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ORIGINAL ARTICLE

Tooth extraction in patients taking nonvitamin K antagonist oral anticoagulants

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KEYWORDS
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Abstract *Background/purpose:* The nonvitamin K antagonist oral anticoagulants direct-thrombin inhibitor dabigatran and the Xa inhibitors rivaroxaban and apixaban are now being used clinically. The course of the patients on these anticoagulants who underwent tooth extraction was assessed.
Materials and methods: The medical charts of these patients were investigated. Tooth extraction was performed while maintaining conventional anticoagulant therapy.
Results: Twenty-three teeth were extracted in 19 patients, including two surgical extractions. Among the 19 patients, nine patients ingested rivaroxaban, six apixaban, and four dabigatran. One patient on rivaroxaban showed persistent postoperative bleeding following two surgical extractions. Mild oozing was observed in five patients (two on rivaroxaban and three on apixaban). There was no bleeding episode in the patients on dabigatran.
Conclusion: The patients on rivaroxaban with a prolonged prothrombin time value have a higher risk of bleeding, especially undergoing surgical extraction. Apixaban correlates to neither activated partial thromboplastin time nor prothrombin time values and the countermeasures should be employed based on the clinical findings.

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Introduction

Nonvitamin K antagonist oral anticoagulants (NVKAs) have been developed as an alternative to warfarin. The direct thrombin inhibitor dabigatran and the Xa inhibitors rivaroxaban and apixaban are now being used clinically.

In mega-studies on efficacy for stroke prevention of each drug [RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study for dabigatran,[1] the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) study for rivaroxaban,[2] and the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) study for apixaban[3]], each drug was compared with warfarin in atrial fibrillation (AF) patients and found to be not inferior for prevention of stroke (stroke incidence: dabigatran 1.53%/y vs. warfarin 1.69%/y; rivaroxaban 1.7%/y vs. warfarin 2.2%/y; apixaban 1.27%/y vs. warfarin 1.60%/y), with less hemorrhagic incidence (major bleeding: 110 mg of dabigatran, 2.71%/y vs. warfarin 3.36%/y; apixaban 2.13%/y vs. warfarin 3.09%/y; intracranial hemorrhage: rivaroxaban 0.5%/y vs. warfarin 0.7%/y).[1–3]

With regard to metabolism of dabigatran and rivaroxaban, 70% is excreted by the kidneys and 30% is metabolized by the liver, followed by excretion in the urine and feces,[4,5] while 30% of apixaban is excreted by the kidney and 70% metabolized by the liver. The peak plasma levels of dabigatran, rivaroxaban, and apixaban were measured after 3—4 hours. The half-life was 11—13 hours for dabigatran, 9—13 hours for rivaroxaban, and 8—15 hours for apixaban.[4,5]

The dose adjustments based on prothrombin time-international normalized ratio values, as with warfarin, are not necessary for these drugs. Therefore, NVKAs are increasingly being prescribed based on ease of use by both patients and physicians.

Continued treatment with dabigatran, rivaroxaban, or apixaban of patients undergoing tooth extraction is recommended because of a low rate of major bleeding.[6] However, there have been few reports of surgery-related hemorrhagic events and no uniform consensus exists regarding the management strategy. The purpose of this case series was to assess the course of patients on dabigatran, rivaroxaban, or apixaban who underwent tooth extraction. Additionally, a strategy for hemostatic management is discussed.

Materials and methods

Patients

The present study protocols were approved by the institutional review board and ethics committee of Kyushu University Hospital in compliance with the Helsinki Declaration. In the present study, the medical charts of patients were retrospectively reviewed to investigate the items below.

Tooth extraction was performed in patients on conventional dabigatran, rivaroxaban, or apixaban therapy between April 2013 and January 2015 at the Special Patient Oral Care Unit, Kyushu University Hospital.

