Oral surgery in patients under antithrombotic therapy: perioperative bleeding as a significant risk factor for postoperative hemorrhage

Amanda L. Rocha[a], Alessandra F. Souza[b], Maria A.P. Martins[c], Marina G. Fraga[a], Denise V. Travassos[b], Ana C.B. Oliveira[b], Daniel D. Ribeiro[d] and Tarcília A. Silva[a]

To investigate perioperative and postoperative bleeding, complications in patients under therapy with anticoagulant or antiplatelet drugs submitted to oral surgery. To evaluate the risk of bleeding and safety for dental surgery, a retrospective chart review was performed. Medical and dental records of patients taking oral antithrombotic drugs undergoing dental surgery between 2010 and 2015 were reviewed. Results were statistically analyzed using Fisher's exact test, *t* test or the χ^2 test. One hundred and seventy-nine patients underwent 293 surgical procedures. A total of eight cases of perioperative and 12 episodes of postoperative bleeding were documented. The complications were generally managed with local measures and did not require hospitalization. We found significant association of postoperative hemorrhage with increased perioperative bleeding ($P = 0.043$) and combination of anticoagulant and antiplatelet therapy ($P < 0.001$). The chance of postoperative hemorrhage for procedures with increased perioperative bleeding is 8.8 times bigger than procedures without perioperative bleeding. Dental surgery in patients under antithrombotic therapy might be carried out without altering the regimen because of low risk of perioperative and postoperative bleeding. However, patients with increased perioperative bleeding should be closely followed up because of postoperative complications risk. *Blood Coagul Fibrinolysis* 28:000–000

Blood Coagulation and Fibrinolysis 2017, **28**:00–00

Keywords: anticoagulants, antithrombotic agents, hemorrhage, tooth extraction, warfarin

[a]Department of Oral Surgery and Pathology, [b]Department of Community and Preventive Dentistry, Faculty of Dentistry, [c]Department of Pharmaceuticals Products, Faculty of Pharmacy and [d]Department of Hematology, Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

Correspondence to Tarcília A. da Silva, PhD, Department of Oral Surgery and Pathology, Faculty of Dentistry, Universidade Federal de Minas Gerais – UFMG, Av. Presidente Antônio Carlos, 6627 – Pampulha, Belo Horizonte 31270-901, Minas Gerais, Brazil.
Tel: +55 31 34092478; fax: +55 31 34092430; e-mail: silva.tarcilia@gmail.com

Received 6 July 2017 **Revised** 29 September 2017
Accepted 16 October 2017

Introduction

Anticoagulant and antiplatelet therapies are widely used for long-term prevention and treatment of thromboembolic events [1]. These drugs act by altering the procoagulant and anticoagulant pathways, preventing clot formation or reducing progression of existing clots [2]. Systemic conditions that require antithrombotic therapy are atrial fibrillation and other cardiac arrhythmias; venous thromboembolism, acute coronary syndrome and myocardial infarction; pulmonary hypertension, cardiac valve disease and prosthetic valve replacement [3,4]. The number of patients with chronic illnesses receiving antithrombotic therapy is growing due to the increase of elderly population and long life-expectancy [5]. Accordingly, the probability of this population requiring dental surgery also increased [6].

Despite the fact that dental extractions are considered minor surgical procedures and associated with low blood loss, it is known that anticoagulant therapy may increase the risk of perioperative and postoperative bleeding [7]. The increased risk of postoperative major bleeding over 2 days in the postoperative period is approximately 0–2% for general invasive procedures [8].

Currently, most of studies do not recommend discontinuing the use of medication for performing tooth extractions due to life-threatening risk associated with the suspension of therapy [9–12]. Accordingly, minor oral surgeries, such as tooth extractions and biopsies, can be performed without changes in the antithrombotic regimen [4,5]. However, some measures are essential to avoid bleeding complications. In patients on warfarin therapy, monitoring of international normalized ratio (INR) values and use of local hemostatic measures are recommended [13–15].

