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DENTAL EXTRACTIONS IN PATIENTS ON NOVEL ORAL ANTICOAGULANTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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SUMMARY

Background: Anticoagulation therapy is the "gold standard" in treating and preventing thromboembolic disease. The indications for its use include prophylaxis against and management of venous thromboembolism (prior thromboembolism, physically constrained patients, post-complex operation patients, etc.) as well as the prevention of embolic stroke (patients with non-valvular atrial fibrillation, prosthetic heart valves). Due to a great percentage of patients receiving anticoagulation therapy, it is of fundamental importance that dental practitioners are familiar with such patients and their medical condition and needs. Dental practitioners should be well informed in advance of any prescription medications their patient is on, such as antiplatelet therapy, as well as of any other concurrent use of drugs. Interruption of anticoagulants is not commonly recommended, because the catastrophic risk of embolism, following anticoagulant suspension prevails over the risk of increased bleeding from tooth removal to a considerable extent. **Material and Methods:** The study's design provided for two patient groups: patients on Novel Oral Anticoagulants (NOACs) and patients on Vitamin K Antagonists (VKAs) that undergo simple dental extractions. The search technique encompassed navigation through and diligent exploration of electronic databases, supplemented by hand searches. Applying the advance search option, i.e. from 1990 up to 2019, we conducted a search in MEDLINE, improving the accessed articles via Ovid interface. Our key words were primarily oriented towards a composite based on MeSH terms and text words. Other advance search options included "Randomized Controlled Trials (RCTs)", "cohort studies" and "case-control studies" reporting post-extraction bleeding complications definable according to the Bleeding Academic Research Consortium (BARC). All retrieved articles were written in English.

Results: The search in the literature yielded 190 studies. After reviewing their title and summary, 82 of them were found to meet the inclusion criteria and, thus, their full text articles were reviewed. Of these, 77 studies were excluded from systematic research, as they would no longer fulfill our inclusion criteria. The systematic review and meta-analysis comprised 5 clinical trials in total. Using the Cochran's Q test, non-significant heterogeneity was established between the studies of meta-analysis ($p = 0.77 > 0.10$). Moreover, the value of I^2 statistic is 0.0%, thus confirming the lack of significant heterogeneity. The pooled risk ratio (RR) is 1.005 (0.98, 1.03); this demonstrates that the appearance of Type I haemorrhage bears no distinction between NOACs and VKAs, given the unit is contained in the 95% confidence interval. In addition, it is observed that the results of the random-effects model are identical to those of the fixed-effects model due to the lack of significant heterogeneity. **Conclusions:** Due to the large-scale administration of NOACs, it is highly significant and determining that dentists are well informed on and knowledgeable of such newer drugs and their mechanisms of action. Accessing whether to switch oral surgery patients from NOACs to other medications is an essential parameter requires the conduction of more clinical trials.

INTRODUCTION

Anticoagulant treatment is essential for the prevention of thromboembolic events in a large number of patients, particularly those with atrial fibrillation or venous thromboembolic disease. According to the guidelines of the American College of Chest Physicians (AACP), patients are determined as "high risk" for a thromboembolic event if they fulfill one of the following criteria: mitral valve prosthesis, recent ischemic stroke in the previous 6 months, venous thromboembolism in the previous 3 months, severe thrombophilia or protein C, protein S, antithrombin or antiphospholipid antibodies.[1,2] Such patients are managed with anticoagulation therapy to avert the occurrence of thromboembolic events.[1] From a pathophysiological point of view, however, the anticoagulants' mechanism of action also increases the risk of bleeding. Heparin was first launched as an anticoagulant in the 1930s; nonetheless, it can only be used parenterally, thus limiting its route of administration, and its therapeutic range must be subject to close monitoring.[3] Typically, to prevent venous thromboembolic disease in acute thromboembolic events or to manage patients admitted to hospital after a surgery, heparin's route of administration is either subcutaneous or intravenous.[4] Vitamin K antagonists (VKAs), i.e. warfarin and acenocoumarol, were developed in 1940 and, until recently, they enjoyed their exclusivity in the category of orally administered anticoagulants.[3] To a certain degree, any challenging issues encountered with

