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Original Article

Risk factors for bleeding after dental extractions in patients receiving antithrombotic drugs - A case control study

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Abstract *Background/purpose:* Patients receiving antithrombotic drugs are more likely to suffer bleeding after tooth extraction and multiple factors are related to it. The aim of this study was to investigate the incidence of bleeding and risk factors for bleeding after dental extractions in patients receiving antithrombotic drugs.

Materials and methods: This retrospective case control study included patients receiving oral antithrombotic drugs or not. Tooth extractions were conducted under ECG monitoring and local hemostatic measures were performed. Risk factors for postoperative hemorrhage after tooth extraction were evaluated using univariate and multivariate analyses.

Results: Bleeding events were reported in 27 (27%) patients receiving antithrombotic drugs and 9 (9%) patients who didn't use antithrombotic drugs, the difference between which was significant ($p < 0.01$). Univariate analyses showed that age (OR = 2.717, $p = 0.028$), oral hygiene (OR = 4.110, $p = 0.043$), inferior nerve block (OR = 4.285, p = 0.038) and number of extracted tooth (OR = 4.758, p = 0.029) were significantly correlate with bleeding incidence. Multivariate analysis revealed that age (OR = 2.824, p = 0.036) and number of extracted tooth (OR = 5.268, p = 0.016) were significant risk factors for postextraction bleeding.

Conclusion: The results suggest that there is higher incidence of postextraction bleeding in patients receiving antithrombotic drugs compared to patients who don't. Age (>75 years), oral

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hygiene, inferior nerve block and number of extracted tooth may be related to bleeding after tooth extraction.

Introduction

Cardiovascular diseases (CVDs), principally ischemic heart disease (IHD) and stroke, are the leading cause of global mortality and a major contributor to disability.[1] It is estimated that CVD prevalence excluding hypertension (CHD, HF, and stroke only) is 9.3% overall in America in 2018.[2] Antithrombotic regimens remain a central part of therapy in many cardiovascular diseases including atherosclerosis, atrial fibrillation, and valvular diseases and reduces ischaemic events and all-cause mortality.[3] However, significant increase in major bleeding was noted in patients receiving antithrombotic therapy when undergoing invasive procedures.[3]

Invasive procedures are common in the field of dentistry. Evidences show that patients who take antithrombotic drugs especially anticoagulants have a higher risk of bleeding after tooth extraction than those who don't.[4—6] Different recommendations on whether the oral antithrombotic therapy should be stopped had been proposed.[7—9] It is now generally believed that patients taking antithrombotic drugs do not need to stop the drug during tooth extractions.[5,10—14] However, there have been reports in the literature that such patients suffered severe bleeding complications after tooth extraction.[15—17] which makes it difficult for oral and maxillofacial surgeons to make a choice when facing such patients. There are many factors that may increase the risk of bleeding after tooth extraction in these patients. Although lots of investigations have been conducted, there haven't been consensus on the risk factors for bleeding after tooth extractions in patients receiving antithrombotic drugs. To figure out those risk factors would undoubtedly ensure the safety of tooth extraction in such patients. Therefore, in the present study, patients who took antithrombotic drugs were followed up after tooth extraction to study the incidence of bleeding and related risk factors in these patients.

Material and methods

This was a case-control study of postextraction bleeding events in patients receiving and not receiving oral antithrombotic drugs.

Ethical guidelines

All procedures were performed in compliance with relevant laws and institutional guidelines and the study protocol was approved by the ethics committee of West China Hospital of Stomatology, Sichuan University and the approving number was WCHSIRB-2020-407. The research followed the guidelines established in the Declaration of Helsinki (revised 2002 version). A written informed consent was given to every patient who take part in the study.

Patients

Patients admitted at the electrocardiogram (ECG) monitoring Dental Extraction Department of the West China Hospital of Stomatology between May 2020 and December 2021 were included. Inclusion criteria were as follows: 1) Meeting the indications for tooth extraction; 2) 18—90 years old; 3) Signed the informed content. Exclusion criteria including: 1) Blood diseases such as hemophilia and coagulation factor deficiency, or other coagulation disorders; 2) Pregnancy; 3) Contraindications of tooth extraction, for instance, recent myocardial infarction. Patients meeting the inclusion criteria were assigned to study group and control group according to whether had been receiving oral antithrombotic drugs.

Study design

The operation was scheduled to be performed, and a professional anesthesiologist would assess whether the exodontia could be conducted. Radiological examinations and laboratory examinations including blood routine, blood chemistry and four coagulation tests within one week were completed before the surgery. All operations were performed by a doctor with rich experience in oral maxillofacial surgery. Postoperative evaluation and follow-up were accomplished by a doctor who also recorded variables of every patient.