To evaluate the risk of bleeding and safety for dental surgery, a retrospective chart review was performed. Herein, we evaluated the frequency of postoperative bleeding complications after surgical dental procedures in patients under antithrombotic therapy with warfarin and/or antiplatelet agents. In addition, the current study aimed to propose standards for safely management bleeding complications in patients on antithrombotic therapy without discontinuing the use of medication.

0957-5235 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved. DOI:10.1097/MBC.0000000000000677

Materials and methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This retrospective study was approved by Universidade Federal de Minas Gerais Ethics Committee (48122215.4.0000. 5149). For this type of study, formal consent is not required. All data were anonymized and deidentified prior to analysis.

The sample consisted of patients in antithrombotic regimen referred by in-hospital departments, as hematology and cardiology, between 2010 and 2015, and the study was conducted in a Hospital's Dentistry Service.

Medical and dental records of patients undergoing oral surgery procedures and taking oral antithrombotic drugs were evaluated. The data collected were age, sex, indication for oral antithrombotic therapy, use of anticoagulants and/or antiplatelet drugs, dental surgery, INR, time in the therapeutic range (TTR) and perioperative or postoperative bleeding outcomes. The records of procedures with incomplete data were excluded.

The type of antithrombotic regimen was classified as anticoagulant or antiplatelet. Patients undergoing oral anticoagulant therapy and antiplatelet therapy were divided into two groups, analyzed and presented separately in results section. Data from patients in use of dual therapy, warfarin and acetylsalicylic acid (ASA), were presented with that of patients under anticoagulant therapy. For statistical analysis, this sample was clustered with anticoagulant group or considered as an independent group.

For patients on warfarin therapy, effectiveness of anticoagulant therapy was assessed based on INR. The proportion of time spent in the therapeutic range was evaluated by TTR was calculated according to F.R. Rosendaal's algorithm, as the proportion of days with INR values between the target INR (2.0–3.0 or 2.5–3.5) [16]. The calculation was established from the day of the procedure INR and the two previous measures of patient's INR.

Number and type of surgical procedures and number of teeth extracted were recorded. The extraction was classified as surgical or simple extraction. A surgical extraction was defined as a procedure with need of raising a mucoperiosteal flap and removal of bone with a bur. All procedures were performed under local anesthesia and sutures were standard measures for all procedures.

Antibiotic prophylaxis was only used in those patients with risk for bacterial endocarditis as defined by American Heart Association [3].

The occurrence of perioperative and/or postoperative hemorrhage was analyzed. The perioperative bleeding was characterized by register on dental records of increased bleeding during surgery. It was classified as effective hemostasis employing local measures or without the possibility of local hemostasis.

The data of postoperative bleeding were based on these following outcomes: return to our or other service because of postoperative bleeding; telephone call to our service with a concern of postoperative bleeding; require hospitalization without blood transfusion; report of postoperative bleeding in dental records at the postoperative visit but did not seek care.

Data were analyzed using IBM SPSS Statistics version 20.0 software (IBM Corp., Armonk, New York, USA). Descriptive data analyses, including mean, SD and percentages, were determined. Categorical data such the occurrence of postoperative bleeding in relation to other variables were analyzed using Fisher's exact test, *t* test or the χ^2 test. Statistical significance was set at a *P* value less than 0.05.

Results

A total of 179 patients in antithrombotic therapy underwent 293 surgical procedures. Of these, 126 patients were in use of anticoagulant (216 procedures) and 53 patients in exclusive antiplatelet therapy (77 procedures). Fourteen patients (23 procedures) were in use of dual therapy (anticoagulant and antiplatelet therapy), and these data were presented in the section of patients under anticoagulant therapy.

Patients under anticoagulant therapy

In a period of 5 years (2010–2015), we identified 134 patients in anticoagulant therapy submitted to a total of 235 dental surgery procedures. Eight patients were excluded due to lack of data in dental records. Therefore, a total of 126 records of patients were included in the study. Of these, 76 (60%) were women and the mean age was 51 ± 13.62 years (range, 11–86 years). The indication for anticoagulation and the therapeutic INR values are described in Table 1.