parenteral heparin were partly addressed with oral anticoagulants.[3] Warfarin (Coumadin, Bristol-Myers Squibb Srl, Italy), a VKA of widespread use, is effeciently absorbed by the upper gastrointestinal tract; the other VKA is acenocoumarol (Sintrom, Novartis Farma, Italy). Albeit warfarin being rapidly absorbed, it takes 8-12 hours for its effects to become evident, with its peak value reaching 36 hours.[4] Thus, heparin remains an indispensable treatment solution in patients in need of prompt anticoagulation treatment.[5] Cytochrome P450 complex is the primary component for the hepatic metabolism of Warfarin and may demonstrate major pharmacological variability among individuals.[4-6] Due to their close therapeutic effect and exhibited variable effects among patients, VKAs are subject to International Normalized Ratio (INR) measurement, i.e. comparison of patient prothrombin time (PT) to the PT control.[4, 7] A physiological value of INR is assumed to be 1.0, with the typical treatment range under anticoagulant treatment being between 2 and 3.[8]

In making efforts to deliver anticipated effects to a greater extent, medications were developed as clotting factors-specific, namely thrombin and factor Xa.[5] The novel oral anticoagulant drug (NOAC) group seems to overwhelm any obstacles related to commonly used anticoagulants, inhibiting the direct production of thrombin or inhibiting thrombin.[5, 6, 9] The first new oral anticoagulant, Dabigatran, was initially authorised by the EU in 2008, and received its subsequent authorisation by the FDA two years later, i.e. 2010. It is marketed under the name Pradaxa (Boehringer, Ingelheim, Germany) and acts as an unmediated inhibitor of thrombin to avert fibrinogen being converted to fibrin, thus blocking thrombus formation.[10] In patients with nonvalvular atrial fibrillation (NVAF), it prevents possible strokes and systemic embolism.[10] The pharmacokinetic properties of dabigatran include a 3% -7% bioavailability after oral administration with a rapid onset; maximum plasma concentration is achieved 2-4 hours after administration[11, 12] and its terminal half-life is 12-17 hours. In terms of elimination, kidneys excrete 80% of dabigatran, with the rest 20% being hepatically metabolised. It should be noted that renal patients are administered a reduced dose, especially those with creatinine levels below 50 mL / min.[11] Dabigatran constitutes a model oral anticoagulant, as, in contrast to VKAs, it does not interact with other drugs or foods, so its action remains unaffected. Rivaroxaban, marketed as Xarelto (Bayer HealthCare, Germany), was the next NOAC to succeed the FDA approval process[13] for the following indication: to limit the risk of stroke and systemic embolic events in patients with NVAF presenting one or more risk factors, from hypertension and diabetes to heart failure or stroke. In addition, rivaroxaban is indicated for the treatment and recurrence reduction of pulmonary

embolism and deep venous thrombosis.[13] Regarding its pharmacokinetic properties, rivaroxaban demonstrates superior bioavailability over all other NOACs, which ranges between 60% - 80% after being orally administered. Its absorption is very fast and it reaches its post-intake maximum plasma concentration in about 2.5-4 hours. Apixaban, marketed as Eliquis (Bristol-Myers Squibb, USA), is the NOAC third in line to have been authorised by the FDA and the European Medicines Agency in 2012 for the management of deep venous thrombosis, pulmonary embolism and the limitation of stroke and systemic embolic events risks in NVAF patients.[14] Apixaban is an additional NOAC inhibiting FXA. Unlike rivaroxaban, apixaban acts reversibly and selectively inhibits free and blocked FXa, while it also inhibits prothrombinase. Similarly to the NOACs mentioned above, it reaches its post-intake maximum plasma concentration in 3-4 hours after being orally administered.[14]

