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Risk factors associated with post-extraction bleeding in patients on warfarin or direct-acting oral anticoagulants: a retrospective cohort study

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HAS-BLED score

Short title: Post-extraction bleeding in patients taking warfarin or DOACs

Abstract

Purpose

The purpose of this study was to investigate the risk factors associated with post-extraction persistent bleeding in patients on warfarin or direct-acting oral anticoagulants (DOACs) and the ability of risk scores to predict post-extraction bleeding.

Methods

391 patients taking warfarin or DOACs underwent tooth extractions. Various risk factors for post-extraction bleeding, including number of tooth extraction, with antiplatelet therapy, and risk scores, were investigated by univariate and multivariate analyses. A post-extraction bleeding was classified into Grade 1-3.

Results

The incidence of post-extraction bleeding was 26.8% (77 out of 287 patients; Grade 1: 63, Grade 2:14) in patients taking warfarin, and 26.0% (27 out of 104 patients; Grade 1: 20, Grade 2:7) in patients taking warfarin DOACs. Multivariate analyses showed that multiple teeth extractions and HAS-BLED scores (above 3 points) in patients taking warfarin, and only multiple teeth extractions in patients taking DOAC, were significantly associated with post-extraction bleeding, respectively.

Conclusion

Most of the post-extraction bleedings were Grade 1, which can be stopped by eligibly pressing gauze by surgeons. If patients taking anticoagulants are scheduled to undergo multiple teeth extractions or their HAS-BLED score are above 3 points (if warfarin), we recommend informing patients risk of post-extraction bleeding before operation, taking carefully hemostasis, and instruction patients to bite down accurately on the gauze for longer than usual.

1. INTRODUCTION

Tooth extraction of patients taking anticoagulants is currently recommended to be performed without discontinuing anticoagulant therapy, in order to prevent the development of thromboembolisms [1-5]. This recommendation also applies to direct oral anticoagulants (DOACs), and tooth extractions in patients taking those can be performed safely [6,7].

Previous reports have investigated the incidence and risk factors of post-extraction bleeding that required additional treatments such as suturing [8-14], however no reports have focused on the incidence and risk factors of post-extraction bleeding, which cannot be stopped just by patient's biting down on the gauze.

In the cardiovascular field, risk scores are used to evaluate the risk of bleeding in patients taking anticoagulants. The risk scores which are often used are HAS-BLED score, ORBIT score, and ATRIA score. These scores can be obtained from interviews and blood test data [15-17]. However, reports that investigate the relationship between risk scores and post-extraction bleeding in patients taking anticoagulants are rare [18].

In the present study, we retrospectively investigated the risk factors associated with post-extraction persistent bleeding in patients on warfarin or direct-acting oral anticoagulants and the ability of risk scores to predict post-extraction bleeding.

2. PATIENTS & METHODS

2.1.Patients

In this study, inclusion criteria were set as patients above eighteen years old, and exclusion criteria were set as patients who hoped non-participate after the publication of this study. From January 2014 to March 2020, 391 patients taking anticoagulants underwent tooth extraction at Kakogawa Central City Hospital. Before the tooth extraction, all patients consulted their patient's primary physicians regarding their general medical status and the use of anticoagulants. Most patients on warfarin or direct-acting oral anticoagulants are regularly underwent blood test most every month at clinics of primary physicians. The blood test includes some items including coagulation blood test, hemoglobin (Hb), hematocrit (Ht), or estimated glomerular filtration rate (eGFR) to investigate risk scores. We checked these results of blood test which was done within one month before the surgery in all patients. If their prothrombin time-international normalized ratio (PT-INR) was over 3.0, they were advised to postpone the extraction, according to the Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction [19]. All patients underwent coagulation blood tests including INR values on the day of their tooth extractions in order to confirm whether INR values were under 3.0. On the day of extraction, all patients took anticoagulants as usual and surgeons checked

that.