Anticoagulant therapy consisted only of vitamin K antagonists. Warfarin monotherapy was used for 109 patients (87%) and a total of 14 patients (11%) underwent combination therapy with warfarin and antiplatelet drug ASA. Three patients in warfarin monotherapy had the anticoagulation regimen interrupted by the attending physician previously to dental intervention. These patients were not excluded from the analysis as one of them presented postoperative bleeding complication (Table 1). The INR average was 2.31 for procedure in whole sample and mean INR of 2.50 for those patients who developed postoperative bleeding.

The TTR value, or, the proportion of time spent with the INR in the therapeutic range, considering the RNI at day of the procedure and the two previous measures of INR,

Table 1 Clinic and demographic characteristics of anticoagulated patients

	Total sample *n*	%	Patients with postop hemorrhage	Therapeutic INR
Patients	126	–	$n=10$ (8%)	–
Mean age (years)	51 (±13.62)	–	49	
Men	50	40	5 (50%)	–
Women	76	60	5 (50%)	–
Deep-vein thrombosis[a]	38	30	3 (30%)	2.00–3.00
Atrial fibrilation[a]	36	29	3 (30%)	2.00–3.00
Cerebrovascular ischemic accident[a]	17	13	1 (10%)	2.00–3.00
Mechanical heart valve Mi[a]	14	11	2 (20%)	2.50–3.50
Pulmonary embolus[a]	13	10	1 (10%)	2.00–3.00
Mechanical heart valve Ao[a]	10	8	1 (10%)	2.00–3.00
Biological heart valve[a]	9	7	0	2.00–3.00
Other conditions[a,b]	16	13	3 (30%)	2.00–3.00
Mean INR before surgery/procedure	2.31 (±0.56)	–	2.50 (±0.61)	–
TTR above 60% /procedure	66	56	6 (66%)	–
TTR below 60% /procedure	52	44	3 (33%)	–
Mean TTR/procedure	118	64	9 (67%)	–
Warfarin monotheraphy	109	87	5 (50%)	–
Warfarin + ASA	14	11	4 (40%)	–
Suspension of antithrombotic therapy	3	2	1 (10%)	–

Ao, aortic; ASA, acetylsalicylic acid; INR, international normalized ratio; Mi, mitral; Postop, postoperative; TTR, time in therapeutic range. [a] The same patient may have more than one diagnosis. [b] Valvular disorders, intracardiac embolus, thrombophilia, portal vein thrombosis.

was calculated for 57% of the cases (118 procedures) and 60% of patients ($n=76$)(Table 1).

A total of 426 teeth were extracted. The mean of teeth extracted for dental appointment was 1.96 and the mean of teeth extracted for patient was 3.38. The percentage of simple extraction was 86% and surgical extractions were 14%, with eight and two cases of postoperative bleeding, respectively. No significant influence of dental procedure in bleeding outcome was observed.

The outcomes studied were bleeding complications in perioperative and postoperative period. In 97% of the surgical procedures, there were no reports of bleeding in perioperative time. In the seven cases of perioperative bleeding, hemostasis was achieved by local measures in all those occasions but two cases progressed with postoperative bleeding.

Overall, in 216 appointments, 11 episodes (5%) of postoperative bleeding were documented. Among a total of 126 patients, 8% presented postoperative bleeding (10 patients), one of which had two reports of postoperative bleeding in different procedures. Seven of the 11 cases returned to our service or were treated at another secondary care. All cases were managed with local hemostatic measures, such as hemostatic gelatin sponges, tranexamic acid and/or new sutures. Tranexamic acid paste (one 250-mg pill macerated and mixed with saline) was used to soak the gelatin sponge, to fill the alveolar socket. Another layer of the paste was applied on the wound after sutures and covered with gauze under compression. Local use of tranexamic acid mouthwash was prescribed for the following seven postoperative days. In one case, the patient made telephone contact and orientations, like compression of the oral site and do not spit, were given without the need of return to service. In another situation, the patient reported, 7 days after surgery, an episode of postoperative bleeding, but did not seek care for this complication due to spontaneous resolution. In two cases, the patients were hospitalized for hemorrhage control through local measures and suspension of anticoagulant therapy, but no blood transfusion was required (Table 2).

