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REVIEW ARTICLE

Dental Implant Surgery for Patients Receiving Non-vitamin K Antagonist Oral Anticoagulants (NOACs); Clinical Considerations and Management: A Mini-review

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Abstract:

Background:

Dental implants are one of the most prevalent operations in dental clinics, as they are the ideal solution to replace teeth. However, many patients who need this treatment are older and suffering from heart diseases, especially atrial fibrillation, which requires anticoagulants. Non-vitamin K antagonist oral anticoagulants (NOACs) are considered modern anticoagulants, and they include four common medications: dabigatran, rivaroxaban, apixaban, and edoxaban.

Materials and Methods:

In this study, we review the literature regarding the proper management of patients receiving NOACs in dental implant clinics based on papers published in the last decade (2010-2022). A comprehensive search on the PubMed, Scopus, and Web of Science databases was conducted to identify articles evaluating the relationship between Non-vitamin K dependent oral anticoagulants and dental implant surgery.

Results:

Despite the limitations of this study, it has been found that dental implants require discontinuation of NOACs for 24 hours or more prior to implant surgery. This depends on the type of anticoagulant and the creatinine clearance (CrCl).

Conclusion:

Implant surgery requires interruption of NOACs ≥ 24 hours preoperatively. However, there is a need for further clinical studies in order to establish more evidence-based guidelines.

Keywords: Dental implant, NOACs, Discontinuation, Anticoagulants, Creatinine clearance, Dabigatran.

Article History

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1. INTRODUCTION

Nowadays, ischemic heart diseases and cerebral ischemia are common worldwide. They represent the leading cause of death [1, 2]. In Europe, they kill more than 1.7 million people annually, accounting for 20% of all deaths, and in the United States, they account for about 30% of all deaths over the age of 35 [3, 4]. These diseases are managed by the regular use of oral anticoagulants [5]. In the past, vitamin K antagonist oral anticoagulants (e.g., warfarin) were commonly used. However, many foods that are rich in vitamin K, such as spinach, broc-

coli, and cashews, are known to be hazardous for patients anticoagulated with vitamin K antagonists [6, 7]. Fortunately, in the last decade, non-vitamin k antagonist oral anticoagulants (NOACs) were discovered. NOACs include the direct thrombin inhibitor (dabigatran) and factor Xa (FXa) inhibitors (rivaroxaban, apixaban, and edoxaban). These drugs have recently been approved for the prevention of stroke [8 - 11].

Bleeding is considered the main side effect of any anticoagulant. However, many clinical trials have shown that the bleeding risk for NOACs is relatively low, and it also depends on the procedure itself [12 - 15].

Dental implants are one of the most requested procedures in the dental clinic by patients. Many of these patients are

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receiving NOACs. Dentists are familiarized with traditional anticoagulants (vitamin K inhibitors) and the methods of monitoring tests by using the international normalized ratio (INR), and thus determine the efficacy and safety of the drug and whether to perform or not an invasive dental procedure that involves bleeding [16, 17]. However, there are still not enough reliable clinical trials and consensus about the protocol to apply to patients on NOACs and undergoing dental procedures. Therefore, it is necessary to address all these issues and summarize them through a review of the literature available for the optimal management of these patients in the dental office [18].

The aim of this study is to review the literature regarding the proper management of patients receiving NOACs in dental implant clinics.

2. MATERIALS AND METHODS

A comprehensive literature search covering the period 2010-2022 was conducted using PubMed, Scopus, and Web of Science databases to locate clinical trials and guidelines that were appropriate and relevant for this review. The following keywords were used in the literature search: Eliquis, Savaysa, Pradaxa, Xarelto, dabigatran, rivaroxaban, apixaban, edoxaban, atrial fibrillation (A-Fib), venous thromboembolism (VTE), FXa inhibitors, direct thrombin inhibitor, novel oral anticoagulants, direct oral anticoagulant (DOAC), new oral anticoagulants, dental implant surgery, oral procedure, and dentistry.

3. CLASSES OF NOACS AND THEIR CONSIDERATIONS FOR PATIENTS UNDERGOING IMPLANT SURGERY

3.1. Direct Thrombin Inhibitor: Dabigatran

Dabigatran is a direct thrombin inhibitor that prevents fibrin formation, thereby hampering clot formation. Therefore, it is used to prevent thrombus and embolus formation [19, 20]. Dabigatran is characterized by a rapid onset that reaches peak concentration in the plasma within 2-4 hours after administration and has a terminal half-life of 12-17 hours [19, 21].

Many sensitive tests could be used to assess dabigatran effects, such as diluted thrombin time, ecarin clotting time, and partial thromboplastin time using HemoClot Thrombin Inhibitor assays [22, 23]. However, using prothrombin time and partial thromboplastin time tests is not reliable [24 - 26].

Dabigatran is eliminated mainly by the kidneys [27]. Therefore, CrCl should be evaluated prior to implant surgery [28, 29]. If CrCl is less than 50 mL/min, dabigatran should be discontinued 3-5 days prior to implant surgery. While if CrCl is 50 mL/min or more, it should be discontinued 1-2 days preoperatively [30, 31]. The randomized clinical trial published in 2012 by Healey et al. recommended that dabigatran should be stopped 2-3 half-lives before the procedure, and for high bleeding risk procedures, dabigatran should be stopped 4-5 half-lives prior to the procedure [32]. Normal dosage can be resumed 8 hours after implant surgery [33].

