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Safety of tooth extraction in patients receiving direct oral anticoagulant treatment versus warfarin: a prospective observation study

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Abstract. The aim of this study was to compare the safety of tooth extraction in patients receiving direct oral anticoagulants (DOACs) or warfarin without cessation of their antithrombotic treatment. This prospective observational study included 367 patients undergoing tooth extraction (119 receiving DOACs and 248 receiving warfarin). All extractions in DOAC patients were performed 6–7 h after taking DOACs in consideration of the half-life in blood under continued antithrombotic treatment. To examine the potential postoperative bleeding risk related to the time of extraction and the drug concentration of blood, activated partial thromboplastin time (APTT) in dabigatran and prothrombin time (PT) in rivaroxaban were measured three times after administration. A total of 390 tooth extractions were performed: 128 in the DOAC patients and 262 in warfarin patients. Postoperative bleeding occurred in four extractions (3.1%) in the DOAC group and in 23 (8.8%) in the warfarin group. There was no statistically significant difference between the two groups (odds ratio: 2.362, 95% confidence interval (CI) 0.819–6.815, $p = 0.112$). APTT and PT prolongation in almost all cases decreased with time after taking the medicine. Our findings suggest that interruption of DOAC therapy is not necessary for tooth extraction if the procedure is performed at least 6 h after the last dose.

Key words: direct oral anticoagulants (DOACs); tooth extraction; warfarin; bleeding.

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Direct oral anticoagulants (DOACs) have recently been introduced as an alternative to warfarin, and the number of patients using them is increasing. DOACs are divided into two subgroups (direct thrombin inhibitors and factor Xa inhibitors) based on differences in the target factor in the coagulation cascade. Dabigatran is a direct thrombin inhibitor, and was the first DOAC to be approved for the prevention of stroke in patients with atrial fibrillation and systemic embolism. Taken twice daily, the drug's peak blood concentration is reached around 1–3 h after dosing. The factor Xa inhibitor group contains three DOACs: rivaroxaban, apixaban and edoxaban. Rivaroxaban and edoxaban are taken once daily, and apixaban twice daily[1]. Each peak blood concentration after dosing is reached at around 1–4 h[1]. DOACs are characterized by rapid efficacy, a short half-life and fewer interactions with other drugs and food in comparison with warfarin[2,3]. The activated partial thromboplastin time (APTT) is responsive to dabigatran, and the prothrombin time (PT) is affected by rivaroxaban and edoxaban, and weakly by apixaban in a dose-dependent manner[1]. The usual coagulation screening assays such as APTT and PT are considered to be unreliable in distinguishing therapeutic from subtherapeutic levels of these agents. Because DOACs have predictable pharmacodynamics and are administered in a fixed-dose regimen, routine therapeutic monitoring is not required as it is with warfarin[1,4].

DOACs are indicated for the prevention of stroke in patients with nonvalvular atrial fibrillation, and the treatment and prevention of deep vein thrombosis[1,5]. Patients treated with DOACs generally belong to the older population, who are likely to have multiple comorbidities. As the number of these patients increases, the management of their dental needs, such as tooth extraction, becomes increasingly important. However, few studies have investigated the perioperative management of such patients. Many of the previous articles consist of small numbers of patients, reviews and case reports[6–8]. Compared with warfarin, there are insufficient scientific data and clinical research on DOACs. Therefore, in this study we focused on the safety of tooth extraction in patients treated with DOACs. This prospective study aimed to: (1) compare the incidence of postoperative bleeding after tooth extraction between patients treated with DOACs and those using warfarin, without cessation or modification of their antithrombotic treatment; and (2) investigate the risk factors for postoperative bleeding after tooth extraction in patients under continued DOAC therapy.

Materials and methods

This prospective observational study included 367 patients who received either DOAC or warfarin therapy and underwent tooth extraction at the Oral Surgery Department of the Kyushu Medical Center in Fukuoka, Japan, between July 2011 and March 2018. They were divided into two groups: the DOAC group and the warfarin group. In all patients receiving warfarin, the international normalized ratio (INR) was measured within 24 h prior to tooth extraction. Tooth extraction could be performed safely in patients taking warfarin without cessation if the INR was controlled within the therapeutic range. In our department, all tooth extractions since 2004 have been performed without cessation of warfarin[9].

