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Postextraction bleeding in patients taking warfarin: Focus on the utility of the HAS-BLED score: a retrospective cohort study

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ABSTRACT

Objective: Post-extraction bleeding is often experienced in our clinical unexpectedly. Therefore, this study aimed to clarify the risk factors for bleeding after tooth extraction in patients taking warfarin and to verify whether the HAS-BLED score is useful in predicting post-extraction bleeding.

Design: Retrospective cohort study.

Setting: Department of Oral and Maxillofacial Surgery, Tokyo Women's Medical University.

Participants: Subjects comprised 258 sequential cases (462 teeth) of inpatients who had undergone tooth extraction between January 1, 2010 and December 31, 2012 while continuing anticoagulant therapy.

Main outcome measure: Post-extraction risk factors of bleeding. As predicting variables of multivariate logistic analysis, extraction site, teeth type, stability of teeth, and extraction procedure, PT-INR value, platelet count, HAS-BLED score, concomitant antiplatelet agents use were collected.

Results: Post-extraction bleeding was noted in 21 (8.1%) of the 258 cases. The risk of post-extraction bleeding for wisdom teeth extraction was approximately seven times more than that for incisor teeth (RR = 6.894; P = 0.027, univariate analysis). The HAS-BLED score was insufficient for predicting post-extraction bleeding (AUC = 0.548, P = 0.867, multivariate analysis). The risk of post-extraction bleeding was approximately three times more for patients taking oral antiplatelet agents (RR = 2.881, P = 0.035, multivariate analysis).

Conclusions: The HAS-BLED score alone was insufficient to predict post-extraction bleeding. The concomitant use of oral antiplatelet agents is a risk factor for post-extraction bleeding. However, because this was a retrospective study conducted at a single institution, we believe that a large-scale prospective cohort study, including outpatient tooth extraction cases, will be

necessary in the future.

Strengths and limitations of this study

- We investigated all cases of tooth extraction, including wisdom tooth and impacted tooth extractions.
- No previous reports have investigated the effects of each individual tooth extracted, extraction procedure, and effects of concomitant antiplatelet agents on post-extraction bleeding using statistical analyses and demonstrated a high level of evidence for correlations.
- This is the first study to verify the usefulness of the HAS-BLED score for predicting post-extraction bleeding risk.
- Because this is a retrospective cohort study conducted at a single institution, a large-scale, prospective cohort study including outpatients is required in the future.

INTRODUTION

In western countries, patients undergoing anticoagulant therapy and who are scheduled to undergo tooth extraction are typically advised to undergo extraction while continuing anticoagulant therapy [1,2]. In Japan, guidelines, such as the "Guidelines for management of anticoagulant and antiplatelet therapy in cardio-vascular disease [3]" as well as the JCS Joint Working Group's "Guidelines for Pharmacotherapy of Atrial Fibrillation [4]" recommend that tooth extraction be performed while continuing anticoagulant therapy. Performing tooth extraction without temporarily discontinuing or reducing the dosage of anticoagulants offers a significant advantage of preventing the onset of potentially fatal thromboembolism [5]. However, there is an additional risk of bleeding due to the invasive treatment, and thus, sufficient measures must be taken to stop excessive post-extraction bleeding; furthermore, care must be taken to limit post-extraction bleeding. In the past, a number of studies have investigated tooth extraction while continuing anticoagulant therapy, with the frequency of post-extraction bleeding reported to range from 0% to 26% [6-17]. As each study involved significant differences in patient backgrounds (e.g., subjects including simple extraction cases only or differing prothrombin time-international normalized ratio (PT-INR) ranges), simple comparisons of post-extraction bleeding rates across different studies have limited value. Furthermore, anticoagulant therapy is known to be effective in Japanese people because they are highly sensitive to warfarin potassium

(hereinafter: "warfarin") [18]. For example, although the recommended range for PT-INR in cases of valvular heart disease is 2.0–3.0, a slightly less intense treatment range is set for Japanese patients (1.6–2.8) [3,4]. Accordingly, it appears inappropriate to compare the results of reports of patients in western countries, which are likely to include more cases of PT-INR treatment levels of 3.0 or above, with those of patients in Japan. Moreover, as is the case with warfarin, it is recommended to perform tooth extraction on patients taking antiplatelet agents at the maintenance antiplatelet therapy dose[19,20]. However, the effects of taking warfarin and antiplatelet agents on post-extraction bleeding are unclear.

Recently, the HAS-BLED score[21-23] has been used as an index for evaluating the risk of bleeding complications in patients undergoing anticoagulant therapy. The HAS-BLED score evaluates nine risk factors for bleeding. The European Society of Cardiology guidelines[24] has stated that patients who score three points or higher are at a high risk of bleeding complications. No reports to date have investigated whether the HAS-BLED score is useful in predicting the risk of post-extraction bleeding.

The preoperative identification of patients with a high risk of post-extraction bleeding could facilitate appropriate preparations prior to performing tooth extraction. Therefore, we examined post-extraction bleeding risk factors in patients undergoing anticoagulant therapy with PT-INR treatment at levels of ≤3.0 and who underwent tooth extraction, including extraction of wisdom or impacted teeth, and additionally investigated whether the HAS-BLED score is useful in predicting post-extraction bleeding.

MATERIAL AND METHODS

Study design

This was a retrospective cohort study.

Study population and eligibility criteria

This study included patients who were hospitalized at the Department of Oral and Maxillofacial Surgery, Tokyo Women's Medical University and who had undergone tooth extraction between January 1, 2010 and December 31, 2012 while receiving a maintenance dose of anticoagulant therapy. As a rule, tooth extraction for patients undergoing anticoagulant therapy shall be performed after the patient is admitted to the hospital. Antiplatelet agents, which were being

concomitantly taken, were continued to be administered at the maintenance dose. Exclusion criteria were as follows: 1) patients younger than 20 years at the time of hospital admission; 2) presence of comorbid blood disease; and 3) a PT-INR level of ≥3.1 as indicated by the results of the blood tests performed on the day of tooth extraction. Patients underwent follow-up examinations for 1 month after discharge. The physician and nurse records obtained from medical examination records were registered in a database along with the results of the clinical tests. When the same patient was hospitalized and underwent tooth extraction more than once during the study period, all instances were registered.

Tooth extraction procedure

The primary physician for the underlying disease of each patient was preoperatively consulted regarding the general medical status of the patient, including their use of anticoagulants. When acute symptoms, such as periodontal abscesses, apical periodontitis, or pericoronitis were present around the tooth that was determined to be eligible for tooth extraction, antibacterial drugs were administered prior to tooth extraction and anti-inflammation procedures, such as incision and drainage, were performed as necessary. During tooth extraction, electrocardiograms, blood pressure, pulse rate, and percutaneous oxygen saturation levels were monitored. For local anesthesia, 1.8–3.6 ml of 2% lidocaine containing 1/80000 epinephrine was administered. Tooth extraction was performed with minimal invasion. When multiple teeth were indicated for extraction and comprised within 1/3 of the jaw area, all the teeth were extracted in one procedure. When the teeth comprised over 1/3 of the total jaw area, multiple teeth were extracted in one procedure if the procedure was expected to take <30 min while considering the age and any comorbid diseases of the patient. After extraction, a curettage of the inflammatory granulation tissue around the wound border was performed, hemostatic gelatin sponge was inserted into the socket (product name: Spongel, Astellas Pharma Inc.), and suturing was performed to reduce the size of the wound border. The patient was requested to bite down on the absorbent cotton for 20 min after completing tooth extraction to achieve pressure hemostasis. At 30 min after tooth extraction, the patient was examined to confirm that the bleeding had stopped. After extraction, patients were instructed to avoid strong or frequent gargling and to rest as much as possible. Post-extraction meals comprised rice gruel. In the patient group with a high risk of adverse effects due to effective endocarditis onset [25], 2 g ampicillin was administered 30 min prior to

tooth extraction, and 1 g ampicillin was intravenously administered 6 h after the initial dose. Patients who were allergic to penicillin were intravenously administered 600 and 300 mg clindamycin 30 min before tooth extraction and 6 h after the initial dose, respectively. For patients with a heart disease that did not necessarily require IE prophylaxis for dental procedures or patients receiving anticoagulant therapy, oral antibacterial drugs (750–1000 mg/day amoxicillin, 300 mg/day cefditoren pivoxil, 300 mg/day cefcapene pivoxil, and 500 mg/day levofloxacin) were administered for 3 days following tooth extraction. Five doses of analgesics comprising loxoprofen sodium or acetaminophen were prescribed as a potion when pain was experienced.

Post-extraction Bleeding

Patients who complained of bleeding during the examination 30 min after tooth extraction and who underwent some sort of hemostatic procedure were categorized in the post-extraction bleeding group. Hemostatic procedures performed in accordance with the decisions by the examining physician are described below. For mild bleeding, the patient was requested to bite down on a gauze or absorbent cotton placed on the tooth extraction wound to achieve pressure hemostasis. For cases of moderate or higher bleeding in which there was a large amount of bleeding that was determined to be difficult to resolve using primary hemostasis, we aimed to utilize the local vasoconstrictive effects of the local dental anesthetic epinephrine and administered a dose of 1.0–1.8 ml to achieve infiltration anesthesia around the tooth extraction wound. Pressure was then applied to the wound by requesting the patient to bite down on gauze or absorbent cotton. When it was determined that the bleeding could not sufficiently be halted by pressure hemostasis alone, the area was additionally filled with local hemostatic agents or additional or repeat suturing of the wound was performed as necessary. For cases of repeated bleeding or prolonged exudative bleeding after hemostatic procedures, a hemostatic splint was fabricated to apply continuous pressure on the wound and to allow the patient to rest. This was fitted after applying a cavity lining with a periodontal pack or denture base tissue conditioner. For cases in which the patient complained of bleeding and was examined but hemostatic procedures were not deemed necessary, patients were instructed to adequately rest and refrain from excessive gargling; regular follow-up examinations were performed. These patients were not included in the post-extraction hemorrhage group. Patients who did not require treatments,

such as those outlined above for after bleeding, were placed into the non-post-extraction hemorrhage group.

Bleeding risk factors for tooth extraction

Details of extracted teeth, surgical procedure, bleeding tendency, and concomitant antiplatelet agents were investigated as possible factors affecting post-extraction bleeding. With respect to details noted regarding extracted teeth, the extraction site (maxilla/mandible), type of teeth (incisor/premolar/molar/wisdom), and stability of teeth were examined. Regarding the stability of teeth, teeth exhibiting alveolar bone resorption of at least 2/3 of the tooth root length as determined by preoperative X-rays or teeth found to have clinical grade III instability were defined to have poor stability. Other teeth were considered to have good tooth stability. The surgical procedure was classified into simple and surgical extractions. For surgical extraction, the strategy followed was to make an incision in the gingiva, detach and turn the mucoperiosteal flap over, and extract the tooth after cutting off the alveolar bone or root separation. All extractions other than that defined above were simple extractions. With regard to bleeding tendency, PT-INR value and platelet count were investigated.

HAS-BLED score

The HAS-BLED score was evaluated according to the European Society of Cardiology guidelines [24] (Table 1) and is described below. Patients with systolic blood pressure of ≥160 mmHg, which was measured on arrival at the hospital, were categorized as having "hypertension." Patients receiving hemodialysis or those who had a kidney transplant; patients with a serum creatinine level of ≥2.26 mg/dl in the most recent blood test; patients exhibiting chronic liver disease, such as liver cirrhosis, and bilirubin levels of at least two times the normal upper limit; and patients having at least three times the normal upper limit of either alanine transaminase, aspartate aminotransferase, or alkaline phosphatase levels were categorized as having "abnormal renal and liver function." "Stroke" or "bleeding" was determined according to the information of patients obtained from medical interviews on admission to the hospital. "Labile INRs" were described as being in a poorly controlled anticoagulation state in cases, such as directly after initiating anticoagulant therapy or during poor compliance, and additionally during detection of a level of PT-INR ≥ 3.1 on the morning of tooth extraction. The "elderly"

categorization was defined as a patient age ≥65 years at the time of tooth extraction. Patients with long-term administration of antiplatelet agents or non-steroidal anti-inflammatory drug (NSAIDs) or patients with alcohol dependence were categorized as "drug and alcohol." One point was allocated for each of these categories if a patient was applicable. Thus, patients were scored according to a possible full score of nine points.

Selection of representative teeth

One representative tooth was selected when the same patient underwent extraction of multiple teeth. However, when the same patient underwent multiple tooth extraction operations during different hospitalization periods, representative extracted teeth were selected for each instance. The most posterior tooth was selected as the representative tooth, and in cases of multiple posterior teeth, the upper tooth or the tooth showing good stability was selected.

Statistical analyses

Univariate and multivariate logistic analysis were applied to analyze the bleeding risk factor for tooth extraction data with the presence/absence of post-extraction bleeding as the response variable and bleeding risk factor as the explanatory variable. The two variable values were used to describe tooth extraction site (maxilla/mandible), four variable values were used to describe the type of teeth (incisor/premolar/molar/wisdom), two variable values were used to describe stability of teeth (good/poor), and two variable values were used to describe the surgical procedure (simple /surgical extraction). For the PT-INR value and platelet count, the actual measured values were analyzed as continuous variables, and the HAS-BLED score was used in analysis with both a continuous and nominal variable. Concomitant antiplatelet agents were evaluated as two variable values (yes/no). During logistic analysis, we calculated the risk ratio, 95% confidence interval (CI), and p value. The risk ratio was calculated as the ratio of maxilla to mandible for a site, the tooth type within anterior teeth for type of teeth, good to poor for the condition of the periodontium, and from surgical to simple for the surgical procedure. The risk ratio for the HAS-BLED score was calculated for each level. For concomitant antiplatelet agents, the risk ratio of "yes" to "no" was calculated. In multivariate analysis, risk factors were combined to create post-extraction bleeding analysis models. For each model, we plotted the receiver operating characteristic (ROC) curve and calculated the area under the curve (AUC) in

addition to the p value and 95% CI for the C-statistic model overall. Many screening tools used a C-statistic value of ≥0.70. We used C-statistic to compare between each model. Model 1 was constructed from extracted tooth state, surgical procedure, and bleeding tendency. Model 2 was constructed from the HAS-BLED score only. Model 3 was constructed by adding the HAS-BLED score to Model 1. Model 4 was constructed by adding concomitant antiplatelet agents as an explanatory variable to Model 1. Data were analyzed with the use of JMP Pro 11 software (2014 SAS Institute Inc., US) with a two-tailed alpha level of 0.05.