The results of Fisher's exact test to assess the association between postoperative hemorrhage and other variables showed significance for procedures with increased bleeding in perioperative time ($P=0.043$). The chance of postoperative hemorrhage for procedures with increased perioperative bleeding is 8.8 times bigger than procedures without perioperative bleeding (Table 3).

Regarding the type of antithrombotic drugs, the occurrence of postoperative bleeding was higher in procedures performed in patients under use of dual therapy (warfarin and ASA) compared with warfarin monotherapy ($P<0.001$). When analyzing the therapeutic INR range, the patients with target of 2.5–3.5 have more postoperative bleeding complications than those with target of 2.0–3.0 ($P=0.056$) (Table 3).

Patients under antiplatelet therapy

Over the same period, were treated 53 patients in continuous use of antiplatelet agents, which underwent to 77 surgical procedures. The men represented the majority of the sample (57%), and the average age of the population was 57 ± 14.2 (range from 12 to 88 years). Approximately 85% of the patients were treating with ASA monotherapy. The combined therapy, ASA and clopidogrel, was prescribed for 11% of the patients, and 4% were taken clopidogrel monotherapy. The indications for antiplatelet therapy were atherosclerotic cardiovascular disease ($n=42$), cerebrovascular ischemic

Table 2 Clinic and demographic data of patients under anticoagulant therapy with episodes of postoperative bleeding

										Hemorrhage		
N	Sex	Age	Anticoagulant therapy indication	Terapeutic INR range	Anticoagulant therapy	Bleeding history	Type of procedure	INR	TTR (%)	No. of teeth	Periop	Postop	Management
1	F	63	AF + IE	2,0–3,0	W	No	SIMPLE E	2.03	80	2	No	1	S + HGS + TTA
2	M	58	MS	2,0–3,0	WS	No	SIMPLE E	1.22	–	4	No	1	S + HGS
3	F	47	MV (Mi)	2,5–3,5	W + ASA	Yes	SIMPLE E	2.94	–	1	Yes[a]	3	WS
[b]4	M	42	MV (Mi)	2,5–3,5	W + ASA	Yes	SIMPLE E	2.24	41	1	Yes[a]	4	None
4	M	42	MV (Mi)	2,5–3,5	W + ASA	Yes	SIMPLE E	3.59	0	1	No	3	S + WS
5	M	53	DVT	2,5–3,5	W	No	SURGICAL E	2.42	0	1	No	1	O
6	F	34	DVT	2,0–3,0	W	No	SIMPLE E	2.52	100	1	No	1	S + HGS + TTA
7	M	37	MV (Ao)	2,0–3,0	W + ASA	No	SIMPLE E	2.82	100	2	No	1	S + HGS
8	M	70	AF + VD	2,0–3,0	W	No	SIMPLE E	2.46	100	2	No	1	S
9	F	38	AF	2,0–3,0	W	No	SURGICAL E	2.30	86	2	No	1	S + HGS
10	F	47	DVT + PE + CIA	2,0–3,0	W + ASA	No	SCL	2.98	100	0	No	2	O

AF, atrial fibrillation; ASA, acetylsalicylic acid; CIA, cerebrovascular ischemic accident; DVT, deep-vein thrombosis; HGS, hemostatic gelatin sponge; IE, intracardiac embolus; MS, Marfan's syndrome; MV (Ao), mechanical heart valve (aortic valve); MV (Mi), mechanical heart valve (mitral valve); O, orientation; PE, pulmonary embolus; Periop, perioperative; Postop, postoperative; S, sutures; SCL, surgical crown lengthening; SIMPLE E, simple extraction; SURGICAL E, surgical extraction; TTA, topic tranexamic acid; VD, valvular disorders; W, warfarin; WS, warfarin suspension. [a] Controlled with local measures. 1-Return to our or other service because of postoperative bleeding; 2-telephone call to our service with a concern of postoperative bleeding; 3-require hospitalization without blood transfusion; 4-report of postoperative bleeding in dental records at the postoperative visit but did not seek care. [b] The patient four had two reports of postoperative bleeding in different procedures.

accident ($n = 6$), deep-vein thrombosis ($n = 3$), pulmonary embolus ($n = 1$) and thrombocythemia ($n = 1$).