The items investigated were patient characteristics (age and sex), dose of dabigatran, rivaroxaban, or apixaban, degree of anticoagulant effects [prothrombin time (PT) or activated partial thromboplastin time (APTT) value on the nearest day of tooth extraction], site and number of extracted teeth, type of tooth extraction (simple or surgical), time of extraction, and incidence of cases of postoperative hemorrhage. Furthermore, platelet count, blood urine nitrogen (BUN), creatinine, aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) were also recorded as laboratory data.

In patients at risk for infective endocarditis, amoxicillin was administered according to guidelines published by the Japanese Circulation Society in order to prevent infective endocarditis.[7] As analgesics, either loxoprofen sodium or acetaminophen was administered as needed.

Tooth extraction and local hemostatic management

Tooth extraction was performed while continuing to maintain doses of dabigatran, rivaroxaban, or apixaban. Local anesthesia was induced using 3% prilocaine (containing 0.054 IU of felypressin). Teeth were extracted in a minimally invasive manner using elevators and forceps, and inflamed granulation tissue was completely curetted. As for local hemostatic measures after tooth extraction, extraction wounds were packed with oxidized cellulose (Surgicel; Ethicon, Somerville, NJ, USA) or atelocollagen sponge (Telpulug, Terumo, Tokyo, Japan), and then horizontal mattress sutures using 4-0 silk were given. When hemostasis could not be achieved using these procedures, bleeding points in soft tissue were cauterized using electrocautery, when necessary. Each patient was asked to bite down on gauze for 30 minutes for compression, and hemostasis was confirmed. The wounds were protected by a surgical acrylic splint with periodontal pack when needed. Sutures were removed after 1 week. Tranexamic acid mouth wash was not used, as use of this agent is not approved in Japan. Likewise, fibrin glue was not used because this agent is not indicated for use during tooth extraction in Japan.

Results

Patient characteristics

The patients (19) included 17 men and two women, with ages ranging from 43 years to 86 years. Twenty-three teeth were extracted, including two surgical extractions (Table 1). Among the 19 patients, nine took rivaroxaban, six apixaban, and four dabigatran. Most of the teeth were extracted 4—9 hours after taking the anticoagulant. Two patients (Cases 15 and 17) received concomitant aspirin (100 mg/d). All patients receiving rivaroxaban indicated prolonged PT values, and most patients receiving dabigatran indicated prolonged APTT values. There were no patients with severe renal or liver dysfunction or thrombocytopenia.

One patient on rivaroxaban showed persistent postoperative bleeding, and mild oozing for short durations was observed in five patients (Table 1). Adequate hemostasis was achieved in all other patients postoperatively.

Table 1 Patient characteristics.