Ethics

This study was approved by the ethical review board of the Tokyo Women's Medical University (approval number: 3079). The first and second authors take complete responsibility for the integrity of the data and the accuracy of the data analysis.

RESULTS

A total of 462 extracted teeth in 258 patients (males: 157, females: 101, mean age: 66.4 years) were analyzed. Post-extraction bleeding was observed in 21 patients (8.1%).

Patient characteristics

Post-extraction bleeding was noted in 21 patients (males: 14, females: seven, mean age: 63.4 ± 13.2 years). Table 2 shows the underlying diseases for anticoagulant therapy. Mean warfarin dosage was 3.9 ± 1.4 mg, and median PT-INR was 2.1 (1.8–2.5). Mean platelet count was $16.8 \pm 5.3 \times 10^4/\mu l$. Eleven patients were taking only warfarin, whereas 10 were taking an antiplatelet agent in addition to warfarin. Aspirin was administered as the antiplatelet agent to all cases.

The non-post-extraction hemorrhaging group included 237 patients (males: 143, females: 94, mean age: 66.6 ± 13.7 years). Underlying diseases for anticoagulant therapy are shown in Table 2. Mean warfarin dosage was 3.2 ± 1.3 mg. The mean (25 percentile, 75 percentile) of PT-INR was 2.0 (1.8, 2.3). Mean platelet count was $18.2 \pm 5.8 \times 10^4/\mu l$. A total of 174 patients were taking warfarin only, whereas 63 patients were taking warfarin and an antiplatelet agent. Table 2 shows a breakdown of the antiplatelet agents. Seven patients who were taking two types of antiplatelet agents were all included in the non-post-extraction hemorrhaging group. A statistically significant difference was noted for warfarin dosage; however, no difference was

noted for PT-INR. No differences were noted for age, sex, platelet count, or concomitant use of antiplatelet agents.

Details of extracted tooth

In the post-extraction hemorrhaging group, the tooth extraction site in 14 and seven cases was the maxilla and mandible, respectively. For the non-post-extraction hemorrhaging group, it was the maxilla and mandible in 122 and 115 cases, respectively. Thus, no differences were noted between the two groups ($P = 0.254$, Fisher's exact test).

Results for teeth type

Numbers of incisor:premolar:molar:wisdom teeth were 1:2:9:9, respectively, in the post-extraction hemorrhaging group and 36:65:89:47, respectively, in the non-post-extraction hemorrhaging group. Thus, a statistically significant difference was noted between the two groups ($P = 0.039$, Fisher's exact test).

In the post-extraction hemorrhaging group, the stability of teeth was good in 17 cases and poor in four. In the non-post-extraction hemorrhaging group, stability was good in 158 cases and poor in 79. No statistically significant difference was noted between the two groups ($P = 0.227$, Fisher's exact test).

Extraction procedure

In the post-extraction hemorrhaging group, the extraction procedure selected was simple extraction in 17 cases and surgical extraction in four cases. In the non-post-extraction hemorrhaging group, the procedure selected was simple extraction in 165 cases and surgical extraction in 72 cases. No differences were noted between the two groups ($P = 0.328$, Fisher's exact test).

Number of teeth extracted per operation

The number of teeth extracted per operation was 1.7 ± 0.6 in the post-extraction hemorrhaging group and 1.8 ± 1.1 in the non-post-extraction hemorrhaging group. There were no cases of multiple extractions of four or more teeth in the post-extraction hemorrhaging group. No differences were noted between the two groups with regards to the number of teeth extracted per operation ($P = 0.576$, Student's t-test).

HAS-BLED score

The highest HAS-BLED score obtained was three points. The mean score was 1.3 ± 0.9 in the

post-extraction hemorrhaging group and 1.2 ± 0.8 in the non-post-extraction hemorrhaging group. No statistically significant differences were noted between the two groups ($P = 0.467$, Student's t-test). In both the post-extraction and non-post-extraction hemorrhaging groups, scores were highest for the "elderly" group, followed by the "drug and alcohol" group, and then the "stroke" group.

Statistical examination

Univariate analysis demonstrated statistically significant differences between the wisdom teeth and incisor (RR = 8.894, $P = 0.027$) and for between concomitant antiplatelet agents (yes/no) (RR = 2.511, $P = 0.500$). RR was ≤1 for surgical procedure and platelet count. No statistically significant difference was noted for a HAS-BLED score of ≥3 compared with a HAS-BLED score of ≤2 (RR = 1.362, $P = 0.7033$).

No statistically significant differences were noted within multivariate analysis for any of the parameters in the models 1, 2, or 3. In Model 4, a statistically significant difference was noted for antiplatelet agents (yes) in the non-post-extraction hemorrhaging group (RR = 2.881, $P = 0.035$). AUCs for models 1, 3, and 4 were 0.7, with a statistically significant difference noted in Model 4 only. AUC for Model 2 was the lowest at 0.5, and a statistically significant difference was noted between models 2 and 3 ($P = 0.004$).

Discussion

Many cases of tooth extraction performed while continuing anticoagulant therapy have been reported; tooth extraction may be performed while the patient continues the maintenance dose of anticoagulants if PT-INR is within the treatment range (PT-INR < 3.5–4.0) and local hemostasis is properly performed [26-28]. The optimal treatment range for warfarin in Japanese patients is considered to be PT-INR in a range of 1.6–3.0[4], and it is recommended that tooth extraction be performed while continuing the maintenance dose of anticoagulants. However, in clinical settings, it is not uncommon to encounter post-extraction hemorrhaging during tooth extraction in cases of PT-INR ≤ 3. Iwabuchi et al.[29] reported through a multicenter, large-scale study that risk factors for post-extraction bleeding in patients taking warfarin were age, PT-INR, and inflammation at the extraction site. Although many reports to date have not included cases of surgical extraction, such as the extraction of wisdom teeth and impacted teeth, these types of surgical extraction are often performed within clinical settings. Therefore, this study targeted

cases that were managed according to the optimal treatment range for Japanese patients (PT-INR ≤ 3.0) and investigated all cases of tooth extraction, including the extraction of wisdom teeth, impacted teeth, and multiple teeth concurrently. Our investigation of risk factors for bleeding included extracted tooth state and surgical procedure. The HAS-BLED score is used in the field of cardiology to evaluate the risk of hemorrhagic complications. We verified whether the score is additionally useful for the evaluation of post-extraction hemorrhaging risk.

We have many patients receiving anticoagulant therapy because of circulatory diseases at our facility. As a rule, tooth extraction is performed on an inpatient basis because preoperative antibacterial agent administration and monitoring of post-invasive procedures are necessary. Approximately 50% of patients in this study had undergone heart valve replacement surgery prior to tooth extraction.

Our investigation of 258 tooth extraction patients indicated that post-extraction bleeding occurred in 21 patients (8%) or in 39 of the total 462 extracted teeth (8.4%). Various methods of hemostasis have been reported for cases of tooth extraction performed while continuing anticoagulant therapy. These include pressure hemostasis only, wound suturing, and the application of local hemostatic agents [30–33]. To implement hemostasis, we placed a hemostatic gelatin sponge in the extraction socket and routinely conducted pressure hemostasis using absorbent cotton with suturing of the wound. Patients were examined 30 min after tooth extraction to confirm whether the bleeding had stopped. Hemostasis was determined to have been sufficient for all cases. As all patients underwent tooth extraction on an inpatient basis, the patient could rapidly be examined by a physician or nurse and could receive early diagnosis and appropriate treatment if post-extraction bleeding was suspected. However, although patients were examined, many did not require hemostatic treatment. Of the patients who exhibited post-extraction bleeding, no systemic hemostatic treatment, such as blood transfusion, was required in any case.

Investigation of conditions of the individual teeth extracted indicated that post-extraction bleeding risk was five to six times higher for wisdom teeth compared with that for anterior teeth. Extraction site and stability had little effect. Although no differences were observed for the number of teeth extracted in one treatment, there were no cases of multiple extractions of four teeth or more in the post-extraction hemorrhaging group. Results indicated that surgical extraction hardly had any effect on post-extraction bleeding (RR = 0.539, $P = 0.256$). However,

because cases that we defined as invasive tooth extraction also included many cases showing a short tooth root remaining , we believe that this may have greatly affected the results.

The effects of warfarin are easily influenced by factors, such as interaction with meals and/or drugs, and additionally by the general state of the patient. In this study, to accurately determine the anticoagulation state directly before tooth extraction, all blood tests were performed before breakfast on the tooth extraction day or the first tooth extraction day if tooth extraction was planned on consecutive days. Although post-extraction bleeding cases were being administered high doses of warfarin, no difference was observed for PT-INR. There were no cases showing an unstable anticoagulation state directly after warfarin introduction or with poor compliance. Because cases of PT-INR > 3.1 were excluded on the basis of the eligibility criteria, no cases were classified as labile INRs according to the HAS-BLED score. Accordingly, the PT-INR value was investigated using actual measured values as the continuous variable. There were no statistically significant differences noted for PT-INR values by either univariate or multivariate analysis ($P \geq 0.1$), suggesting that the PT-INR value had little effect on post-extraction bleeding in patients undergoing anticoagulant therapy while being managed within the optimal treatment range (PT-INR ≤ 3.0).

The HAS-BLED score is used in the field of cardiology to evaluate the risk of hemorrhaging in patients showing good anticoagulation. As it would be highly significant if the HAS-BLED score could be additionally used for predicting the risk of post-extraction hemorrhaging, we evaluated its use in this study. In our study, the highest HAS-BLED score was three points. A score of one point was the most commonly achieved among the 137 patients (53%). The most common risk factor was found to be age (174 patients; 67%). No difference was noted for the mean HAS-BLED score between the post-extraction hemorrhaging and non-post-extraction hemorrhaging groups. The European Society of Cardiology has proposed that a score of HAS-BLED ≥ 3 indicates a high risk of hemorrhagic complications. In cases of post-extraction hemorrhaging, we compared patients with a HAS-BLED score of three or higher and those with a score of two or lower but did not detect any statistically significant difference (univariate analysis; RR = 1.362, $P = 0.703$). Multivariate analysis indicated that there was little risk associated with the score increasing by one (Table 6). AUC for HAS-BLED score alone (Model 2) was 0.55, which was the lowest for all of the models we constructed. In Model 3, to which the details of extracted teeth were added to the HAS-BLED score, AUC was 0.745, suggesting that this model is useful

for predicting post-extraction bleeding. However, a statistically significant difference was noted for Model 2 versus Model 3 ($P = 0.004$), indicating that the HAS-BLED score alone was insufficient for predicting post-extraction bleeding.

No fixed consensus has been reached regarding the concomitant use of warfarin and antiplatelet agents because some reports have indicated that this increases the risk of post-extraction bleeding [1,34], whereas other reports have suggested that antiplatelet agents have little effect [35]. Both of our univariate and multivariate analyses results indicated that the use of concomitant antiplatelet agents was a significant factor affecting post-extraction bleeding. Of the models that we created in this study, Model 4 exhibited the highest predictive ability for post-extraction bleeding (AUC = 0.76, $P = 0.0309$). It has been reported that the concomitant use of two antiplatelet agents significantly increases the frequency of intracranial hemorrhaging [36]. Furthermore, a prospective observational study of hemorrhagic complications in Japanese cerebral infarction patients [37] found that compared with patients taking one antiplatelet agent only; those taking two or three antiplatelet agents along with warfarin clearly exhibited higher annual onset rates of intracranial hemorrhaging. We believe that these results suggest that concomitant antiplatelet agents are a risk factor for post-extraction bleeding.

The limitations of this study included the fact that data were obtained only at a single facility and that outpatients were not included in the subjects investigated. Many patients treated at our facility suffer from circulatory diseases (post-operative valve replacement patients are particularly common). Furthermore, because our study excluded patients who exhibited PT-INR of ≥3.1 during the blood testing performed on the day of tooth extraction, the current study included patients whose anticoagulant therapy was being well managed. Thus, our subjects did not exactly constitute generalized cases of tooth extraction patients taking warfarin. Moreover, because this was a retrospective study, we believe that a large-scale, prospective, cohort study including outpatient tooth extraction cases required to be conducted in the future.

Moreover, we could not examine the drug interaction effects because our subjects included both patients who intravenously received antibacterial agents and those who received oral administration. Warfarin use results in a number of drug interactions, and many antibacterial agents and NSAIDs have been reported to increase anticoagulant effects [38]. However, some reports have stated that in most stable anticoagulant therapy patients, exposure to antibacterial agents causes no clinical problems [39]; furthermore, other reports have found that NSAIDs and

antibacterial agents often increased warfarin effects in cases of long-term administration [17]. We also believe that the short-term or low-dose administration of NSAIDs or antibacterial agents does not cause any prolongation of clinically problematic PT-INR.

Of the models used for our multivariate analysis, Model 4 exhibited the highest AUC, demonstrating that it could predict post-extraction bleeding. However, because there were no significant differences observed between Model 1 or 3 versus Model 4, we were unable to construct an optimal model for predicting post-extraction bleeding. To increase model precision, it may be optimal to add factors demonstrating surgeon skill (e.g. years of surgeon experience or time required for one tooth extraction), which were not included in our current investigation. Furthermore, it will be necessary to put all extraction data from outpatients into analysis set to conduct a multilevel analysis.

CONCLUSIONS

1. We investigated post-extraction bleeding risk factors for all types of tooth extraction, including wisdom teeth and impacted teeth in patients taking warfarin (PT-INR $\leq$ 3.0). Post-extraction bleeding requiring hemostatic treatment was observed in 8% patients.
2. The risk of post-extraction bleeding was five to six times more for the wisdom teeth than that for the incisor teeth.
3. Post-extraction bleeding could not be predicted using the HAS-BLED score alone.
4. Concomitant use of antiplatelet agents is a risk factor for post-extraction bleeding. More care must be taken regarding post-extraction bleeding within these cases than in cases with the administration of warfarin alone.