Dabigatran was first approved for use in Japan in 2011, and rivaroxaban and apixaban were approved in 2012 and 2013, respectively. All four DOACs, including edoxaban, have been approved and used from 2015. We had no clinical experience in the perioperative management of patients taking dabigatran who required extraction of teeth, and there was limited information available about dental surgery in these patients. Therefore, we developed a protocol for tooth extraction in patients taking dabigatran based on the report of Stangier et al.[10]. The peak plasma concentration and the maximum pharmacodynamic effect of dabigatran were attained approximately 2 h after dosing. APTT was responsive to dabigatran, and the time curve for APTT paralleled the plasma concentration–time curve with values increasing rapidly and in a dose-dependent manner[10]. On average, APTT prolongation declined to almost half of the maximum within 6–8 h of dosing[10]. Therefore, we decided to perform tooth extraction more than 6 h after taking dabigatran without interruption or modification[11]. Because the half-lives of all DOACs were similar, we decided to perform tooth extraction in patients taking rivaroxaban, apixaban and edoxaban in the same time period using the same method, without interruption or modification. Investigated items were patient characteristics (age, sex), history of stroke, indications for anticoagulant therapy, type of oral anticoagulant therapy (dabigatran, rivaroxaban, apixaban, edoxaban, warfarin), antiplatelet combination therapy, number and type of teeth extracted, type of tooth extraction (nonsurgical, surgical, impacted) and number of cases of postoperative bleeding.

All tooth extractions in patients receiving DOACs and warfarin were performed under local anaesthesia in accordance with established clinical protocols by several oral surgeons. The patients receiving DOACs were hospitalized for a few days because of the limited information available about the perioperative management. Local haemostasis was achieved by applying a resorbable gelatin sponge in the extraction socket, and the wound was closed with 3-0 silk sutures, as in tooth extraction in patients taking warfarin. After surgery, the patients were asked to bite on sterile gauze for at least 1 h to compress the surgical area. After release of the biting pressure, the wound was examined for haemostasis. In patients taking dabigatran and apixaban, the next dose was administered when haemostasis was maintained. The follow-up appointment was 7 days after surgery to remove the sutures. Patients were discharged from hospital after confirmation of haemostasis on the day after surgery. Postoperative bleeding was defined as oozing or marked haemorrhage that could not be stopped by wound compression with gauze, and haemostasis that required medical intervention such as haematoma removal, curettage, suturing, or splint placement. Tooth extraction was divided into three groups: nonsurgical extraction (extraction using forceps and/or elevator); surgical extraction (extraction with elevation of a mucoperiosteal flap and/or osteotomy); and impacted tooth extraction.

APTT was responsive to dabigatran, and PT was affected by rivaroxaban and edoxaban and weakly by apixaban in a dose-dependent manner. To examine the potential postoperative bleeding risk related to the time of tooth extraction and the drug concentration in the blood, APTT was measured in dabigatran patients and PT was measured in rivaroxaban patients 3 h after taking the drug (almost peak drug concentration) and 6–7 h after taking the drug (just before tooth extraction). In patients taking rivaroxaban, the third PT measurement was made before the drug was taken on the next day (trough value). In patients taking dabigatran, because the next dose after tooth extraction was postponed or skipped depending on the condition of haemostasis, the third APTT measurement was also made before the drug was taken on the next day.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation or median

(interquartile range) depending on distribution; categorical variables were expressed as number and percentages. On statistical analysis, independent two-sample *t*-tests and χ^2 tests were used to compare the patients' characteristics. Univariable, age- and sex-related, or multivariable adjusted odds ratios and 95% confidence intervals (CIs) for postoperative bleeding of each anticoagulant medicine group were determined using a logistic regression model adjusted for potential confounding covariates.

As subanalysis, we used a univariable mixed linear model to evaluate APTT in patients taking dabigatran and PT in patients taking rivaroxaban at all time points: 3 h after taking the anticoagulant medicine, before extraction (about 6–7 h after taking it), and before taking it the next day. In this analysis, we only used the patients from whom APTT and PT data were collected through all time points. All analyses were performed using R version 3.3.4. For all analyses, the level of significance was set at $p < 0.05$.