The variables analyzed in this study were: relative volume of bleeding and bleeding events, patient's sex and age, body mass index (BMI), drugs taken (anticoagulant or antiplatelet drugs), preoperative use of antibiotics, oral hygiene, local anesthesia, surgical extraction or not, number of tooth extracted, granulation in the sockets, duration of surgery, history of smoking, comorbidities with diabetes and hypertension.

Surgical procedures

Priority was given to local infiltration anesthesia with PRIMACAINE (PRODUITS DENTAIRES PIERRE ROLLAND, Mérignac, France) while block anesthesia with 2% lidocaine hydrochloride (RONSHYN, Jiaozuo, China) was selected for poor anesthesia or mandibular impacted teeth. All patients' operations were performed under ECG monitoring.

During the entire extraction process, the ECG, blood oxygen saturation and blood pressure changes before and after anesthesia and during the extraction were monitored in real time. Minimally invasive extraction techniques were used during the extraction process. After extraction of the tooth, local hemostatic measures such as suturing the wound and padding of absorbable gelatin sponge were selected according to the size of the wound and the movement of the soft tissue flap, and the duration of surgery was recorded. Patients were requested to bite medical tampons for half an hour after tooth extraction and then receive a reassessment of the socket. Extra measures were applied if the socket was still bleeding to ensure successful hemostasis. Postoperative cautions were explained to patients before they left.

Assessment of postoperative bleeding

The relative volume of bleeding was measured by putting the medical tampons that had been compressed for half an hour in the socket into a centrifuge tube containing 40 ml of double distilled water and submitting the solution to a multifunctional microplate reader (Thermo, Waltham, MA, USA) to measure the absorbance (seen in supplementary materials).

A "postoperative bleeding event" was defined as an oozing or marked hemorrhage after mechanical compression with gauze for 30 min. Bleeding events were monitored from the day of surgery up to 1 week after the tooth extractions with a telephone follow-up. The oral surgeon's cellphone number was also given to patients so that they could reach him in case of problems. Patients were asked to return 7 days after surgery to remove the stitches, evaluate the healing. The number of patients with postoperative bleeding were recorded for each group. Furthermore, in patients with postoperative bleeding, the time of onset of the post-operative bleeding ($<$24 h, $>$24 h and$<$48 h, $>$48 h and$<$72 h, $>$72 h and$<$7 days), management of the bleeding (site compression, local hemostatic measures, hospital readmission, length of hospital stay) were recorded.

Statistical analysis

Fisher's exact test or the chi-square test was conducted to compare bleeding events and T test was applied to compare relative volume of bleeding between the two group. For univariate analyses, Fisher's exact test or the chi-square test was used and binary logistic regression analysis was conducted for multivariate analysis. In all analyses, differences were considered significant for $p < 0.05$. All analyses were performed using SPSS 20.0 (SPSS, Chicago, IL, USA).

Results

Totally, 212 patients were submitted from the participating investigators. Of these, 12 cases were eliminated because of lost of follow-up, leaving 200 for further analysis.

Postextraction bleeding volume and incidence

Characteristics of patients in study and control group were listed in Table 1. No significance was noted between the two groups in terms of sex, age, BMI, oral hygiene, number of tooth extracted, tooth condition, duration of surgery, comorbidity of hypertension or diabetes and history of smoking ($p > 0.05$). While difference of comorbidity of diseases that require antithrombotic therapy was found to be significant ($p < 0.01$).

Bleeding events were reported for 27 of 100 patients (27%) of the study group and for 9 of 100 patients (9%) of the control group, and the difference was significant ($p < 0.01$, Table 2). Besides, relative volume of bleeding after tooth extraction was found to be significant between the two groups ($p = 0.028$, Fig. 1).

Eight (8/27) patients in study group had active bleeding within 24 h and the other 19 (19/27) bleeding events took place in 1–3 days after surgery. Successful hemostasis was accomplished by prolonging the time of cotton ball compression (24/27) and packing gelatin Sponge (3/27). There were four (4/9) bleeding events within 24 h in the control group and the other five (5/9) cases of bleeding occurred within in 1–3 days after operation. All bleedings were successfully stopped by cotton ball compression. No serious bleeding occurred in all patients.

Risk factors for postextraction bleeding in patients receiving antithrombotic drugs

Univariate analyses showed that age (OR = 2.717, $p = 0.028$), oral hygiene (OR = 4.110, $p = 0.043$), inferior nerve block (OR = 4.285, p = 0.038) and number of extracted tooth (OR = 4.758, p = 0.029) were significantly correlated with postextraction bleeding (Table 3). Consequently, these parameters were included as explanatory variables in the logistic regression analysis (Table 4). The results showed that age (OR = 2.824, p = 0.036) and number of extracted tooth (OR = 5.268, p = 0.016) were significant risk factors for postextraction bleeding (Table 5).