Of 77 extractions analyzed, 69 were considered as simple and in eight cases were surgical extraction. A total of 211 teeth were extracted, and the largest number of extracted teeth in the same session was 18. The mean of teeth extracted for occasion was 2.7 and the mean of teeth extracted for patient was 4.

Based on the analysis of bleeding complications, only two reports were identified. These reports represented 2% of the procedures performed. The first outcome refers to increased bleeding on the perioperative period, in which the patient underwent to surgical extraction of four teeth under use of ASA monotherapy. Hemostasis was effectively done employing local measures, and the patient had no postoperative complications. The second episode of postoperative bleeding occurred after simple extraction of five teeth in a patient in use of clopidogrel monotherapy. Patient did not seek care due to spontaneous resolution of the episode.

Discussion

In this retrospective study, the surgical dental procedures were taken without discontinuing the antithrombotic medication [4,9–12]. From a total of 293 surgical dental procedures, 12 episodes of postoperative bleeding were found (4%), and in most of the cases, the complication was managed without hospitalization. The occurrence of perioperative bleeding and combination of warfarin and

Table 3 Comparison between variables regarding postoperative bleeding ($n = 216$)

	Procedures group			
Independent variable	With postop bleeding *n* (%)	Without postop bleeding *n* (%)	*P* value[a]	Odds ratio (95% CI)
Age	48.27 (±11.50)	52.42 (±14.55)	0.354[b]	–
Sex				
Male	6 (6.7)	84 (93.3)	0.374	1
Female	5 (4.0)	121 (96.0)		0.58 (0.17–1.95)
INR	2.50 (±0.61)	2.31 (±0.56)	0.324[b]	–
TTR	0.67 (±0.42)	0.64 (±0.35)	0.804[b]	–
Perioperative bleeding				
Absent	9 (4.3)	200 (95.7)	**0.043**[c,*]	1
Present	2 (28.6)	5 (71.4)		8.88 (1.51–52.2)
Therapeutic INR				
2.00–3.00	7 (3.8)	178 (96.2)	0.056[c]	1
2.50–3.50	4 (12.9)	27 (87.1)		3.76 (1.033–13.73)
Drug therapy				
Warfarin	5 (2.6)	185 (97.4)	**<0.001***	1
Warfarin + ASA	5 (21.7)	18 (78.3)		1.85 (1.43–2.50)
Other[d]	1 (33.3)	2 (66.7)		1.89 (1.13–24.39)
Total procedures	11 (5.1)	205 (94.9)	–	–

* 5% Significance level/95% CI. ASA, acetylsalicylic acid; CI, confidence interval; INR, international normalized ratio; Postop, postoperative. [a] χ^2 Test. [b] *t* Test. [c] Fisher's test. [d] Anticoagulation regimen altered.

antiplatelet therapy significantly increased the risk of postoperative bleeding.

The literature supports the evidence that patients who require minor dental procedure undergoing warfarin and/or antiplatelet regimen should continue the medication [4,9,11]. The interruption of therapy exposes patients to an increased risk for thromboembolic events, which can result in major disability or death [9,10,12]. On a review of the English literature, of 542 documented cases with 493 patients of withdrawing continuous anticoagulation, five had serious embolic complications, wherein resulted in four deaths [17]. Furthermore, no well documented case of serious bleeding from dental surgery in patients receiving therapeutic levels of warfarin therapy was previously reported [11,17]. Moreover, bleeding complications indicating more than local hemostatic measures are very rare [9,12].

In this study, the postoperative bleeding was significantly higher in patients under dual therapy compared with those on warfarin monotherapy. This result was consistent with previous reports that described an increased risk of hemorrhagic events in patients who are on concomitant warfarin and antithrombotic therapy, like ASA or Low-Molecular-Weight Heparin [18,19]. On the other hand, some authors do not found significant differences when analyzing postoperative hemorrhage between these groups [10,20].