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Contributors

TA and TK were involved in the planning of the study concept and design. TK wrote the drafting of the manuscript. KH and TK were involved in the statistical analysis. TA and TK reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

The authors have no conflicts of interest to declare regarding this study.

Data sharing statement

No additional data are available.

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Table 1 HAS-BLED bleeding risk score		
	risk factor	clinical characteristics
H	Hypertension	uncontrolled, >160mmHg systolic
A	Abnomal renal and liver function (1point each)	presence of chonic dialysis, renal pramsplantation or serum creatinine ≧200 μmol/L
		chornic hepatic disease(eg, cirrhosis), bilirubin >2X upper limit of nomal,
		AST/ALT/ALP >3X upper limit of nomal
S	Stroke	previous history
B	Bleeding	bleeding history or predisposition
L	Labile INRs	unstable/high INRs (PT-INR>3.1)
E	Elderly	>65 years
D	Drugs or alcohol (1point each)	concomitantly antiplatelet agents and NSAIDs,
		alcohol excess
Criteria from the European Society of Cardiology[24] were used.		
AST=aspartate aminotransferase, ALT=alanine aminotransferase, ALP=alkaline phosphatase,		
NSAIDs=nonsteroidal antiinflammatory drugs		

Table 2 Clinical profile

	post-extraction bleeding group	non post-extraction bleeding group	p value		X^2 value
	N=21	N=237			
	number of patients	number of patients			
Age (mean ± SD)	63.4±13.2	66.6±13.7	0.2944[a]		
Gender(Male/Female)	14/7	143/94	0.6463[c]		0.32
Primary disease					
post Heart Valve Prosthesis Implantation	17	120			
atrial fibrillation	2	76			
cerebral infarction	2	13			
dilated cardiomyopathy	1	9			
myocardial infarction	0	23			
deep vein thrombosis	0	11			
arteriosclerosis obliterans	0	3			
intracardiac thrombus	0	2			
Anticoagulation					
warfarin dose(mg) (mean ± SD)	3.9±1.4	3.2±1.3	0.0241[a]	*	
PT-INR value (mean［25%tile, 75%tile］)	2.1[1.8, 2.5]	2.0[1.8, 2.3]	0.3296[b]		
Platelet count($\times 10^4/\mu l$)	16.8±5.3	18.2±5.8	0.2978[a]		
Concomitant antiplatelet agents					
yes	10	63	0.0732[c]		4.21
aspirin	10	52			
ticlopidine	0	8			
ethyl icosapentate	0	6			
cilostazol	0	2			
limaprost	0	1			
dipyridamole	0	1			

SD:standard deviation, Multiple factors possible for underlying disease,

All seven patients using two types of antiplatelet agents were included in the non-post-extraction hemorrhaging group.

a; Student's t-test, b:Mann-Whitney U test, c:Fisher's exact test

*:$p < 0.05$ was considered significant.

Table 3 Situation of extracted teeth					
	post-extraction bleeding group	non post-extraction bleeding group	p value		X^2 value
	N=21	N=237			
	number of patients or mean ± SD	number of patients or mean ± SD			
Extraction site					
maxilla	14	122	0.254[c]		1.79
mandibula	7	115			
Teeth type					
incisor	1	36	0.039[c]	*	8.70
premolar	2	65			
molar	9	89			
wisdom	9	47			
Stability of teeth					
good	17	158	0.227[c]		1.80
poor	4	79			
Extraction procedure					
simple	17	165	0.328[c]		1.19
surgical	4	72			
Number of teeth extracted in one procedure	1.7 ±0.6	1.8 ±1.1	0.576[a]		
One tooth	8	125	0.188[c]		9.12
Two tooth	12	65			
Three tooth	1	24			
Four tooth	0	18			
Five tooth	0	3			
Six tooth	0	1			
Seven tooth	0	1			
SD:standard deviation,					
a; Student's t-test, c;fisher's exact test					
*:p〈0.05 was considered significant.					

Table 4 HAS-BLED score					
	post-extraction bleeding group N=21	non post-extraction bleeding group N=237	p value		X^2 value
	mean ± SD or number of patients	mean ± SD or number of patients			
HAS-BLED score	1.3±0.9	1.2±0.8	0.467[a]		
0	3	41	0.804[c]		0.75
1	10	127			
2	6	52			
3	2	17			
4	0	0			
5	0	0			
6	0	0			
7	0	0			
8	0	0			
9	0	0			
risk factor					
H	1	3			
A	1	11			
S	2	38			
B	0	5			
L	0	0			
E	13	161			
D	11	63			
SD:standard deviation,					
a; Student's t-test, c;Fisher's exact test					

Table 5 Univariate analysis of bleeding risk factor in teeth extraction

		95%CI			
	RR	lower	upper	p value	
Extraction site					
maxilla/mandibula	1.885	0.756	5.128	0.177	
Teeth type					
premolar/incisor	1.108	0.103	24.300	0.934	
molar/incisor	3.640	0.649	68.346	0.160	
wisdom/incisor	6.894	1.213	130.039	0.027	*
Stability of teeth					
good/poor	2.125	0.756	7.572	0.161	
Extraction procedure					
surgical/simple	0.539	0.151	1.518	0.256	
PT-INR value	1.782	0.597	5.387	0.300	
Platelet count($\times 10^4/\mu l$)	0.959	0.887	1.037	0.296	
HAS-BLED score					
1/0	1.076	0.312	4.968	0.914	
2/0	1.577	0.391	7.825	0.529	
3/0	1.608	0.199	10.551	0.626	
2/1	1.465	0.477	4.157	0.487	
3/1	1.494	0.218	6.305	0.636	
3/2	1.020	0.140	4.922	0.982	
3/ less than 2	1.362	0.206	5.255	0.703	
Concomitant antiplatelet agents use					
yes/no	2.511	1.001	6.238	0.050	*

・Criteria from the European Society of Cardiology[24] were used.
RR:risk ratio
*:p〈0.05 was considerred significant.

Table 6 Multivariate analysis of postextraction hemorrhage

	model 1				model 2				model 3				model 4				
		95%CI				95%CI				95%CI				95%CI			
	risk ratio	lower	upper	p value	risk ratio	lower	upper	p value	risk ratio	lower	upper	p value	risk ratio	lower	upper	p value	
Extraction site																	
maxilla/mandibula	1.855	0.7	5.286	0.216	—	—	—	—	1.914	0.716	5.494	0.198	1.936	0.722	5.585	0.192	
Teeth type																	
premolar/incisor	1.118	0.102	24.727	0.928	—	—	—	—	1.045	0.095	23.222	0.972	1.159	0.104	25.901	0.906	
molar/incisor	3.468	0.594	65.974	0.188	—	—	—	—	3.388	0.579	64.544	0.199	3.730	0.630	71.468	0.164	
wisdom/incisor	5.228	0.85	101.628	0.078	—	—	—	—	5.380	0.860	105.301	0.075	5.113	0.804	100.719	0.804	
Stability of teeth																	
good/poor	1.790	0.551	6.994	0.344	—	—	—	—	1.961	0.588	7.893	0.283	1.916	0.568	7.780	0.304	
Extraction procedure																	
surgical/simple	0.624	0.166	1.915	0.425	—	—	—	—	0.674	0.177	2.125	0.515	0.670	0.175	2.117	0.509	
PT-INR value	2.078	0.681	6.606	0.204	—	—	—	—	2.288	0.727	7.543	0.162	2.687	0.831	9.349	0.107	
Platelet count(x10^4/ul)	0.970	0.892	1.053	0.461	—	—	—	—	0.968	0.889	1.053	0.443	0.970	0.894	1.052	0.465	
HAS-BLED score																	
1/0	—	—	—	—	1.076	0.312	4.968	0.914	1.197	0.325	5.777	0.798	—	—	—	—	
2/0	—	—	—	—	1.577	0.391	7.825	0.529	2.271	0.515	12.242	0.284	—	—	—	—	
3/0	—	—	—	—	1.608	0.199	10.551	0.626	2.338	0.269	16.989	0.410	—	—	—	—	
2/1	—	—	—	—	1.465	0.477	4.157	0.487	1.897	0.580	5.871	0.279	—	—	—	—	
3/1	—	—	—	—	1.494	0.218	6.305	0.636	1.954	0.266	9.403	0.463	—	—	—	—	
3/2	—	—	—	—	1.020	0.14	4.922	0.982	1.030	0.130	5.605	0.975	—	—	—	—	
Concomitant antiplatelet agents use																	
yes/no	—	—	—	—	—	—	—	—	—	—	—	—	2.881	1.079	7.740	0.035	*

・Criteria from the European Society of Cardiology[24] were used.

・*: p〈0.05

Table 7 Comparison of the model					
		95%CI			
	AUC	lower	upper	p value	
model 1	0.738	0.630	0.824	0.083	
model 2	0.548	0.425	0.666	0.867	
model 3	0.745	0.632	0.832	0.148	
model 4	0.763	0.650	0.847	0.031	*
model 1vs3				0.727	
model 1vs4				0.441	
model 2vs3				0.004	*
model 3vs4				0.398	
・*：p〈0.05					
AUC;area under the curve					

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HAS-BLED score alone could not be predict post-extraction bleeding: a retrospective cohort study.

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ABSTRACT

Objective: Post-extraction bleeding is often experienced in our clinical unexpectedly. It is very beneficial if the determination is post-extraction bleeding risk prior to surgery in the anticoagulant therapy patient. Therefore, this study aimed to verify whether the HAS-BLED score is useful in predicting post-extraction bleeding in patients taking warfarin.

Design: Retrospective cohort study.

Setting: Department of Oral and Maxillofacial Surgery, Tokyo Women's Medical University.

Participants: Subjects comprised 258 sequential cases (462 teeth) of inpatients who had undergone tooth extraction between January 1, 2010 and December 31, 2012 while continuing warfarin therapy.

Main outcome measure: Post-extraction risk factors of bleeding. As predicting variables of multivariate logistic analysis, HAS-BLED score, extraction site, teeth type, stability of teeth, and extraction procedure, PT-INR value, platelet count, concomitant antiplatelet agents use were collected.

Results: Post-extraction bleeding was noted in 21 (8.1%) of the 258 cases. Whole post-extraction bleeding was hemostasis in localized hemostatic procedure. The HAS-BLED score was insufficient for predicting post-extraction bleeding (AUC = 0.548, P = 0.867, multivariate analysis). The risk of post-extraction bleeding was approximately three times more for patients taking oral antiplatelet agents (RR = 2.881, P = 0.035, multivariate analysis).

Conclusions: The HAS-BLED score alone could not be predict post-extraction bleeding. The concomitant use of oral antiplatelet agents is a risk factor for post-extraction bleeding. This study was no post-extraction bleeding that required more than localized hemostatic procedure. However, because this was a retrospective study conducted at a single institution, we believe that a large-scale prospective cohort study, including outpatient tooth extraction cases, will be

necessary in the future.

Strengths and limitations of this study

- This is the first study to verify the usefulness of the HAS-BLED score for predicting post-extraction bleeding risk.
- We investigated all cases of tooth extraction, including wisdom tooth and impacted tooth extractions.
- No previous reports have investigated the effects of each individual tooth extracted, extraction procedure, and effects of concomitant antiplatelet agents on post-extraction bleeding using statistical analyses and demonstrated a high level of evidence for correlations.
- In this study, we think need to prospective cohort studies, including a large-scale outpatient in the future. Because it is a retrospective cohort study conducted at a single institution.

INTRODUTION

Patients undergoing anticoagulant therapy and who are scheduled to undergo tooth extraction are typically advised to undergo extraction while continuing anticoagulant therapy [1-4]. Although post-extraction bleeding is often experienced in our clinical unexpectedly. In the past, a number of studies have investigated tooth extraction while continuing anticoagulant therapy, with the frequency of post-extraction bleeding reported to range from 0% to 26%[5-16].

Recently, the HAS-BLED score[17-19] has been used as an index for evaluating the risk of bleeding complications in patients undergoing anticoagulant therapy. The HAS-BLED score evaluates nine risk factors for bleeding. The European Society of Cardiology guidelines[20] has stated that patients who score three points or higher are at a high risk of bleeding complications. No reports to date have investigated whether the HAS-BLED score is useful in predicting the risk of post-extraction bleeding. The preoperative identification of patients with a high risk of post-extraction bleeding could facilitate appropriate preparations prior to performing tooth extraction. Therefore, we examined whether the HAS-BLED score is useful in predicting post-extraction bleeding in patients undergoing warfarin therapy.

MATERIAL AND METHODS

Study design

This was a retrospective cohort study.

Study population and eligibility criteria

This study subject included 258 sequential cases that were hospitalized at the Department of Oral and Maxillofacial Surgery, Tokyo Women's Medical University and who had undergone tooth extraction between January 1, 2010 and December 31, 2012 while receiving a maintenance dose of warfarin therapy. As a rule, tooth extraction for patients undergoing warfarin therapy shall be performed after the patient is admitted to the hospital. Antiplatelet agents, which were being concomitantly taken, were continued to be administered at the maintenance dose. Exclusion criteria were as follows: 1) patients younger than 20 years at the time of hospital admission; 2) presence of comorbid blood disease; and 3) a PT-INR level of ≥3.1 as indicated by the results of the blood tests performed on the day of tooth extraction. Patients underwent follow-up examinations for 1 month after discharge. The doctors and nurse records obtained from medical examination records were registered in a database along with the results of the clinical tests. When the same patient was hospitalized and underwent tooth extraction more than once during the study period, all instances were registered.

