Is it necessary to alter anticoagulation therapy for tooth extraction in patients taking direct oral anticoagulants?

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Abstract

Background: The number of patients using direct oral anticoagulants (DOACs) instead of vitamin K antagonists (VKA) is increasing and there is limited data on the safety of tooth extractions in patients taking DOACs. The aim of this study was to compare the amount of bleeding (AOB) and postoperative complications after tooth extractions between patients taking VKAs and patients taking DOACs without altering the anticoagulation therapy. Material and Methods: The study consisted of four groups: Direct thrombin inhibitor group, factor Xa inhibitor group, warfarin group and a control group. A single tooth was extracted in each patient and routine coagulation test values were recorded prior to extraction. AOB was measured for 20 minutes after tooth extraction. The patients were evaluated on 2nd and 7th days after extraction for bleeding. Status of bleeding was classified as no bleeding, mild bleeding controlled by gauze pads, moderate bleeding controlled by hemostatic agents and severe bleeding required hospitalization. Analysis of variance, chi square test and correlation analysis were used for statistical analysis of data.

Results: A total of 84 patients (48 male, 36 female) were included in this study. The mean age of patients was 57 (38-87) years. Mean AOB was 1388.6±913.0, 1909.29±1063.1, 3673±1415.4, 1593.33±672.5 mg for direct thrombin inhibitor, factor Xa inhibitor, warfarin and control groups respectively. Mean AOB was significantly higher for warfarin group, compared to other groups (p<0.05). The number of patients showing mild and moderate bleeding was significantly higher in warfarin group compared to other groups (p<0.05). The number of patients showing mild and moderate bleeding was significantly higher in warfarin group compared to other groups on the 2nd postextraction day (p=0.001). No bleeding was occurred in control group on 2nd and 7th postextraction days and no bleeding was occurred in direct thrombin inhibitor group on 7th postextraction day. The number of bleeding events among groups was not statistically significant on 7th postextraction day (p=0.251).

Conclusions: Patients taking warfarin had more bleeding compared to patients taking direct oral anticoagulants after tooth extractions. In patients taking direct oral anticoagulants simple tooth extractions can be safely carried out without altering the anticoagulant regimen with the use of local hemostatic agents.

Key words: Direct oral anticoagulants, dabigatran, rivaroxaban, apixaban, tooth extraction, oral surgery.
Introduction
Treatmen of prothrombotic embolism in several
diseases and medical conditions including prothrombotic
cardiac valves, chronic atrial fibrillation, stroke, recur-
rent myocardial infarction, deep vein thrombosis and
pulmonary embolism may require extended anticoagu-
lation therapy. For more than 50 years VKAs have been
the only oral anticoagulant drugs available (1). Warfarin
is a coumarin derived drug that shows its anticoagulant
effect by reduced synthesis of Vitamin K dependent
factors II, VII, IX, X, proteins C and S. Warfarin is the
most commonly prescribed VKA however it has many
disadvantages like food and drug interactions, the need
for individual dosing, regular monitoring and dose ad-
justment, slow onset and offset of action and a hyperco-
agulable state as a result of warfarin-mediated protein
C and S deficiency that develops in some patients (2,3).
To overcome these disadvantages and difficulties new
oral anticoagulants or DOACs have been developed in the
recent years (4). Unlike warfarin, DOACs act by in-
hibiting a specific targeted step in the coagulation cas-
cade. The majority of DOACs including rivaroxaban(5)
and apixaban (6) inhibit FXa. Dabigatran etexilate is the
only available oral direct thrombin inhibitor for clinical
use (7). The use of DOACs for thromboembolic disease
treatment in place of VKAs has increased over the past
years. The management of patients taking VKAs who
require tooth extractions/oral surgery is well document-
ed in the literature (8-14). However, there are only limit-
ed amount of clinical studies in patients taking DOACs
who require dental extractions/oral surgery (15-18).
The aim of this prospective, observational study was to
compare the AOB and postoperative complications af-
ther tooth extractions in patients taking warfarin, direct
thrombin inhibitors and factor Xa inhibitors.