The most common side effects experienced by more than 15% of patients are epigastric pain, dyspepsia, and bloating [34, 35]. Events of minor bleeding have been reported in 8-33% of patients and events of major bleeding in $\leq 6\%$ of patients [32, 36 - 37,]. In this situation, these can be managed by local measures, such as local pressure, sutures, and tranexamic acid [38]. In severe cases, these can be reversed within minutes by idarucizumab or hemodialysis [31, 39].

3.2. Factor Xa Inhibitors

3.2.1. Rivaroxaban

Rivaroxaban is a direct FXa inhibitor (xabans), preventing thrombin formation [40, 41]. It is rapidly absorbable and reaches peak plasma concentration approximately 2.5-4 hours after administration and exhibits a terminal half-life of 5-9 hours. The effect of rivaroxaban is evaluated using an anti-FXa test [36, 42, 43].

Literature regarding the **interruption of rivaroxaban therapy** is limited. However, several studies recommend discontinuing rivaroxaban one day prior to implant surgery [44 - 48]. In another study, Moreno *et al.* concluded that dental implant surgery in patients taking rivaroxaban is safe, with no need to discontinue the medication and emphasize the importance of performing postoperative local hemostatic measures [49 - 52]. While Hanken *et al.* concluded that rivaroxaban has a higher risk of bleeding than other oral anticoagulants [20]. A retrospective single-center observational study in 2015 showed postoperative bleeding complications to occur after oral surgery significantly more often in patients under continued rivaroxaban therapy (11.5%) than in the control cases without anticoagulation/antiplatelet medication (0.7%). All of the bleeding events were manageable, and all of them occurred during the first postoperative week [20].

Adverse effects are experienced by 1-10% of the patients. 1-2% of the patients have been reported to have major bleeding, and minor bleeding has been reported in 4-7% [41, 53, 54]. In cases where major bleeding has occurred, "Andexanet alfa" can be used as a reversal agent for rivaroxaban (Xarelto) and apixaban (Eliquis) [55 - 57].

3.2.2. Apixaban

Apixaban has a similar mechanism of action to rivaroxaban. It acts as a direct inhibitor of Fxa [58]. It is characterized by a rapid onset of action, which reaches the peak concentration in the plasma within 3-4 hours after oral administration. 25-30% is excreted by renal metabolism. Apixaban's half-life is 8-13 hours [59], which represents the longest half-life of current FXa inhibitors [60, 61]. In contrast to rivaroxaban, apixaban works in a reversible manner to selectively inhibit free and bound FXa as well as inhibit prothrombinase [60]. The effect of apixaban can be measured using the anti-FXa test [36, 62, 63].

Regarding implant surgery, some studies recommend apixaban interruption 24 hours prior to the procedure with low bleeding risks and 48 hours prior to procedures with high bleeding risks [59]. While other studies show no need to interrupt apixaban [64]. In general, it is recommended to let

patients ignore or postpone their morning dose on the day of the dental treatment. The patients can restart their medication only when haemostasis has been achieved [65 - 67].

3.2.3. Edoxaban

Edoxaban is a direct, reversible, and selective inhibitor of Fxa [68 - 70]. It is able to achieve peak plasma concentration more rapidly than all previously mentioned NOACs at 1-2 hours after administration [71]. Additionally, edoxaban has an approximate terminal half-life of approximately 10 hours [72]. Edoxaban's excretion is 35% renal. Therefore, renal function assessment could be helpful preoperatively [73]. If CrCl is less than 50 mL/min, dabigatran should be discontinued 2-4 days prior to implant surgery. While if CrCl is 50 mL/min or more, it should be discontinued 1-2 days preoperatively [74 - 76].

Table 1. Summary of NOACs with its considerations in the implant surgery clinic.

Classes of NOACs	Subclasses	Antidote	Considerations for Implant Surgery
Direct thrombin inhibitor	Dabigatran	Idarucizumab	CrCl should be evaluated prior to implant surgery [28, 29]. If CrCl is less than 50 mL/min, dabigatran should be discontinued 3-5 days prior to implant surgery. While if CrCl is 50 mL/min or more, it should be discontinued 1-2 days preoperatively [30, 31]
	Apixaban		
Factor Xa inhibitors	Rivaroxaban	Andexanet alfa	CrCl should be evaluated prior to implant surgery. If CrCl is less than 50 mL/min, it should be discontinued 2-4 days prior to implant surgery. While if CrCl is 50 mL/min or more, it should be discontinued 1-2 days preoperatively [74 - 76].
	Edoxaban		

CONCLUSION

Implant surgery requires interruption of NOACs ≥ 24 hours prior to the operation. The recommended duration of interruption depends on the NOAC subclass and the patient's renal function. The effects of direct thrombin inhibitor "dabigatran" can be measured using HemoClot Thrombin Inhibitor assays, while the anti-FXa test is used for FXa inhibitors "rivaroxaban, apixaban and edoxaban". In case of severe bleeding, dabigatran can be reversed by idarucizumab, while other NOACs can be reversed by andexanet alfa.

Despite an increase in the number of patients receiving NOACs, as listed in Table 1, the available evidence-based guidelines are still weak. Therefore, additional studies and the collaboration of dental and medical professionals are needed.

LIST OF ABBREVIATIONS

INR	=	International Normalized Ratio
A-Fib	=	Atrial Fibrillation
VTE	=	Venous Thromboembolism
DOAC	=	Direct oral Anticoagulant

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data supporting this study's findings are available from the corresponding author, [E.L.], on special request.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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