Discussion

In this study, bleeding events were noted to be more in patients receiving antithrombotic drugs than those who don't, which was consistent with other studies.[4,6] However, the incidence of was 27% in study group, which was higher than that in some studies where the incidence was reported to be 2–26%.[18] The discrepancies on definition of bleeding, condition of patients and medications taken may account for the difference. The incidence in this study was higher due to the sensitivity of definition of bleeding and the results were in accordance with another report which reported the incidence to be 25.7%.[18] Besides, average age of patients in study group was 71.4 and incidence of bleeding in elderly people was noted to be even higher at 32.4% in another study among elderly population.[19]

Table 1 Summary statistics of the patients.

Factor		Study group	Control group	χ^2	*p*-value
Sex	Male	41	48	0.992	0.319
	Female	59	52		
Age	>75 years	38	48	2.04	0.153
	≤75 years	62	52		
BMI	≤24	47	48	0.020	0.887
	>24	53	52		
Oral hygiene	Periodontitis	50	55	2.976	0.084
	Non-periodontitis	50	45		
Anesthesia	Block	29	23	0.936	0.333
	Infiltration	71	77		
Pre-operative antibiotics use	Yes	23	15	1.125	0.289
	No	77	85		
Number	<4	88	82	1.412	0.235
	≥4	12	18		
Granulation	Yes	37	45	1.323	0.250
	No	63	55		
Surgical extraction	Yes	20	30	2.667	0.102
	No	80	70		
Duration of surgery	≤10 min	77	84	1.561	0.212
	>10 min	23	16		
Smoking history	Yes	5	8	0.740	0.390
	No	95	92		
Systematic diseases	Requiring antithrombotic therapy	98/2	0/100	192.157	**<0.01***
	Hypertension	55/45	47/53	1.281	0.258
	Diabetes	22/78	26/74	0.439	0.508

BMI: body mass index; *Fisher's exact test, $p < 0.05$.

Table 2 Bleeding events in the two groups.

Group	Cases			Incidence	*p*-value
	Bleeding	No bleeding	Total		
Study	27	73	100	27.0%	**<0.01***
Control	9	91	100	9.0%	
Total	36	164	200	18.0%	

*Chi-square test, $p < 0.05$.

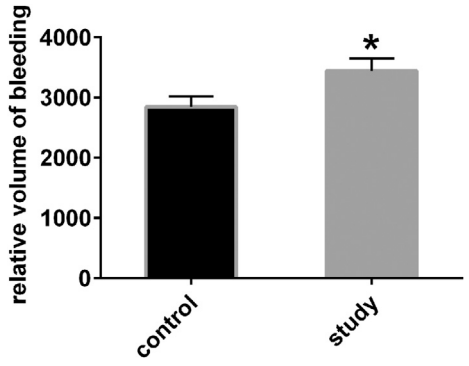

Figure 1 Relative volume of bleeding within 30 min after tooth extraction. *t test, $p < 0.05$.

Several studies had reported the risk factors for bleeding after tooth extraction in patients receiving antithrombotic therapy.[18,20,21] Univariate analyses in this study demonstrated that inferior nerve block and age were significantly correlated with postextraction bleeding. Inferior nerve block was noted to be correlated with bleeding in another study but the authors didn't explain the possible reasons.[21] In the present study, we attributed it to the effect of epinephrine on constricting blood vessels: lidocaine that did not contain epinephrine was used for nerve block anesthesia in the present study, while the articaine used for infiltration anesthesia contained epinephrine, which decreased the incidence of bleeding in patients underwent infiltration anesthesia. In addition, nerve block anesthesia is generally used for the removal of impacted teeth, which means greater trauma and therefore may increase the bleeding rate. Age was also reported to be correlated with postextraction bleeding in the above-mentioned study where the result was contradictory to that in this study.[21] The authors found that mean PT-INR in the patients who experienced clinically significant postextraction bleeding was higher in older patients than that in younger, so they hypothesized that younger patients experienced bleeding at lower PT-INR, which might have contributed to the lower bleeding risks in the elderly patients. However, incidence of bleeding was higher in elder patients in the present study. Few studies reported to date examined the relationship between age and the incidence of bleeding after tooth extraction, but studies in other fields have reported that advanced age is a risk factor for postoperative bleeding,[22–25] which was consistent with the present study. Although patients with diagnosed liver and kidney diseases were excluded in this study, the physiological functions of liver and kidney of the elderly would be weakened with the increase of age,

Table 3 Univariate analysis of postextraction bleeding events by potential risk factors in patients receiving antithrombotic agents.