Material and Methods
Sixty-two patients taking oral anticoagulants and 24
healthy patients taking no anticoagulant were enrolled
in this study. A medical history was taken, clinical and
radiographic examinations were performed at first visit.
Çukurova University Local Ethics Committee approved
the study protocol and the guidelines established in the
Declaration of Helsinki were followed during the study.
The patients who participated in the study signed an in-
formed consent.
The inclusion criterion was having a tooth indicated
for extraction. Exclusion criteria were: local infection,
inflammation or pathology associated with the tooth;
conditions that may complicate the extraction includ-
ing extensive caries, large restorations, roots that have
severe dilaceration, ankylosis and hypercementosis;
hematologic diseases; thrombocytopenia; hepatic/renal
dysfunction; using an anti-platelet drug; INR>4 in pa-
tients taking warfarin.

The study was consisted of three anticoagulant groups
and a control group; Patients taking direct thrombin in-
hibitor, patients taking factor Xa inhibitor, patients tak-
ing warfarin, patients taking no anticoagulants (control
group). All patients in direct thrombin inhibitor group
were taking dabigatran etexilate 150mg/12h (Pradaxa®,
Boehringer Ingelheim Pharma GmbH & Co. KG). Three
patients in FXa inhibitor group were taking apixaban
5mg/12h (Eliquis®, Bristol-Myers Squibb Co. & Pfiz-
er) and 18 patients were taking rivaroxaban 20mg/24h
(Xarelto®, Bayer Schering Pharma AG). The warfarin
(Coumadin®, Zentiva, Istanbul) dosage was adjusted
for a target INR value of 2.0 to 3.0 depending on the
patient’s INR levels.

Blood samples were taken from all patients for BUN,
creatinine, AST, ALT, prothrombin time (PT), INR and
platelet count measurements on the day of extraction.
Thrombin Time (TT) and anti-FXa measurements were
performed for patients in direct thrombin inhibitor and
factor Xa inhibitor groups respectively. When neces-
sary, 2gr. amoxicillin were given to the patients for bac-
terial endocarditis prophylaxis 30-60 minutes before
the extraction. A single tooth was extracted from each
patient without stopping anticoagulants.

Extractions were performed under local anesthesia
without epinephrine (3% Mepivacaine, Safecaine®, Vem
Ilac, Istanbul, Turkey). Prior to extraction, the oral cav-
ity was isolated from salivary secretions by specific
saliva blocking barriers (Neodrys®, Henry Schein,
Germany) placed on orifices of parotid glands, gauze
pads placed on the submandibular gland ducts and by
continuous suctioning with a surgical aspirator. All ex-
tractions were performed in an atraumatic fashion us-
ing elevators and forceps by the same surgeon who was
blinded to the type of patient’s anticoagulant therapy.
The method previously described by Karsli et al. was
used to measure the AOB (10). At completion of the ex-
traction, gauze pads were used to control bleeding from
the extraction sockets, and these were subsequently
changed for 20 minutes. Each gauze pad was placed
over the extraction socket and changed with a new
pad once it absorbed a sufficient amount of blood. The
weights of gauze pads used before and after tamponade
were measured using a fine electronic weight measure-
ment device (Shimadzu, Kyoto, Japan). Weight differ-
ences before and after tamponades were interpreted as
the AOB (in miligrams). After 20 minutes, each extrac-
tion socket was packed with oxidized cellulose dressing
(Surgicel; Ethicon, Neuchatel, Switzerland) and sutured
with 3.0 silk sutures (Dogsan, Istanbul, Turkey). Par-
acetamol 500 mg three times a day was prescribed for
pain control. Patients were given additional gauze pads
to be used if bleeding continued and instructed to call
the surgeon or visit the oral and maxillofacial surgery
department in case of severe bleeding. Patients were
seen again on 2nd and 7th days after extraction for suture removal and evaluation of any postextraction bleeding. Status of postextraction bleeding was classified as no bleeding, mild bleeding controlled by gauze pads, moderate bleeding controlled by hemostatic agents and severe bleeding required hospitalization.