Results

A total of 367 patients were included: 119 were being treated with DOACs (82 males and 37 females) and 248 with warfarin (163 males and 85 females). In the DOAC group, 32 patients were taking dabigatran, 31 were taking rivaroxaban, 39 were taking apixaban and 17 were taking edoxaban. The mean age was 74.6 ± 10.1 years in the DOAC group and 71.6 ± 10.1 years in the warfarin group. The DOAC group was significantly older than the warfarin group ($p = 0.015$). Table 1 lists the patients' characteristics. Almost 90% of DOAC patients were medicated to prevent stroke in nonvalvular atrial fibrillation, whereas the warfarin patients were medicated to prevent stroke in valvular heart disease, artificial heart valves and atrial fibrillation, or to prevent recurrence of myocardial infarction. Antiplatelet combination therapy was more frequent in the warfarin group than in the DOAC group. There was no significant difference in sex and history of stroke between the two groups.

A total of 390 tooth extractions were performed: 128 in the DOAC group and 262 in the warfarin group. The DOAC group included patients taking dabigatran (37 extractions), rivaroxaban (34 extractions), apixaban (39 extractions) and edoxaban (18 extractions). Data on the number and type of extractions are summarized in Table 2. Nonsurgical extraction in the DOAC group was more frequent ($p = 0.023$) than in the warfarin group. Postoperative bleeding occurred after four tooth extractions (3.1%) in the DOAC group and after 23 tooth extractions (8.8%) in the warfarin group. The risk of postoperative bleeding in the warfarin group was significantly higher (odds ratio 2.983, 95% CI 1.017–8.748, $p = 0.046$) than in the DOAC group by univariable logistic analysis, taking into consideration repeated extraction for the same patient. Multivariable analysis was performed using age, male sex, antiplatelet combination therapy, atrial fibrillation and impacted or surgical/nonsurgical as a regulatory factor, and the results showed no statistically significant difference ($p = 0.113$) in postoperative bleeding between the two groups (Table 3).

APTT was measured in 21 patients receiving dabigatran, and PT was measured in 28 patients taking rivaroxaban.

Table 1. Patient characteristics.

	Antithrombotic therapy		
	DOACs	Warfarin	*p*
No. of patients	119	248	
Age (years)	74.6 ± 10.1	71.6 ± 10.1	0.015
Male/female	82/37	163/85	0.557
Indication of anticoagulant therapy			
Atrial fibrillation	107 (89.9)	128 (51.6)	<0.001[a]
Valvular heart disease	0 (0)	67 (27)	
Myocardial infarction, other heart disorders	1 (0.8)	32 (12.9)	
Deep vein thrombosis	9 (7.6)	6 (2.4)	
Stroke	2 (1.7)	7 (2.8)	
Others	0 (0)	8 (3.2)	
History of stroke	21 (17.6)	51 (20.6)	0.575
Antiplatelet combination therapy	18 (15.1)	83 (33.5)	<0.001
INR, mean	–	2.08 ± 0.47	–
Oral anticoagulant therapy			
Dabigatran	32 (26.9)	0 (0)	
Rivaroxaban	31 (26.1)	0 (0)	
Apixaban	39 (32.8)	0 (0)	
Edoxaban	17 (14.3)	0 (0)	

Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation. DOACs, direct oral anticoagulants; INR, international normalized ratio.

[a] Compared the reason of anticoagulant therapy between Af or others.

Table 2. Tooth extraction and bleeding characteristics.

	Antithrombotic therapy		
	DOACs	Warfarin	*p*
No. of tooth extractions (occasions)	128	262	–
No. of teeth extracted	288	567	–
Nonsurgical extraction	279 (96.9)	523 (92.2)	0.023
Surgical extraction	6 (2.1)	25 (4.4)	–
Impacted extraction	3 (1)	19 (3.4)	–
Surgical or impacted extraction	9 (3.1)	44 (7.8)	0.007
No. of removed teeth	2 (1, 3)	1 (1, 2)	0.759
1 tooth	57 (44.5)	122 (46.6)	0.746
More than 2 teeth and impacted	71 (55.5)	140 (53.4)	0.746
More than 3 teeth and impacted	41 (32)	77 (29.4)	0.639
More than 4 teeth and impacted	23 (18)	56 (21.4)	0.503
More than 5 teeth and impacted	18 (1.6)	49 (6.9)	0.317
Impacted tooth	2 (1.6)	18 (6.9)	0.027
No. of postoperative bleeding	4 (3.1)	23 (8.8)	0.054
Dabigatran	37 (28.9)	0 (0)	
Rivaroxaban	34 (26.6)	0 (0)	
Apixaban	39 (30.5)	0 (0)	
Edoxaban	18 (14.1)	0 (0)	
Management of bleeding			
Local compression	2 (50)	11 (47.8)	1
Reoperation	2 (50)	12 (52.2)	1

Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median (interquartile range). DOACs, direct oral anticoagulants.