Due to a great percentage of patients receiving anticoagulation therapy, it is of fundamental importance that dental practitioners are familiar with such patients and their individual medical conditions and needs. Patients on antiplatelet and/or anticoagulant treatment run a higher risk of bleeding. Conversely, discontinuation of anticoagulants is usually not advised, as the risk of catastrophic embolism outweighs the risk of greater post-operative bleeding from tooth removal by far.[15-19] The American College of Chest Physicians (AACP) recommended continuing anticoagulation for dental extractions in its 2001, 2004, and 2008 statements. In 2012[1], the AACP recommended the option of either continuing anticoagulation using a prohemostatic mouthwash, e.g. tranexamic acid, to aid in hemostasis for minor dental procedures including extractions or discontinuing anticoagulants for 2 or 3 days prior to the procedure. Warfarin has a well-documented management protocol, according to which treatment is delayed on condition that the INR is greater than 4.0[20] –that being the sole indication. Upon identification of haemorrhage risk, haemostasis can be effected using topical means, i.e. mechanical pressure, haemostatic agents (e.g. Gelfoam™ or Surgicel™), and suture and oral tranexamic acid solution.[16-19] In cases of minor bleeding events, local means, such as mechanical pressure, haemostatic agents and sutures, can be used to achieve the desirable outcome.[16-18] If haemorrhage persists and any local measures taken do not prove applicable and/or effective, or if automatic bleeding occurs, urgent care is deemed imperative, and patient referral to a hospital setting should always be considered.[16] The novel oral anticoagulant drug (NOAC) group seems to overcome any disadvantages related to conventional anticoagulants, however, further clinical studies are needed in order to establish more evidence-based guidelines for such patients. The aim of this systematic review

and metanalysis is to investigate post-extraction bleeding after simple tooth extraction in patients on NOACs and in patients on VKAs.

MATERIALS AND METHODS

Design of the study

This systematic review was performed based on the recommendations and principles of the Cochrane Collaboration as well as on the PRISMA statement. Prior to starting this systematic review, an all-encompassing protocol was elaborated that received consecutive approval by all authors. The said highly thorough protocol integrated a number of sections and research techniques, i.e. search approach, determination of eligibility, inclusion requirements, screening methods, data extraction, quality assessment, and data synthesis/analysis. The core question was determined according to the PICO framework, i.e. "In patients who undergo routine dental extractions (P) and are under NOACs treatment (I) compared to those under VKAs (C), what are the outcomes of post-extraction bleeding complications according to the BARC bleeding definition (O)?"

Inclusion requirements

1. Randomized controlled trials (RCTs), cohort studies and case-control studies reporting post-extraction bleeding complications that can be transformed in BARC bleeding definition.
2. Articles written in English

Exclusion requirements

3. Case reports, case series, reviews, editorials, and retrospective studies.
4. Single arms of prospective studies on patients under NOACs

Population characteristics

The study's design provided for two patient groups: patients on Novel Oral Anticoagulants (NOACs) and patients on Vitamin K antagonists who undergo simple dental extractions. Simple dental extraction refers to atraumatic tooth removal by applying rotational and traction movements with the assistance of dental forceps and elevators, without raising a mucoperiosteal flap and/or in absence of alveolar bone excision.

Outcome measurements

Outcomes from the included studies were transformed to BARC classification according to the proposal of *Lillis et al*.[21], as following.

Bleeding Academic Research Consortium (BARC) 5 types. Type 0 corresponds to no bleeding. Type 1 has two categories, i.e. minor bleeding, which is an immediate post-extraction bleeding from socket that can be controlled on a first attempt with pressure pack and/or other local haemostatic measures (suturing, oxidized cellulose, gelatin or collagen sponge etc); mild oozing, i.e. occurring from the post-extraction socket, which does not require special intervention for its control and management. Type 2 BARC can be either clinically significant with persisting immediate post-extraction bleeding from the socket that cannot be controlled on a first attempt with local haemostatic measures in a primary dental setting, or any other clinical sign of recurrent aggressive post-extraction bleeding with the formation of "liver clot", large facial ecchymosis or persisting aggressive oozing continuing for more than 12 h that may require intervention by a healthcare professional to be controlled, however, it does not fit the life-threatening bleeding criteria. Type 3 BARC classification is a life-threating bleeding with clinical, laboratory and/or imaging findings requiring medical attention by a specialist healthcare provider, on condition that haemoglobin drops from 3 to < 5 g/dL* or any transfusion with overt bleeding corresponds to Type 3a BARC. Type 3b BARC corresponds to post-extraction bleeding and haemoglobin drop at ≥ 5 g/dL* or bleeding requiring intravenous vasoactive agents or bleeding requiring surgical intervention for control and management. Lastly, fatal bleeding corresponds to Type 5 BARC and probable fatal bleeding; no autopsy or imaging confirmation, but clinically suspicious (Type 5a BARC) and a definite fatal bleeding; overt bleeding or autopsy or imaging confirmation (Type 5b BARC).[21]