- Statistical analysis
All analyses were performed using SPSS 20.0 statistical software (SPSS, IBM, Chicago, IL). Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation where appropriate. Chi-square test was used to compare categorical variables between the groups. For normal distributed data, One-Way ANOVA test was used to compare more than two groups. Bonferroni test was used for multiple comparisons of groups. Pearson’s correlation was used to assess the correlation between the AOB and TT in thrombin inhibitor group and between the AOB and Anti-FXa value in factor Xa inhibitor group. The statistical level of significance for all tests was considered to be 0.05.

**Results**
Two patients taking direct thrombin inhibitor were excluded from the study because of elevated ALT-AST levels. A total of 84 patients (48 male, 36 female) were included in this study. The mean age of patients was 57 (38-87) years. Demographic data of the patients, type of extracted tooth and indication for anticoagulant therapy were summarized in Table 1. There was no statistically significant difference among groups, in terms of age and type of extracted tooth ($p>0.05$). No patients required flap elevation, root separation or bone removal. No intraoperative complications or severe intraoperative bleeding occurred in any patient. The mean AOB after tooth extraction and bleeding status on 2nd and 7th postextraction days according to groups were summarized in Table 2. The mean AOB in warfarin group was significantly higher than the other groups ($p<0.05$). The difference between thrombin inhibitor, factor Xa inhibitor and control groups was not statistically significant in terms of AOB ($p_{1-2}=0.798$, $p_{1-4}=1.00$, $p_{2-4}=1.00$) (Fig. 1). No patient in control group had bleeding on 2nd and

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**Table 1. Patient characteristics, indications for anticoagulant therapy and type of extracted tooth**

|                          | Thrombin inhibitor n=17 | FXa inhibitor n=21 | Warfarin n=22 | Control n=24 | Total n=84 | $p$  |
|--------------------------|-------------------------|-------------------|--------------|-------------|-----------|------|
| Gender                   |                         |                   |              |             |           |      |
| Female, n (%)            | 8 (47%)                 | 9 (43%)           | 6 (27%)      | 12 (50%)    | 36        | 0.427* |
| Male, n (%)              | 9 (53%)                 | 12 (57%)          | 16 (73%)     | 12 (50%)    | 48        |      |
| Age (years)              |                         |                   |              |             |           | 0.138**|
| Mean (+SD)               | 59.35(+13.63)           | 60.81(+11.84)     | 60.68(+10.35)| 54(+9.727) | 57.04     |      |
| Min-Max                  | 39-87                   | 44-82             | 39-78        | 38-70       | 38-87     |      |
| Indication for anticoagulant therapy |                   |                   |              |             |           |      |
| Prosthetic Cardiac Valve, n (%) | 4                   | 6                 | 5            | 15          |          |
| Atrial Fibrillation, n (%) | 5                   | 5                 | 5            | 15          |          |
| Thromboembolism(PE/DVT), n (%) | 3                   | 7                 | 8            | 18          |          |
| Myocard Infarctus, n (%) | 1                     | -                 | -            | 1           | $0.562*$ |
| Cerebrovascular Accident, n (%) | 1                   | -                 | -            | 1           |          |
| Acute Coronary Syndrome, n (%) | 3                   | 3                 | 4            | 10          |          |
| Type of extracted tooth   |                         |                   |              |             |           | 0.472* |
| Incisor, n (%)           | 5 (29.4)               | 8 (38.1)          | 7 (31.8)     | 3 (13.6)    |          |
| Premolar, n (%)          | 4 (23.5)               | 3 (14.3)          | 6 (27.3)     | 4 (18.2)    |          |
| Molar, n (%)             | 8 (47.1)               | 10 (47.6)         | 9 (40.9)     | 15 (68.2)   |          |

* Pearson Chi-square test was used for this result.
** OneWay ANOVA test was used for this result.
Tooth extraction in patients taking oral anticoagulants

No severe bleeding requiring hospitalization was encountered following the extractions. The number of patients showing mild and moderate bleeding was significantly higher in warfarin group compared to other groups on the 2nd postextraction day \((p=0.001)\). No bleeding occurred on the 7th day for thrombin inhibitor and control groups. One patient in factor Xa inhibitor group (4.8%) and 1 patient in warfarin group (4.5%) had mild bleeding, and 2 patients in warfarin group (9.1%) had moderate bleeding on the 7th day. However, these results were not statistically significant \((p=0.251)\).