Table 3. Comparison of direct oral anticoagulants (DOACs) and warfarin in postoperative bleeding.

	Odds ratio	95% confidence interval	*p*
Model 1			
Warfarin vs. DOACs	2.983	1.017–8.748	0.046
Model 2			
Warfarin (vs. DOACs)	2.619	0.893–7.683	0.080
Age, 1 year	0.958	0.932–0.985	0.002
Male gender (vs. female)	0.964	0.422–2.202	0.931
Model 3			
Warfarin (vs. DOACs)	2.362	0.819–6.815	0.112
Age, 1 year	0.968	0.940–0.995	0.023
Male gender (vs. female)	1.111	0.464–2.662	0.813
Antiplatelet combination therapy	2.032	0.762–5.417	0.157
Atrial fibrillation	0.504	0.218–1.163	0.108
Model 4			
Warfarin (vs. DOACs)	2.380	0.814–6.961	0.113
Impacted or surgical/non-surgical	0.873	0.257–2.963	0.827
Age, 1 year	0.966	0.938–0.996	0.025
Male gender (vs. female)	1.106	0.382–2.142	0.819
Antiplatelet combination therapy	2.041	0.762–5.462	0.156
Atrial fibrillation	0.499	0.217–1.150	0.103

APTT and PT were both most prolonged at 3 h after drug administration. The APTT declined from 46.3 (95% CI 40.8–51.9) to 44.4 (95% CI 39.8–49.0) in dabigatran ($p = 0.139$), and the PT declined from17.9 (95% CI 15.9–19.9) to 17.3 (95% CI 15.8–18.8) in rivaroxaban before tooth extraction ($p = 0.133$). Before the dose on the following day was taken, the anticoagulant effect (prolonged APTT) decreased significantly from 46.3 (95% CI 40.8–51.9) to 41.8 (95% CI 37.8–45.7) in dabigatran ($p = 0.003$), and the prolonged PT decreased significantly from 17.9 (95% CI 15.9–19.9) to 14.2 (95% CI 13.4–15.0) in rivaroxaban ($p < 0.001$) when compared with the values 3 hours after taking the dose (Figs. 1 and 2).

All cases of postoperative bleeding in the warfarin group were managed by local haemostatic measures such as compression with gauze, curettage and sutures without the cessation of warfarin. In the DOAC group, two bleeding events occurred with apixaban, one with dabigatran, and one with edoxaban. Two of the postoperative bleeding events (apixaban and edoxaban) were easily stopped by haematoma removal and wound compression with gauze. The remaining two bleeding events (one in a dabigatran patient and one in an apixaban patient) were associated with systemic factors described below, making it necessary to skip the next DOAC dose after additional local haemostatic measures such as curettage and suturing to ensure wound haemostasis. The dabigatran patient was a 75-year-old man with moderate kidney dysfunction and a prolonged APTT of 71.8 s, 3 h after dosing (32.9 s before the introduction of dabigatran). Because the APTT decreased to 60.5 s before the procedure, four teeth were extracted. Postoperative bleeding occurred after taking the next dose. Although the bleeding event was controlled with haematoma removal and suturing, the APTT was prolonged to 63 s even before taking dabigatran on the next day, so the dose was skipped to avoid further bleeding. The next dose was restarted after confirming haemostasis. The apixaban patient who experienced a bleeding event was an 80-year-old man with anemia associated with liver metastasis of oesophageal cancer (the liver dysfunction was considered to be a systemic factor). Five teeth were extracted. Postoperative bleeding occurred on day 5 after the procedure. Although local haemostasis measures were successful, the next dose of apixaban was skipped to avoid further bleeding. No thromboembolic complications were reported in either case.

