Clinical study of bleeding index in oral surgery in patients under anticoagulant or antiplatelet therapy

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Introduction: It was performed a clinical evaluation of the incidence of bleeding in various oral surgical procedures in patients taking anticoagulants (such as warfarin sodium and heparin) or antiplatelet therapy (such as acetylsalicylic acid), as well as the efficacy of tranexamic acid, maintaining patient's protection against the occurrence of thromboembolic episodes. **Methods:** 31 surgeries were performed, 17 in male patients and 14 in female patients, having as inclusion criteria the use of anticoagulant or antiplatelet therapy, and INR value within the therapeutic range. In none case, medication was suspended or altered. It was evaluated the type of surgical intervention, thromboembolic risk, bleeding during surgery and post-surgery, and the need for local measures to control hemorrhage. **Results:** The maintenance of anticoagulant or antiplatelet medication did not trigger an increase in the bleeding index. Only 2 patients (6.45%) were observed with bleeding that was not normal in the intraoperative period, both of which were reversed through tranexamic acid tamponade. Considering the postoperative bleeding index, classified as mild, moderate or severe, only 1 patient (3.22%) developed severe hemorrhage after the fourth day, due to external factors, with the others presenting mild bleeding. There was no thromboembolic episode recorded during the study. **Conclusions:** The trans and postoperative bleeding index in the performed surgical procedures remained, in the great majority of our patients, within normal, that is, controlled and with good visibility of the operative field. Still, new studies may contribute to further elucidations. **Keywords:** Thromboembolism. Anticoagulants. Tranexamic acid.

How to cite: Salvi C, Formighieri LA, Berticelli RS, Seguin F, Oliveira GR. Clinical study of bleeding index in oral surgery in patients under anticoagulant or antiplatelet therapy. J Clin Dent Res. 2017 Oct-Dec;14(4):92-100.

DOI: https://doi.org/10.14436/2447-911x.14.4.092-100.oar

Submitted: September 28, 2016 - **Revised and accepted**: September 11, 2017.

» The authors report no commercial, proprietary or financial interest in the products or companies described in this article.

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INTRODUCTION

Anticoagulants agents and antiplatelet drugs are the pillars of the treatment of cardiovascular diseases, which represent, according to the World Health Organization, 17.5 million deaths annually.[1-9] Frequently, they present a challenge for the oral and maxillofacial surgeon, in order to manage their patients who are chronically medicated.[1,2,3,10,11] This is because the incidence of hemorrhage in oral surgeries can increase in cases in which the medication is maintained or changed.[1,2,3,10] On the other hand, there is an increased risk of thromboembolic episodes caused by the suspension of the medication, bringing risks to the patient's life, but this is a much-debated and controversial topic, having various protocols and therapies for management.[1,2,10,11,12,13]

The treatment of patients in therapy with anticoagulants or antiplatelet agents aims at the maintenance of protection against thromboembolism and, at the same time, minimizing of the risk of trans and post-surgery hemorrhage, through methods of local hemostasis as the use of tranexamic acid.[1,5,7,10,11,14]

LITERATURE REVIEW

The antiplatelet and anticoagulants agents act, respectively, in the process of primary and secondary hemostasis, being used specifically for the treatment of patients with pulmonary embolism, cardiac valvular prostheses, chronic atrial fibrillation, acute myocardial infarction, Hypercoagulable states (i.e. , C protein deficiency, S protein deficiency, mutation of factor V Leiden, deficiency of antithrombin III, antibody-antiphospholipid syndrome), pulmonary hypertension, venous or arterial thromboembolism and cerebral vascular accident.[4,6,8,11,15,16] Among the drugs, we have the following listed.