2.2.Surgical procedures

All patients continued anticoagulant therapy and were hospitalized from the day of tooth extraction to the following day. Tooth extraction was performed under local anesthesia, and local anesthesia was administered using 1.8-3.6 mL of 2% lidocaine containing 1/80000 units of epinephrine. The teeth were extracted by a rotation and traction movement with forceps or elevators. If immediate hemostasis was not achieved by dry gauze compression for five minutes, then a hemostatic agent composed of oxidized cellulose (surgical; Ethicon, Somerville, NJ, USA), suturing with 3-0 absorbent thread, or a surgical splint was used at the surgeon's discretion. After confirming hemostasis during tooth extraction, all patients were instructed to bite down on the gauze for a few hours in each hospital room. Preoperative antibiotics were administered in order to all patients to prevent surgical site infection (SSI).

2.3.Post-extraction bleeding

In all patients, the presence of bleeding was checked by surgeons an hour after tooth extraction. Bleedings were classified as Grade 1-3. When bleeding from the extraction

socket was observed, bleeding which can be stopped by eligibly pressing gauze by surgeons, we defined it as Grade 1. If the bleeding required additional treatment such as re-suturing, we defined it as Grade 2. If the bleeding required a systemic treatment such as vitamin K or clotting factor replacement, we defined it as Grade 3.

2.4.Variables

The objective of this study was to investigate risk factors associated with post-extraction bleeding in patients taking anticoagulants. The following variables from medical records were retrospectively reviewed and investigated: (1) patient factors—: gender, age, HAS-BLED score, ORBIT score, ATRIA score, PT-INR, serum creatinine, with antiplatelet therapy (single or dual) , and preoperative NSAIDs; (2) clinical findings factors—: preoperative complaint, number of tooth extractions, and the jaw of tooth extraction; and (3) surgical factors—: surgeon's experience, incision, bone removal, and the use of a hemostatic agent. Moreover, patients taking DOACs were investigated for some patient factors: the type of DOACs (apixaban, edoxaban, dabigatran, or rivaroxaban), prothrombin time (PT), and activated partial thromboplastin time (APTT).

For patient factors, we used three scores— the HAS-BLED score, the ORBIT score

and the ATRIA score. First, the HAS-BLED score assigned points depending on the presence of risk factors: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition (anemia), elderly (>65 years), and a history with drugs or alcohol (Table 1) [20,21]. In patients taking DOACs, 0 points were assigned to labile PT-INR. The ORBIT score was calculated using the following factors: older age (>74 years), reduced Hb or Ht (<40% in men and <36% in women), bleeding history, insufficient kidney function (eGFR <60 mg/dL/1.73m^2), and treatment with antiplatelets (Table 1) [20,21]. Finally, the ATRIA score was calculated using the following factors: anemia, severe renal disease (eGFR <30 mL/min or dialysis-dependent), age≥75 years, any prior bleeding diagnosis, and diagnosed hypertension (Table 1) [20,21].

2.5.Statistical analyses

Statistical analyses were performed using SPSS 26.0 (SPSS, Chicago, IL). The association of each variable with the post-extraction bleeding was analyzed by the non-parametric Mann-Whitney U test for ordinal variables, and either Fisher's exact test or chi-squared test was used for categorical variables. All of the variables associated with post-extraction bleedings were introduced into a multiple logistic regression model. Forward Selection (Likelihood Ratio) of Stepwise selection method was used; variables

that did not fit the model significantly were rejected. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Probabilities of less than 0.05 were considered statistically significant.

3 RESULTS

3.1 Patient factors in patients taking warfarin

Post-extraction bleeding occurred in 77 out of 287 extractions (26.8%); 63 patients had a Grade 1 bleeding and 14 patients had Grade 2 bleeding. No patients had a severe Grade 3 bleeding (Table 2). According to a univariate analysis, there was a significant difference between the occurrence of post-extraction bleeding and HAS-BLED score (Table 2). The multivariate analysis showed that HAS-BLED score above three points (OR: 1.78, 95% CI: 1.01–3.11) was a significant risk factor for the occurrence of post-extraction bleeding (Table 3). Conversely, other scores (the ORBIT score and the ATRIA score) and the antiplatelet therapy did not have statistically significant correlations according to the univariate and multivariate analysis outcomes (Table 2 and 3).