Tooth extraction procedure

The primary physician for the underlying disease of each patient was preoperatively consulted regarding the general medical status of the patient, including their use of anticoagulants. When acute symptoms, such as periodontal abscesses, apical periodontitis, or pericoronitis were present around the tooth that was determined to be eligible for tooth extraction, antibiotics were administered at least three days and anti-inflammation procedures, such as incision and drainage, were performed as necessary. During tooth extraction, electrocardiograms, blood pressure, pulse rate, and percutaneous oxygen saturation levels were monitored. For local anesthesia, 1.8–3.6 ml of 2% lidocaine containing 1/80000 epinephrine was administered. Tooth extraction was performed with minimal invasion. When multiple teeth were indicated for extraction and comprised within 1/3 of the jaw area, all the teeth were extracted in one procedure. When the teeth comprised over 1/3 of the total jaw area, multiple teeth were extracted in one procedure if the procedure was expected to take <30 min while considering the age and any comorbid diseases of the patient. After extraction, a curettage of the inflammatory granulation tissue around the wound border was performed, hemostatic gelatin sponge was inserted into the socket

(product name: Spongel, Astellas Pharma Inc.), and suturing was performed to reduce the size of the wound border. The patient was requested to bite down on the absorbent cotton for 20 min after completing tooth extraction to achieve pressure hemostasis. At 30 min after tooth extraction, the patient was examined to confirm that the bleeding had stopped. After extraction, patients were instructed to avoid strong or frequent gargling and to rest as much as possible. Post-extraction meals comprised rice gruel. In the patient group with a high risk of adverse effects due to infective endocarditis onset [21], antibiotics were administered before surgery intravenously, after tooth extraction was prescribed to oral antibiotics for three days. For patients with a heart disease that did not necessarily require IE prophylaxis for dental procedures or patients receiving anticoagulant therapy, oral antibacterial drugs were administered for 3 days following tooth extraction. Five doses of analgesics comprising loxoprofen sodium or acetaminophen were prescribed as a potion when pain was experienced.

Post-extraction Bleeding

For cases in which the patient complained of bleeding and was examined but hemostatic procedures were not deemed necessary, patients were instructed to adequately rest and refrain from excessive gargling; regular follow-up examinations were performed. In mild bleeding as oozing, the patient was requested to bite down on a gauze or absorbent cotton for twenty minutes placed on the tooth extraction wound to achieve pressure hemostasis. Patients who did not require treatments, such as those outlined above for post-extractive bleeding, were placed into the non post-extraction bleeding group.

Patients who complained of bleeding since the examination after tooth extraction and who underwent some medical hemostatic procedures were categorized in the post-extraction bleeding group. Hemostatic procedures performed in accordance with the decisions by the examining oral surgeon are described below. For cases of moderate or higher bleeding in which there was a large amount of bleeding that was determined to be difficult to resolve using primary hemostasis, we aimed to utilize the local vasoconstrictive effects of the local dental anesthetic epinephrine and administered a dose of 1.0–1.8 ml to achieve infiltration anesthesia around the tooth extraction wound. Pressure was then applied to the wound by requesting the patient to bite down on gauze or absorbent cotton. When it was determined that the bleeding could not sufficiently be halted by pressure hemostasis alone, the area was additionally filled with local hemostatic agents

or additional or repeat suturing of the wound was performed as necessary. For cases of repeated bleeding or prolonged exudative bleeding after hemostatic procedures, a hemostatic splint was fabricated to cover of wound. This was fitted after applying a cavity lining with a periodontal pack or denture base tissue conditioner.

Bleeding risk factors for tooth extraction

Details of extracted teeth, surgical procedure, bleeding tendency, and concomitant antiplatelet agents were investigated as possible factors affecting post-extraction bleeding. With respect to details noted regarding extracted teeth, the extraction site (maxilla/mandible), type of teeth (incisor/premolar/molar/wisdom), and stability of teeth were examined. Regarding the stability of teeth, teeth exhibiting alveolar bone resorption of at least 2/3 of the tooth root length as determined by preoperative X-rays or teeth found to have clinical grade III instability were defined to have poor stability. Other teeth were considered to have good tooth stability. The surgical procedure was classified into simple and surgical extractions. For surgical extraction, the strategy followed was to make an incision in the gingiva, detach and turn the mucoperiosteal flap over, and extract the tooth after cutting off the alveolar bone or root separation. All extractions other than that defined above were simple extractions. With regard to bleeding tendency, PT-INR value and platelet count were investigated.

HAS-BLED score

The HAS-BLED score was evaluated according to the European Society of Cardiology guidelines [20] (Table 1) and is described below. Patients with systolic blood pressure of ≥160 mmHg, which was measured on arrival at the hospital, were categorized as having "hypertension." Patients receiving hemodialysis or those who had a kidney transplant; patients with a serum creatinine level of ≥2.26 mg/dl in the most recent blood test; patients exhibiting chronic liver disease, such as liver cirrhosis, and bilirubin levels of at least two times the normal upper limit; and patients having at least three times the normal upper limit of either alanine transaminase, aspartate aminotransferase, or alkaline phosphatase levels were categorized as having "abnormal renal and liver function." "Stroke" or "bleeding" was determined according to the information of patients obtained from medical interviews on admission to the hospital. "Labile INRs" were described to unstable/high INRs or poor time in therapeutic range (e.g.

<60%). The "elderly" categorization was defined as a patient age ≥65 years at the time of tooth extraction. Patients with long-term administration of antiplatelet agents or non-steroidal anti-inflammatory drug (NSAIDs) or patients with alcohol dependence were categorized as "drug and alcohol." One point was allocated for each of these categories if a patient was applicable. Thus, patients were scored according to a possible full score of nine points.

Selection of representative teeth

Since the subject is sequential cases in this study, the same patient will duplicate where the tooth extraction was done in other period, but age and PT-INR value and tooth extraction site is different. There is a case that extraction of multiple teeth in the same patient. Therefore, it was an independent data for each period by selected representative teeth following procedure. The most posterior tooth was selected as the representative tooth, and in cases of multiple posterior teeth, the upper tooth or the tooth showing good stability was selected.

Statistical analyses

Statistical analysis was processing the data of the patient with a representative tooth. Univariate and multivariate logistic analysis were applied to analyze the bleeding risk factor for tooth extraction data with the presence/absence of post-extraction bleeding as the response variable and bleeding risk factor as the explanatory variable. The two variable values were used to describe tooth extraction site (maxilla/mandible), four variable values were used to describe the type of teeth (incisor/premolar/molar/wisdom), two variable values were used to describe stability of teeth (good/poor), and two variable values were used to describe the surgical procedure (simple /surgical extraction). For the PT-INR value and platelet count, the actual measured values were analyzed as continuous variables, and the HAS-BLED score was used in analysis with both a continuous and nominal variable. Concomitant antiplatelet agents were evaluated as two variable values (yes/no). During logistic analysis, we calculated the risk ratio, 95% confidence interval (CI), and p value. The risk ratio was calculated as the ratio of maxilla to mandible for a site, the tooth type within anterior teeth for type of teeth, good to poor for the condition of the periodontium, and from surgical to simple for the surgical procedure. The risk ratio for the HAS-BLED score was calculated for each level. For concomitant antiplatelet agents, the risk ratio of "yes" to "no" was calculated. In multivariate analysis, risk factors were

combined to create post-extraction bleeding analysis models. For each model, we plotted the receiver operating characteristic (ROC) curve and calculated the area under the curve (AUC) in addition to the p value and 95% CI for the C-statistic model overall. Many screening tools used a C-statistic value of ≥0.70. We used C-statistic to compare between each model. Model 1 was constructed from extracted tooth state, surgical procedure, and bleeding tendency. Model 2 was constructed from the HAS-BLED score only. Model 3 was constructed by adding the HAS-BLED score to Model 1. Model 4 was constructed by adding concomitant antiplatelet agents as an explanatory variable to Model 1. Data were analyzed with the use of JMP Pro 11 software (2014 SAS Institute Inc., US) with a two-tailed alpha level of 0.05.

Ethics

This study was approved by the ethical review board of the Tokyo Women's Medical University (approval number: 3079). The first and second authors take complete responsibility for the integrity of the data and the accuracy of the data analysis.

RESULTS

A total of 462 extracted teeth in 258 patients (males: 157, females: 101, mean age: 66.4 years) were analyzed. Post-extraction bleeding was observed in 21 patients (8.1%). Whole post-extraction bleeding was hemostasis in localized hemostatic procedure, and none died patients due to hemorrhage.

Patient characteristics

Post-extraction bleeding was noted in 21 patients (males: 14, females: 7, mean age: 63.4 ± 13.2 years). Table 2 shows the underlying diseases for anticoagulant therapy. Mean warfarin dosage was 3.9 ± 1.4 mg, and median (25 percentile, 75 percentile) of PT-INR was 2.1 (1.8,2.5). Mean platelet count was $16.8 \pm 5.3 \times 10^4/\mu l$. Eleven patients were taking only warfarin, whereas 10 were taking an antiplatelet agent in addition to warfarin. Aspirin was administered as the antiplatelet agent to all cases.

The non post-extraction bleeding group included 237 patients (males: 143, females: 94, mean age: 66.6 ± 13.7 years). Underlying diseases for anticoagulant therapy are shown in Table 2. Mean warfarin dosage was 3.2 ± 1.3 mg. The mean (25 percentile, 75 percentile) of PT-INR was

2.0 (1.8, 2.3). Mean platelet count was 18.2 ± 5.8 × 10^4/μl. A total of 174 patients were taking warfarin only, whereas 63 patients were taking warfarin and an antiplatelet agent. Table 2 shows a breakdown of the antiplatelet agents. Seven patients who were taking two types of antiplatelet agents were all included in the non post-extraction bleeding group. A statistically significant difference was noted for warfarin dosage; however, no difference was noted for PT-INR. No differences were noted for age, sex, platelet count, or concomitant antiplatelet agents use.

Details of extracted tooth

In the post-extraction bleeding group, the tooth extraction site in 14 and seven cases was the maxilla and mandible, respectively. For the non post-extraction bleeding group, it was the maxilla and mandible in 122 and 115 cases, respectively. Thus, no differences were noted between the two groups (P = 0.254, Fisher's exact test; table 3).

Results for teeth type

Numbers of incisor:premolar:molar:wisdom teeth were 1:2:9:9, respectively, in the post-extraction bleeding group and 36:65:89:47, respectively, in the non post-extraction bleeding group. Thus, a statistically significant difference was noted between the two groups (P = 0.039, Fisher's exact test; table 3).

In the post-extraction bleeding group, the stability of teeth was good in 17 cases and poor in four. In the non post-extraction bleeding group, stability was good in 158 cases and poor in 79. No statistically significant difference was noted between the two groups (P = 0.227, Fisher's exact test; table 3).

Extraction procedure

In the post-extraction bleeding group, the extraction procedure selected was simple extraction in 17 cases and surgical extraction in four cases. In the non post-extraction bleeding group, the procedure selected was simple extraction in 165 cases and surgical extraction in 72 cases. No differences were noted between the two groups (P = 0.328, Fisher's exact test; table 3).

Number of teeth extracted per operation

The number of teeth extracted per operation was 1.7 ± 0.6 in the post-extraction bleeding group and 1.8 ± 1.1 in the non post-extraction bleeding group. There were no cases of multiple extractions of four or more teeth in the post-extraction bleeding group. No differences were noted between the two groups with regards to the number of teeth extracted per operation

(*P* = 0.576, Student's t-test; table 3).

HAS-BLED score

The highest HAS-BLED score obtained was three points. The mean score was 1.3 ± 0.9 in the post-extraction bleeding group and 1.2 ± 0.8 in the non post-extraction bleeding group. No statistically significant differences were noted between the two groups (*P* = 0.467, Student's t-test; table 4). In both the post-extraction and non post-extraction bleeding groups, scores were highest for the "elderly" group, followed by the "drug and alcohol" group, and then the "stroke" group.

Statistical examination

Univariate analysis demonstrated statistically significant differences between the wisdom teeth and incisor (RR = 8.894, *P* = 0.027) and for between concomitant antiplatelet agents (yes/no) (RR = 2.511, *P* = 0.500). RR was ≤1 for surgical procedure and platelet count. No statistically significant difference was noted for a HAS-BLED score of ≥3 compared with a HAS-BLED score of ≤2 (RR = 1.362, *P* = 0.7033) (table 5).

No statistically significant differences were noted within multivariate analysis for any of the parameters in the models 1, 2, or 3. In Model 4, a statistically significant difference was noted for antiplatelet agents (yes) in the non post-extraction bleeding group (RR = 2.881, *P* = 0.035) (table 6). AUCs for models 1, 3, and 4 were 0.7, with a statistically significant difference noted in Model 4 only. AUC for Model 2 was the lowest at 0.5, and a statistically significant difference was noted between models 2 and 3 (*P* = 0.004) (table 7).

Discussion

Our investigation of 258 tooth extraction patients indicated that post-extraction bleeding occurred in 21 patients (8%) or in 39 of the total 462 extracted teeth (8%). Whole post-extraction bleeding was possible hemostasis in localized hemostatic procedure. The HAS-BLED score alone it was not possible to predict post-extraction bleeding. As a result of considering the risk factors for post-extraction bleeding statistically, the concomitant antiplatelet agents use were risk factors. It has reported that the incidence of bleeding in the anticoagulation group is the same (about 6-7%) as in the anticoagulation withdrawal group[22]. The post-extraction bleeding in this

study was in accordance with their report.

Many cases of tooth extraction performed while continuing anticoagulant therapy have been reported[23-25]. However, in clinical settings, it is not uncommon to encounter post-extraction bleeding during tooth extraction in cases of optimal INR value range. Iwabuchi et al.[26] reported through a multicenter, large-scale study that risk factors for post-extraction bleeding in patients taking warfarin were age, PT-INR, and inflammation at the extraction site. Although many reports to date have not included cases of surgical extraction, such as the extraction of wisdom teeth and impacted teeth, these types of surgical extraction are often performed within clinical settings. Therefore, this study targeted cases that were managed according to the optimal treatment range and investigated all cases of tooth extraction, including the extraction of wisdom teeth, impacted teeth, and multiple teeth concurrently.

Various methods of hemostasis have been reported for cases of tooth extraction performed while continuing warfarin therapy. These include pressure hemostasis only, wound suturing, and the application of local hemostatic agents[27-30]. To implement hemostasis, we placed a hemostatic gelatin sponge in the extraction socket and routinely conducted pressure hemostasis using absorbent cotton with suturing of the wound. Patients were examined 30 min after tooth extraction to confirm whether the bleeding had stopped. Hemostasis was determined to have been sufficient for all cases. As all patients underwent tooth extraction on an inpatient basis, the patient could rapidly be examined by a physician or nurse and could receive early diagnosis and appropriate treatment if post-extraction bleeding was suspected. However, although patients were examined, many did not require hemostatic treatment. Of the patients who exhibited post-extraction bleeding, no systemic hemostatic treatment, such as blood transfusion, was required in any case.