Acetylsalicylic Acid

Aspirin is one of the most classical antiplatelet agents.[2,8,17] The pharmacological effect in platelets is through acetylation and irreversible inhibition of platelet cyclooxygenase-1, a key enzyme involved in the production of thromboxane A2. In other words, the aspirin blocks production of thromboxane A2. The release of this stimulates the recruitment, activation and increases the aggregation of platelets.[2,16,18,19] The effect of these drugs continues through the lifetime of a platelet (7-10 days).[19] There is no specific reversible agent for the effect of these drugs.[2]

Warfarin Sodium

It has been accepted for use as an oral anticoagulant therapy in 1954 and is the most used throughout the world. The time of plasma half-life of warfarin is from 36 to 42 hours, and it may take 3 to 5 days for the complete reversal.[2,10] The return to normal coagulation after stopping the warfarin requires their removal, followed by synthesis of new coagulation factors.[11] Its effect is predominantly in the reduction of factor II of coagulation, the prothrombin.[2,10] Due to the fact that the derivatives of warfarin sodium can affect the synthesis of active coagulation factors, alteration of the doses of these anticoagulants do not have an immediate effect on coagulation.[1]

Heparin

The unfractionated heparin acts through activation of antithrombin III. This induces a conformational change that accelerates the speed at which the antithrombin III inhibits the factor Xa. In addition, are inactivated several coagulation enzymes, factor thrombin (IIa) and the factors IXa, Xa, XIa, and XIIa. The anticoagulant effect has a half-life that is dose-dependent and is 30 to 150 minutes.[2] The unfractionated heparin

produces a pattern of anticoagulant response unpredictable because it is inhibited by binding protein and activated platelets.[20]

The half-life of low-molecular-weight heparin is approximately 6 hours and is not dose dependent. Reverse activity of anti-f.Xa of low-molecular-weight heparin may be incomplete (60 %), obtained with protamine. Because of their long half-lives, the repeated administration may be required.[2]

The impetus for the development of anticoagulants safer has resulted in New Oral Anticoagulants, (NOACs), as dabigatrana, rivaroxabana and apixabana.[8,9] However, scientific evidence regarding their relationship in dental environment is is still required.[8]

For the achievement of the most various dentistry surgical procedures, without any interruption or modification of treatment, it is necessary the systemic evaluation of the patient in question. The test of INR (International Normalized Ratio) is used as a parameter for analyzing the possibility or not of suspension of the drug oral anticoagulants in use.[11] The reference value of INR is 1, and the higher the value of INR, the lower is blood coagulation, being that this varies according to the underlying pathology of the patient.[21]

As a measure of local hemostasis, studies have demonstrated the efficacy of tranexamic acid, an antifibrinolytic drug.[2,4,6,10,14,22]

Tranexamic acid prevents proteolytic degradation of fibrin, preventing the connection of plasminogen and plasmin.[21] This mechanism locks the systemic treatment of connection of plasmin to fibrin, acting as well as a powerful inhibitor of fibrinolysis.[7,15,20]

For adequate decisions, we should also take into account the factors that increase the risk of hemorrhage, such as the power of the medicinal product, associated diseases, age, dietary habits, alcohol, smoking, concomitant use of drugs that interfere with hemostasis and duration of treatment.[11,23]

Considering the risks involved already described, the objective of this study was to clinically evaluate the patients on anticoagulants or antiplatelet agents regarding the incidence of bleeding during and after several oral surgeries, without suspension or amendment of the medication, as well as the efficacy of tranexamic acid, being maintained to protect the patient against the occurrence of thromboembolic episodes.

MATERIAL AND METHODS

For the study, 31 oral surgical procedures were performed in 17 male (6 using anticoagulant and 11 antiplatelet) and 14 female patients (5 using anticoagulant and 9 antiplatelet), having as inclusion criteria the use of anticoagulant therapy or antiplatelet and the value of INR within the therapeutic range. Patients with hepatic dysfunction were excluded, as well as those in which it has been necessary to use cautery to stop hemorrhage.

The patients were evaluated and listed according to the thromboembolic risk. The classification system used was Beirne's, 2005.[11] This author subdivides it into low, moderate and high thromboembolic risk (Table 1).

Following this classification, we subdivided our patients for a general assessment: 36.36% of patients taking anticoagulants were low risk, 27.27% moderate and 36.36% high thromboembolic risk. In antiplatelet therapy, 100% were low risk.