Case	Age (y)	Sex	NVKA	Dose (/d)	PT (s)	APTT (s)	Extracted tooth (*n*)	Extraction type	Postope rative bleeding	Extraction time	Laboratory test					
											PLT ($\times 10^4/\mu L$)	BUN (mg/dL)	Crea (mg/dL)	AST (U/L)	ALT (U/L)	ALP (U/L)
1	74	Male	Rivaroxaban	10 mg	UM	UM	18	Simple	None	10:30	26.0	15	1.40	20	12	UM
2	69	Male	Rivaroxaban	15 mg	17.1	53.7	27	Simple	Mild	11:30	26.4	13	0.86	20	18	197
3	60	Male	Rivaroxaban	10 mg	18.5	46.0	38 37	Surgical hemisection	Severe	13:00	11.7	44	1.47	21	14	UM
4	86	Female	Rivaroxaban	10 mg	16.8	49.5	12,14	Simple	Mild	12:30	18.6	21	1.10	18	9	140
5	74	Male	Rivaroxaban	15 mg	13.5	UM	46	Simple	None	11:30	14.5	13	0.95	70	64	UM
6	84	Female	Rivaroxaban	10 mg	UM	UM	24	Simple	None	11:30	11.2	34	1.10	18	9	UM
7	80	Male	Rivaroxaban	10 mg	16.2	UM	46	Simple	None	13:00	11.1	23	1.08	25	15	336
8	76	Male	Rivaroxaban	10 mg	15.9	38.0	46,47	Simple	None	16:30	13.4	11	0.91	24	10	UM
9	81	Male	Rivaroxaban	10 mg	UM	UM	17	Simple	None	14:00	35.8	16	0.81	43	29	441
10	64	Male	Apixaban	5 mg $\times$ 2 times	12.6	35.7	48	Simple	Mild	14:00	21.9	12	0.73	14	15	175
11	76	Male	Apixaban	5 mg $\times$ 2 times	14.7	37.3	37	Simple	Mild	17:00	18.7	21	0.92	21	12	211
12	61	Male	Apixaban	5 mg $\times$ 2 times	14.4	36.6	16	Simple	None	10:00	17.5	13	0.91	25	23	UM
13	50	Male	Apixaban	5 mg $\times$ 2 times	15.4	UM	34,36	Simple	Mild	11:00	12.3	13	0.94	18	13	UM
14	79	Male	Apixaban	5 mg $\times$ 2 times	14.8	40.0	48	Simple	None	11:00	15.3	28	0.73	32	21	325
15	83	Male	Apixaban	2.5 mg $\times$ 2 times	16.0	53.0	11	Simple	None	14:00	12.4	36	0.87	20	13	220
16	62	Male	Dabigatran	110 mg $\times$ 2 times	UM	45.1	47	Simple	None	10:30	24.4	19	1.02	37	23	150
17	61	Male	Dabigatran	110 mg $\times$ 2 times	UM	UM	24	Simple	None	10:30	UM	UM	UM	UM	UM	UM
18	78	Male	Dabigatran	110 mg $\times$ 2 times	UM	34.0	13	Simple	None	13:00	20.8	24	1.34	28	20	UM
19	43	Male	Dabigatran	150 mg $\times$ 2 times	16.2	48.6	36	Simple	None	15:00	10.2	17	0.62	20	11	424

ALP = alkaline phosphatase (normal limit: 115–359 U/L); ALT = alanine transaminase (normal limit: 6–30 U/L); APTT = activated partial thromboplastin time (normal limit: <41.0 s); AST = aspartate transaminase (normal limit: 13–33 U/L); BUN = blood urine nitrogen (normal limit: 8–22 mg/dL); Crea = creatinine (normal limit: 0.6–1.1 mg/dL); NVKA = nonvitamin K antagonist; PT = prothrombin time (normal limit: <13.5 s); PLT = platelet; UM = unmeasured.

Case report of the patients with significant postoperative hemorrhage

Case 3 was a 60-year-old man with pericoronitis of the left mandibular third molar and extensive dental caries of the left mandibular second molar, for which extraction of the left mandibular wisdom tooth and distal root of the left mandibular second molar was planned. The patient had a history of AF, corrected transposition of the great arteries, severe cardiac failure, tricuspid valve prolapse, and chronic renal failure.

On the day of tooth extraction, the patient took rivaroxaban (10 mg) at 7:00 AM and amoxicillin (1.5 g) at noon. Tooth extraction began at 1:00 PM. For extraction of the wisdom tooth, the gingiva was incised and reflected, the crown was removed after being split, and the root was extracted after removing a small amount of bone. The distal root of the second molar was extracted by splitting the tooth at the bifurcation of the root. Then, oxidized cellulose was inserted, the incisions were sutured with 4-0 silk suture, hemostasis was confirmed, and a splint was applied.

At follow-up examination the next day at 11:00 AM, there was no bleeding from the extraction wounds, but oozing was noted at 4:00 PM. The oozing continued overnight, and the patient was again examined at 11:00 AM on postoperative Day 2. Because oozing from the extraction wound was persistent, hemostasis was again performed. The splint was removed and when the sutures and hematoma were removed, oozing from the extraction cavity was observed. The oozing did not subside even with gauze compression, so the bleeding point was coagulated by electrocautery, oxidized cellulose was again inserted, the surgical site was resutured, and hemostasis was achieved. Blood test results at this time were: platelets $11.4\times10^4/\mu L$, PT 20.3 seconds, and APTT 53.7 seconds.