The HAS-BLED score is used in the field of cardiology to evaluate the risk of hemorrhaging in patients showing good anticoagulation. As it would be highly significant if the HAS-BLED score could be additionally used for predicting the risk of post-extraction hemorrhaging, we evaluated its use in this study. In our study, the highest HAS-BLED score was three points. A score of one point was the most commonly achieved among the 137 patients (53%). The most common risk factor was found to be age (174 patients; 67%). No difference was noted for the mean HAS-BLED score between the post-extraction hemorrhaging and non-post-extraction hemorrhaging groups. The European Society of Cardiology has proposed that a score of HAS-BLED ≥ 3

indicates a high risk of hemorrhagic complications. In cases of post-extraction hemorrhaging, we compared patients with a HAS-BLED score of three or higher and those with a score of two or lower but did not detect any statistically significant difference (univariate analysis; RR = 1.362, $P = 0.703$). Multivariate analysis indicated that there was little risk associated with the score increasing by one (Table 6). AUC for HAS-BLED score alone (Model 2) was 0.55, which was the lowest for all of the models we constructed. In Model 3, to which the details of extracted teeth were added to the HAS-BLED score, AUC was 0.745, suggesting that this model is useful for predicting post-extraction bleeding. However, a statistically significant difference was noted for Model 2 versus Model 3 ($P = 0.004$), indicating that the HAS-BLED score alone was insufficient for predicting post-extraction bleeding.

As a bleeding risk factors for tooth extraction, investigation of conditions of the individual teeth extracted indicated that post-extraction bleeding risk was five to six times higher for wisdom teeth compared with that for anterior teeth. Extraction site and stability had little effect. Although no differences were observed for the number of teeth extracted in one treatment, there were no cases of multiple extractions of four teeth or more in the post-extraction hemorrhaging group. Although we had predicted Surgical extraction as a risk factor of post-extraction bleeding, results indicated that surgical extraction hardly had any effect on post-extraction bleeding (RR = 0.539, $P = 0.256$).

The effects of warfarin are easily influenced by factors, such as interaction with meals and/or drugs, and additionally by the general state of the patient. In this study, to accurately determine the anticoagulation state directly before tooth extraction, all blood tests were performed before breakfast on the tooth extraction day or the first tooth extraction day if tooth extraction was planned on consecutive days. Although post-extraction bleeding cases were being administered high doses of warfarin, no difference was observed for PT-INR. There were no cases classified as labile INRs. Accordingly, the PT-INR value was investigated using actual measured values as the continuous variable. There were no statistically significant differences noted for PT-INR values by either univariate or multivariate analysis ($P \geq 0.1$), suggesting that the PT-INR value had little effect on post-extraction bleeding in patients undergoing anticoagulant therapy while being managed within the optimal treatment range.

No fixed consensus has been reached regarding the concomitant use of warfarin and antiplatelet agents because some reports have indicated that this increases the risk of post-extraction

bleeding[1,31], whereas other reports have suggested that antiplatelet agents have little effect [14,32]. In this study, incidence of 13.7% of post-extraction bleeding in concomitant antiplatelet drugs, in the warfarin alone was 5.9%. Both of our univariate and multivariate analyses results indicated that the use of concomitant antiplatelet agents was a significant factor affecting post-extraction bleeding. It has been reported that the concomitant use of two antiplatelet agents significantly increases the frequency of intracranial hemorrhaging[33]. Furthermore, a prospective observational study of hemorrhagic complications in Japanese cerebral infarction patients[34] found that compared with patients taking one antiplatelet agent only; those taking two or three antiplatelet agents along with warfarin clearly exhibited higher annual onset rates of intracranial hemorrhaging. We believe that these results suggest that concomitant antiplatelet agents are a risk factor for post-extraction bleeding.

The limitations of this study included the fact that data were obtained only at a single facility and that outpatients were not included in the subjects investigated. In our facility were many cardiovascular disease patients (especially post-operative valve replacement patients was about 50%). Furthermore, because our study excluded patients who exhibited PT-INR of ≥3.1 during the blood testing performed on the day of tooth extraction, the current study included patients whose anticoagulant therapy was being well managed. Thus, our subjects did not exactly constitute generalized cases of tooth extraction patients taking warfarin. Moreover, because this was a retrospective study, we believe that a large-scale, prospective, cohort study including outpatient tooth extraction cases required to be conducted in the future.

Moreover, we could not examine the drug interaction effects because our subjects included both patients who intravenously received antibacterial agents and those who received oral administration. Warfarin use results in a number of drug interactions. Holbrook et al.[35] has stated to enhance anti-infective agents, lipid-lowering drugs, NSAIDs including COX-2 selective NSAIDs, selective serotonin reuptake inhibitors, amiodarone, omeprazole, fluorouracil, a and cimetidine of warfarin anticoagulant effects. In these drugs suggest to consider changes to the small alternative agent of interaction with warfarin. However, some reports have stated that in most stable anticoagulant therapy patients, exposure to antibacterial agents causes no clinical problems [36]; furthermore, other reports have found that NSAIDs and antibacterial agents often increased warfarin effects in cases of long-term administration [16]. We also believe that the short-term or low-dose administration of NSAIDs or antibacterial agents does not cause any

prolongation of clinically problematic PT-INR.

Of the models that we created in this study, Model 4 exhibited the highest predictive ability for post-extraction bleeding (AUC = 0.76, $P = 0.0309$). However, because there were no significant differences observed between Model 1 or 3 versus Model 4, we were unable to construct an optimal model for predicting post-extraction bleeding. To increase model precision, it may be optimal to add factors demonstrating surgeon skill (e.g. years of surgeon experience or time required for one tooth extraction), which were not included in our current investigation. Furthermore, it will be necessary to put all extraction data from outpatients into analysis set to conduct a multilevel analysis.

Finally, all the patients had post-extraction bleeding be hemostasis in localized hemostatic procedure, there was no systemic hemostatic treatment was required cases. There was no case that was extended hospitalization period by post-extraction bleeding. Wahl et al.[22] has stated that bleeding complications requiring more than local hemostatic measures after dental surgery are exceedingly rare. It was also our results. In order to not cause the onset of fatal severe thromboembolism[37], there is no need of warfarin interruption or pause for tooth extraction. The special environment to the post-extraction bleeding procedure is not necessary. If condition are prepared, we believe extraction of warfarin therapy patient is possible in a private office.

CONCLUSIONS

1. We investigated post-extraction bleeding risk factors for all types of tooth extraction, including wisdom teeth and impacted teeth in patients taking warfarin. Post-extraction bleeding requiring hemostatic treatment was observed in 8% patients.

2. Whole post-extraction bleeding was hemostasis in localized hemostatic procedure. There was no systemic hemostatic treatment was required cases, and none died patients due to hemorrhage.

3. The HAS-BLED score alone could not be predict post-extraction bleeding in patients taking warfarin.

4. Concomitant antiplatelet agents use is a risk factor for post-extraction bleeding. More care must be taken regarding post-extraction bleeding within these cases than in cases with the administration of warfarin alone.

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Contributors

TA and TK were involved in the planning of the study concept and design. TK wrote the drafting of the manuscript. KH and TK were involved in the statistical analysis. TA and TK reviewed and revised the manuscript. All authors read and approved the final manuscript.

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The authors have no conflicts of interest to declare regarding this study.

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Table 1 HAS-BLED bleeding risk score

risk factor		clinical characteristics
H	Hypertension	uncontrolled, >160mmHg systolic
A	Abnomal renal and liver function （1point each)	presence of chonic dialysis, renal pramsplantation or serum creatinine ≧200μmol/L
		chornic hepatic disease(eg, cirrhosis), bilirubin >2X upper limit of nomal,
		AST/ALT/ALP >3X upper limit of nomal
S	Stroke	previous history
B	Bleeding	bleeding history or predisposition
L	Labile INRs	unstable/high INRs or poor time in therapeutic range (e.g. 60%)
E	Elderly	>65 years
D	Drugs or alcohol （1point each)	concomitantly antiplatelet agents and NSAIDs,
		alcohol excess

Criteria from the European Society of Cardiology[20] were used. AST=aspartate aminotransferase, ; table 3 ALT=alanine aminotransferase, ALP=alkaline phosphatase, NSAIDs=nonsteroidal antiinflammatory drugs

Table 2 Patient characteristics

	post-extraction bleeding group	non post extraction bleeding group	p value	significant difference	χ^2 value
	N=21	N=237			
	number of patients	number of patients			
Age (mean ± SD)	63.4±13.2	66.6±13.7	0.2944[a]		
Gender(Male/Female)	14/7	143/94	0.6463[c]		0.32
Primary disease					
post Heart Valve Prosthesis Implantation	17	120			
atrial fibrillation	2	76			
cerebral infarction	2	13			
dilated cardiomyopathy	1	9			
myocardial infarction	0	23			
deep vein thrombosis	0	11			
arteriosclerosis obliterans	0	3			
intracardiac thrombus	0	2			
Anticoagulation					
warfarin dose(mg) (mean ± SD)	3.9±1.4	3.2±1.3	0.0241[a]	*	
PT-INR value (mean［25%tile, 75tile］)	2.1[1.8, 2.5]	2.0[1.8, 2.3]	0.3296[b]		
Platelet count($\times 10^4$/μl)	16.8±5.3	18.2±5.8	0.2978[a]		
Concomitant antiplatelet agents					
yes	10	63	0.0732[c]		4.21
aspirin	10	52			
ticlopidine	0	8			
ethyl icosapentate	0	6			
cilostazol	0	2			
limaprost	0	1			
dipyridamole	0	1			

SD:standard deviation, Multiple factors possible for underlying disease, All seven patients ; table 3using two types of antiplatelet agents were included in the non post-extraction bleeding group. A;Student's t-test, b;Mann-Whitney U test, c;Fisher's exact test, *:p〈0.05 was considered significant.

Table 3 Details of extracted teeth

	post-extraction bleeding group	non post-extraction bleeding group	p value	significant difference	χ^2 value
	N=21	N=237			
	number of patients or mean ± SD	number of patients or mean ± SD			
Extraction site					
maxilla	14	122	0.254[c]		1.79
mandibula	7	115			
Teeth type					
incisor	1	36	0.039[c]	*	8.70
premolar	2	65			
molar	9	89			
wisdom	9	47			
Stability of teeth					
good	17	158	0.227[c]		1.80
poor	4	79			
Extraction procedure					
simple	17	165	0.328[c]		1.19
surgical	4	72			
Number of teeth extracted in operation	1.7 ±0.6	1.8 ±1.1	0.576[a]		
One tooth	8	125	0.188[c]		9.12
Two tooth	12	65			
Three tooth	1	24			
Four tooth	0	18			
Five tooth	0	3			
Six tooth	0	1			
Seven tooth	0	1			

SD:standard deviation, a;Student's t-test, c;fisher's exact test, ; table 3

*:p〈0.05 was considered significant.

Table 4 HAS-BLED score

	post-extraction bleeding group	non post-extraction bleeding group	p value	significant difference	χ^2 value
	N=21	N=237			
	mean ± SD or number of patients	mean ± SD or number of patients			
HAS-BLED score	1.3±0.9	1.2±0.8	0.467 [a]		
0	3	41	0.804 [c]		0.75
1	10	127			
2	6	52			
3	2	17			
4	0	0			
5	0	0			
6	0	0			
7	0	0			
8	0	0			
9	0	0			
risk factor					
H	1	3			
A	1	11			
S	2	38			
B	0	5			
L	0	0			
E	13	161			
D	11	63			

SD:standard deviation, a;Student's t-test, c;Fisher's exact test; table 3

Table 5 Univariate analysis of bleeding risk factor in teeth extraction

		95%CI			significant difference
	RR	lower	upper	p value	
Extraction site					
maxilla/mandibula	1.885	0.756	5.128	0.177	
Teeth type					
premolar/incisor	1.108	0.103	24.300	0.934	
molar/incisor	3.640	0.649	68.346	0.160	
wisdom/incisor	6.894	1.213	130.039	0.027	*
Stability of teeth					
good/poor	2.125	0.756	7.572	0.161	
Extraction procedure					
surgical/simple	0.539	0.151	1.518	0.256	
PT-INR value	1.782	0.597	5.387	0.300	
Platelet count($\times 10^4/\mu l$)	0.959	0.887	1.037	0.296	
HAS-BLED score					
1/0	1.076	0.312	4.968	0.914	
2/0	1.577	0.391	7.825	0.529	
3/0	1.608	0.199	10.551	0.626	
2/1	1.465	0.477	4.157	0.487	
3/1	1.494	0.218	6.305	0.636	
3/2	1.020	0.140	4.922	0.982	
3/ less than 2	1.362	0.206	5.255	0.703	
Concomitant antiplatelet agents use					
yes/no	2.511	1.001	6.238	0.050	*

Criteria from the European Society of Cardiology[20] were used. ;

RR:risk ratio *:p〈0.05 was considerred significant.