The incidence of postoperative hemorrhage in patients receiving warfarin varies from 2 [17], 3.5 [10], 3.9 [13], 4.8 [18], 6.6 [9] to 26% [15]. A systematic review shown that clinically significant bleeding occurred in 15 of 275 patients who continued warfarin therapy (5.5%), against 25 of 278 who discontinued or altered their dose (9%) [21]. In our study of 11 episodes of postoperative bleeding (5%), in two cases, the patient was hospitalized, but without the need of blood transfusion. For the other bleeding episodes, only local hemostatic measures like curettage and irrigation of wound, gelatin sponges, new sutures and local use of tranexamic acid [20,22] were performed.

We found seven cases of perioperative bleeding and in all those procedures hemostasis was possible only with local measures like gauze compression and more sutures. Moreover, for seven cases of perioperative bleeding, two had postoperative bleeding in the same procedure. Importantly, we obtained that perioperative bleeding significantly increased the probability for postoperative bleeding (eight times). Accordingly, bleeding should be assessed in perioperative time, and if there is concern, additional measures for hemostasis must be implemented [23].

Our data also pointed for a tendency of association between postoperative bleeding and larger therapeutic INR range, between 2.5 and 3.5. This INR target increased the probability of postoperative bleeding outcome in 3.76 times when compared with INR target of 2.0–3.0. The therapeutic range is usually kept between 2.0 and 3.5 to prevent thromboembolic events [24]. Nevertheless, several studies have demonstrated that dental extraction in patients receiving warfarin who have an INR up to 4.0 could be carried out without a significant risk of bleeding [7,10–12,14,15,20].

The TTR level, a measure referred to the proportion of time spent in the 2.0–3.0 or 2.5–3.5 INR target range, was also calculated for patients of this study. We did not find significant influence of TTR and the bleeding outcome. The TTR has been closely associated with adverse outcomes, that is stroke, hemorrhage, mortality and the literature shows that the poor control of INR is defined as TTR less than 60%, resulting in higher rates of mortality and major bleeding [16].

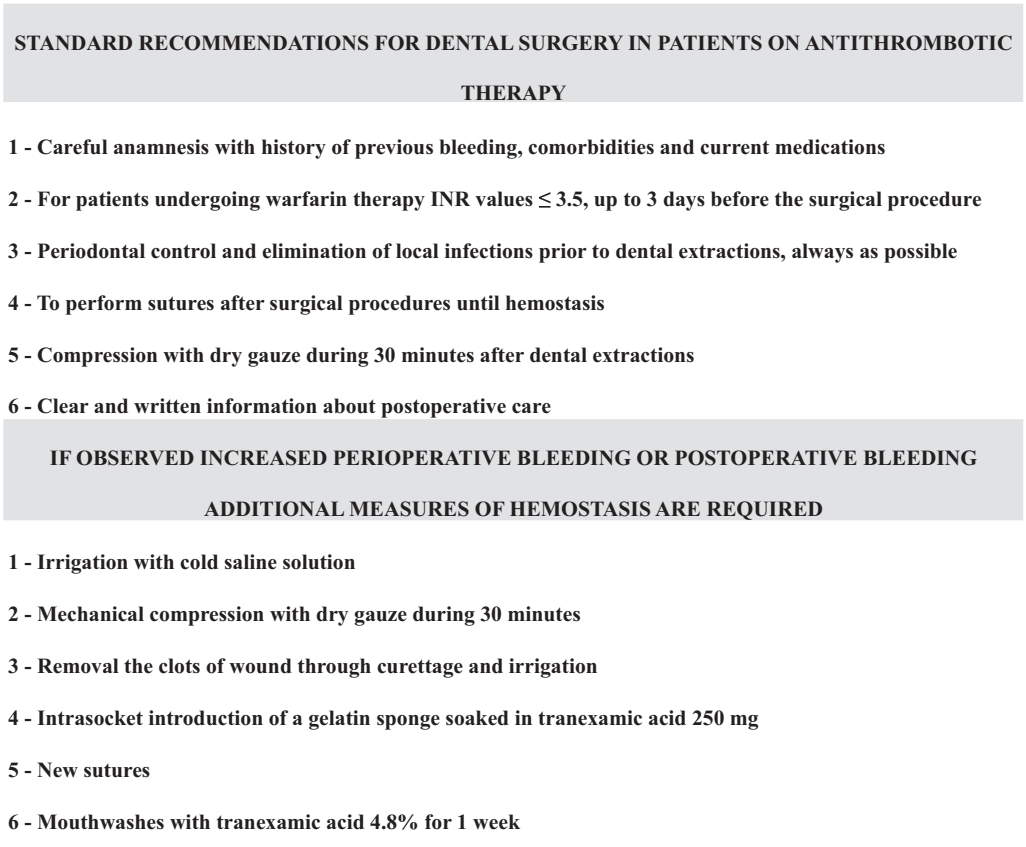
In this current study, none significant episode of postoperative bleeding was found in patients with only antiplatelet therapy. Based on these results and previous literature [10,13,25,26], we do not recommend to discontinue this therapy to perform tooth extractions.