However, mild oozing occurred again, continued though that night, and gauze was used to bite on as needed. The patient was subsequently followed up every other day. A small amount of oozing was noted, but the bleeding finally stopped by Day 7 with epithelization of the extraction cavities. Because the physician of the patient recommended continuation of rivaroxaban due to past history of multiple ischemic strokes, the patient continued to take rivaroxaban (10 mg) in the mornings during this time.

In Cases 2 and 4 (rivaroxaban), and 10, 11, and 13 (apixaban), slight oozing for approximately 8—12 hours following simple tooth extraction was observed, requiring the patients to bite down on gauze for hemostasis. There was no bleeding episode in the patients on dabigatran.

Discussion

Coagulation tests in patients on NVKAs showed prolongation of both the PT and APTT. Plasma dabigatran levels showed a good linear correlation with prolongation of APPT, whereas plasma rivaroxaban levels showed a good linear correlation with PT.[4,5] However, both PT and APTT are likely to show poor responsiveness in apixaban.[4,5]

The patient on rivaroxaban who showed significant postoperative bleeding (Case 3) had a PT of 18.5 seconds on the day of tooth extraction, which was within baseline values during follow up over a few months. Tooth extraction was performed 6 hours after the patient took rivaroxaban, which was presumably past the peak plasma drug level. Moreover, oxidized cellulose, suturing, and a splint were used for local hemostasis. The patient again took rivaroxaban the following day at 7:00 AM, and oozing began 9 hours after the patient took rivaroxaban. The time of re-evaluation on postoperative Day 2 for bleeding was 4 hours after rivaroxaban was taken, the time of the peak plasma level. Local hemostasis at this time was difficult despite cauterization by electrocautery, use of oxidized cellulose, and resuturing, and mild oozing continued for another 5 days. Bleeding continued even at the rivaroxaban plasma half-life and trough value times, thus suggesting that plasma levels of rivaroxaban may have remained higher than expected due to renal dysfunction. In a discussion with the physician of the patient, a decision had been made not to discontinue rivaroxaban for the extraction because the patient was at high risk for thromboembolism. Therefore, measures for local hemostasis were taken.

In a review paper, an increased risk for bleeding was reported when the APTT was 1.2—1.5-fold greater than the normal upper limit in dabigatran, and the PT was 1.2—1.5 greater than the normal upper limit in rivaroxaban.[4,8] In Case 3, the PT value at the time of bleeding (4 hours post-dose) was 20.3 seconds, 1.5-fold greater than the normal upper limit. The plasma peak level during that time frame may have contributed to the bleeding. In the patients with mild oozing (Cases 2 and 4), PT also exceeded the normal upper limit by 1.3-fold. Therefore, the risk of bleeding after tooth extraction increases when PT exceeds the normal upper limit. However, in the patients on apixaban, three cases experienced mild oozing (Cases 10, 11, and 13), suggesting almost normal PT or APTT values. As only the serum anti-Xa activity indicates the serum agent concentration in patients receiving apixaban, assessment of anti-Xa activity may be needed when bleeding continues after tooth extraction.[9,10]

In the management of patients on NVKAs during surgery, drug cessation is not necessary for minor surgery when the risk of bleeding is low. Appropriate measures include avoiding surgery at a time when the plasma drug level is at a peak or delaying the time of the next dose.[9,10] In patients with renal dysfunction, drug cessation for longer times has also been reported.[9,10]

When a hemorrhagic event occurs, if measurement of PT (for rivaroxaban) or APTT (for dabigatran) is within the normal range, plasma levels of rivaroxaban or dabigatran can be regarded as being in a therapeutic range and local hemostasis is indicated. If the PT or APTT value is prolonged, plasma levels of rivaroxaban or dabigatran can be regarded as exceeding the therapeutic range and either the procedure can be delayed for 4—12 hours, or, in the case of emergency surgery for a life-threatening condition, prothrombin complex concentrate or recombinant activated factor VII agent can be used to immediately reverse the effects of anticoagulation.[9,10] However, as neither PT nor APTT correlates with the serum level of apixaban, the same measures should be taken based on clinical findings when bleeding occurs.