Search strategy

The search technique encompassed navigation through and diligent exploration of electronic databases, supplemented by hand searches. Applying the advance search option, i.e. from December 1990 up to May 2019, we conducted a search in MEDLINE, improving the accessed articles via Ovid interface. Our key words were primarily oriented towards a composite based on MeSH terms and text words. Our online search was conducted according to the PICO framework in the following fashion: (dabigatran OR rivaroxaban OR apixaban OR edoxaban OR antithrombotic) AND (dental OR tooth OR teeth).

Study eligibility evaluation and data extraction criteria

A PRISMA flowchart was prepared and used as a standardized screening form; both the reviewers used the form to unilaterally enter all valuable data retrieved from the studies screened at various steps of the review. Following the initial literature search, all article titles were screened anew to rule out any non-pertinent publications, review articles, case reports, and animal studies (AM.V. and T.L.). As a result, several studies were omitted after viewing and reading data contained in their abstracts (AM.V. and T.L.). Our closing screening eligibility step involved the same two reviewers (AM.V. and T.L.) reading the full-text in the light of both the inclusion and exclusion requirements.

Statistical Analysis

The results of the meta-analysis were expressed using risk ratio (RR) and 95% confidence interval (CI). Heterogeneity was assessed by the *P* value of Cochran's Q test and I^2 statistics, and heterogeneity was deemed significant if the I^2 statistic was greater than 50% or if the *P* value was less than 0.1. The random-effects model was used to conduct the meta-analysis. In the case of non-significant heterogeneity, the random-effects model is the same as the fixed-effects model.The statistical analysis was performed using the RStudio (R version 3.5.2).

Methodological quality evaluation

The quality evaluation of all studies meeting the inclusion requirements was carried out by each reviewer unilaterally (AM.V. and T.L.) and during the data extraction process. All selected studies were also evaluated in terms of methodological quality evaluation, by applying the Newcastle-Ottawa Scale (NOS).[22]

The NOS system contains eight items, which are classified under three pillars including selection, comparability, and depending on the study type outcome (cohort studies) or exposure (case control studies). Each item is followed by multiple choice responses. A star scoring system facilitates a semiquantitative quality evaluation of each study, i.e. studies of the highest quality are awarded a maximum of one star for each item, save for the item pertaining to comparability that grants the assignment of two stars. The maximum number of assigned stars is nine, provided all the aforementioned items are fulfilled.

Article	Selection	Comparability	Outcome
Andrade 2018	1) * 2) * 3) * 4) *	1) *	1) * 2) * 3) *
Berton 2018	1) * 2) * 3) * 4) *	1) *	1) - 2) - 3) -
Caliskan 2017	1) * 2) - 3) * 4) *	1) *	1) - 2) * 3) *
Mauprivez 2016	1) * 2) * 3) * 4) *	1) *	1) * 2) * 3) *
Yagyuu 2017	1) * 2) * 3) - 4) *	1) *	1) - 2) - 3) -