Table 2. Amount of bleeding (AOB), bleeding on 2nd and 7th days after tooth extraction

|                | Thrombin Inhibitor \(n=17\) | FXa inhibitor \(n=21\) | Warfarin \(n=22\) | Control \(n=24\) | \(p\)   |
|----------------|-----------------------------|------------------------|-------------------|-----------------|---------|
| AOB (mg) Mean±SD | 1388.6±913.0                | 1909.2±1063.1          | 3673.0±1415.4     | 1593.3±672.5    | <0.05*  |
| Bleeding on 2nd day, n (%) | \(p=0.001**\) |                       |                   |                 |         |
| No bleeding     | 15 (88.2)                   | 17 (81)                | 10 (45.5)         | 24 (100)        |         |
| Mild bleeding   | 1 (5.9)                     | 2 (9.5)                | 6 (27.3)          | 0               |         |
| Moderate bleeding | 1 (5.9)              | 2 (9.5)                | 6 (27.3)          | 0               |         |
| Heavy bleeding  | 0                          | 0                      | 0                 | 0               |         |
| Bleeding on 7th day, n (%) | \(p=0.251**\) |                       |                   |                 |         |
| No bleeding     | 17 (100)                    | 20 (95.2)              | 19 (86.4)         | 24 (100)        |         |
| Mild bleeding   | 0                          | 1 (4.8)                | 1 (4.5)           | 0               |         |
| Moderate bleeding | 0                     | 0                      | 2 (9.1)           | 0               |         |
| Heavy bleeding  | 0                          | 0                      | 0                 | 0               |         |

* OneWay ANOVA test was used for this result.
** Pearson Chi-square test was used for this result.

Fig. 1. Graphic shows the AOB (mg) among groups.

7th postextraction days. No severe bleeding requiring hospitalization was encountered following the extractions. The number of patients showing mild and moderate bleeding was significantly higher in warfarin group compared to other groups on the 2nd postextraction day \((p=0.001)\). No bleeding occurred on the 7th postextraction day for thrombin inhibitor and control groups. One patient in factor Xa inhibitor group (4.8%) and 1 patient in warfarin group (4.5%) had mild bleeding, and 2 patients in warfarin group (9.1%) had moderate bleeding, and 2 patients in warfarin group (9.1%) had moderate bleeding on the 7th day. However, these results were not statistically significant \((p=0.251)\). Table 3 shows the distribution of the laboratory results of the patients according to the groups. The mean INR and PT measurements were statistically significant between the groups \((p<0.05)\). The direct thrombin inhibitor group and the control group were found to have similar INR and PT values. However, higher INR and PT values were measured in fac-
tor Xa and warfarin groups compared to direct thrombin inhibitor group and control group. On the other hand, no statistically significant difference was found between factor Xa and warfarin group (p=0.099). The mean platelet counts was not statistically significant among the groups (p=0.089). The mean TT in thrombin inhibitor group was 106.0±29.8 seconds, which was higher than normal range of TT (14-21 seconds). The mean anti-FXa was 2.98±9.2 UI/ml in factor Xa inhibitor group was also higher than the normal range (0-0.1 UI/ml). However no statistically significant correlation was found between the AOB and TT in thrombin inhibitor group (r=0.04; p=0.870), and the AOB and Anti-FXa value in factor Xa inhibitor group (r=-0.10; p=0.657).