Factors		Patients receiving antithrombotic agents			χ^2	*p*-value
		Bleeding	No bleeding	Incidence		
Sex	Male	10	31	24.4%	0.240	0.624
	Female	17	42	28.8%		
Age	>75 years	15	23	39.5%	4.838	**0.028***
	≤75 years	12	50	19.4%		
BMI	>24	14	39	26.4%	0.020	0.889
	≤24	13	34	27.7%		
Agents	Anticoagulant	10	19	34.8%	1.160	0.281
	Antiplatelet	17	54	23.9%		
Pre-operative antibiotics use	Yes	9	14	39.1%	2.230	0.135
	No	18	59	23.4%		
Oral hygiene	Periodontitis	18	32	36.0%	4.110	**0.043***
	Non-periodontitis	9	41	18.0%		
Anesthesia	Block	12	17	41.4%	4.285	**0.038***
	Infiltration	15	56	21.1%		
Number	≥4	7	5	58.3%	4.758	**0.029***
	<4	20	68	22.7%		
Surgical extraction	Yes	6	14	30.0%	0.114	0.735
	No	21	59	26.3%		
Granulation	Yes	11	26	29.3%	0.222	0.637
	No	16	47	25.4%		
Duration	>10 min	7	16	30.4%	0.179	0.672
	≤10 min	20	57	26.0%		
Smoking history	Yes	0	5	—	0.772	0.380
	No	27	68	28.4%		
Diabetes	Yes	8	14	36.4%	1.255	0.263
	No	19	59	24.3%		
Hypertension	Yes	16	39	29.1%	0.271	0.603
	No	11	34	24.4%		

BMI: body mass index;*Chi-square test, $p < 0.05$.

Table 4 Assignment of variables for logistic regression analysis.

Variable	Definition	Assignment
X1	Age	1 = >75 years, 2 = ≤75 years
X2	Oral hygiene	1 = periodontitis, 2 = non-periodontitis
X3	Anesthesia	1 = block, 2 = infiltration
X4	Number of tooth	1 = ≥4, 2 = <4
Y	Bleeding	1 = bleeding, 2 = no bleeding

Table 5 Logistic regression analysis.

	B	S.E.	Sig	Exp (B)	95%CI	
					Lower	Upper
Age	1.038	0.494	**0.036***	2.824	1.073	7.434
Number of tooth	1.662	0.692	**0.016***	5.268	1.358	20.437
Anesthesia	0.997	0.513	0.052	2.710	0.991	7.407
Constant	−2.011	0.416	0.000	0.134		

*Logistic regression analysis, $p < 0.05$.

which were related to the coagulation function. In addition, the inferior healing function and increased blood pressure associated with advanced age may also lead to an increased risk of bleeding.

In addition, the results of univariate analysis also showed that oral hygiene status is related to the risk of bleeding after tooth extraction in patients taking anticoagulant/antiplatelet drugs, which is consistent with the previous study: the history of inflammation or acute infection at the tooth extraction site during the surgery was considered to be a risk factor for bleeding after tooth extraction in patients receiving anticoagulation therapy.[20,21,26] Periodontitis is the most common oral inflammation. The clinical manifestations are loss of attachment, bleeding, and bad mouth odor; in an inflammatory state, periodontal soft tissues are congested and edema, fragility increases, and tearing and bleeding are more likely to occur. Periodontitis is also related to cardiovascular system diseases. Studies have reported that periodontal pathogens can enter the cardiovascular system.[27,28] Periodontitis may interfere with the coagulation function of the circulatory system through these ways, but the specific pathogenic mechanism is not clear yet.[29]

The present study demonstrated a significant correlation between the number of extracted teeth and post-surgery

bleeding in the patients undergoing anticoagulant therapy, which was consistent with previous study.[6] Another study reported that extraction of multiple teeth (≥2) was a risk factor for post-extraction bleeding in patients receiving anticoagulation therapy,[18] while the "multiple" in this study was defined to be 4. Studies have shown that trauma can cause increased bleeding rates,[30] thus the severer trauma caused by multiple tooth extractions led to an increased bleeding rate.

Above all, the present study provided clinical evidence to support the consensus that it is safe and feasible for patients taking anticoagulant and antiplatelet drugs to perform tooth extraction without stopping the drug. Age (>75 years), oral hygiene, inferior nerve block and number of extracted tooth were related to higher risk of bleeding after tooth extraction, suggesting special attention should be paid to patients with these risk factors to minimize the occurrence of bleeding events. Of course, prospective experiments with a larger sample size are needed to further explore the risk factors of tooth extraction bleeding in anticoagulant patients.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2021.10.005.

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