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Post-extraction bleeding in patients on direct oral anticoagulants

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Abstract (J Korean Assoc Oral Maxillofac Surg 2024;50:189-196)

Objectives: This study aimed to evaluate the association between use of direct oral anticoagulants (DOACs) and post-extraction bleeding and to quantify bleeding risk in patients receiving DOACs.

Materials and Methods: The study included 293 patients who were taking DOACs and underwent tooth extraction (414 teeth). The patients were divided into those who had the extraction while taking DOACs and those who discontinued DOACs before the extraction. Bleeding complications were recorded and compared between the patient groups and types of DOACs.

Results: Of the 293 patients, 12 patients (6.9%) had post-extraction bleeding. Post-extraction bleeding occurred in 12 of the 414 tooth extraction sites. Among the 246 patients who underwent dental extraction while continuing DOAC therapy, 12 patients (8.5%) had post-extraction bleeding. Among the 47 patients who underwent dental extraction after discontinuing the administration of DOACs, none reported post-extraction bleeding. There was no significant difference in the number of patients with post-extraction bleeding between the two groups (P=0.122).

Conclusion: Continuing DOAC therapy during dental extraction does not increase post-extraction bleeding tendency. These results are consistent with those of previous studies.

Key words: Postoperative hemorrhage, Tooth extraction, Antithrombins, Factor Xa inhibitors, Anticoagulants

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I. Introduction

Currently, direct oral anticoagulants (DOACs) are widely used for the prevention of thrombosis in cases of cardiovascular and cerebrovascular disorders. DOACs directly inhibit coagulation factors. Dabigatran is a direct thrombin inhibitor; and rivaroxaban, apixaban, and edoxaban inhibit coagulation factor Xa. Patients on anticoagulants requiring dental treatment may experience an increased risk of bleeding[1,2].

Each dental disorder requires a different treatment approach. These treatment options include apicoectomy, periodontal surgery, tooth extractions, and osteoplasty; and some techniques may be accompanied by hemorrhage. Of these, tooth extraction is the most performed procedure. Therefore, predicting and preventing hemorrhagic complications after dental extraction in patients on anticoagulants are necessary[3-6].

Previous studies have reported that dental extractions do not significantly cause postoperative hemorrhagic complications in patients on DOAC therapy[3,4,7]. Korean studies on this issue are, however, lacking. No research on the need for short-term DOAC discontinuation among Korean dental extraction patients has been conducted[2].

Recently, an increasing number of patients have undergone dental extractions without discontinuing anticoagulant therapy for systemic conditions. In some cases, both patient and surgeon considered dental extraction as the only option despite the risk of hemorrhage after the procedure. These cases emphasize the need to assess the risk of severe hemorrhage in tooth extraction patients taking DOACs. This study aimed to evaluate the association between DOACs and post-extraction bleeding in patients on DOACs and to quantify the bleeding risk in these patients.

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II. Materials and Methods

This study reviewed the medical data of patients having accurate prescription records who received DOACs at National Health Insurance Service Ilsan Hospital and underwent dental extractions between 2015 and 2021. The DOACs assessed included dabigatran (Pradaxa; Boehringer-Ingelheim Pharmaceuticals), rivaroxaban (Xarelto; Janssen), apixaban (Eliquis; Bristol-Myers Squibb/Pfizer Pharmaceuticals), and edoxaban (Lixiana; Daiichi Sankyo).

Exclusion criteria were: (1) patients undergoing dental extractions before institution of DOAC therapy, (2) patients on DOACs but not requiring tooth extraction, (3) patients receiving DOACs without sufficient or accurate data on the administered drug and its dosage, (4) pregnant women, (5) patients aged <19 years, (6) those with a history of radiation therapy on the mandibular area or surgery to remove tumors from the maxillofacial area, and (7) patients with osteonecrosis or osteomyelitis in the maxillomandibular area. After implementation of these criteria, a total of 293 patients were included in the study. Patients were divided into two groups: those who underwent dental extractions while continuing DOAC therapy and those who underwent dental extraction after discontinuing DOAC therapy. Post-extraction patients with persistent bleeding were instructed to return to our hospital's outpatient clinic or emergency medical center for treatment. Determination of postoperative bleeding was made by an oral surgeon. Positive signs of postoperative hemorrhage were active bleeding or blood seepage; and this bleeding was controlled by suturing, direct pressure, or biting down. Cases in which a patient's postoperative bleeding complaint could not be confirmed were excluded from statistical analysis.