RESULTS

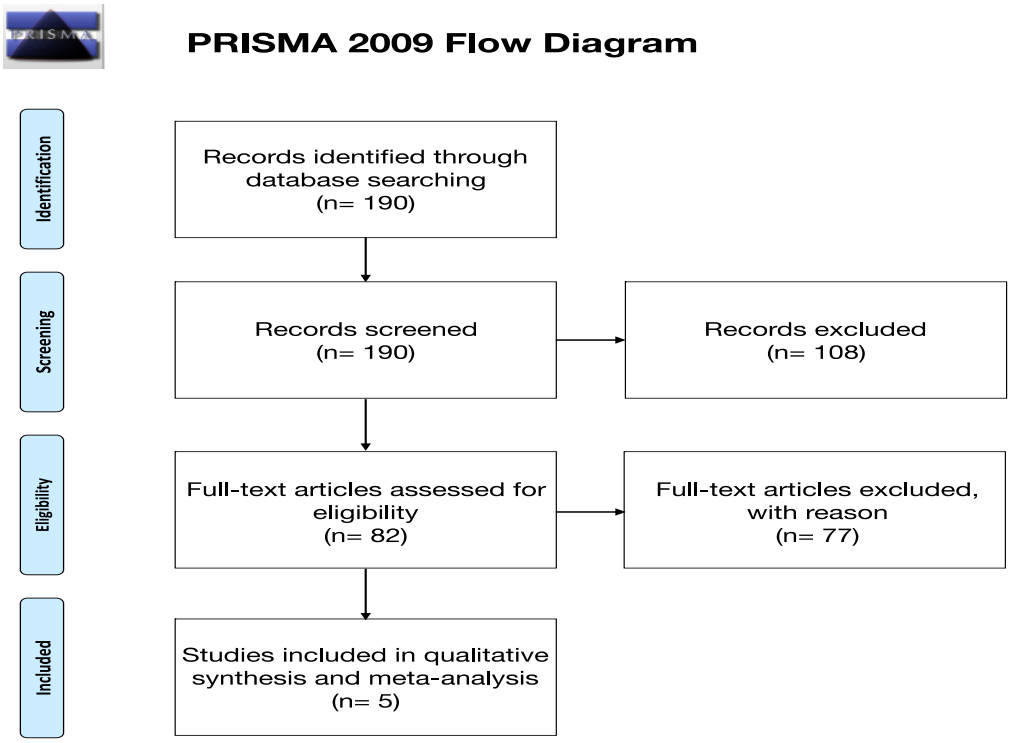
The search in the literature yielded 190 studies. After reviewing their title and summary, 82 of them were found to meet the inclusion criteria and, next, the full-text articles were reviewed. Of these, 77 studies were excluded from systematic research, as they would no longer meet the inclusion criteria. A total of 5 studies were considered for systematic review and meta-analysis, and the data obtained were summarized on the PRISMA FLOW CHART.

The forest plot presents data from five studies which were collected for meta-analysis purposes. Type I haemorrhage was considered to be the fact of interest, because most of the events were identified as such. Observing the forest plot, one notes that the there is no difference in the appearance of Type I haemorrhage between the NOACs and the VKAs for all of the five studies, as the 95% confidence interval of the risk ratio is involved the unit. Using the Cochran's Q test, non-significant heterogeneity was found between the studies of meta-analysis ($p = 0.77 > 0.10$). Moreover, the value of I^2 statistic is 0.0%, thus confirming the absence of significant heterogeneity. The pooled risk ratio (RR) is 1.005 (0.98, 1.03), demonstrating that the appearance of Type I haemorrhage does not differ between NOACs and VKAs, given the unit is contained in the 95% confidence interval. In addition, it is perceived that the results of the random-effects model are the same as those of the fixed-effects model due to the lack of significant heterogeneity.