3.2 Clinical findings factors in patients taking warfarin

According to the univariate analysis, the number of tooth extractions and the jaw of tooth extraction had statistically significant correlations to post-extraction bleeding (Table 2). The multivariate analysis showed that multiple teeth extractions in single individuals (OR: 3.65, 95% CI: 1.98–6.74) were significant risk factors for the occurrence of post-extraction bleeding (Table 3).

3.3 Surgical factors in patients taking warfarin

According to the univariate and multivariate analyses, no surgical factors had a statistically significant correlation to post-extraction bleeding (Table 2).

3.4 Patient factors in patients taking DOAC

Post-extraction bleeding occurred in 27 out of 104 extractions (26.0%); 20 patients had Grade 1 bleeding and 7 patients had Grade 2 bleeding. No patient had a severe bleeding of Grade 3 (Table 4). None of scores (HAS-BLED score, ORBIT score and ATRIA score), coagulation factors (PT, PT-INR, and APTT), nor the antiplatelet therapy had statistically significant correlations, according to the univariate analysis outcomes (Table 4).

3.5 Clinical findings factors in patients taking DOAC

According to the univariate analysis, the number of tooth extractions had a statistically significant correlation to post-extraction bleeding (Table 4). A multivariate analysis showed that multiple teeth extractions in single individuals (OR: 3.55, 95% CI: 1.37–9.21) were a significant risk factor in the occurrence of post-extraction bleeding (Table 5).

3.6 Surgical factors in patients taking DOACs

According to the univariate and multivariate analyses, no surgical factors had statistically significant correlations to post-extraction bleeding (Table 4).

3.7 Comparison of patients taking warfarin and patients taking DOACs

No significant differences were found in post-extraction bleeding between two group.

4. DISCUSSION

In the present study, we investigated risk factors associated with post-extraction bleeding in patients taking anticoagulants. In patients taking warfarin, multivariate analyses showed that HAS-BLED score above three points and multiple teeth extractions were significantly correlated with post-extraction bleeding. In the patients taking DOACs, multivariate analyses showed that just multiple teeth extractions in an individual were significantly related to post-extraction bleeding.

In the past, many reports have investigated the post-extraction bleeding of patients taking anticoagulants and reported that the incidence of post-extraction bleeding was 0-26% [8-14]. In the present study, the incidence of post-extraction bleeding was 26.8% (77 out of 287 patients taking warfarin) and 26.0% (27 out of 104 patients taking DOACs), respectively. These results were higher than those reports in other studies. This is because most reports did not include Grade 1 bleeding when studying post-extraction bleeding. The incidence of Grade 2 bleeding was 4.9% (14 out of 287 patients taking warfarin) and 6.7% (7 out of 104 patients taking DOACs), respectively. These results were similar to those of other reports [8-14]. Most of the post-extraction bleedings were Grade 1 in this study. One possible reason for this is that hemostasis by biting down on gauze by the patients themselves was difficult, due to the fact that most of the patients taking

anticoagulants were elderly and had a small number of remaining teeth. Our report suggest that HAS-BLED score may be useful for predicting post-extraction bleeding including Grade 1 in patients taking warfarin.

Univariate and multivariate analyses showed that multiple teeth extractions were a found to be significant predictor of post-extraction bleeding in patients taking warfarin and DOACs (Tables 2-5). In addition, we found that PT-INR was not significant risk factor of post-extraction bleeding when under 3.0, as seen in the univariate and multivariate analyses. Studies have reported that PT was prolonged with -xabans and APTT was responsive to dabigatran [22,23]. Hillarp et al. showed that APTT was also sensitive to the effect of rivaroxaban [24]. In this study, no significant differences were found in post-extraction bleeding between PT and -xabans, nor between APTT and rivaroxaban or rivaroxaban. There were no postoperative cases of thrombosis such as cerebral embolisms in patients taking warfarin and DOACs.