The patients were also classified according to the type of surgical intervention in accordance with Ferrieri et al., 2007,[5] being divided into high surgical risk (simple single extractions;

Table 1: Risk of thromboembolism, according Beirne, 2005.[11]

LOW RISK	MODERATE RISK	HIGH RISK
Atrial fibrillation without stoke	Bileaflet tilting disc aortic valve with ≤ stroke risk factors	Mechanical mitral valve
Cardiomyopathy without atrial fibrillation	Chronic atrial fibrillation with >2 stroke risk factors	Ball-cage valve replacement
Venous thrombosis > 6 months	Venous thrombosis <6 months	Venous thrombosis <3 months
Bileaflet aortic valve and <2 stroke risk factors	-	Hypercoaguable state Atrial fibrillation with history of stroke Acute myocardial infarction <3 months Recent (1 month) stroke or transient ischemic attack

simple multiple (<4) extractions) or low surgical risk (complicate single extractions; simple multiple (>5) extractions; biopsies; implant installation). Prior to performing any procedure, was delivered the Free and Informed Consent and each patient was advised about the survey, which was duly registered by the Committee for Ethics in Human Research of the University, number CAAE 02614212.4.0000.0107.

In all cases, none had the suspension or amendment of medication. It was obtained a complete coagulogram for all patients, evaluating the INR of at most 72 hours prior to those in treatment with warfarin, verifying the effectiveness of anticoagulant therapy. The INR values considered appropriate for certain procedures, follows measurement as described by Ferrieri et al. , 2007[5] (table 2). With regard to the patients on antiplatelet therapy, where there is no activity in the coagulation cascade and consequently the INR should not be used as a parameter to know the efficiency of the medication, the exams were used for exclusion of any coexisting blood irregularity. All patients had platelet count greater than or equal to 10x104/mm^3.

During the surgery, were adopted local measures for the control of hemorrhage, if it occurred, for both anticoagulant and antiplatelet users.. For this, we chose to follow 3 different protocols to control hemorrhage. The first option (Protocol I) was based on use of gauze soaked in saline 0.9 %, with local pressure for 10 minutes. If not occur hemostasis, our second option (Protocol II) consisted of use of tranexamic acid through local pressure with gauze soaked for 10 minutes and/or irrigation with 10 mL. The last option (Protocol III), if the above were not effective, would be the referral to the hospital to control through medication and/or cautery when indicated.

After finalized all procedures, the hemorrhage was evaluated until a week after the surgery. Post-surgery hemorrhage was classified as mild when lasted less than 10 minutes, moderate when lasted 10 to 20 minutes, and severe when greater, requiring hospitalization for adequate treatment.

Prophylactically, there were instructions for

Table 2: INR values and procedures.

	INR	PROCEDURES
Level 1	Until 3	Where major bleeding is expected
Level 2	Until 3.5	Moderate bleeding cases, third molar surgery or multiple tooth extractions
Level 3	Until 4	Single tooth extraction or when the expected bleeding is minimal
Level 4	Above 5	No surgery

oral hygiene and use of 0,12% Chlorhexidine digluconate. The preoperative medication consisted of antibiotics and anti-inflammatories. In the postoperative period, the recommendations were mainly in relation to the light and cold diet for 24 hours, local ice for 24 to 48 hours, do not perform mouth rinses or suctions in the first day, avoid efforts or physical activities and contact the responsible before any amendment of the clinical picture. As for the medication, antibiotics, anti-inflammatory drugs and analgesics were used only when indicated.

RESULTS

The INR values obtained were in the range between 0.9 and 2.7, being the mean value for the patients on anticoagulants of 2.14 and antiplatelet agents of 1.29, staying in the acceptable range for surgical procedures in a safe manner.

Data were obtained by comparing the information regarding the various types of surgical procedures performed and the use of anticoagulants and antiplatelet agents, respectively, for patients with high, intermediate and low thromboembolic risk, getting the overview given in table 3. The most common procedures in the study were the dental extractions (49), followed by the installation of dental implants (19).

Considering the procedures of dental implants, some were needed concurrent reconstructive surgical procedures, involving the removal of autogenous bone and/or gingival tissue, as well as the use of bone substitutes (Table 4).

The results regarding the type of trans-surgical protocol used for bleeding control are shown in Table 5.

In relation to the bleeding after finalization of the surgical procedures, according our classification in mild, moderate and severe, follows Graphic 6.

It is important to note that no thromboembolic episode was recorded during the research.

Table 3: Total surgical procedures and the thromboembolism risk in patients with anticoagulants and antiplatelet.