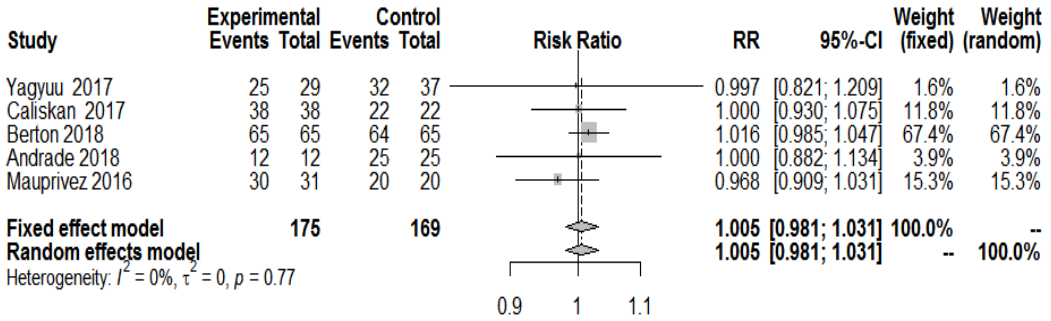
Mauprivez et al.[23] conducted a prospective observational study and performed simple tooth extraction on 51 patients who had received anticoagulant treatment. Of the 51 patients, 31 had received NOAC and 20 received VKA, with INR range between 2.0 and 3.0. In both groups, teeth were extracted without interrupting the anticoagulant treatment, while the same local hemostatic measures were applied. All patients were characterized as type I; only one case of post-operative bleeding occurred, which was managed with fibrin glue to facilitate re-suturing of the socket (type II). Bleeding events, if any, manifested within 3 days after the surgical procedure, and none of them was of serious nature mandating for medical attention, i.e. either hospitalization or blood transfusion. *Caliskan et al*.[24], studied the post-operative hemorrhage among patients receiving NOACs and VKAs. Out of 60 patients on anticoagulants, 22 patients had received VKAs, while the rest 38 patients had received NOACs. All tooth extractions were performed as atraumatically as possible, using only elevator and forceps. Both groups exhibited the same haemorrhagic type according to BARC classification (type I), and none of them was identified with automatic haemorrhage that could not be managed by local haemostatic measures.[24] A recent retrospective study by *Yagyuu et al*. 2017[25] was based on patient records, and tooth extractions were classified corresponding to whether patients were on NOACs and VKAs. A total of 172 routine teeth extractions in 66 patients met the inclusion criteria, with 72 extractions being performed on patients on NOACs and 100 extractions on patients on VKAs.

For all patients participating in the study, their anticoagulant therapy was not interrupted during the procedure. All bleeding events were according to the BARC classification observed in the NOACs group and were of type I for 25 patients and of type II for 4 patients, while the VKAs group had 32 patients and 5 patients, respectively.[25] The prospective controlled study of *Andrade et al*. 2018[26] selected atrial fibrillation patients of both genders, aged 18 years and older, who were on oral anticoagulants, i.e. either warfarin or NOAC. Prior to extraction, the vital signs of all subjects were assessed, namely blood pressure, heart rate, weight, and height. On the same day of the extraction, patients from the warfarin group had their blood sampled for PT and INR measurement purposes. All extractions were carried out in accordance with the protocol of anticoagulant therapy in patients with heart disease at Santa Izabel Hospital. Local haemostatic measures included socket suturing, placement of a collagen sponge and tranexamic acid administration. Of the patients enrolled in the study, 25 were in the warfarin group and 12 in the NOAC group. The results of the aforementioned study demonstrated no statistically significant difference between the two patient groups in

terms of post-operative bleeding events following routine teeth extractions, with both groups being included in as type I according to BARC.[26] In 2018, *Berton et al*.[27] studied two groups of a total of 130 patients requiring tooth extraction while receiving anticoagulant treatment: 65 patients on NOACs and 65 patients on VKAs. Preoperatively blood pressure and INR were measured in order to identify any changes in prothrombin time dependent on factors other than pharmacological treatment. Preoperative chemoprophylaxis (amoxicillin 2 g 1 hour before surgery or clarithromycin 500 mg in case of allergy) was required and patients were prompted to rinse their oral cavity with 0.2% chlorhexidine shortly before their dental procedure –after the tooth removal, all patients were closely monitored for 30 minutes. In case of inadequate bleeding control, an absorbable cellulose sponge (Gelita-Spon, Gelita Medical GmbH, Eberbach, Germany) or gauze impregnated with tranexamic acid 500 mg/ml (Acido Tranexamico, Bioindustria LIM, Novi Ligure) was placed in the socket. In case of local bleeding control measurements being ineffective, patients were referred to a dental emergency department. The number of bleeding events following simple tooth extractions among the patients who participated in this study was low. More specifically, the 65 patients of the NOAC group and the 64 patients of VKA group reported no serious postoperative bleeding and their BARC transformation was type I. Only 1 patient in the VKA group required medical evaluation and wound suturing (type II).[27]