Discussion
Discontinuation of oral anticoagulants may lead to severe thromboembolic complications, and in case of minor surgery these medications should not be stopped if feasible. There is a considerable amount of literature that supports the continuation of VKAs in minor surgical procedures such as tooth extraction. Recent studies have shown that in patients taking warfarin, tooth extractions can be carried out safely with the aid of local hemostatic measures if the INR is less than 4 (11,14,19). Predictable pharmacokinetics, rapid onset of action, lower risk of food-drug interaction and a short half-life are advantages of DOACs compared to VKAs. Unlike VKAs, DOACs do not require regular monitoring or dose titration. Thus, management of patients taking these medications during tooth extraction may be safer and easier (3,20). However, a high level of scientific evidence for direct oral anticoagulant use during tooth extractions is limited. In a review by Muñoz-Corcuera et al. the authors suggest that each case should be treated individually in accordance to the risk of embolism, postoperative bleeding and renal function (21). Depending on the risk of bleeding Curto et al. classified dental treatments in two groups: procedures with a low risk of bleeding and procedures with medium to high risks of bleeding (22). Low-risk procedures include simple tooth extractions, oral surgery lasting less than 45 minutes and mucogingival surgical procedures. The extraction of more than three teeth at once and oral surgery lasting more than 45 minutes were considered medium-high risk procedures. In this group, the instructions to stop DOACs should be consulted with the specialist physician. The authors suggest that for low risk procedures discontinuation of dabigatran is not necessary and apixaban can be administered at a usual dose on the day, after the procedure (23). For medium and high risk procedures apixaban and dabigatran should be suspended for at least 24h and 48h respectively. Also the time of suspension should be extended for patients with altered renal function. If the drug suspension period is prolonged bridging therapy with low molecular weight heparin should be considered. Beyer-Westendorf et al. took data from a larger ongoing study of 2179 patients to evaluate the peri-procedural safety and management of DOACs(24). The majority of patients in the study were taking rivaroxaban (76%), followed by dabigatran (23.5%) and apixaban (0.5%). The authors defined three categories of procedures as minimal, minor and major according to the severity of tissue trauma and the risk of bleeding. In minor procedures category that included tooth extractions, the authors identified 3 (0.5%) major bleeding, 20 (3.1%) non-major clinically relevant bleeding and 6 (0.9%) minor bleeding. The prevalence of bleeding was found to be higher in the group of patients who had received heparin bridging, compared to patients continued DOACs or patients interrupted anticoagulants. In conclusion of the study heparin bridging was not recommended. In the present study, tooth extraction was performed without interruption of DOACs and no major bleeding was observed in any patient. Morimoto et al. extracted twenty-three teeth including two surgical extractions in 19 patients while continuing DOACs (17). The teeth were extracted in a minimally invasive fashion and the authors used local hemostatic measures after extraction. Three patients taking apixaban, and two patients taking rivaroxaban showed mild bleeding however one patient taking rivaroxaban who

|                  | Thrombin Inhibitor | FXa inhibitor | Warfarin | Control | p     |
|------------------|--------------------|---------------|----------|---------|-------|
| **PT (sec)**     | 12.8±1.4           | 20.4±13.7     | 24.8±8.9 | 11.5±0.8| p<0.05|
| Mean ± SD       |                    |               |          |         |       |
| **INR**          | 1.11±0.1           | 1.81±1.3      | 2.33±0.5 | 1.00±0.1| p<0.05|
| Mean ± SD       |                    |               |          |         |       |
| **Platelet**     | 243.2±51.8 x 10³   | 220.0±76.8 x 10³ | 241.7±53.1 x 10³ | 269.4±68.3 x 10³ | 0.089 |
| Mean ± SD       |                    |               |          |         |       |

