extractions except in the study of Omar., *et al*. [24] and of Tabrizi., *et al*. [25] in which also pre-prosthetic surgery and implant surgery was performed. Few cases of prolonged or postoperative bleeding were found: Tang., *et al*. [26] found a 47% of patients with prolonged bleeding while not discontinuing the antiplatelet agent in contrast with 15% of patients discontinuing it.

Once revised if it is better one situation or the other, the attention was focused on those patients that did not discontinue the antiplatelet agent; looking for the risk of bleeding among the different antiplatelet drugs and the antihemorrhagic measures available.

Table 8 shows only the number of patients divided in monotherapy and dual antiplatelet therapy in the different studies and the treatment performed.

Table 9 shows the protocol of management used: anesthetic, % of bleeding depending on the therapy and the anti-hemorrhagic measure used to stop bleeding.

In all the studies a positive association was found between bleeding in patients on dual antiplatelet therapy and bleeding in patients on monotherapy during different dental surgeries such as extraction, implant surgeries, osteotomies, cyst removal. The % of prolonged bleeding in DAPT was in most of cases higher the double than the % of bleeding in monotherapy. On the other end, this association could always be controlled with local hemostatic measures varying from gauze compression, gel foam with tranexamic acid, gelatine sponge, topical thrombin and sutures. Two studies used articaine 4% as anaesthetic while most of the others perform all the treatments under lidocaine 2% with vasoconstrictor.

	N. Patient discontinue the antiplatelet	N. Patient Not discontinue the antiplatelet agent	Treatment done	% of prolonged or postoperative bleeding (Discontinued)	% of prolonged or postoperative bleeding (not discontinued)
Sadhasivam., *et al*. [27] 2016	100	100	Multiple extractions	15%	9%
Omar., *et al*. [24] 2015	22	46	Full Mouth Extractions/ Pre-prosthetic surgery	0%	9%
A. Dinkova [28] 2017	65	65	Multiple extractions	3%	5%
K. Varghese [29] 2015	95	95	Multiple extractions	8%	11%
M. Tang [26] 2018	85	253	Multiple extractions	15%	47%
F.Akhlaghi [30] 2017	38	38	Extractions	4,68%	4,95%
Tabrizi [25] 2018	42	42	Implant surgery	4,2%	4,45%

Table 7: *Main differences in the percentage of prolonged bleeding between those patients that discontinue or not the medication.*

	N.Patients	Monotherapy	DAPT	Treatment
S.-Y Lu [31] 2016	274	250	24	Surgical Extractions
Lillis [32] 2011	111	78	33	Multiple Extractions
Sadhasivam [27] 2016	300	131	69	Multiple Extractions
Omar [24] 2015	68	37	9	Full mouth Extraction
Cañigral [33] 2010	36	27	9	Multiple extractions
Napeñas [23] 2009	43	14	29	Invasive surgeries
Bajkin [34] 2015	160	117	43	Multiple extractions
Varghese [29] 2015	95	64	31	Multiple extractions
Girotra [35] 2014	546	407	139	Invasive surgeries
Gröbe [36] 2015	124	64	60	Oral osteotomy
Tang [26] 2018	338	268	70	Multiple extractions
Lu [37] 2018	275	250	24	Multiple extractions
Nagao [38] 2017	79	65	14	Multiple extractions
Doganay [39] 2018	222	162	60	Invasive surgeries

Table 8: *Shown for each study the number of patients under mono or dual antiplatelet therapy and the related treatments performed.*

The last objective to be evaluated was the risk of bleeding in those patients that were taking combined therapy (antiplatelet and anticoagulant) and were subjected to tooth extraction. In table 10 three out of four studies found a strong correlation between bleeding and patients on combined therapy antiplatelet/anticoagulant.

Discussion

Evaluating preoperative management

In order to evaluate the correct management of antiplatelet agents, it is essential to have a complete vision of the main parts which can make clear the choice between one protocol or another and the subsequent management of patients.