This study was approved by the Institutional Review Board (IRB) of the National Health Insurance Service Ilsan Hospital (IRB No. NHIMC 2022-03-004). The written informed consent was waived by the IRB due to the retrospective nature of the study.

1. Tooth extraction procedures

Dental extractions were performed in all patients receiving DOACs who required extraction. These included patients who presented directly to the Department of Maxillofacial Surgery and those who were transferred from other departments, such as prosthodontics or periodontics. A complete medical history was taken, and dental panoramic radiography and clinical examination were performed.

Indications for dental extraction included retained dental roots, serious dental caries for which restoration was not possible, fractured teeth, severe periodontitis, and pericoronitis. Extraction techniques included simple dental extraction, dental extraction with sutures, surgical extraction requiring alveolar osteotomy, and extraction requiring splitting of the maxillary and mandibular teeth under local anesthesia. After tooth extraction, the socket was not filled with bone grafts or substitute materials, such as collagen and fibrin. For infection prophylaxis, the patients were administered oral antibiotics 1 hour before the extraction.

We divided dental extractions in this study into two groups: simple extractions and surgical extractions. The simple dental extractions involved the removal of teeth by using only extraction forceps or elevation tools without the use of scalpels or burs. These devices were mainly used to remove intact teeth with serious periodontitis or having a poor prosthodontic prognosis. Surgical dental extraction involved the removal of teeth via an incision using a No. 12 or No. 15 blade or via an osteotomy or odontotomy using a fissure bur. Both of these techniques are commonly used for removing retained dental roots or impacted teeth. We used sutures to close all surgical extraction sites and some simple extraction sites. When multiple teeth were removed or primary closure was deemed necessary, suturing was performed using 3-0 braided silk (Mersilk; Ethicon). For pre-extraction local anesthesia, 2% lidocaine with epinephrine (1:80,000) was administered. The area was infiltrated with local anesthetic or an inferior alveolar nerve block was performed. Post-extraction, patients were instructed to apply site pressure for a few hours using gauze and were discharged with cessation of bleeding.

2. Peri-tooth extraction medication and post operative bleeding complication

Clotting time testing to assess the prothrombin time (PT) and international normalized ratio (INR) levels was not performed. However, if available, recent INR level tests documented by other departments were used. Before the dental extraction, the DOAC prescriber was contacted to determine if the DOAC therapy could be discontinued. Discontinuation of therapy was based on the prescriber's recommendation.

All patients were prescribed a prophylactic oral antibiotic (cefadroxil 1,000 mg, clindamycin 300 mg, or amoxicillin 1,000 mg) before dental extraction. Those at increased risk of developing an infection, such as those with comorbidi-

ties like diabetes mellitus, were also administered antibiotics post-extraction. No antibiotics were administered post-extraction to any other patients. In addition, all patients were prescribed pain relievers pre- and post-procedure (3 to 7 days) pain medication, either ibuprofen 300 mg or acetaminophen 300 mg.

Before discharge after the extraction, bleeding cessation was confirmed, and all patients were informed of the possibility of hemorrhagic complications. In the event of bleeding, patients were instructed to return to the hospital. Prior to discharge, post-extraction bleeding was controlled with direct pressure by biting down on gauze applied to the extraction site. For patients with persistent bleeding, an absorbable hemostatic gelatin sponge was applied to the extraction socket to achieve hemostasis by compression. In some cases, hemostasis was also achieved through suturing adjacent areas.

A chi-square test was used to compare differences in the number of patients with post-extraction bleeding between the two groups. Additionally, the frequency of post-extraction hemorrhagic complications for each DOAC was determined.