For dental procedures with a low risk of bleeding, Mingarro-de-Leon et al[11] recommended that, for simple extraction of three teeth or less and surgery lasting ≤45 minutes, measures for local hemostasis should be used without discontinuing NVKAs. For surgery with a higher risk of bleeding, for example extraction of three or more teeth, surgery ≥45 minutes, or head and neck neoplasm surgery, they recommend discontinuing NVKAs for a few days, depending on the type of surgery, severity of renal dysfunction, and risk of bleeding.[11] Firriolo et al[6] and Breik et al,[12] like Mingarro-de-Leon et al,[11] also recommended local hemostasis without discontinuation of NVKAs in patients undergoing tooth extraction. However, Breik et al[12] reported a case of significant postoperative bleeding following extraction of 18 teeth while taking dabigatran.[12] Based on this report and the present study, surgical tooth extraction can increase the bleeding risk in patients on NVKAs. When bleeding is sustained, discontinuation of these drugs must be considered after discussion with the physician of the patient and measures for sufficient local hemostasis must be taken.

In a subanalysis of the RE-LY trial for periprocedural bleeding, when the last dose of dabigatran was given 49 hours (median) before the procedure, in comparison with 114 hours (median) in patients receiving warfarin, dabigatran and warfarin were associated with similar rates of periprocedural major bleeding (dabigatran 110 mg: 3.8% vs. dabigatran 150 mg: 5.1% vs. warfarin 4.6%), and ischemic stroke or systemic embolism (1.2% vs. 1.5% vs. 1.2%) until 30 days after invasive procedures. Both doses of dabigatran were associated with a lower risk of perioperative bleeding or thromboembolism when these were discontinued within 48 hours of surgery.[13] However, in the ARISTOTLE trial, when anticoagulation therapy was discontinued in two-thirds of patients receiving apixaban or warfarin before the procedure, the rate of periprocedural major bleeding (apixaban: 1.62% vs. warfarin: 1.93%) or stroke and systemic embolism (0.35% vs. 0.57%) were also low and similar between apixaban and warfarin until 30 days after invasive procedures.[14] However, discontinuation of these agents indicates approximately 0.5—1.5% of thromboembolism occurrence and conventional anticoagulant therapy with these drugs should be maintained during tooth extraction as possible.

In the ROCKET AF trial, when rivaroxaban was discontinued for ≥3 days, the incidence of stroke or noncentral nervous system thromboembolism within 30 days was 6.42/100 patient-years; significantly higher than the incidence when warfarin was discontinued (1.73/100 patient-years). Therefore, rivaroxaban should be discontinued with caution in patients undergoing surgery.[15] In patients with a high risk for thromboembolic events, use of low-molecular weight heparin is recommended.[9,10]

Based on these findings, the recommendations for patients on NVKAs who undergo tooth extraction can be summarized as follows: (1) NVKAs can generally be continued during tooth extraction, with some patients experiencing mild oozing postoperatively on the day of extraction; (2) tooth extraction should be avoided during the time of peak plasma levels of NVKAs (3—4 hours post-dose); (3) as surgical tooth extraction can increase the bleeding risk in patients on NVKAs, sufficient local hemostasis and careful follow up are required; (4) if bleeding occurs, local hemostasis should be provided after the time of peak plasma levels; (5) if hemostasis is anticipated to be difficult, delaying the next dose of NVKAs or skipping one dose should be considered and discussed with the physician of the patient; and (6) caution is necessary in patients with renal dysfunction or severe liver dysfunction because NVKA plasma levels may be elevated.

In conclusion, NVKAs can usually be continued in patients undergoing tooth extraction. However, patients with a prolonged APTT (for dabigatran) or PT (for rivaroxaban) value have a higher risk of bleeding, therefore, adequate local hemostasis and careful follow up are required. As apixaban correlates with neither APTT nor PT, the same clinical countermeasures should be employed based on the clinical findings.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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