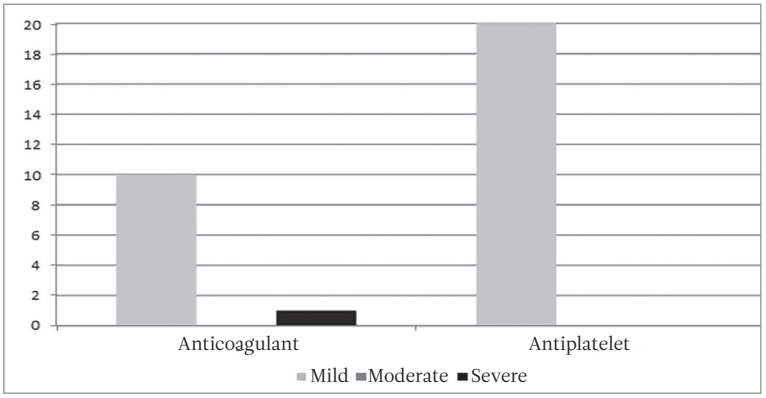
DRUG	NUMBER OF PATIENTS	NUMBER OF PROCEDURES	LOW RISK	MODERATE RISK	HIGH RISK
Anticoagulant	7	15 Extractions	2	2	3
Antiplatelet	10	34 Extractions	10	-	-
Anticoagulant	-	0 Soft tissue biopsies	-	-	-
Antiplatelet	4	04 Soft tissue biopsies	4	-	-
Anticoagulant	-	0 Bone tissue biopsies	-	-	-
Antiplatelet	1	01 Bone tissue biopsies	1	-	-
Anticoagulant	-	0 Bucossinusal close	-	-	-
Antiplatelet	1	01 Bucossinusal close	1	-	-
Anticoagulant	3	09 Implants	2	1	-
Antiplatelet	3	10 Implants	3	-	-
Anticoagulant	1	03 Healings	-	1	-
Antiplatelet	1	04 Healings	1	-	-

Table 4: Implants and other procedures concomitant.

DRUG	THROMBOEMBOLISM RISK	IMPLANTS	HEALING IMMEDIATELY	AUTOGENOUS BONE GRAFT	BONE GRAFT WITH BIOMATERIAL	GINGIVAL GRAFT
Anticoagulant	Moderate	3	-	Tuber	-	Tuber
Anticoagulant	Low	4	4	-	-	-
Anticoagulant	Low	2	2	-	-	-
Antiplatelet	Low	4	2	-	Sinus lifting	-
Antiplatelet	Low	5	-	-	-	-
Antiplatelet	Low	1	1	-	-	-

Table 5: Protocol to control bleeding.

PATIENTS	PROTOCOL I	PROTOCOL II	PROTOCOL III
Anticoagulants			
Male	6	-	-
Female	5	-	-
Antiplatelet			
Male	11	-	-
Female	7	2	-



Graph 1: Postoperative bleeding.

DISCUSSION

The more used conduct for years, in relation to anticoagulant or antiplatelet agents, was the recommendation of the interruption or reduction of the dose a few days before oral surgery.[3] However, recently the continuation of therapy in oral surgeries won more attention in the literature, emphasizing preventive measures and the role of local hemostatics.[1,4,5,6,10,22,23]

In our study, none of the 31 patients discontinued the use of anticoagulants or antiplatelet agents, showing values of INR within the therapeutic range suitable for oral procedures. In the study by Morimoto et al., 2008,[24] the therapy with warfarin was continued in all patients, and there were no significant differences in the incidence of postoperative hemorrhage among patients with INR< 2.0 and those with an INR> 2.0. These results suggest that, if the antithrombotic therapy is properly maintained, the hemostasis can be performed in the postoperative period by means of local measures while the therapy with warfarin is continued.

Considering the risk of hemorrhage during surgery in patients on medication, our study showed only 02 patients (6.45 %) with bleeding outside the normal range (longer than 10 minutes ceasing only with tamponade of gauze soaked in saline 0.9 %). Only 1 patient (3.22%) evolved with postoperative bleeding. This bleeding was difficult to control after the fourth day of the procedure, required hospitalization for use of vitamin K intravenously and adjust the dose of warfarin (which was with an overdose), not being the extraction the triggering reason of hemorrhage. Our results are in agreement with the comprehensive study by Wahl in 2000[13], in which more than 2.000 dental surgical procedures (extractions and alveoplasties) were performed in more than 800 patients. In these cases, 12 patients (1.3 %) had major hemorrhage (not controlled with local measures).