Table 6 Multivariate analysis of postextraction hemorrhage

	model 1				
		95%CI			
	risk ratio	lower	upper	p value	significant difference
Extraction site					
maxilla/mandibula	1.855	0.7	5.286	0.216	
Teeth type					
premolar/incisor	1.118	0.102	24.727	0.928	
molar/incisor	3.468	0.594	65.974	0.188	
wisdom/incisor	5.228	0.85	101.628	0.078	
Stability of teeth					
good/poor	1.790	0.551	6.994	0.344	
Extraction procedure					
surgical/simple	0.624	0.166	1.915	0.425	
PT-INR value	2.078	0.681	6.606	0.204	
Platelet count(x10^4/ul)	0.970	0.892	1.053	0.461	
HAS-BLED score					
1/0	—	—	—	—	
2/0	—	—	—	—	
3/0	—	—	—	—	
2/1	—	—	—	—	
3/1	—	—	—	—	
3/2	—	—	—	—	
Concomitant antiplatelet agents use					
yes/no	—	—	—	—	

Criteria from the European Society of Cardiology[20] were used. ・*:p〈0.05

Table 6 continuation

	model 2				
		95%CI			
	risk ratio	lower	upper	p value	significant difference
Extraction site					
maxilla/mandibula	—	—	—	—	
Teeth type					
premolar/incisor	—	—	—	—	
molar/incisor	—	—	—	—	
wisdom/incisor	—	—	—	—	
Stability of teeth					
good/poor	—	—	—	—	
Extraction procedure					
surgical/simple	—	—	—	—	
PT-INR value	—	—	—	—	
Platelet count(x10^4/ul)	—	—	—	—	
HAS-BLED score					
1/0	1.076	0.312	4.968	0.914	
2/0	1.577	0.391	7.825	0.529	
3/0	1.608	0.199	10.551	0.626	
2/1	1.465	0.477	4.157	0.487	
3/1	1.494	0.218	6.305	0.636	
3/2	1.020	0.14	4.922	0.982	
Concomitant antiplatelet agents use					
yes/no	—	—	—	—	

Criteria from the European Society of Cardiology[20] were used. ・*:p〈0.05

Table 6 continuation

	model 3				
		95%CI			
	risk ratio	lower	upper	p value	significant difference
Extraction site					
maxilla/mandibula	1.914	0.716	5.494	0.198	
Teeth type					
premolar/incisor	1.045	0.095	23.222	0.972	
molar/incisor	3.388	0.579	64.544	0.199	
wisdom/incisor	5.380	0.860	105.301	0.075	
Stability of teeth					
good/poor	1.961	0.588	7.893	0.283	
Extraction procedure					
surgical/simple	0.674	0.177	2.125	0.515	
PT-INR value	2.288	0.727	7.543	0.162	
Platelet count(x10^4/ul)	0.968	0.889	1.053	0.443	
HAS-BLED score					
1/0	1.197	0.325	5.777	0.798	
2/0	2.271	0.515	12.242	0.284	
3/0	2.338	0.269	16.989	0.410	
2/1	1.897	0.580	5.871	0.279	
3/1	1.954	0.266	9.403	0.463	
3/2	1.030	0.130	5.605	0.975	
Concomitant antiplatelet agents use					
yes/no	—	—	—	—	

Criteria from the European Society of Cardiology[20] were used. ・*:p〈0.05

Table 6 continuation

	model 4				
		95%CI			
	risk ratio	lower	upper	p value	significant difference
Extraction site					
maxilla/mandibula	1.936	0.722	5.585	0.192	
Teeth type					
premolar/incisor	1.159	0.104	25.901	0.906	
molar/incisor	3.730	0.630	71.468	0.164	
wisdom/incisor	5.113	0.804	100.719	0.804	
Stability of teeth					
good/poor	1.916	0.568	7.780	0.304	
Extraction procedure					
surgical/simple	0.670	0.175	2.117	0.509	
PT-INR value	2.687	0.831	9.349	0.107	
Platelet count(x10^4/ul)	0.970	0.894	1.052	0.465	
HAS-BLED score					
1/0	—	—	—	—	
2/0	—	—	—	—	
3/0	—	—	—	—	
2/1	—	—	—	—	
3/1	—	—	—	—	
3/2	—	—	—	—	
Concomitant antiplatelet agents use					
yes/no	2.881	1.079	7.740	0.035	*

Criteria from the European Society of Cardiology[20] were used. ・*:p〈0.05

Table 7 Comparison of the model

		95%CI			
	AUC	lower	upper	p value	significant difference
model 1	0.738	0.630	0.824	0.083	
model 2	0.548	0.425	0.666	0.867	
model 3	0.745	0.632	0.832	0.148	
model 4	0.763	0.650	0.847	0.031	*
model 1vs3				0.727	
model 1vs4				0.441	
model 2vs3				0.004	*
model 3vs4				0.398	

*:p〈0.05, AUC;area under the curve

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✔
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✔
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✔
Objectives	3	State specific objectives, including any prespecified hypotheses	✔
Methods			
Study design	4	Present key elements of study design early in the paper	✔
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✔
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	✔
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✔
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✔
Bias	9	Describe any efforts to address potential sources of bias	✔
Study size	10	Explain how the study size was arrived at	✔
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✔
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	✔
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	✔
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✔
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✔
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	✔
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✔
		(*b*) Report category boundaries when continuous variables were categorized	✔

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	✔
Discussion			
Key results	18	Summarise key results with reference to study objectives	✔
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✔
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✔
Generalisability	21	Discuss the generalisability (external validity) of the study results	✔
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✔

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Is the HAS-BLED score useful in predicting post-extraction bleeding in patients taking warfarin?: a retrospective cohort study.

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Is the HAS-BLED score useful in predicting post-extraction bleeding in patients taking warfarin? a retrospective cohort study

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ABSTRACT

Objective: Unexpected post-extraction bleeding is often experienced in clinical practice. Therefore, determining the risk of post-extraction bleeding in patients receiving anticoagulant therapy prior to surgery is beneficial. This study aimed to verify whether the HAS-BLED score was useful in predicting post-extraction bleeding in patients taking warfarin.

Design: Retrospective cohort study.

Setting: Department of Oral and Maxillofacial Surgery, Tokyo Women's Medical University.

Participants: Subjects 258 sequential cases (462 teeth) who had undergone tooth extraction between January 1, 2010 and December 31, 2012 while continuing warfarin therapy.

Main outcome measure: Post-extraction risk factors for bleeding. The following data were collected as the predicting variables for multivariate logistic analysis: the HAS-BLED score, extraction site, tooth type, stability of teeth, extraction procedure, prothrombin time-international normalized ratio value, platelet count, and the use of concomitant antiplatelet agents.

Results: Post-extraction bleeding was noted in 21 (8.1%) of the 258 cases. Hemostasis was achieved with localized hemostatic procedures in all the cases of post-extraction bleeding. The HAS-BLED score was found to be insufficient in predicting post-extraction bleeding (area under the curve = 0.548, P = 0.867, multivariate analysis). The risk of post-extraction bleeding was approximately three time greater in patients taking concomitant oral antiplatelet agents (risk ratio= 2.881, P = 0.035, multivariate analysis).

Conclusions: The HAS-BLED score alone could not predict post-extraction bleeding. The concomitant use of oral antiplatelet agents was a risk factor for post-extraction bleeding. No episodes of post-extraction bleeding required more than local measures for hemostasis. However, because this was a retrospective study conducted at a single institution, large-scale prospective cohort studies, which include cases of outpatient tooth extraction, will be necessary in the future.

Strengths and limitations of this study

- This is the first study to investigate the usefulness of the HAS-BLED score for predicting the risk of post-extraction bleeding. We investigated all cases of tooth extraction, including wisdom teeth and impacted tooth extractions.
- No previous reports have investigated the effects of each individual tooth extracted, the extraction procedure, and the effects of concomitant antiplatelet agents on post-extraction bleeding using statistical analyses or demonstrated a high level of evidence for these correlations.
- As this study was a retrospective cohort study conducted at a single institution, large-scale prospective cohort studies, including outpatients, are needed in the future.

INTRODUTION

Patients on anticoagulant therapy who are scheduled to undergo tooth extraction are typically advised continue anticoagulant therapy [1-4]. Unexpected post-extraction bleeding is often experienced in clinical practice; however, the Development of thromboembolism after tooth extraction because of the discontinuation or reduction of anticoagulant therapy has been reported[5, 6]. Although fatal adverse events must be prevented, there is the additional risk of bleeding because of invasive treatment in these patients, and sufficient measures must be taken to prevent and limit excessive post-extraction bleeding. In the past, a number of studies have investigated tooth extraction with continued anticoagulant therapy and have reported that the frequency of post-extraction bleeding was in the range of 0%–26%[7-18]. Blinder et al.[9] and Evans et al.[10] reported that there were no differences in the incidences of post-extraction bleeding between a group of patients who had discontinued anticoagulant therapy and a group of those who had continued anticoagulant therapy. Even if the uniform consensus was to perform tooth extraction with continued anticoagulant therapy, the risk of post-extraction bleeding remains. Morimoto et al.[19] suggested that post-extraction bleeding was strongly affected by local inflammatory conditions. However, there are few reports on the systemic factors contributing to post-extraction bleeding. Recently, the HAS-BLED score[20-22] has been used as an index for evaluating the risk of bleeding complications in patients taking anticoagulant therapy. The HAS-BLED score evaluates nine risk factors for bleeding. The European Society of Cardiology guidelines[23] has stated that patients who score three points or higher are at a high risk of

bleeding complications. However, to date, no reports have examined the relationship between post-extraction bleeding and the HAS-BLED score.

Preoperative identification of patients at high risk of post-extraction bleeding could facilitate appropriate preparations prior to performing tooth extraction. Therefore, we examined whether the HAS-BLED score was useful in predicting post-extraction bleeding in patients on warfarin therapy.

MATERIAL AND METHODS

Study design

This was a retrospective cohort study.

Study population and eligibility criteria

The study subjects were included from 258 sequential inpatient cases at the Department of Oral and Maxillofacial Surgery, Tokyo Women's Medical University, who underwent tooth extraction between January 1, 2010 and December 31, 2012, while receiving a maintenance dose of warfarin. As a general rule, we performed inpatient tooth extraction in patients taking warfarin. Concomitant antiplatelet agents were continued at the maintenance dose. The exclusion criteria were as follows: 1) patients younger than 20 years in age at the time of hospital admission; 2) the presence of comorbid blood diseases; and 3) a prothrombin time-international normalized ratio (PT-INR) level of ≥3.1, as indicated by blood tests performed on the day of the tooth extraction. Patients underwent follow-up examinations for 1 month after discharge. The doctors' and nurses' records obtained from the medical examination records were registered in a database along with the results of the clinical tests. When the same patient was hospitalized and underwent tooth extraction more than once during the study period, all instances were included in the analysis.

Tooth extraction procedure

Each patient's primary physician was consulted preoperatively regarding the general medical status and the use of anticoagulants. When acute symptoms, such as periodontal abscesses, apical periodontitis, or pericoronitis were present around the tooth to be extracted, antibiotics were administered for at least 3 days and anti-inflammation procedures, such as incision and drainage, were performed as necessary. During the tooth extraction, electrocardiograms, blood pressure,

pulse rate, and percutaneous oxygen saturation levels were monitored. For local anesthesia, 1.8–3.6 ml of 2% lidocaine containing 1/80,000 units of epinephrine was administered. Tooth extraction was performed with minimal invasion. When multiple teeth were indicated for extraction and comprised within 1/3 of the jaw area, all the teeth were extracted in one procedure. When the teeth comprised over 1/3 of the total jaw area, multiple teeth were extracted in one procedure if the procedure was expected to take <30 min, while at the same time considering the age of the patient and any comorbid diseases. After extraction, curettage of inflammatory granulation tissue around the wound border was performed, a hemostatic gelatin sponge was inserted into the socket (Spongel, Astellas Pharma Inc.), and suturing was performed to reduce the size of the wound border. The patient was requested to bite down on a piece of absorbent cotton for 20 min after completion of the tooth extraction in order to achieve pressure hemostasis. At 30 min after the tooth extraction, the patient was examined to confirm that the bleeding had stopped. After extraction, patients were instructed to avoid strong or frequent gargling and to rest as much as possible. Post-extraction meals were comprised of rice gruel. In patients with a high risk of developing infective endocarditis[24)], intravenous antibiotics were administered before surgery and oral antibiotics were administered for 3 days after the tooth extraction. For patients with heart disease on anticoagulant therapy who did not require infectious endocarditis prophylaxis, oral antibiotics were administered for 3 days following tooth extraction. Five doses of analgesics, which comprised loxoprofen sodium or acetaminophen, were prescribed as a medication when pain was experienced.

Post-extraction Bleeding

Patients who had bleeding but in whom hemostatic procedures were not deemed necessary were instructed to get adequate rest and refrain from excessive gargling. Regular follow-up examinations were performed. When patients had mild bleeding and oozing, the patient was requested to bite down for 20 min on a piece of gauze or absorbent cotton placed on the tooth extraction wound in order to achieve pressure hemostasis. These patients who did not require medical treatment for post-extraction bleeding were categorized into the non-post-extraction bleeding group.

Patients who had bleeding on examination after the tooth extraction and who underwent some form of medical hemostatic procedure were categorized into the post-extraction bleeding group.

The hemostatic procedures that were performed in accordance with the decision of the examining oral surgeon are described below. In cases of moderate to severe bleeding, which were difficult to resolve using primary hemostasis alone, the local dental anesthetic epinephrine, which has vasoconstrictive effects, was infiltrated at a dose of 1.0–1.8 ml around the tooth extraction wound. Pressure was then applied to the wound by asking the patient to bite down on a piece of gauze or absorbent cotton. When it was determined that the bleeding could not sufficiently be halted by pressure hemostasis alone, the area was additionally filled with local hemostatic agents or additional suturing of the wound was performed as necessary. For cases of repeated bleeding or prolonged exudative bleeding after hemostatic procedures, a hemostatic splint was fabricated to cover the wound. This was fitted after applying a cavity lining with a periodontal pack or denture-based tissue conditioner.

Bleeding risk factors for tooth extraction

The details of extracted teeth, surgical procedure, bleeding tendency, and the use of concomitant antiplatelet agents were investigated as possible factors affecting post-extraction bleeding. Details regarding the extracted teeth, extraction site (maxilla/mandible), type of teeth (incisor/premolar/molar/wisdom), and stability of teeth were examined. Teeth exhibiting alveolar bone resorption of at least 2/3 of the tooth root length, as determined by preoperative X-rays, or teeth found to have clinical grade III instability were defined as having poor stability. The surgical procedure was classified into simple extraction and surgical extraction. For surgical extraction, the strategy followed was to make an incision into the gingiva, detach and turn over the muco-periosteal flap, and extract the tooth after cutting off the alveolar bone or root separation. All other extractions were defined as simple extractions. With respect to the bleeding tendency, the PT-INR value and platelet count were examined.