Discussion

Four DOACs, namely dabigatran, rivaroxaban, apixaban and edoxaban, have been increasingly used worldwide as an alternative to warfarin. In this study, DOACs were predominantly prescribed to prevent stroke in nonvalvular atrial fibrillation, whereas warfarin has been commonly used to prevent stroke in persons with valvular heart disease, artificial heart valves and atrial fibrillation, and to prevent recurrence of myocardial infarction. In this study, more than twice as many patients were enrolled in the warfarin group ($n = 248$) than in the DOAC group ($n = 119$). After dabigatran was first approved in Japan in 2011, rivaroxaban, apixaban and edoxaban were approved in 2012, 2013 and 2014, respectively. Our study was conducted under the same conditions during the same period without adding any special considerations regarding patient selection. The number of patients taking DOACs is increasing year on year. However, warfarin has more broad indications than DOACs, and is still prescribed for many patients even now in Japan. Patients in whom treatment with DOACs is contraindicated (e.g., renal dysfunction, left ventricular thrombus, atrial valve implantation) will continue to be treated with warfarin.

The average age in the DOAC group was significantly higher than that in the warfarin group. DOACs have been reported to be more successful than warfarin in reducing the rate of major bleeding and intracranial haemorrhage[4,12]. In Japan, the number of older patients being treated with DOACs has increased because of the advantage of a reduced incidence of intracranial haemorrhage and major bleeding, as well as a rapid onset and short half-life. These factors may have increased the average age in the DOAC group.

It has been reported that in patients treated with warfarin, thromboembolic events occurred at a frequency of between 0.02% and 1% when warfarin was discontinued prior to tooth extraction[13,14]. Therefore, tooth extraction without cessation of warfarin has become a standard procedure when the INR is controlled under the therapeutic range[15–17]. DOAC treatment, by contrast, is novel, and there are still few studies that have investigated perioperative management of patients taking DOACs. A review by Johnston[8] reported that most of the literature consisted of non-structured review articles and guidance documents based on assumptions from nondental data and expert opinion, and recommendations about best practice varied throughout. Our study was focused on tooth extraction in patients being treated with DOACs. We performed 128 tooth extractions under continued DOAC therapy to evaluate the incidence of postoperative bleeding, and compared our findings with those for 262 tooth extractions in warfarin patients. According to past studies, the incidence of postoperative bleeding in patients receiving DOAC therapy ranged from 5.5% to 40%[3,19–22] as compared with 2% to 26%[15–18] in patients receiving warfarin therapy. Mauprivez et al.[3] compared the incidence of postop-

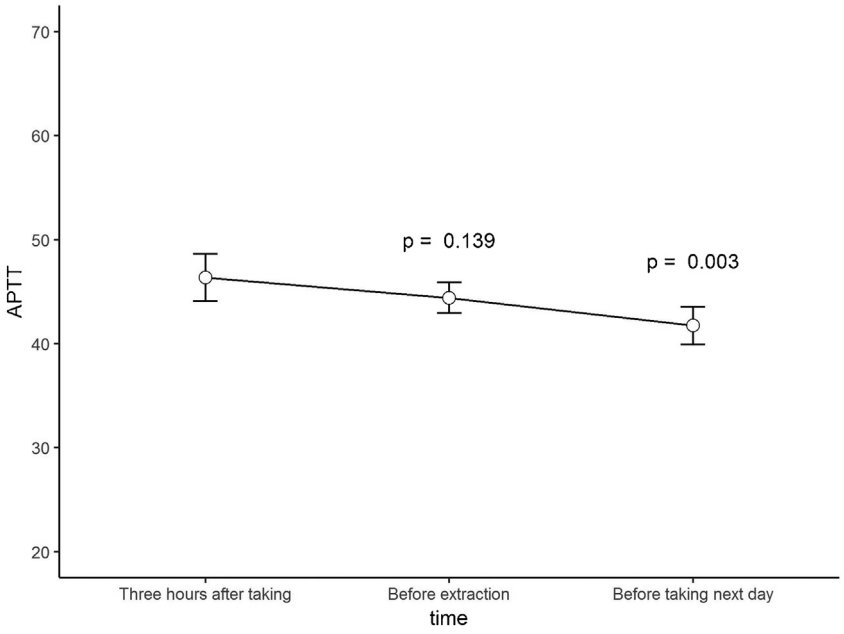

Fig. 1. Change in activated partial thromboplastin time (APTT) before and after extraction in patients taking dabigatran. APTT was measured in 21 patients taking dabigatran. The APTT decreased from 46.3 (95% confidence interval (CI) 40.8–51.9) at 3 h after taking dabigatran to 44.4 (95% CI 39.8–49.0) before extraction ($p = 0.139$), and decreased significantly to 41.8 (95% CI 37.8–45.7) before taking the medication the next day ($p = 0.003$).