III. Results

This study included a total of 293 patients, 133 males and 160 females. Of the total, 246 patients underwent dental extraction while continuing their DOAC regimen; and 47 patients underwent extraction after discontinuing DOAC therapy.(Table 1)

In the 293 patients, 414 teeth were removed, 231 and 183 maxillary and mandibular teeth, respectively. The maxillary extractions included 50 incisors, 89 canines and premolars, and 92 molars; the mandibular extractions included 31 incisors, 71 canines and premolars, and 81 molars.(Table 2)

Of the total 293 patients, 12 patients had post-extraction bleeding. Among the 414 removed teeth, post-extraction bleeding occurred at 12 tooth extraction sites. Among the 246 patients who underwent dental extraction while continuing DOACs therapy, 12 patients had post-extraction bleeding. Among the 47 patients who underwent dental extraction after discontinuing the administration of DOACs, none reported post-extraction bleeding. There was no significant difference in the number of patients with post-extraction bleeding between the two groups (P=0.122).

The mean INR and standard deviation for the group continuing DOAC therapy was 1.15±0.50, and this value was 1.13±0.55 for the group who discontinued DOAC use. There was no difference in the INR between the two groups (P=0.866).

For the groups taking and not taking DOACs, the mean age was 77.4±8.9 years and 74.5±10.6 years, respectively. There

Table 1. Characteristics and incidence of post-extraction bleeding according to the preoperative discontinuation method of DOACs

Variable	Groups according to the preoperative discontinuation of DOACs (n=293)		
	DOACs continuation (n=246)	DOACs discontinuation (n=47)	*P*-value
Sex, male:female	110:136	23:24	0.594
Age (yr)	77.4±8.9	74.5±10.6	0.087
Post-extraction bleeding patient	12 (4.9)	0	0.122
INR	1.15±0.50	1.13±0.55	0.866

(DOACs: direct oral anticoagulants, INR: international normalized ratio)
Values are presented as number only, mean±standard deviation, or number (%).
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Table 2. Characteristics of tooth extraction and postoperative bleeding according to the type of prescribed DOAC

Variable	No. of tooth extractions according to the DOAC (n=414)			
	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Lixiana)
Maxilla (n=231) [4]				
Anterior sim-surg:Premolar sim-surg:Molar sim-surg	13[1]-1:11-6:17[1]-5	3-0:7-0:17-3	19-5:39-10[1]:31-5[1]	9-0:10-6:9-5
Sim-surg	41[1]-12[1]	27-3	89-20[2]	28-11
Mandible (n=183) [8]				
Anterior sim-surg:Premolar sim-surg:Molar sim-surg	2-0:3-2:9[1]-6	5-0:6[1]-2:8-2[1]	15-1:36[2]-11:33[2]-11[1]	8-0:9-2:8-4
Sim-surg	14[1]-8	19[1]-4[1]	84[4]-23[1]	25-6
Total (maxilla+mandible) [12]	55[2]-20[1]	46[1]-7[1]	173[4]-43[3]	53[0]-17[0]

(DOAC: direct oral anticoagulant, Anterior: central and lateral incisor, Premolar: canine and first and second premolar, Molar: first to third molar, Sim: simple extraction with/without primary closure, Surg: surgical extraction with osteotomy)
[ ]: post-extraction bleeding case.
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was no significant difference in age between the two groups (*P*=0.087).(Table 1)

Eighty-seven teeth were extracted using osteotomy, 46 maxillary and 41 mandibular teeth. Post-extraction bleeding occurred in 3 maxillary and 2 mandibular extractions. Among the 327 teeth removed using a simple extraction technique, post-extraction bleeding occurred in 7 cases.(Table 2)

IV. Discussion

There was no statistically significant difference in the number of patients who had post-extraction bleeding between the two groups. Among the 246 who underwent dental extraction while continuing DOAC therapy, 12 (4.9%) reported post-extraction hemorrhagic complications. No post-extraction hemorrhagic complications were reported in patients who underwent dental extraction after discontinuing DOAC use.