	Protocol followed	Anesthetic	% of prolonged bleeding Monotherapy	% of prolonged bleeding DAPT	Hemostatic measures
S.-Y Lu [31] 2016	Not discontinue	Lidocaine 2% with epinephrine 1:80000	2%	4%	Gel foam with tranexamic acid and sutures
Lillis [32] 2011	Not discontinue	Lidocaine 2% with epinephrine 1:80000	3%	67%	Gauze compression and sutures
Sadhasivam [27] 2016	-	Lidocaine 2% with epinephrine 1:80000	Not reported		Gelatin sponge
Omar [24] 2015	Not discontinue	General Anesthesia and lidocaine	8%	11%	Gel foam with tranexamic acid and sutures
Cañigral [33] 2010	Not discontinue	Not reported	15%	44%	Gauze compression
Napeñas [23] 2009	Not discontinued	Local Anestesia and 5 General anesthesia	0%	0%	Gelatin sponge, sutures and topical thrombin
Bajkin [34] 2015	Not discontinued	Not reported	0%	2%	Gelatin Sponge
Varghese [29] 2015	Not discontinued	Lidocaine 2% with epinephrine 1:80000	9%	16%	Gauze compression and sutures *
Girotra [35] 2014	Not discontinued	Lignocaine 2% 1:80000 epinephrine	0%	6%	Gealfoam with tranexamic acid and sutures, surgical diathermy
Gröbe [36] 2015	Not discontinued	Articaine 4%	2%	3%	Sutures, collagen sponge, acrilic splint
Tang [26] 2018	-	Not reported	32%	64%	Gelatin sponge, hemostatic gauze and sutures
Lu [37] 2018	Not discontinue	Lidocaine 2% with epinephrine 1:80000	2%	4%	Gel foam with tranexamic acid and sutures
Nagao [38] 2017	Not discontinue	Lidocaine 2% with epinephrine 1:80000	5%	21%	Gauze and sutures
Doganay [39] 2018	Not discontinue	Articaine 4%	4%	8%	Gauze, collagen sponge, tranexamic acid

Table 9: *Protocol of management used, anaesthetic, % of bleeding depending on the therapy and the anti-haemorrhagic measures used in order to stop bleeding.*

	N. patients Monotherapy and % postoperative bleeding	N. patients DAPT and % postoperative bleeding	N. patients Combined therapy and % postoperative bleeding
Morimoto [19] 2008	87 (2%)	-	49 (4%)
Morimoto [40] 2011	128 (1,5%)	-	66 (9%)
Bajkin [41] 2012	71 (0%)	-	71 (4,2%)
Ohba [20] 2015	34 (32,3%)	20(40%)	17 (35%)

Table 10: *Number of patients in each study and related prolonged or postoperative bleeding.*

The condition and the clinical history of the patient are the starting point of the dentist's decision; for this reason, it is advisable to use a scale that tries to predict the risk of a thromboembolic event. The most used one is the CHA2DS2-VASc [18] in which different parameters are evaluated.

CHADS	VAS
C	Congestive heart failure
H	Hypertension
A	Age > 75
D	Diabetes
S	Stroke/TIA
V	Vascular disease
A	Age 64 - 75
S	Sex

Table 11: *CHADS/VAS values.*

The following point would be the assessment of bleeding risk. Regarding this tool, different hematological tests can be performed in order to assess the effect of the antiplatelet medication depending on the inhibition provoked by the drug: Cox-1 by aspirin, ADP-induced platelet aggregation by thienopyridines and glycoprotein IIb/IIIa antagonist by abciximab and tirofiban. Among the different tests, the most used are Light transmittance aggregometry, verifynow, platelet function analyzer-100, vasodilator-stimulated phosphoprotein phosphorylation assay [42]. In the dental field, with the help of these tests it is possible to assess if, during extraction or any other dental surgery, the oral area involved is going to bleed more or less.

Moreover, the bleeding risk can be evaluated depending on the treatment the dentist is going to perform. The ESC suggests that dental surgery has a low risk of bleeding (< 1%) but among the different treatments there can be more or fewer complications. For this reason, there is a differentiation between high-risk treatment and low-risk treatments: simple extractions, incision and drainage, periodontal examination, subgingival scaling, restoration with subgingival margins are included in low risk, while complex extraction, flap raising, periodontal surgery, pre-prothesis surgery, peri-radicular surgery, crown lengthening, implant surgery, and biopsies are included in high risk [15,18]. On the other hand, in the different studies analysed, the bleeding risk was strongly related to the anti-hemorrhagic measure the dentist was able to perform in order to prevent excessive bleeding [43].

Of course, the type of antiplatelet agent and dosage assumed by the patient can help for this assessment, knowing that dual antiplatelet therapy or combined therapy increases the risk of a hemorrhagic event [11].

Independently from antiplatelet therapy, the dentist should focus also on the presence of other systemic pathology or risk derived from the intervention. In particular, in all those patients undergone heart valve replacement with mechanical or bioprosthetic valve, the antibiotic prophylaxis for infective endocarditis is needed. Antibiotic prophylaxis would be also necessary for all dental surgeries performed in the first 6 months after any cardiac surgery [44,45].