Article	Patients	BARC
Mauprivez 2016	VKAs: 20 pts NOACs: 31 pts	VKAs: 20 I NOACs: 30 I/ 1 II
Caliskan2017	VKAs: 22 pts NOACs: 38 pts	VKAs: 22 I NOACs: 38 I
Yagyuu 2017	VKAs: 37 pts NOACs: 29 pts	VKAs: 32 I/ 5 II NOACs: 25 I/ 4 II
Andrade 2018	VKAs: 25 pts NOACs: 12 pts	VKAs: 25 I NOACs: 12 I
Berton 2018	VKAs: 65 pts NOACs: 65 pts	VKAs: 64 I/ 1 II NOACs: 65 I



DISCUSSION

Several studies have shown a major decrease in the risk of thromboembolic events due to anticoagulant treatment.[28,29] Other studies report serious embolic complications, including death, in patients who discontinue anticoagulant treatment, with the complications being three times as likely.[30,31] Regarding oral surgery procedures, no cases of fatal post-operative bleeding have been reported in patients who continued their anticoagulant treatment[30, 32], but thromboembolic events have been reported after tooth extraction.[33, 34]

The American College of Chest Physicians suggests patients discontinue warfarin 5 days prior to any surgical operation, as well as that warfarin should be bridged with heparin of low molecular weight.[35, 36] On the other hand, the American Heart Association suggests that the INR be between 2.0 and 2.5, with strict follow-up.[37] Simple tooth extractions are likely to cause bleeding, as the complexity of the removal itself or its possible complications may have an impact on the bleeding risk in highly susceptible patients. Patients should be thoroughly evaluated, because there is a great lack of consensus on adjusting warfarin therapy prior to any dental procedure.[38, 39] The existence of rebound hypercoagulability after a sudden discontinuation of warfarin therapy has been reported in literature.[40, 41]

According to the guidelines of 2007, the risk of bleeding in patients on oral anticoagulants and stable INR within therapeutic limits 2-4 (i.e.<4) is very low; on the contrary, the risk of thrombosis may be elevated if dental patients interrupt their anticoagulant treatment for a short period of time. Oral anticoagulants are not recommended to be discontinued in most patients requiring dental treatment and tooth extraction.[42]

Bacci et al.[43] demonstrated that tooth extractions can be safely conducted in patients receiving anticoagulant therapy without any treatment adjustment. Although such recommendations do appear in literature, a number of dental practitioners remain skeptical about observing the current guidelines.[44] In patients with a heavy medical history, such as diabetes mellitus, liver disease and chronic renal failure, the INR should be between 2.5 and 2.8 in order to prevent major bleeding complications in the course of their oral surgery.[41, 45]

On a global basis, the new oral anticoagulants (NOACs), i.e. dabigatran, rivaroxaban and apixaban are progressively used as a backup choice for warfarin. NOACs were primarily administered to prevent stroke in atrial fibrillation patients, while warfarin is used to prevent stroke in people with valve diseases, artificial heart valves, atrial fibrillation as well as to avoid the recurrence of myocardial infarction. Although the number of patients taking NOACs increases every year, warfarin remains among widely prescribed medications, especially in patients who are contraindicated to NOACs (as in the case of renal dysfunction or left ventricular thrombus or metal prosthetic valve). Even though dental extractions are now carried out without discontinuation of anticoagulant drugs (warfarin), given the INR is regularly controlled and within the therapeutic range[46-48], contrary to NOAC treatment, there are still few studies investigating intraoperative treatment of patients.[49]

The advantages of NOACs are their predictable pharmacokinetic properties, rapid onset of action, lesser risk of food-drug interactions as well as their reduced half-life time. Unlike VKAs, NOACs do not require regular monitoring.[24, 50, 51]

A systematic review by *Johnston* reported that the majority of the literature is composed of unstructured review articles based on assumptions of non-dental data.[52]

Muñoz-Corcuera et al. propose that each patient receives customized treatment, depending on the risk of embolism, post-operative haemorrhage and renal function.[53] Determined by the haemorrhage risk, *Curto et al*. divided dental treatments into two groups: patients that run

a minor risk of haemorrhage and patients that run a medium to major risk of haemorrhage.[54] Minor-risk dental procedures include routine tooth extractions, surgical extractions lasting less than 45 minutes, and soft tissue surgery. Simultaneous extractions of more than three teeth, and interventions lasting more than 45 minutes, were considered as medium or major risk procedures, always in the light of effective and critical communication with the physician treating the patient.