The DOAC agents used in this study included dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Lixiana). The incidence of post-extraction hemorrhage for each drug was determined. Post-extraction bleeding occurred in three of 75 extractions on dabigatran, three of 53 extractions on rivaroxaban, and seven of 216 extractions on apixaban. In the patients who received edoxaban, no post-extraction bleeding was reported. However, the differences in bleeding incidence among the drugs were not statistically significant.

A retrospective study by Müller et al.[8] compared bleeding after tooth extraction in patients on DOACs and phenprocoumon, a coumarin derivative, to those not on anticoagulants. A higher incidence of delayed bleeding occurred in the patients taking DOACs and phenprocoumon[8]. In that study, delayed bleeding occurred in 9 of 16 (56.3%) patients taking DOACs, 19 of 22 (86.4%) patients taking phenprocoumon, and 8 of 26 (30.8%) patients not taking anticoagulants. Bleeding events in the DOAC and phenprocoumon groups were similar in that these cases required a longer length of stay in the emergency department (ED) and a higher frequency of surgical intervention. The patients who were not taking anticoagulants demonstrated a significantly shorter duration of bleeding and length of stay in the ED. In contrast, only 12 (6.9%) patients had post-extraction hemorrhagic complications among the 173 patients on DOACs in our study.

Warfarin, a representative oral anticoagulant, exhibits anticoagulant activity by inhibiting the conversion of vitamin K to its active form. In contrast, DOACs are drugs that directly inhibit coagulation factors. Dabigatran is a direct thrombin inhibitor; and rivaroxaban, apixaban, and edoxaban inhibit coagulation factor Xa. In a meta-analysis by Hua et al.[9] in which bleeding outcomes after dental extraction were reviewed, the risk of bleeding for patients taking DOACs was significantly lower than the risk in patients taking vitamin K antagonists (VKAs). The outcome of this meta-analysis should be interpreted with caution, however[9].

A multicenter study by Hiroshi et al.[3] evaluated the frequency of hemorrhage after tooth extraction in patients treated with DOACs and VKAs; and the frequency of hemorrhage after tooth extraction was 1.65%, 3.41%, and 3.41% in those treated with dabigatran, rivaroxaban, and warfarin, respectively. In those who were not treated with anticoagulants, the frequency was 3.63%[3]. Post-extraction bleeding was significantly higher in the rivaroxaban group than in patients who did not receive anticoagulants (*P*=0.008). No significant difference in frequency was observed in the dabigatran and rivaroxaban groups compared to that in the warfarin group (*P*=0.221 and *P*=1.000, respectively). Therefore, the frequency of post-extraction hemorrhage was similar in patients receiving dabigatran, rivaroxaban, and warfarin. Comparable results were reported in a study by Yoshikawa et al.[10] in which postoperative bleeding occurred in four extractions (3.1%) in the DOAC group and in 23 (8.8%) in the warfarin group; the difference was not statistically significant between the two groups.

The studies comparing post-extraction bleeding with DOAC use and warfarin use showed either a statistically insignificant difference or an increased risk of bleeding with warfarin use[9,11]. The implication is that patients on DOACs or warfarin can undergo dental extraction with expectations of similar outcomes.

A retrospective cohort study compared the risk of post-extraction bleeding between patients receiving DOACs and patients on warfarin. In that study, there was no difference in the incidence of post-extraction bleeding between the DOAC and warfarin groups. The findings suggest that dentists and physicians should exercise the same degree of caution when extracting teeth in DOAC and warfarin patients[5].

A study by Yoshikawa et al.[10] compared the incidences of post-extraction bleeding in patients receiving DOACs and in those on warfarin and demonstrated no difference between the two groups. The study reported that among 262 patients in the warfarin group, 23 (8.8%) experienced post operative bleeding. These findings differed from the results of our study in which 12 of 246 (4.9%) who underwent dental extraction while continuing DOAC therapy experienced post-extraction

bleeding. A study by Yagyuu et al.[12] compared post-extraction bleeding in patients on DOACs and those on VKAs, such as warfarin. That group found no difference in incidence of post operative bleeding between the two groups. However, the warfarin group experienced post-extraction bleeding in 12 (12.0%) of 100 extractions.