The European Society of Cardiology has proposed that HAS-BLED score above three points indicates a high risk of hemorrhagic complications [25]. In the present study, in both patients taking warfarin and DOACs, the median HAS-BLED score was three points. When patients taking warfarin were compared with the patients with more than three points and those with lower scores, HAS-BLED score above three points was a significant

risk factor of post-extraction bleeding, according to the univariate and multivariate analyses. However, in the patients taking DOACs, a HAS-BLED score above three points was not significantly associated with post-extraction bleeding in both the univariate and multivariate analyses. Kataoka et al. reported that HAS-BLED score could not predict post-extraction bleedings in 258 patients taking warfarin [18]. This may be because this report did not define Grade 1 bleeding as a post-extraction bleeding. If limited to Grade 2 bleeding, there was no significant difference between post-extraction bleeding and the HAS-BLED score in patients taking warfarin in our study.

Our study has limitations. At first, the number of patients taking DOACs was much smaller than the number of patients taking warfarin. In the future, we plan to conduct a multicenter prospective observational study. Next, this study set the upper limit of the INR value 3 point. However, this is still controversial as some dental and maxillofacial associations claim 1.5 the maximum INR value for oral surgery, this is the INR value accepted for the Spanish Society of Oral and Maxillofacial Surgery for instance [26]. Therefore, it may be more ideal to investigate by classification into groups (e.g., one group with patient's INR less than 1.5 and a second group from 1.5 to 3).

In conclusion, this is the first report to investigate the risk factors associated with post-extraction persistent bleeding in patients on warfarin or DOACs and the ability of risk

scores to predict post-extraction bleeding. In the present study, most of the post-extraction bleedings were Grade 1, which can be stopped by eligibly pressing gauze by surgeons. If the patients taking anticoagulants are scheduled to undergo multiple teeth extractions or their HAS-BLED score are above 3 points (only if patients taking warfarin), we recommend the following; informing patients risk of post-extraction bleeding before operation, taking carefully hemostasis by sutures or using hemostatic agent, and instruction patients to bite down accurately on the gauze for longer than usual.

5. Compliance with Ethical Standards

5.1. Funding

No funding received.

5.2. Competing Interest:

The authors declare that they have no competing interest.

5.3. Ethical approval

This retrospective study has been conducted in full accordance with the World Medical Association Declaration of Helsinki and was approved by Ethical Committee of

Kakogawa Central City Hospital approved the study design (authorization number: 2019-84).

5.4. Consent to participate

Not applicable.

5.5. Consent to publish

Not applicable.

5.6. Author's contribution

Study design: E Iwata

Acquisition of data: E Iwata, R Kadoya, Y Enomoto

Analysis and interpretation of data: E Iwata, A Tachibana, M Akashi

Manuscript preparation: E Iwata, A Tachibana, J Kusumoto, T Hasegawa, R Kadoya, Y Enomoto, N Takata, M Akashi

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Statistical analysis: E Iwata, A Tachibana, J Kusumoto, M Akashi

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TABLE AND FIGURE CAPTIONS

Table 1: Components of the three bleeding risk scores

*Presence of chronic dialysis, a renal transportation, or a serum creatinine>2.26mg/dL.

**Presence of chronic hepatic disease (e.g., cirrhosis) or a biochemical abnormality (e.g., bilirubin>2 upper limit of normal, in association with an aspirate aminotransferase/alanine aminotransferase/alkaline phosphatase>3 upper limit of normal).

***Anti-platelets and non-steroidal anti-inflammatory drugs.

****Hb 13g/dL in men and 12g/dL in women.

Table 2: The results of univariate logistic regression analysis of the risk factors for post-extraction bleeding in patients taking warfarin

Values are expressed as absolute numbers, with the corresponding percentage of the total in parentheses. Values in the right-hand column indicate the statistical significance of the difference between subgroups. Age is expressed as the mean ± standard deviation in a parametric ratio scale. In scores and blood test data, the patients were divided into two groups at the median.

*significant

Table 3: The results of multivariate logistic regression analysis of the risk factors for post-extraction bleeding in patients taking warfarin

Data are the p-value, ORs and CIs for those factors found to be significantly associated with an increased risk of post-extraction bleeding.