Table 3. PT, INR and platelet count in groups
had a surgical extraction showed persistent post-operative bleeding on 2nd postextraction day. This patient had mild oozing from the surgical site even after local intervention using electrocautery and oxidized cellulose until the 7th day. No postoperative bleeding event was observed in other patients. Breik et al. reported a case series of 5 patients taking dabigatran who underwent tooth extraction (25). In one patient dabigatran was stopped 48 hours prior to extractions, in 3 patients a single tooth was extracted without drug interruption and there was no adverse bleeding in these 4 patients. However in one patient 18 teeth were extracted with drainage of a facial abscess under general anesthesia without drug interruption, which resulted in a significant bleeding. The patient needed to return to operating room and dabigatran was stopped to control the bleeding. Hanken et al. compared the postoperative bleeding events after 52 oral procedures including bone removal for tooth extraction and implant placement, performed while taking factor Xa inhibitor (rivaroxaban) with 285 oral procedures performed in patients taking no anticoagulant (18). The authors described postoperative bleeding event as a condition requiring additional treatment, which may correspond to moderate bleeding in our study. In this study 11.5% bleeding events incidence was reported for rivaroxaban, which was similar to our results for moderate bleeding (9.5%). The authors concluded that, although it is manageable, continuing anticoagulation therapy with rivaroxaban significantly increases the risk of postoperative bleeding after oral surgery. Slightly increased incidence of bleeding events seen in this study may be explained by the bone removal for tooth extraction in the majority of the cases (97%). Mauprivez et al. compared the number of bleeding events after tooth extraction in 31 patients taking DOACs and 20 patients taking VKAs with an INR between 2.0 and 3.0 without interrupting their medications (15). The authors defined a bleeding event as persistent oozing or marked hemorrhage despite mechanical compression with gauze pads for 20 minutes. Five patients taking DOACs had seven bleeding events, and four patients taking VKAs had five bleeding events during the postoperative follow-up period. The difference between two groups was not statistically significant in terms of number of bleeding events. Eleven (91.67%) bleeding events were mild and controlled by gauze pads, and one (8.33%) was managed with a revision of the wound, application of fibrin glue, and resuturing. Similar to our study, the authors reported no bleeding that required hospitalization or blood transfusion. In contrast to our study no bleeding events were occurred after the first 3 postoperative days. Total bleeding events reported in this study (22.58%) was slightly higher than our results for thrombin inhibitor group and FXa inhibitor groups combined (18.42%). Two (9.52%) bleeding events were observed in 21 simple tooth extractions for patients taking dabigatran, which was similar to our study (11.8%). Eight (%29.63) bleeding events were observed in 27 simple extractions for patients taking Factor Xa inhibitor, which was slightly increased, compared to our results (23.8%).

In the present study the mean INR value was significantly higher in factor Xa inhibitor and warfarin groups compared to other groups. In patients taking warfarin, INR>2 is the therapeutic goal of anticoagulant therapy. Additionally, in patients taking factor Xa inhibitor an increase can be observed in INR. However, in patients using FXa inhibitor, there is no need for regular INR monitoring and a fixed dose is preferred. TT measured in the direct thrombin inhibitor group and anti-FXa measured in the FXa inhibitor group was higher than the normal ranges. However, no correlation could be found between these blood tests and AOB. Therefore, these tests are questionable for clinical practice.

The comparison of bleeding both quantitatively and in terms of postextraction bleeding events, the fixed dosage of DOACs and the prospective design were the main strengths of this study. It wasn’t possible to extract the same type of tooth from all patients and this could be considered as a weakness of this study. However the distribution of types of tooth among the groups wasn’t different statistically. Perhaps a more important weakness of this study is that the time period between drug intake and tooth extraction was not recorded, which could be an important issue when considering the short half-life of these drugs. The most important limitation of this study was only a single uncomplicated tooth extraction was carried out for each patient. Multiple extractions or more invasive oral surgical procedures may show a different outcome and should be evaluated with further studies. Another limitation of this study was only 3 patients using apixaban was included in the study.

In conclusion, for simple tooth extractions DOACs are safe drugs in terms of bleeding and extractions can be carried out without interrupting or altering anticoagulant regimen with the aid of local hemostatic measures. Further studies are needed to evaluate the necessity of alteration in drug regimen for patients taking DOACs who underwent oral surgical procedures.

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