Morimoto et al., 2011[12] observed a postoperative bleeding in 3.9% of cases of extraction, a total of 433 dental extractions. Of these, 9 patients received monotherapy with warfarin, 6 received combination therapy with warfarin and antiplatelet drugs and 2 patients received antiplatelet monotherapy. Results suggest that the hemostasis can be achieved after dental extraction in most patients with therapy of warfarin and those in antiplatelet therapy, even if the administration of these agents is maintained.

Regarding the new anticoagulants, or "direct oral anticoagulants" (DOACs), recent studies show the risk of bleeding in dental patients is low with no major consequences. The data support not stopping DOACs prior to dental treatment, regardless of the complexity or the extent of the procedure.[25] In addition, the NOACs might be safer than the vitamin K antagonists in dental implant surgery. However, more well-designed studies are required for future research.[26]

About the antiplatelet drugs, Napenas et al., 2000,[27] found no hemorrhagic complications in the postoperative period among 43 patients who received treatment with single or dual antiplatelet agents. Ardekian et al., 2000,[28] reported that the antiplatelet therapy maintenance did not increase the incidence of postoperative hemorrhage after dental extraction.

Furthermore, our study did not identify the presence of any thromboembolic problem resulting from the completion of surgery, probably because it was not indicated the suspension or amendment of medication in use. Wahl, 2000,[13] estimated a risk of thromboembolism of 1% for patients who interrupt or change the dose of warfarin, because 4 patients had fatal thromboembolism and 2 had non-fatal thromboembolic events in his research. Thromboembolic events, although less common than clinically significant hemorrhagic episodes, represent a major threat to the patient. Should also be considered that the bleeding after oral surgeries can be easily seen and are usually self-limiting.[4,6,13,14]

The potential of thromboembolic risk was observed in 1 patient in our study. This patient was in use of warfarin sodium 20 years ago by mitral valvuloplasty and presence of aortic valve, and had already suffered 2 previous thromboembolic episodes by discontinuation of medication in an attempt to achieve dental implants.

Considering procedures that increase the risk of transoperative hemorrhage and the success of local measures, we highlighta patient who developed abnormal bleeding during the surgical procedure, which consisted of excisional biopsy of peripheral lesion of giant cells. Despite the characteristics and even having occurred hypertensive peak in trans-surgical time (210x110mmHg), the increased hemorrhage was reversed with local pressure with gauze soaked in tranexamic acid during 10 minutes, with the postoperative evolution within the normal range.

In our study, tranexamic acid was elected as the first option for hemostasis due to their availability and low cost. Blinder et al., 1999,[23] compared three different modalities of hemostatic: fibrin glue, tranexamic acid and gelatin sponge. The data in anticoagulated patients did not show any significant difference in the occurrence of postoperative bleeding.

In the present study, instructions for oral hygiene and 0,12% chlorhexidine mouth rinses prior to procedures are supported by the literature, which reiterates the importance of reducing or removing outbreaks of acute oral inflammation.[5,6,12]

Prophylaxis and maintenance of antibiotics were performed in cases of dental implants (with and without grafts) and in more invasive procedures. Antibiotic therapy in the postoperative period should be prescribed only when necessary, because its use by 5 to 10 days can change the intestinal bacterial floral and decrease the vitamin K in the body, resulting in an increase of INR.[11,12,15,24] Non-steroidal anti-inflammatory agents should also be avoided, because of its power to change the metabolism of warfarin and its effects.[6,11,12,14] The management of post-surgical pain can be performed with lower doses of acetaminophen, as necessary.[5,8,12,24] Narcotic analgesics may be safely used in patients taking oral anticoagulants.[11]

CONCLUSIONS

According to the methodology used in this study, the trans and postoperative bleeding index in the surgical procedures performed in patients who used anticoagulants or antiplatelet medication remained mostly normal, that is, controlled and with good visibility of the operative field. Our results are in agreement with the current literature, allowing us to perform oral surgeries without suspending the antithrombotic medication used by the patient, as long as the latter is controlled and we have available topical means to perform bleeding. New studies with larger samples and metrologies that can measure blood loss may contribute to further elucidation.

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