Table 4: The results of univariate analysis of the risk factors for post-extraction bleeding in patients taking DOACs

Values are expressed as absolute numbers, with the corresponding percentage of the total in parentheses. Values in the right-hand column indicate the statistical significance of the difference between subgroups. Age is expressed as the mean ± standard deviation in a parametric ratio scale. In scores and blood test data, the patients were divided into two groups at the median.

*significant

Table 5: The results of multivariate logistic regression analysis of the risk factors for post-extraction bleeding in patients taking DOACs

Data are the p-value, ORs and CIs for those factors found to be significantly associated

with an increased risk of post-extraction bleeding.

Table 1.

HAS-BLED score

Variable	Points
Hypertension (uncontrolled, >160mmgHg)	1
Abnormal renal*/liver function**	1-2
Stroke (previous history, particular lacunar)	1
Bleeding history or predisposition (anemia***)	1
Elderly (>65 years)	1
Concomitant drugs****/alcohol	1-2

ORBIT score

Variable	Points
Older age (>74 years)	1
Reduced hemoglobin*** or Hct (<40% in men and <36% in women)	2
Bleeding history	2
Insufficient kidney function (eGFR<60mg/dL/1.73m^2)	1
Treatment with antiplatelets	1

ATRIA score

Variable	**Points**
Anemia***	3
Severe renal disease (eGFR <30mL/min or dialysis-dependent)	3
Age≥75years	2
Any prior hemorrhage diagnosis	1
Diagnosed hypertension	1

Table 2.

Variables		Post-extraction bleeding		P value
		Present (n; %)	Absent (n; %)	
Sample size		77 (26.8)	210 (73.2)	
Hemorrhage Grade	Grade 1	63 (81.8)	-	
	Grade 2	14 (18.2)	-	
	Grade 3	0 (0.0)	-	
Gender	Male	47 (61.0)	136 (64.8)	0.581
	Female	30 (39.0)	74 (35.2)	
Age	Mean ± SD	72.1 ± 10.9	73.9 ± 9.2	0.179
HAS-BLED score	< 3 (median)	28 (36.4)	105 (50.0)	0.045*
	≥3	49 (63.6)	105 (50.0)	
ORBIT score	< 2 (median)	32 (41.6)	83 (39.5)	0.787
	≥2	45 (58.4)	127 (50.5)	
ATRIA score	< 3 (median)	39 (50.6)	102 (48.6)	0.791
	≥3	38 (49.4)	108 (51.4)	
PT-INR	Mean ± SD	2.0 ± 0.4	2.0 ± 0.4	0.085
Serum creatinine (mg/dl)	Mean ± SD	1.0 ± 0.5	1.1 ± 1.1	0.231
With antiplatelet therapy	No	58 (75.3)	157 (74.8)	1.000
	Single	18 (23.4)	50 (23.8)	
	Dual	1 (1.3)	3 (1.4)	
Preoperative NSAIDs	No	72 (93.5)	201 (95.7)	0.536
	Yes	5 (6.5)	9 (4.3)	
Preoperative complaint	Severe periodontitis	19 (24.7)	54 (25.7)	0.779
	Apical periodontitis	44 (57.1)	125 (59.5)	
	Deep caries	14 (18.2)	31 (14.8)	
Number of tooth extractions	Mean ± SD	3.2 ± 2.6	2.3 ± 2.0	0.001*
	Single tooth	17 (22.1)	110 (52.4)	<0.001*
	Multiple teeth	60 (77.9)	100 (47.6)	
The jaw of tooth extraction	Upper jaw	25 (32.5)	86 (41.0)	0.020*
	Lower Jaw	25 (32.5)	80 (38.0)	
	Upper and lower jaw	27 (35.0)	44 (21.0)	
Surgeon’s experience	1-5 years	13 (16.9)	53 (25.2)	0.267
	6-10Years	52 (67.5)	133 (63.4)	
	>11 years	12 (15.6)	24 (11.4)	
Incision	No	72 (93.5)	199 (94.8)	0.772
	Yes	5 (6.5)	11 (5.2)	
Bone removal	No	72 (93.5)	196 (93.3)	1.000
	Yes	5 (6.5)	14 (6.7)	

The use of hemostatic agent	No	2 (2.6)	11 (5.2)	0.525
	Yes	75 (97.4)	199 (94.8)	

Table 3.