Due to retrospective characteristic of this current study, it had some limitations. The relatively small sample size and a small number of postoperative bleeding outcomes are a conflicting aspect once it could complicate the analysis of possible risk factors. The information on the dental and periodontal condition was not performed and it may influence bleeding. Another factors that might increase the risk of bleeding are drug interaction with other medications as antibiotics (e.g. cephalosporins, macrolides and quinolones), antifungals (azoles), nonsteroidal anti-inflammatory agents, age, systemic diseases (liver disease) and diet (changes in vitamin K intake) [6,23,27].

Despite the fact that patients of this study were attended in an ambulatory service of a hospital, our results should be exploited for general population that could be safely managed in primary care services. The literature supports this suggestion once limiting the assistance to secondary and tertiary care will cause increase the waiting lists and reduce access to dental treatment [12,15]. Thus, there is a need for clinical practice guidelines for the management of this population [28].

For the safety surgical management of patients receiving antithrombotic therapy, the professional should be aware of some criteria and care. All patients should have a preoperative (no longer than 2 or 3 days) INR value up to 3.5. Investigation of previous bleeding, comorbidities and drugs interactions must be carefully performed. In cases of bleeding complications, hemostatic measures to local control like gauze compression, sutures, gelatin sponges and topic tranexamic acid are recommended for effective hemostasis (Fig. 1).

Fig. 1



Six steps for surgical management of patients on antithrombotic therapy.

Conclusion

The results of this study demonstrated a low risk of perioperative and postoperative bleeding associated with dental surgery in patients under antithrombotic therapy, thus suggesting that treatment might be carried out without altering the therapy. The use of appropriated hemostatic measures can avoid hemorrhagic outcomes and postoperative complications, especially in cases with increased perioperative bleeding.

Acknowledgements

The study was supported by FAPEMIG, CNPq and CAPES.

Conflicts of interest

There are no conflicts of interest.