A study by Rocha et al.[13] compared post-extraction bleeding in patients receiving warfarin and those not receiving warfarin. The study demonstrated that among 66 patients who underwent dental extraction while on VKA therapy, 3 (4.3%) had post operative bleeding; and 2 of 67 (2.9%) patients who did not receive anticoagulants had post operative bleeding. The difference was not statistically significant.

Previous studies reported variable results including a higher incidence of bleeding compared to that observed in this study. The different dental extraction techniques used and the quick response to successfully treat bleeding before patients were discharged in our study contributed to a lower incidence of bleeding. A study by Svensson et al.[14] reported that among 124 patients on warfarin who had their extraction sockets packed with an absorbable hemostatic gelatin sponge or a collagen fleece, 5 (4%) patients experienced post-extraction bleeding. Therefore, application of less traumatic dental extraction techniques, use of hemostatic materials, and use of different hemostatic techniques can contribute to a reduction in incidence of post-extraction bleeding in patients on DOAC therapy.

In the present study, 12 of 293 (4.1%) patients experienced post-extraction bleeding, and these 12 (4.9%) were included in the group of 246 patients who underwent dental extraction while continuing DOAC therapy. Given that there was no post-extraction bleeding in the 47 patients who discontinued DOACs before dental extraction, further research should be conducted with a greater number of patients and participating hospitals to determine if this difference is truly insignificant.

In our pre-extraction INR level study, no correlation was observed between the tendency for post-extraction bleeding and INR level[15]. DOACs are significantly less likely to be associated with INR levels than warfarin owing to their specific mechanisms of action. A prospective study by Berton et al.[16] that compared DOAC and VKA use in single tooth extractions demonstrated similar results for pre-, intra-, and post operative variables. In addition, patients on DOACs and VKAs had the same incidence of post-extraction bleeding after single tooth extractions[16]. The study concluded that the bleeding event differences were not statistically significant and clinically unrelated. Therefore, patients on DOACs can be treated in similar ways to those on VKAs whose INR levels are between 2 and 3; and removing teeth without discontinuing DOACs therapy is an appropriate course of action for single tooth extractions.

No statistically significant difference in post-extraction bleeding between patients who continued anticoagulant therapy and those who discontinued anticoagulant use was reported[5,11,17]. Those findings are consistent with the results of our study. A meta-analysis of patients who continued oral anticoagulant therapy during dental extractions concluded that continuing anticoagulant therapy would not increase the likelihood of post-extraction bleeding[17].

In the present study, bleeding occurred in four maxillary extractions and eight mandibular extractions. In a study of warfarin use by Febbo et al.[18], a higher tendency for bleeding was observed in mandibular extractions than in maxillary extractions and in multiple versus single tooth extraction.

In this study, bleeding occurred in 5 of 87 extractions requiring osteotomy and 7 of 327 simple extractions. Another study reported that surgical extractions requiring osteotomy were more likely to cause a higher incidence of post-extraction bleeding than simple extractions in patients treated with warfarin[14].

A retrospective cohort study by Iwata et al. investigated risk factors associated with post-extraction bleeding in patients on warfarin or DOACs and concluded that most of the post-extraction bleeding episodes were grade 1. These can be controlled by the application of gauze and pressure[11]. If patients on DOACs are scheduled to undergo multiple teeth extractions or HAS-BLED score is 3 points with warfarin therapy, the recommendation is to inform patients of the risk of post-extraction bleeding before surgery, take meticulous care to achieve hemostasis, and instruct patients to apply pressure by biting down firmly on the gauze for longer than usual.

In addition, a randomized clinical trial by Ockerman et al.[19] suggested using a 10% tranexamic acid (TXA) mouthwash to prevent post-extraction bleeding in patients treated with non-vitamin K oral anticoagulants. The study demonstrated that TXA does not reduce the rate of periprocedural or early post-operative oral bleeding compared to placebo but appears to reduce delayed bleeding, especially in cases of multiple tooth extractions. Based on these findings, dental extraction with careful hemostasis and proper use of sutures, discharge of patients on DOACs after confirming bleeding cessation, and appropriate use of TXA mouthwash are expected to reduce post-extraction bleeding.