Evaluating discontinuation or not of the antiplatelet therapy

At the time of the decision for discontinuing or not the agent, all these factors should be evaluated and a consultation with the cardiologist would be necessary especially in complicated surgeries. In the research performed, one of the objectives was to know if there are benefits in choosing one protocol of action or the other.

In the different studies chosen to help dentists in taking a correct decision of management: Sadhasivam., *et al*. [27], Omar., *et al*. [24], Dinkova., *et al*. [28], Varghese., *et al*. [29], Tang., *et al*. [26], Akhlaghi., *et al*. [30], Tabrizi., *et al*. [25], there was an absolute agreement in not discontinuing antiplatelet therapy. Results show that there is not always present an association between excessive bleeding and continuation of the antiplatelet agent and that if it is present is not strong enough to stop the medication putting the patient in an increased condition of suffering a thromboembolic event. Dinkova., *et al*. [28] focus also on the importance of managing the situation of hemorrhage with local hemostatic measures such as gelatine sponge and sutures. Only the study of Tang., *et al*. [26] found a discrete number of patients with prolonged or postoperative bleeding both when discontinuing (15%) or not the medication (47%). This can be due to the fact that all the population chosen was a high-risk patient. It should be also noted that in the study, the interruption of

antiplatelet agents was performed four days before the intervention which is a time not enough to allow recovery of the activity of platelet as the inhibition by the antithrombotic drug last from 7-10 days. Fortunately, it agrees on the fact that the surgical approach and local hemostatic measure should be preferred to discontinuation of antiplatelet agents.

F Akhlaghi., *et al*. [30] explain the importance of giving the patient instructions of postoperative management in order to help in a correct healing and diminish the risk of possible hemorrhagic complications that can occur away from the dental practice.

To conclude, even though there is a higher risk of bleeding continuing the drug, this risk is statistically irrelevant due to the fact that all the cases where excellently managed without any severe complication and the quantity of blood loss was not enough to talk about major bleeding. For these reasons, the European Society of Cardiology (ESC) explains the importance of not discontinuing the antiplatelet agent in order to safeguard patients' life reducing the risk of a thromboembolic event [15]. The risk of hemorrhage does not carry the same risks of cardiovascular complications [15].

Risk of bleeding in monotherapy and dual antiplatelet therapy

Once evaluated the efficacy of non-discontinuing the medication, the attention was focused on the different main forms the drug can be prescribed, meaning monotherapy or dual therapy.

The treatments selected in the studies were multiple extractions, osteotomies as well as invasive surgeries for implant placing, pre-prosthetic surgery, flap raising, periodontal surgery, and biopsies.

The anesthetic used in most of the cases was Lidocaine 2% with 1:100000 of epinephrine, only Napeñas [23] used general anesthesia and few cases: Gröbe., *et al*. [36] and Doganay., *et al*. [39] use Articaine 4% probably due to more complicated treatments.

The main Dual antiplatelet therapy was aspirin associated with clopidogrel. All the studies found a positive association between DAPT and increased risk of bleeding versus monotherapy except the one by Napeñas., *et al* [23]. This can be due to the fact that clinical cases were excellently managed with local hemostatic measures such as sutures, gelatine sponge and also topical thrombin.

Cañigral., *et al*. [33] and Nagao., *et al*. [38] recommend that the use of platelet function tests in high risks patients to know the possible hemostatic troubles and increase safety at the moment of the intervention.

Girotra., *et al*. [35] explain that the risks of prolonged bleeding are independent from the treatment performed and that patients on single antiplatelet medication can be treated as healthy individuals but with the awareness of possible bleeding.

On the other hand, Doganay., *et al*. [39] insist on the idea that multiple extractions and more complicated surgery carry the risk of increased bleeding.

Gröbe., *et al*. [36] show the efficacy of using acrylic splint in oral osteotomies while Girotra., *et al*. [35] explain the efficacy of electrosurgery with surgical diathermy; in fact, electrocautery is very useful to achieve a bloodless site of intervention and nowadays is becoming more and more used, not only in dental surgery but also in the other specialties [46].

The percentage of people who experienced prolonged or postoperative bleeding in dual antiplatelet therapy was in the majority of the cases the double or more than monotherapy. Even if all the cases were properly managed by the dentist, the professional should be aware of the fact that if a patient is taking two antiplatelet agents, there is an increased risk of bleeding and should be prepared to manage it with local anti-hemorrhagic measures [21].

Risk of bleeding in combined antiplatelet anticoagulant therapy

The last clinical situation compared in this revision, was related to a drug combination of antiplatelet and anticoagulant agents. In the four studies reviewed, regarding the combined therapy, the main anticoagulant agent was warfarin, a vitamin K antagonist, and the main antiplatelet agent was aspirin.