Variable	P value	Odds ratio	95% CI	
			Lower	Upper
HASBLED score ≥3	0.046	1.78	1.01	3.11
Multiple teeth extractions	<0.001	3.65	1.98	6.74

CI. Confidence interval

Table 4.

Variables		Post-extraction bleeding		P value
		Present (n; %)	Absent (n; %)	
Sample size		27 (26.0)	77 (74.0)	
Hemorrhage Grade	Grade 1	20 (74.1)	-	
	Grade 2	7 (25.9)	-	
	Grade 3	0 (0.0)	-	
Gender	Male	19 (70.4)	46 (59.7)	0.365
	Female	8 (29.6)	31 (40.3)	
Age	Mean ± SD	74.8 ± 8.8	75.4 ± 8.2	0.722
The type of DOACs	Apixaban	5 (18.5)	26 (33.8)	0.128
	Edoxaban	8 (29.6)	13 (16.9)	
	Dabigatran	2 (7.4)	14 (18.2)	
	Rivaroxaban	12 (44.5)	24 (31.1)	
HAS-BLED score	< 3 (median)	10 (37.0)	23 (29.9)	0.484
	≥3	17 (63.0)	54 (70.1)	
ORBIT score	< 2 (median)	11 (40.7)	27 (35.1)	0.646
	≥2	16 (59.3)	50 (64.9)	
ATRIA score	< 2 (median)	10 (37.0)	24 (31.2)	0.636
	≥2	17 (63.0)	53 (68.8)	
PT (s)	Mean ± SD	14.7 ± 3.2	13.9 ± 1.7	0.252
PT-INR	Mean ± SD	1.2 ± 0.2	1.3 ± 0.3	0.199
APTT (s)	Mean ± SD	38.2 ± 10.2	37.7 ± 7.2	0.800
Serum creatinine (mg/dl)	Mean ± SD	1.0 ± 0.4	0.9 ± 0.3	0.142
With antiplatelet therapy	No	21 (77.8)	69 (89.6)	0.186
	Single	5 (18.5)	7 (9.9)	
	Dual	1 (3.7)	1 (0.5)	
Preoperative NSAIDs	No	27 (100.0)	75 (97.4)	1.000
	Yes	0 (0.0)	2 (2.6)	
Preoperative complaint	Severe periodontitis	4 (14.8)	8 (10.4)	0.794
	Apical periodontitis	18 (66.7)	52 (67.5)	
	Severe caries	5 (18.5)	17 (22.1)	
Number of tooth extractions	Mean ± SD	2.7 ± 1.6	2.2 ± 1.9	0.179
	Single tooth	7 (25.9)	40 (51.9)	0.025*
	Multiple teeth	20 (74.1)	37 (48.1)	
The jaw of tooth extraction	Upper jaw	8 (29.6)	33 (42.9)	0.287
	Lower Jaw	11 (40.8)	31 (40.3)	
	Upper and lower jaw	8 (29.6)	13 (16.8)	
Surgeon’s experience	1-5 years	7 (25.9)	21 (27.3)	0.949

	6-11 Years	17 (63.0)	46 (59.7)	
	>11 years	3 (11.1)	10 (13.0)	
Incision	No	26 (97.1)	75 (97.4)	1.000
	Yes	1 (2.9)	2 (2.6)	
Bone removal	No	25 (92.6)	75 (97.4)	0.276
	Yes	2 (7.4)	2 (2.6)	
The use of hemostatic agent	No	1 (3.7)	2 (2.6)	1.000
	Yes	26 (96.3)	75 (97.4)	

Table 5.

Variable	P value	Odds ratio	95% CI	
			Lower	Upper
Multiple teeth extractions	0.009	3.55	1.37	9.21

CI. Confidence interval