HAS-BLED score

The HAS-BLED score was evaluated according to the European Society of Cardiology guidelines[23] (Table 1) and is described below. Patients with a systolic blood pressure of ≥160 mmHg, which was measured on arrival at the hospital, were categorized as having "hypertension." Patients were categorized as having "abnormal renal or liver function" based on

the following conditions: 1) patients receiving hemodialysis or those who had a kidney transplant; 2) patients with a serum creatinine level of ≥2.26 mg/dl in the most recent blood test; 3) patients exhibiting chronic liver disease, such as liver cirrhosis, and bilirubin levels of at least two times the normal upper limit; and 4) patients with at least three times the normal upper limit of either alanine transaminase, aspartate aminotransferase, or alkaline phosphatase levels. Patients were categorized as having "stroke" or "bleeding" based on the information obtained from the medical interviews on admission to the hospital. "Labile INRs" were described as unstable/high INRs or poor time in therapeutic range (e.g., <60%). Patients who were ≥65 years in age at the time of tooth extraction were categorized as "elderly." Patients with long-term administration of antiplatelet agents or non-steroidal anti-inflammatory drugs (NSAIDs) or patients with alcohol dependency were categorized into "drug and alcohol" group. One point was allocated for each of these categories with a possible full score of nine points.

Selection of representative teeth

Of the sequential cases in this study, some patients had duplicate tooth extractions at different time periods; however, the age of the patient, PT-INR values, and the tooth extraction site were different for each extraction. In cases of extraction of multiple teeth in the same patient, each period was treated as independent data with the representative tooth following the procedure. The most posterior tooth was selected as the representative tooth, and in cases of multiple posterior teeth, the upper tooth or the tooth showing the best stability was selected.

Statistical analyses

Statistical analysis involved processing the data of the patient with the representative tooth. Univariate and multivariate logistic analyses were applied to analyze the bleeding risk factors for the tooth extraction data with the presence/absence of post-extraction bleeding as the response variable and the bleeding risk factor as the explanatory variable. Two variable values were used to describe the tooth extraction site (maxilla/mandible), four variable values were used to describe the type of teeth (incisor/premolar/molar/wisdom), two variable values were used to describe the stability of teeth (good/poor), and two variable values were used to describe the surgical procedure (simple/surgical extraction). For the PT-INR value and platelet count, the actual measured values were analyzed as continuous variables, and the HAS-BLED score was

used in the analysis as both a continuous and a nominal variable. Concomitant antiplatelet agents were evaluated as two variable values (yes/no). During logistic analysis, we calculated the risk ratio (RR), 95% confidence interval (CI), and *P* value. The RR was calculated as the ratio of "maxilla" to "mandible" for the site, the tooth type within the anterior teeth for the type of teeth, "good" to "poor" for the condition of the periodontium, and from "surgical" to "simple" for the surgical procedure. The RR for the HAS-BLED score was calculated for each level. For concomitant antiplatelet agents, the RR of "yes" to "no" was calculated. In the multivariate analysis, RRs were combined to create post-extraction bleeding analysis models. For each model, we plotted the receiver operating characteristic (ROC) curve and calculated the area under the curve (AUC) in addition to the *P* value and 95% CI for the C-statistical model overall. Many screening tools have used a C-statistical value of ≥0.70. We used the C-statistic for comparisons between each model. Model 1 was constructed from the extracted tooth state, surgical procedure, and bleeding tendency. Model 2 was constructed from the HAS-BLED score only. Model 3 was constructed by adding the HAS-BLED score to Model 1. Model 4 was constructed by adding concomitant antiplatelet agents as an explanatory variable to Model 1. Data were analyzed with the use of JMP Pro 11 software (2014 SAS Institute Inc., US) with a two-tailed alpha level of 0.05.

Ethics

This study was approved by the ethical review board of the Tokyo Women's Medical University (approval number: 3079). The first and second authors take complete responsibility for the integrity of the data and the accuracy of the data analysis.

RESULTS

A total of 462 extracted teeth in 258 patients (males: 157, females: 101) were analyzed. Post-extraction bleeding was observed in 21 patients (8.1%). Hemostasis with a localized hemostatic procedure was performed in all the cases of post-extraction bleeding and no patients died because of hemorrhage.

Patient characteristics

Post-extraction bleeding was noted in 21 patients (males: 14, females: 7; mean age: 63.4 ±

13.2 years). Table 2 shows the underlying diseases for which anticoagulant therapy was prescribed. The mean warfarin dosage was 3.9 ± 1.4 mg, and the median (25th percentile, 75th percentile) PT-INR was 2.1 (1.8, 2.5). The mean platelet count was 16.8 ± 5.3 × 10^4/μl. Eleven patients were taking only warfarin, and 10 patients were taking an antiplatelet agent in addition to warfarin. Aspirin was administered as the antiplatelet agent in all cases.

The non-post-extraction bleeding group included 237 patients (males: 143, females: 94; mean age: 66.6 ± 13.7 years). The underlying diseases for which anticoagulant therapy was prescribed are shown in Table 2. The mean warfarin dosage was 3.2 ± 1.3 mg. The median (25th percentile, 75th percentile) PT-INR was 2.0 (1.8, 2.3). The mean platelet count was 18.2 ± 5.8 × 10^4/μl. A total of 174 patients were taking only warfarin, and 63 patients were taking warfarin and an antiplatelet agent. Table 2 shows a breakdown of the antiplatelet agents. Seven patients who were taking two types of antiplatelet agents were all categorized into the non-post-extraction bleeding group. Between the two groups, a statistically significant difference was noted for the warfarin dosage; however, no significant difference was noted for PT-INR. In addition, no significant differences were noted for age, sex, platelet count, or concomitant antiplatelet agent use.

Details of the extracted tooth

In the post-extraction bleeding group, the maxilla was the tooth extraction site in 14 cases and the mandible was that in 7 cases. For the non-post-extraction bleeding group, the maxilla was the tooth extraction site in 122 cases and the mandible was that in 115 cases. No significant differences were noted between the two groups (P = 0.254, Fisher's exact test; Table 3).

Results for tooth type

The numbers of incisor, premolar, molar, and wisdom teeth were 1, 2, 9, and 9, respectively, for the post-extraction bleeding group, and 36, 65, 89, and 47, respectively, for the non-post-extraction bleeding group. A statistically significant difference was noted between the two groups (P = 0.039, Fisher's exact test; Table 3).

In the post-extraction bleeding group, 17 cases showed good stability of teeth, whereas 4 cases showed poor stability. In the non-post-extraction bleeding group, 158 cases showed good stability, whereas 79 cases showed poor stability. No statistically significant difference was noted between the two groups (P = 0.227, Fisher's exact test; Table 3).

Extraction procedure

In the post-extraction bleeding group, the selected extraction procedure was simple extraction in 17 cases and surgical extraction in 4 cases. In the non-post-extraction bleeding group, the selected extraction procedure was simple extraction in 165 cases and surgical extraction in 72 cases. No significant differences were noted between the two groups ($P = 0.328$, Fisher's exact test; Table 3).

Number of teeth extracted per operation

The number of teeth extracted per operation was 1.7 ± 0.6 in the post-extraction bleeding group and 1.8 ± 1.1 in the non-post-extraction bleeding group. There were no cases of multiple extractions of four or more teeth in the post-extraction bleeding group. No significant difference was noted between the two groups with respect to the number of teeth extracted per operation ($P = 0.576$, Student's t-test; Table 3).

HAS-BLED score

The highest HAS-BLED score obtained was three points. The mean score was 1.3 ± 0.9 in the post-extraction bleeding group and 1.2 ± 0.8 in the non-post-extraction bleeding group. No statistically significant difference was noted between the two groups ($P = 0.467$, Student's t-test; Table 4).

Statistical examination

Univariate analysis demonstrated statistically significant differences between the wisdom teeth and incisors (RR = 8.894, $P = 0.027$) and between concomitant antiplatelet agents (yes/no) (RR = 2.511, $P = 0.500$). RR was ≤1 for the surgical procedure and platelet count. No statistically significant difference was noted between a HAS-BLED score of ≥3 and a HAS-BLED score of ≤2 (RR = 1.362, $P = 0.7033$; Table 5).

No statistically significant differences were noted within multivariate analysis for any of the parameters in Models 1, 2, or 3. In Model 4, a statistically significant difference was noted for antiplatelet agents (yes) in the non-post-extraction bleeding group (RR = 2.881, $P = 0.035$; Table 6). The AUCs for Models 1, 3, and 4 were 0.7, with a statistically significant difference noted only in Model 4. The AUC for Model 2 was the lowest at 0.5, and a statistically significant difference was noted between Models 2 and 3 ($P = 0.004$; Table 7).

Discussion

Our investigation of 258 tooth extraction patients indicated that post-extraction bleeding occurred in 21 patients (8%), in 39 of the total 462 extracted teeth (8%). In all the cases of post-extraction bleeding, hemostasis was possible with localized hemostatic procedures. The HAS-BLED score alone could not predict post-extraction bleeding. On considering all the risk factors for post-extraction bleeding statistically, concomitant antiplatelet agent use was a risk factor. It has been reported that the incidence of bleeding in an anticoagulation group was the same (approximately 6%–7%) as in an anticoagulation withdrawal group[25]. The post-extraction bleeding in this study was in accordance with this report.

Many cases of tooth extraction that have been performed while continuing anticoagulant therapy have been reported[1, 7-18, 26, 27]. However, in the clinical setting, it is not uncommon to encounter post-extraction bleeding during tooth extraction in cases with an optimal INR value range. In a multicenter large-scale study, Iwabuchi et al.[28] reported that the risk factors for post-extraction bleeding in patients taking warfarin were age, PT-INR, and inflammation at the extraction site. To date, although many reports did not include cases of surgical extraction, such as the extraction of wisdom teeth and impacted teeth, these types of surgical extraction are often performed in the clinical setting. Therefore, this study targeted cases that were managed in the optimal treatment range and concurrently investigated all cases of tooth extraction, including the extraction of wisdom teeth, impacted teeth, and multiple teeth.

Various methods of hemostasis have been reported for cases of tooth extraction performed while continuing warfarin therapy. These include pressure hemostasis alone, wound suturing, and the application of local hemostatic agents[2, 29-31]. To implement hemostasis, we placed a hemostatic gelatin sponge in the extraction socket and routinely conducted pressure hemostasis using absorbent cotton with suturing of the wound. Patients were examined 30 min after tooth extraction to confirm whether the bleeding had stopped. Hemostasis was determined to have been sufficient in all cases. As all patients underwent tooth extraction on an inpatient basis, the patient could rapidly be examined by an oral surgeon or a nurse and could receive early diagnosis and appropriate treatment if post-extraction bleeding was suspected. However, although the patients were examined, many did not require hemostatic treatment. Of the patients who exhibited post-extraction bleeding, no systemic hemostatic treatment, such as blood transfusion, was required in any of the cases.

The HAS-BLED score is used in cardiology to evaluate the risk of hemorrhage in patients with adequate anticoagulation. It would be highly significant if the HAS-BLED score could be used to predict the risk of post-extraction bleeding, and therefore, we evaluated its use in this study. We found that the highest HAS-BLED score was three points. A score of one point was the most commonly achieved score among the 137 patients (53%). The commonest risk factor was age (174 patients; 67%). No significant difference was noted for the mean HAS-BLED score between the post-extraction bleeding and non-post-extraction bleeding groups. The European Society of Cardiology has proposed that a HAS-BLED score ≥ 3 indicates a high risk of hemorrhagic complications. In the cases of post-extraction bleeding, we compared patients with a HAS-BLED score of three or higher with those having a score of two or lower but did not detect any statistically significant difference (univariate analysis; RR = 1.362, $P = 0.703$). Multivariate analysis indicated that there was little risk associated with the score increasing by one (Table 6). The AUC for the HAS-BLED score alone (Model 2) was 0.55, which was the lowest for all of the models that we constructed. In Model 3, to which the details of extracted teeth were added to the HAS-BLED score, AUC was 0.745, suggesting that this model is useful for predicting post-extraction bleeding. However, a statistically significant difference was noted for Model 2 versus Model 3 ($P = 0.004$), indicating that the HAS-BLED score alone was insufficient for predicting post-extraction bleeding.

As bleeding risk factors for tooth extraction, investigation of the conditions of the individual teeth extracted indicated that the post-extraction bleeding risk was five to six times higher for wisdom teeth compared with that for anterior teeth. The extraction site and stability had little effect. Although no differences were observed for the number of teeth extracted in one treatment, there were no cases of multiple extractions of four or more teeth in the post-extraction bleeding group. Although we predicted that surgical extraction was a risk factor for post-extraction bleeding, the results indicated that surgical extraction hardly had any effect on post-extraction bleeding (RR = 0.539, $P = 0.256$).

Effects of warfarin can be possibly affected by the interactions between meals and medicine and by the general state of the patient. Therefore, in this study, to accurately determine the anticoagulation state directly before tooth extraction, all blood tests were performed before breakfast on the tooth extraction day or the first tooth extraction day if tooth extraction was planned on consecutive days. Although post-extraction bleeding cases were receiving high doses

of warfarin, no difference was observed in PT-INR values. There were no cases classified as having labile INRs. Accordingly, the PT-INR value was investigated using actual measured values as the continuous variable. There were no statistically significant differences noted for PT-INR values by either univariate or multivariate analyses ($P \geq 0.1$), suggesting that the PT-INR value had little effect on post-extraction bleeding in patients on anticoagulant therapy while being managed within the optimal treatment range.

There has been no fixed consensus regarding the concomitant use of warfarin and antiplatelet agents because some reports have indicated that these increase the risk of post-extraction bleeding[1,32], whereas other reports have suggested that antiplatelet agents have little effect[16,19]. In this study, the incidence of post-extraction bleeding was 13.7% with concomitant antiplatelet drugs and 5.9% with warfarin alone. Both the univariate and multivariate analyses indicated that the use of concomitant antiplatelet agents was a significant factor affecting post-extraction bleeding. It has been reported that the concomitant use of two antiplatelet agents significantly increases the frequency of intracranial hemorrhaging[33]. Furthermore, a prospective observational study of hemorrhagic complications in Japanese cerebral infarction patients[34] found that compared with patients taking only one antiplatelet agent, those taking two or three antiplatelet agents along with warfarin clearly exhibited higher annual onset rates of intracranial hemorrhaging. These results suggest that concomitant antiplatelet agents are a risk factor for post-extraction bleeding.