References

1 Alquwaizani M, Buckley L, Adams C, Fanikos J. Anticoagulants: a review of the pharmacology, dosing and complications. *Curr Emerg Hosp Med Rep* 2013; **1**:83–97.
2 Thean D, Alberghini M. Anticoagulant therapy and its impact on dental patients: a review. *Aust Dent J* 2015; **3**:1–16.
3 Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, *et al.* 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; **129**:2440–2492.
4 Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, *et al.* Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Pratice Guidelines. *Chest* 2012; **141 (2 Suppl)**:326–350.
5 Cocero N, Mozzati M, Ambrogio M, Bisi M, Morello M, Bergamasco L. Bleeding rate during oral surgery of oral anticoagulant therapy patients with associated systemic pathologic entities: a prospective study of more than 500 extractions. *J Oral Maxillofac Surg* 2014; **72**:58–867.
6 Fakhri HR, Janket SJ, Jackson EA, Baird AE, Dinnocenzo R, Meurman JH. Tutorial in oral antithrombotic therapy: biology and dental implications. *Med Oral Patol Oral Cir Bucal* 2013; **18**:461–472.
7 Karsli ED, Erdogan O, Esen E, Acartürk E. Warfarin and heparin in dental extraction. *J Oral Maxillofac Surg* 2011; **69**:2500–2507.
8 Dunn SA, Turpie AG. Perioperative management of patients receiving oral anticoagulants. *Arch Intern Med* 2003; **163**:901–908.
9 Wahl MJ, Pinto A, Kilham J, Lalla RV. Dental surgery in anticoagulated patients – stop the interruption. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015; **119**:136–157.
10 Bajkin BV, Bajkin IA, Petrovic BB. The effects of combined oral anticoagulant–aspirin therapy in patients undergoing tooth extractions: a prospective study. *J Am Dent Assoc* 2012; **143**:770–776.
11 Sacco R, Sacco M, Carpenedo M, Mannucci M. Oral surgery in patients on oral anticoagulant therapy: a randomized comparison of different intensity targets. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **104**:18–21.
12 Salam S, Yusuf H, Milosevic A. Bleeding after dental extractions in patients taking warfarin. *Br J Oral Maxillofac Surg* 2007; **45**:463–466.
13 Morimoto Y, Niwa H, Minemastu K. Risk factors affecting postoperative hemorrhage after tooth extraction in patients receiving oral antithrombotic therapy. *J Oral Maxillofac Surg* 2011; **69**:1550–1556.
14 Devani E, Lavery KM, Howell CJT. Dental extractions in patients on warfarin: is alteration of anticoagulant regime necessary? *Br J Oral Maxillofac Surg* 1998; **36**:107–111.

15 Evans IL, Sayers MS, Gibbons AJ, Price G, Snooks H, Sugare AW. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. *Br J Oral Maxillofac Surg* 2002; **40**:248–252.
16 Hylek EM. Vitamin K antagonists and time in the therapeutic range: implications, challenges, and strategies for improvement. *J Thromb Thrombolysis* 2013; **35**:333–335.
17 Wahl MJ. Dental surgery in anticoagulated patients. *Arch Intern Med* 1998; **158**:1610–1616.
18 Hong C, Napenas JJ, Brennan M, Furney S, Lochart P. Risk of postoperative bleeding after dental procedures in patients on warfarin: a restrospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; **114**:464–468.
19 Johnson SG, Rogers K, Delate T, Witt DM. Outcomes associated with combined antiplatelet and anticoagulant therapy. *Chest* 2008; **133**:948–954.
20 Morimoto Y, Niwa H, Minematsu K. Hemostatic management of tooth extractions in patients on oral antithrombotic therapy. *J Oral Maxillofac Surg* 2008; **66**:51–57.
21 Nematullah A, Alabousi A, Blanas N, Douketis JD, Sutherland SE. Dental surgery for patients on anticoagulant therapy with warfarin: a systematic review and meta-analysis. *J Can Dent Assoc* 2009; **75**:41.
22 Carter G, Goss A. Tranexamic acid mouthwash – a prospective randomized study of a 2-day regimen vs 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. *Int J Oral Maxillofac Surg* 2003; **32**:504–507.
23 Scully C, Wolf A. Oral surgery in patients on anticoagulant therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **94**: 57–64.
24 Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; **141**: 576S–600S.
25 Girotra C, Padhye M, Mandlik G, Dabir A, Gite M, Dhonnar R, *et al.* Assessment of the risk of haemorrhage and its control following minor oral surgical procedures in patients on antiplatelet therapy: a prospective study. *Int J Oral Maxillofac Surg* 2014; **43**:99–106.
26 Lu SY, Tsai CY, Lin LH, Lu SN. Dental extraction without stopping single or dual antiplatelet therapy: results of a retrospective cohort study. *Int J Oral Maxillofac Surg* 2016; **45**:1293–1298.
27 Lockhart PB, Gibson J, Pond SH, Leitch J. Dental management consideration for the patient with an acquired coagulopathy. Part 2: Coagulopathies from drugs. *Br Dent J* 2003; **195**:495–501.
28 Van Diermen DE, van der Waal I, Hoogvliets MW, Ong FN, Hoogstraten J. Survey response of oral and maxillofacial surgeons on invasive procedures in patients using antithrombotic medication. *Int J Oral Maxillofac Surg* 2013; **42**:502–507.