Results have shown that there was a higher incidence of bleeding in patients with combined therapy in comparison with antiplatelet monotherapy. Only Ohba., *et al*. [20] did not find a strong difference between combined therapy (35% of bleeding) and both

monotherapy (32%) or dual antiplatelet therapy (40%). In all the studies, INR was checked from 72 hours before the intervention and bleeding were successfully managed.

Regarding New oral anticoagulants, all dentist should be aware of the fact that they are insensitive to INR test or for example in the case of Dabigatran the modification of INR is not related with a change in the coagulation, due to this, is necessary in those cases to ask for the dosage of the active substance in blood; however, New oral anticoagulants are more stable in anticoagulation in comparison to the other anticoagulant drugs, for this reason, monitoring is less crucial. Moreover, as anticoagulation can be a precipitating factor in haemorrhage, antidots have been developed in order to counteract the effects of these New Oral Anticoagulants. Idarucizumab is a reversal agent for Dabigatran, in few minutes it reverse the anticoagulant activity in almost all the patients. The way of administration is intravenous: 2,5g two times with intervals of 15 minutes and the effect lasts 24 hours [47]. While Andexanet alfa is the antidote for inhibitor of factor Xa, rivaroxaban and apixaban. The way of administration is through infusion and the effect last 2 - 3 hours from the end of the infusion [48].

Morimoto., *et al*. [19,40] focused on a comparison of risk factors for postoperative hemorrhage such as age, gender, antiplatelet therapy, INR value, treatment, inflammatory signs. For the author, INR in patients on warfarin and antiplatelet drugs should always be less than 3 in oral surgery. And focuses the attention on the use of oxidizing cellulose in the prevention of postoperative infections.

In the study of Ohba., *et al*. [20], 4 patients under aspirin monotherapy (1) and combined therapy (3) developed postoperative hemorrhage of 4 days or more but they were successfully managed with local hemostatic measures.

Bajkin., *et al*. [41] recommend not discontinue the therapy in simple surgery and ask for a consultation with the cardiologist in case of more complex surgeries for changing the oral anticoagulant agent with unfractionated heparin or low molecular weight heparin.

For this reason, regarding oral anticoagulant therapy, for INR values up to 2.5 - 3.5 in the case of simple interventions it is not necessary to change the therapy, while if the INR is higher or for more complex interventions involving significant bleeding, the anticoagulant therapy will be adapted suspending the main agent 2 - 3 days before surgery and it would be replaced by unfractionated heparin or low molecular weight heparin [21]. The return to normal therapy should be after 1 - 5 days from the intervention. In these situations, the consultation with the hematologist is even more important and for a correct dental management the dentist would ask the patient the international normalized ratio (INR), activated partial thromboplastin time (aPPT) (30 - 40 sec), prothrombin time (PT) (1.5 - 1.8) tests, from 72 and 24 hours before the treatment in order to assess the hemorrhagic predictability [21].

Intraoperative management

Due to this and all the information collected, the intraoperative management is essential. First of all, if necessary, the dentist would ask for a complete blood count and hematological test 24 hours prior to the intervention. Moreover, depending on the surgical intervention, the dentist should minimize trauma, avoid flap raising or design a flap suitable for suturing. Local hemostatic measures are key point to control bleeding and surgical intervention.

Among the different study reviewed, the approach was in most of the cases the same: first of all gauze compression for 30 min to try stopping the hemorrhage, then collagen sponge or oxidized cellulose or gelfoam with tranexamic acid or topical thrombin was placed in the socket and lastly, sutures were performed. The aim of using these local hemostatic measures was not only to stop bleeding but also to reduce the incidence of postoperative infection that can appear in the site of the intervention.

Protocol of management of the different therapies

A special protocol for patients on antiplatelet-anticoagulant therapy was made due to the higher risk of bleeding compared with antiplatelet monotherapy.