The authors suggest that for minor-risk procedures, interruption of dabigatran therapy does not constitute a prerequisite and apixaban intake may be take place post-operatively.[55] In mid- and major-risk approaches, taking apixaban and dabigatran should be interrupted for a minimum of 24 and 48 hours, respectively. *Beyer-Westendorf et al*. received data from 2179 patients and evaluated perioperative safety and patient management under NOACs.[56] The major part of patients, 76%, in the study were administered rivaroxaban; 23.5% were administered dabigatran and, lastly, 0.5% were administered apixaban. Subject to the seriousness of tissue injury and haemorrhage risk, the authors determined three separate types of procedures. In the type involving simple tooth extractions, the authors identified 3 cases (0.5%) with severe bleeding, 20 cases (3.1%) with clinically significant haemorrhages and 6 (0.9%) with insignificant bleeding events. The haemorrhage incidence was identified as higher in the heparin-bridged group compared to patients who continued on NOACs or those who interrupted their anticoagulant therapy.[56] *Mauprivez et al*. measured the number of post- tooth extraction haemorrhagic events in 31 patients who had received NOACs against 20 patients who had received VKAs with INR between 2.0 and 3.0 and had discontinued their medication.[23] According to the authors of the study, a “bleeding episode” is an unresolved or intense bleeding that is not responsive to a 20-minute gauze compression. The number of bleeding episodes showed no statistically significant difference across the groups.[23]

Costantinides et al. suggested not to interrupt anticoagulation treatment for patients on NOACs who undergo dental surgery.[57] In their recent study, *Lababidi et al*. reported no statistically significant variation in haemorrhagic events between patients on NOACs and VKAs who underwent surgical oral procedures.[27, 58] The study by *Andrade et al*. suggests that, regarding simple tooth extractions, there is no statistically significant variation in haemorrhagic episodes of patients on dabigatran over those on warfarin. Haemorrhage within the first 24 hours after extraction was less common among dabigatran patients.[26]

Cocero et al. 2019, in a retrospective cohort study on 100 patients under NOACs, they performed teeth extractions after 4 hours of the last dose of drug dose intake. Of the 100 patients, sixty-four had a systemic disease: 32 (50%) had diabetes, 20 (31%) had hepatic disorders and 12 (19%) had renal failure. The study variables were age, gender, NOAC factor (61% Factor Xa inhibitors) and 2- or 3-teeth extraction (30%).[59] The factor that significantly affects bleeding in patients with systemic diseases is the extraction of more than one multirooted tooth (premolars and molars). The study, though, was excluded from the meta-analysis, because it was a singled arm study and did not deploy a control group with VKAs.[59]

In a prospective study of *Micotte et al*. 2017, routine tooth extractions were performed in 26 patients (mean age 76 years, 57% males) managed with dabigatran, rivaroxaban or apixaban, in absence of a control group on VKAs. Regardless of the scheduled time of tooth removal or of their drug regime or renal function status, patients were asked to only omit the morning dose on the same day of the operation. No difference in intraoperative hemorrhage between the two groups (NOAC & control group) was observed, however, postoperative bleeding was more common in patients undergoing anticoagulation therapy. The said study was not included in the meta-analysis, as it did not fulfill our inclusion criteria.[60]

CONCLUSION

Due to the large-scale administration of NOACs, it is highly significant and determining that dentists are well informed on and knowledgeable of such newer drugs and their mechanisms of action. To a great extent, both drug expertise and experience serve clinical practice and handling of possible complications that may arise and are related to their use in dentistry. However, any decision to interrupt anticoagulants must be reached following communication with the patient's attending physician and evaluation of the post-extraction bleeding risk, and in the light of a potential compromise due to thromboembolic event if the treatment is adjusted. Although guidelines are released for perioperative management of patients on NOACs, the field of dentistry continues to lack such guidelines for the NOAC group, the reason being that current dental guidelines only refer to warfarin and, thus, dentists should adhere to them. In conclusion, simple tooth extractions in patients receiving NOACs can be carried out without discontinuation or conversion of their anticoagulant therapy with local haemostatic measures.

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