The limitations of the present study include the fact that the data were obtained only at a single facility and that outpatients were not included in the subjects that we investigated. In our facility, there were many patients with cardiovascular diseases, particularly post-operative valve replacement patients at approximately 50%. Furthermore, because patients with a PT-INR of ≥3.1 during the blood testing performed on the day of tooth extraction were excluded, the current study included patients whose anticoagulant therapy was well managed. Therefore, our subjects were not exactly representative of generalized cases of tooth extraction patients taking warfarin. Moreover, because this was a retrospective study, we believe that a large-scale, prospective, cohort study, including outpatient tooth extraction cases, needs to be conducted in the future.

Moreover, we could not examine drug interaction effects because our subjects included patients who received intravenous antibacterial agents and patients who received oral antibacterial agents. Warfarin has a number of drug interactions. Holbrook et al.[35] stated that anti-infective agents,

lipid-lowering drugs, NSAIDs, including COX-2 selective NSAIDs, selective serotonin reuptake inhibitors, amiodarone, omeprazole, fluorouracil, and cimetidine enhance the anticoagualtion effects of warfarin. It has been suggested that changing to alternative drugs that have a smaller interactive effect with warfarin should be considered. However, some reports have stated that in most stable anticoagulant therapy patients, exposure to antibacterial agents did not cause clinical problems[36]; furthermore, other reports have found that NSAIDs and antibacterial agents often increased warfarin effects only in cases of long-term administration[18]. We also believe that the short-term or low-dose administration of NSAIDs or antibacterial agents does not cause any prolongation of clinically problematic PT-INR.

Of the models that we created in this study, Model 4 exhibited the highest predictive ability for post-extraction bleeding (AUC = 0.76, $P = 0.0309$). However, because there were no significant differences observed between Models 1 or 3 versus Model 4, we were unable to construct an optimal model for predicting post-extraction bleeding. To increase model precision, it may be beneficial to add other factors, such as the surgeon's skill (e.g., years of experience or time required for one tooth extraction), which were not included in our current investigation. Furthermore, the addition of all extraction data from outpatients to the analysis set is necessary to conduct a multilevel analysis.

Finally, all the patients who had post-extraction bleeding achieved hemostasis with localized hemostatic procedures, and no systemic hemostatic treatment was required. There was no case that warranted extended hospitalization because of post-extraction bleeding. In agreement with our results, Wahl et al.[25] stated that bleeding complications requiring more than local hemostatic measures after dental surgery were exceedingly rare. To avoid the onset of fatal thromboembolism[6], there is no need to pause or interrupt warfarin therapy for tooth extraction. A special environment for the post-extraction bleeding procedure is not necessary. If the conditions are adequately prepared, we believe that tooth extraction in a patient on warfarin therapy is possible in a private office.

CONCLUSIONS

1. We investigated post-extraction bleeding for all types of tooth extractions, including impacted teeth, in patients taking warfarin. Minor post-extraction bleeding was observed in 8% of patients; however, no patients required more than local measures for hemostasis.

2. The HAS-BLED score alone could not predict post-extraction bleeding in patients taking warfarin.

3. The use of concomitant antiplatelet agents was a risk factor for post-extraction bleeding. More care must be taken regarding post-extraction bleeding in cases undergoing concomitant use of antiplatelet drugs than in those on warfarin alone.

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Contributors

TA and TK were involved in the planning of the study concept and design. TK wrote the draft of the manuscript. KH and TK were involved in the statistical analysis. TA and TK reviewed and revised the manuscript. All authors have read and approved the final manuscript.

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Conflicts of interest

The authors have no competing interest to declare regarding this study.

Data sharing statement

No additional data are available.

Provenance and peer review

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Table 1 HAS-BLED bleeding risk score

risk factor		clinical characteristics
H	Hypertension	uncontrolled, >160mmHg systolic
A	Abnomal renal and liver function （1point each)	presence of chonic dialysis, renal pramsplantation or serum creatinine ≧200μmol/L
		chornic hepatic disease(eg, cirrhosis), bilirubin >2X upper limit of nomal,
		AST/ALT/ALP >3X upper limit of nomal
S	Stroke	previous history
B	Bleeding	bleeding history or predisposition
L	Labile INRs	unstable/high INRs or poor time in therapeutic range (e.g. <60%)
E	Elderly	>65 years
D	Drugs or alcohol （1point each)	concomitantly antiplatelet agents and NSAIDs,
		alcohol excess

Criteria from the European Society of Cardiology[23] were used., AST=aspartate aminotransferase, ALT=alanine aminotransferase, ALP=alkaline phosphatase, NSAIDs=nonsteroidal antiinflammatory drugs

Table 2 Patient characteristics

	post-extraction bleeding group N=21 number of patients	non post-extraction bleeding group N=237 number of patients	p value	Significant difference	χ^2 value
Age (mean ± SD)	63.4±13.2	66.6±13.7	0.294[a]		
Gender(Male/Female)	14/7	143/94	0.646[c]		0.32
Primary disease					
post Heart Valve Prosthesis Implantation	17	120			
atrial fibrillation	2	76			
cerebral infarction	2	13			
dilated cardiomyopathy	1	9			
myocardial infarction	0	23			
deep vein thrombosis	0	11			
arteriosclerosis obliterans	0	3			
intracardiac thrombus	0	2			
Anticoagulation					
warfarin dose(mg) (mean ± SD)	3.9±1.4	3.2±1.3	0.024[a]	*	
PT-INR value (mean ［25% tile, 75%tile］)	2.1[1.8, 2.5]	2.0[1.8, 2.3]	0.330[b]		
Platelet count($\times 10^4/\mu l$)	16.8±5.3	18.2±5.8	0.298[a]		
Concomitant antiplatelet agents					
Yes	10	63	0.073[c]		4.21
Aspirin	10	52			
Ticlopidine	0	8			
ethyl icosapentate	0	6			
Cilostazol	0	2			
Limaprost	0	1			
Dipyridamole	0	1			

SD: standard deviation, Multiple factors possible for underlying disease, All seven patients using two types of antiplatelet agents were included in the non post-extraction bleeding group. a; Student's t-test, b;Mann-Whitney U test, c;Fisher's exact test, *:$p<0.05$

Table 3 Details of extracted teeth

	post-extraction bleeding group	non post-extraction bleeding group	p value	Significant difference	χ^2 value
	N=21	N=237			
	number of patients or mean ± SD	number of patients or mean ± SD			
Extraction site					
maxilla	14	122	0.254[c]		1.79
mandibula	7	115			
Tooth type					
Incisor	1	36	0.039[c]	*	8.70
premolar	2	65			
molar	9	89			
wisdom	9	47			
Stability of teeth					
good	17	158	0.227[c]		1.80
poor	4	79			
Extraction procedure					
simple	17	165	0.328[c]		1.19
surgical	4	72			
Number of teeth extracted in operation	1.7 ±0.6	1.8 ±1.1	0.576[a]		
One tooth	8	125	0.188[c]		9.12
Two tooth	12	65			
Three tooth	1	24			
Four tooth	0	18			
Five tooth	0	3			
Six tooth	0	1			
Seven tooth	0	1			

SD: standard deviation, a; Student's t-test, c; Fisher's exact test, *: p〈0.05

Table 4 HAS-BLED score

	post-extraction bleeding group	non post-extraction bleeding group	p value	Significant difference	χ^2 value
	N=21	N=237			
	mean ± SD or number of patients	mean ± SD or number of patients			
HAS-BLED score	1.3±0.9	1.2±0.8	0.467[a]		
0	3	41	0.804[c]		0.75
1	10	127			
2	6	52			
3	2	17			
4	0	0			
5	0	0			
6	0	0			
7	0	0			
8	0	0			
9	0	0			
risk factor					
H	1	3			
A	1	11			
S	2	38			
B	0	5			
L	0	0			
E	13	161			
D	11	63			

SD: standard deviation, a; Student's t-test, c;Fisher's exact test

Table 5 Univariate analysis of bleeding risk factor in teeth extraction

	RR	95%CI		p value	significant difference
		lower	Upper		
Extraction site					
maxilla/mandible	1.885	0.756	5.128	0.177	
Tooth type					
premolar/incisor	1.108	0.103	24.300	0.934	
molar/incisor	3.640	0.649	68.346	0.160	
wisdom/incisor	6.894	1.213	130.039	0.027	*
Stability of teeth					
good/poor	2.125	0.756	7.572	0.161	
Extraction procedure					
surgical/simple	0.539	0.151	1.518	0.256	
PT-INR value	1.782	0.597	5.387	0.300	
Platelet count($\times 10^4/\mu l$)	0.959	0.887	1.037	0.296	
HAS-BLED score					
1/0	1.076	0.312	4.968	0.914	
2/0	1.577	0.391	7.825	0.529	
3/0	1.608	0.199	10.551	0.626	
2/1	1.465	0.477	4.157	0.487	
3/1	1.494	0.218	6.305	0.636	
3/2	1.020	0.140	4.922	0.982	
3/ less than 2	1.362	0.206	5.255	0.703	
Concomitant antiplatelet agents use					
yes/no	2.511	1.001	6.238	0.050	*

Criteria from the European Society of Cardiology[23] were used. RR: risk ratio, *:p〈0.05

Table 6 Multivariate analysis of post-extraction bleeding

	model 1				
	risk ratio	95%CI		p value	significant difference
		lower	upper		
Extraction site					
maxilla/mandible	1.855	0.700	5.286	0.216	
Tooth type					
premolar/incisor	1.118	0.102	24.727	0.928	
molar/incisor	3.468	0.594	65.974	0.188	
wisdom/incisor	5.228	0.850	101.628	0.078	
Stability of teeth					
good/poor	1.790	0.551	6.994	0.344	
Extraction procedure					
surgical/simple	0.624	0.166	1.915	0.425	
PT-INR value	2.078	0.681	6.606	0.204	
Platelet count(x10^4/ul)	0.970	0.892	1.053	0.461	
HAS-BLED score					
1/0	—	—	—	—	
2/0	—	—	—	—	
3/0	—	—	—	—	
2/1	—	—	—	—	
3/1	—	—	—	—	
3/2	—	—	—	—	
Concomitant antiplatelet agents use					
yes/no	—	—	—	—	

Criteria from the European Society of Cardiology[23] were used ,*:p〈0.05

Table 6 continuation

	model 2				
	risk ratio	95%CI		p value	significant difference
		Lower	upper		
Extraction site					
maxilla/mandible	—	—	—	—	
Tooth type					
premolar/incisor	—	—	—	—	
molar/incisor	—	—	—	—	
wisdom/incisor	—	—	—	—	
Stability of teeth					
good/poor	—	—	—	—	
Extraction procedure					
surgical/simple	—	—	—	—	
PT-INR value	—	—	—	—	
Platelet count(x10^4/ul)	—	—	—	—	
HAS-BLED score					
1/0	1.076	0.312	4.968	0.914	
2/0	1.577	0.391	7.825	0.529	
3/0	1.608	0.199	10.551	0.626	
2/1	1.465	0.477	4.157	0.487	
3/1	1.494	0.218	6.305	0.636	
3/2	1.020	0.140	4.922	0.982	
Concomitant antiplatelet agents use					
yes/no	—	—	—	—	

Criteria from the European Society of Cardiology[23] were used., *:p〈0.05

Table 6 continuation

	model 3				
	risk ratio	95%CI		p value	significant difference
		lower	upper		
Extraction site					
maxilla/mandible	1.914	0.716	5.494	0.198	
Tooth type					
premolar/incisor	1.045	0.095	23.222	0.972	
molar/incisor	3.388	0.579	64.544	0.199	
wisdom/incisor	5.380	0.860	105.301	0.075	
Stability of teeth					
good/poor	1.961	0.588	7.893	0.283	
Extraction procedure					
surgical/simple	0.674	0.177	2.125	0.515	
PT-INR value	2.288	0.727	7.543	0.162	
Platelet count(x10^4/ul)	0.968	0.889	1.053	0.443	
HAS-BLED score					
1/0	1.197	0.325	5.777	0.798	
2/0	2.271	0.515	12.242	0.284	
3/0	2.338	0.269	16.989	0.410	
2/1	1.897	0.580	5.871	0.279	
3/1	1.954	0.266	9.403	0.463	
3/2	1.030	0.130	5.605	0.975	
Concomitant antiplatelet agents use					
yes/no	—	—	—	—	

Criteria from the European Society of Cardiology[23] were used. *: p〈0.05

Table 6 continuation

	model 4				
	risk ratio	95%CI		p value	significant difference
		lower	upper		
Extraction site					
maxilla/mandible	1.936	0.722	5.585	0.192	
Tooth type					
premolar/incisor	1.159	0.104	25.901	0.906	
molar/incisor	3.730	0.630	71.468	0.164	
wisdom/incisor	5.113	0.804	100.719	0.804	
Stability of teeth					
good/poor	1.916	0.568	7.780	0.304	
Extraction procedure					
surgical/simple	0.670	0.175	2.117	0.509	
PT-INR value	2.687	0.831	9.349	0.107	
Platelet count(x10^4/ul)	0.970	0.894	1.052	0.465	
HAS-BLED score					
1/0	—	—	—	—	
2/0	—	—	—	—	
3/0	—	—	—	—	
2/1	—	—	—	—	
3/1	—	—	—	—	
3/2	—	—	—	—	
Concomitant antiplatelet agents use					
yes/no	2.881	1.079	7.740	0.035	*

Criteria from the European Society of Cardiology[23] were used., *:p〈0.05

Table 7 Comparison of the model

	AUC	95%CI		p value	significant difference
		lower	upper		
model 1	0.738	0.630	0.824	0.083	
model 2	0.548	0.425	0.666	0.867	
model 3	0.745	0.632	0.832	0.148	
model 4	0.763	0.650	0.847	0.031	*
model 1vs3				0.727	
model 1vs4				0.441	
model 2vs3				0.004	*
model 3vs4				0.398	

AUC; area under the curve, * : p〈0.05

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 2,3
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 2,3
Methods			
Study design	4	Present key elements of study design early in the paper	Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 3-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 3-7
Bias	9	Describe any efforts to address potential sources of bias	Page 3
Study size	10	Explain how the study size was arrived at	Page 3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 3-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 6
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	Page 6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 7-9
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 7-9
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 7-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and	Page

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(*b*) Report category boundaries when continuous variables were categorized	Page 7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 14