Antiplatelet monotherapy and DAPT
Continuation of the antiplatelet medication
1. Medical History and CHADS scale for evaluating CV risk. 2. Antiplatelet medication (daily dose, dosage, since when?). 3. Evaluation of the risk of bleeding depending on the surgery. No alteration of the medication, single or dual, for dental surgery: single or multiple extractions, periodontal surgery, implant surgery). 4. Ask for antiplatelet tests in high-risk patients. 5. Possible interconsultation with the cardiologist if an increased risk of bleeding.
Preoperative measure
1. If you need to extract more than 3 teeth, schedule more than 1 visit. 2. Appointments in the early morning and at the beginning of the week. 3. Special attention for antibiotic prophylaxis of infective endocarditis in those patients who are taking antiplatelet agents due to a valve replacement with a mechanical valve.
Operative measures:
1. Inform the patient of possible prolonged or postoperative bleeding. 2. Minimize surgical trauma using conservatives' approaches. 3. Gauze compression 30 min, collagen sponge or oxidize cellulose or gel foam with tranexamic acid (500 mg) or topical thrombin, sutures. If necessary, evaluate electrocautery.
Postoperative measures
1. Do not prescribe NSAID and COX-2 inhibitors due to strong interaction. 2. Paracetamol would be enough or consultation with the health care provider. 3. Give patients postoperative recommendation and tranexamic acid 4.8% mouthwashes for 2 - 3 days. 4. Remove suture after 7 days and check if any signs of infection.

Combined antiplatelet-anticoagulant therapy
Continuation of the antiplatelet medication
1. Medical History and CHADS scale for evaluating CV risk 2. Medication (daily dose, dosage, since when?) 3. Evaluation of the risk of bleeding depending on the surgery 4. No alteration of the antiplatelet medication, single or dual therapy, for dental surgery: single or multiple extractions, periodontal surgery, implant surgery. 5. Check INR, aPTT, PT levels from 72 and 24 hours before the surgery or in case of new oral anticoagulants, check the quantity of the active substance in the blood 6. No alteration of anticoagulant if INR< 3.5 and simple dental surgery 7. If INR > 3.5 or invasive dental procedure, the interconsultation with the cardiologist is necessary and think in substitution with low molecular weight heparin or unfractionated heparin.
Preoperative measures
1. If you need to extract more than 3 teeth, schedule more than 1 visit. 2. Appointments in the early morning and at the beginning of the week. 3. Special attention for antibiotic prophylaxis of infective endocarditis in those patients who are taking antiplatelet agents due to a valve replacement with a mechanical valve.
Operative measures
1. Inform the patient of possible prolonged or postoperative bleeding 2. Minimize surgical trauma using conservatives' approaches 3. Gauze compression 30 min, collagen sponge or oxidize cellulose or gel foam with tranexamic acid (500 mg) or topical thrombin, sutures. If necessary, evaluate electrocautery.

Table 12: *Protocols*

D. Postoperative measures
1. Do not prescribe NSAID and COX-2 inhibitors due to strong interaction
2. Paracetamol would be enough or consultation with the health care provider
3. Give patients postoperative recommendation and tranexamic acid 4.8% mouthwashes for 2 - 3 days
4. Remove suture after 7 days and check if any signs of infection.
5. Refer to the hospital if INR is unstable

Table 13: *Source: Lee JK. Dental management of patients on anti-thrombotic agents. J Korean Assoc Oral Maxillofac Surg. 2018;44(4):143–50.) (Lu SY, Lin LH, Hsue SS. Management of dental extractions in patients on warfarin and antiplatelet therapy. J Formos Med Assoc [Internet]. 2018;117(11):979–86. Available from: https://doi.org/10.1016/j.jfma.2018.08.019) (SDCEP. Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs. Scottish Dent Clin Eff Program [Internet]. 2015;(August):accessed 31/08/2016. Available from: http://www.sdcep.org.uk/wp-content/uploads/2015/09/SDCEP-Anticoagulants-Guidance.pdf).*

Conclusion

1. Bleeding associated with antiplatelet agents is a real fear situation in dentist daily life when approaching a surgical intervention from a simple extraction to multiple extractions, periodontal and implant surgery. For this reason, after a bibliographic review of clinical cases and meta-analysis, a protocol was made in order to help to face these patients, since in the past dentists tried replacement therapies or suspending drugs, exposing patients to a cardiovascular complication.
2. Nowadays stopping antiplatelet agent monotherapy is not anymore acceptable because although the risk of a thromboembolic event associated with antiplatelet discontinuation is low, it outweighs the risk of oral bleeding.
3. It is also important to take into account that patients who are taking dual therapy are exposed to a higher risk of hemorrhage compared to patient monotherapy. For this reason, it is even more necessary, and it is the responsibility of the dentist to use all the available anti-hemorrhagic measures, such as gauze compression, collagen sponge, gel foam with tranexamic acid, electrocautery and sutures, in order to control bleeding in dental surgery.
4. Lastly, the communication with the health care provider and patients is substantial, explaining the risk of increased bleeding but focusing on the benefits of not discontinuing the antiplatelet agents and giving postoperative recommendations and management of the site of the intervention, such as mouthwashes with tranexamic acid and gauze compression.

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