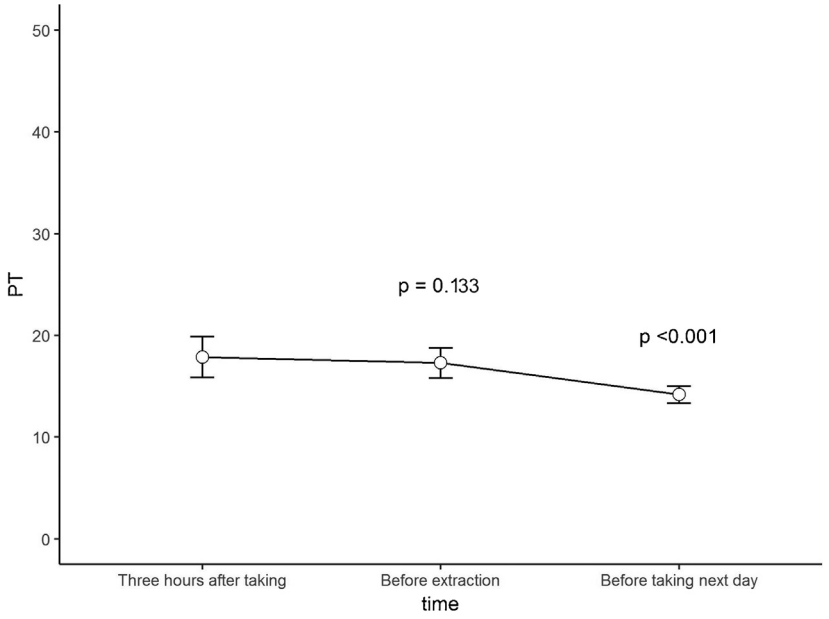

Fig. 2. Change in PT before and after extraction in patients taking rivaroxaban. Prothrombin time (PT) was measured in 28 patients taking rivaroxaban. The PT decreased from 17.9 (95% confidence interval (CI) 15.9–19.9) at 3 h after taking rivaroxaban to 17.3 (95% CI 15.8–18.8) before extraction ($p = 0.133$), and decreased significantly to 14.2 (95% CI 13.4–15.0) before taking the medication the next day ($p < 0.001$).

erative bleeding after tooth extractions between a DOAC group (31 patients) and a vitamin K antagonist (VKA) group (20 patients). Five patients (16.13%) taking DOACs had seven bleeding episodes while four patients (20%) taking VKAs had five bleeding episodes. Patel et al.[21] examined 111 oral surgical procedures including 35 procedures in which DOACs were ceased before and/or after treatment in 82 patients, and reported a postoperative bleeding incidence of 13.5%. The incidence of bleeding events in our study was 3.3%, which was lower than that reported in previous studies. In the present study, all tooth extractions were performed more than 6 h after taking DOACs without interruption or modification of the medication, based on the half-life of the drugs. It is likely that performing the extractions while taking the blood concentration of the drug into account contributed to our low postoperative bleeding rate. To the best of our knowledge, no studies thus far have designated the time of tooth extraction and examined the safety of tooth extractions without cessation of

DOAC therapy. To minimize postoperative bleeding and complications, it is important to consider the time at which the DOAC is usually taken and plan the procedure accordingly.

In our study, to examine the potential postoperative bleeding risk in relation to the time of tooth extraction and the drug concentration in the blood, we measured the APTT in dabigatran and the PT in rivaroxaban 3 h and 6–7 h after drug administration, and before administration the next day. We confirmed that APTT and PT prolongation in almost all cases decreased just before tooth extraction and before taking medication the next day, compared with 3–4 h after dosing. This tendency is assumed to be the same for the other two drugs (apixaban and edoxaban). From our outcomes, we recommend that tooth extraction should be performed at least 6 h after the last dose of the DOAC is taken to take advantage of the lower DOAC plasma level. In this study, because DOACs in all patients were taken in the morning, tooth extraction was performed in the afternoon without skipping or changing the time of administration. In the case of once-daily administration such as rivaroxaban and edoxaban, and taking it in the afternoon or evening, tooth extraction should be performed the next morning when the blood concentration of the drug is at its lowest.