Direct oral anticoagulants work through a different mechanism than VKAs such as warfarin. Direct oral anticoagulants directly inhibit specific proteins in the blood coagulation chain. The mechanism of action of rivaroxaban, apixaban, and edoxaban is the inhibition of factor Xa; dabigatran directly inhibits the coagulation factor IIa (thrombin). DOACs have a more consistent anticoagulant effect than warfarin, which indirectly affects multiple factors. In general, routine INR monitoring is not necessary before prescribing DOACs[20]. With predictable pharmacokinetic and pharmacodynamic profiles, DOACs can be prescribed at fixed doses regardless of monitoring results.

Because PT can be affected by Xa inhibitors, taking DOACs may be related to INR. However, the sensitivity of PT to these drugs varies greatly depending on the reagents used in the blood test, making the blood test an unreliable monitoring tool for DOACs. Blood tests to check for bleeding tendencies associated with taking DOACs include anti-factor Xa assay, thrombin time (TT), ecarin clotting time, diluted thrombin time, and chromogenic assays[21]. Anti-factor Xa assays measure the anticoagulant effect of factor Xa inhibitors such as rivaroxaban, apixaban, and edoxaban.

Thrombin time is prolonged in the presence of dabigatran, a direct thrombin inhibitor. Diluted thrombin time is an anticoagulation test like TT but is more specific and sensitive to dabigatran. Ecarin clotting time is a more specific test for dabigatran that measures the activity of direct thrombin inhibitors and is an effective test for measuring the amount of dabigatran[22]. Chromogenic assays can be used to evaluate the effectiveness of direct thrombin inhibitors and direct factor Xa inhibitors. This test is more specific than coagulation-based tests and can provide quantitative measurements[23].

These tests can be used selectively depending on the specific DOACs prescribed and the clinical situation. These can be useful for patient management in emergency situations such as before surgery or in cases of severe bleeding. However, these tests are not generally recommended for routine monitoring purposes to evaluate the effect of drugs considering the pharmacokinetic, pharmacodynamic, and cost aspects of DOACs[24].

This study investigated post-extraction bleeding in patients taking DOACs for a variety of disorders. Prior to discontinuing DOAC use, we consulted the primary physicians who prescribed DOACs and discontinued use only with their approval. Postoperative bleeding incidence may be reduced due to the advancement in dental extraction techniques and development of hemostatic materials and methods, so the decision to discontinue DOAC use should be made only after careful consideration.

Patients taking DOACs for systemic diseases may not be able to discontinue taking the drugs for a variety of physiological reasons. The present study thoroughly investigated the risk of post-extraction bleeding, considering DOAC type, drug cessation before dental extraction, and dental extraction technique. We concluded that there was no significant difference in the risk of post-extraction bleeding between the DOAC group and the group that discontinued anticoagulant therapy. However, the limitations of this study include a difference in the total number of samples between groups and insufficient data on each DOAC. Further studies should be conducted that include a variety of patients on different DOACs and a much larger sample size comprising patients from multiple clinical sites. However, this study can provide useful initial guidelines for dental extraction management in patients treated with DOACs.

V. Conclusion

In this study, local management of surgical sites was considered important for controlling bleeding. This was confirmed by one case of multiple extractions in which bleeding occurred only at one site. The patient's systemic condition cannot be ignored, however. Currently, maintaining patients on DOACs has become more common because of the prevalence and severity of comorbidities in patients. Our results and those of previous studies support this practice. Continuing DOAC therapy during dental extraction does not increase post-extraction bleeding tendency.

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Authors' Contributions

M.J.K. and S.H.K. obtained data and wrote the manuscript. S.H.K. and M.J.K. drafted the manuscript. S.H.K., M.J.K., and M.K.K. participated in article design and coordination and carefully reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board (IRB) of the National Health Insurance Service Ilsan Hospital (IRB No. NHIMC 2022-03-004).

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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