Postoperative bleeding occurred after four procedures in four patients in our study. Two cases were controlled by haematoma removal and local compression. Because the remaining two bleeding events were associated with systemic factors, it was necessary to skip the next dose to ensure haemostasis of the wound. In patients taking one daily dose of rivaroxaban and edoxaban, the anticoagulation effect almost disappears after 24 h, and the risk of postoperative bleeding decreases in a time-dependent manner. If postoperative bleeding is continuous, insufficient local haemostasis is likely to be the cause rather than the effect of the DOACs. Therefore, additional local haemostasis measurements should be performed before the next dose is taken. However, for dabigatran and apixaban, which are taken twice daily, the anticoagulation effect is maintained even before taking the next dose, and the level in the blood depends on the patient's kidney function and general condition. About 80% of dabigatran is excreted from the kidneys[3,7]. We should be aware that extreme prolongation of APTT may occur in patients with renal dysfunction. Indeed, one case of postoperative bleeding occurred in a patient with moderate renal dysfunction. In cases in which moderate or severe bleeding occurs, and a strong anticoagulation effect is presumed when local haemostasis is not sufficient, the next dose should be skipped or delayed in collaboration with the patient's physician. On the one hand, ATPP can be used as a parameter for risk screening for excess drug concentrations in patients taking dabigatran. On the other hand, PT is sensitive for rivaroxaban; however, the response differs according to the reagents used and cannot be standardized across laboratories. In some situations, including continuous bleeding or emergent surgery such as inflammation and injury, it is useful to assess excessive anticoagulant effects. The measurement of PT before tooth extraction is not necessary for routine screening except for specific patients with renal or liver dysfunction. Recently idarucizumab, a monoclonal antibody fragment, was developed to neutralize the activity of dabigatran. It is not expected that dental practitioners would need to use the reversal agent for haemostasis because postoperative bleeding in the oral cavity is usually visible. Local haemostatic measures are of most importance. Sutures combined with gelatin sponges or cellulose, and compression of the wound with gauze, are essential for reducing the risk of postoperative bleeding.

We investigated the risk factors for postoperative bleeding after tooth extraction in patients under continued DOAC therapy. These risk factors have systemic and local influences. From our results, the timing of tooth extraction, i.e. the drug concentration in the blood, is the most important risk factor. Since DOACs are characterized by a short half-life in blood compared with warfarin, the risk of bleeding after tooth extraction can be reduced by considering the blood concentration of the drug. Age (older population) is usually considered to be a risk factor for postoperative bleeding, although being elderly itself is not a risk factor. Systemic complications such as renal or liver dysfunction can be a risk factor. The mean age of the DOAC group was higher than that of the warfarin group; however, postoperative bleeding did not increase in comparison with the warfarin group. As the incidence of total postoperative bleeding was only 3.3% (four cases), the number of events might be too small to verify the risk factors. Our findings did not identify any local bleeding risk factors such as the type, site, or number of tooth extractions and antiplatelet combination therapy in patients taking DOACs.

In conclusion, our findings suggest that interrupting DOAC therapy is not necessary for tooth extraction. There was no significant difference in postoperative bleeding between the DOAC group and the warfarin group. Tooth extraction in patients under continued DOAC can be performed without high risk. The surgical procedure should be performed at least 6 h after the last dose of the DOAC, decreasing the peak plasma levels of DOACs. In this study the tooth extractions were performed under hospitalization, although our findings suggest that treatment as an outpatient would be possible. The measurement of APTT in dabigatran can be used as a parameter for risk screening for excess drug concentration. PT in rivaroxaban before a surgical procedure is not necessary for routine screening except for specific patients with renal or liver dysfunction. An accurate medical history and physical examination are particularly important for the assessment of bleeding risk in older patients. Further study is needed to confirm our results.

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Competing interests

The authors have no conflicts of interest to declare.

Ethical approval

The study protocol was approved by the ethics committee of the National Hospital Organization Kyushu Medical Center in 2010 (KMC 10-61). The study was conducted as part of MARK research, and the Declaration of Helsinki guidelines were followed.

Patient Consent

All patients gave written informed consent to participate.

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