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A COMPARISON OF BLEEDING RELATED TO DENTAL TREATMENT IN PATIENTS WITH THROMBOEMBOLIC DISORDERS TAKING TWO GROUPS OF ORAL ANTICOAGULANTS - A SYSTEMATIC REVIEW

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ABSTRACT

Providing dental care to patients with systemic comorbidities is difficult as they are on multi drug therapy. One such drug or group of drugs, which require modification in dosing and administration especially during invasive dental treatments, are anticoagulants.Extractions should be done with caution in patients under anticoagulant therapy as it is associated with escalated chances of profuse bleeding and complications associated with morbidity-mortality.To identify, appraise the available evidence on bleeding related to dental treatment in patients with thromboembolic disorders taking two groups of oral anticoagulants – the new/ novel oral anticoagulants and the other conventional oral anticoagulants an electronic search in various databases was performed. Articles were selected if they were studies which evaluated the effect of anticoagulants on peri-, and post-operative bleeding related to dental procedures in patients under NOACs and other oral anticoagulants. The electronic and hand search of studiesyielded 7 studies meeting the inclusion criteria. The available evidence from the included studies show that NOACs are associated with mild to moderate post-operative

bleeding with can be controlled by local hemostatic measures such as mechanical compression using gauze pads and collagen sponges. Severe bleeding requiring hospitalization was not reported in any of the included studies. For simple tooth extractions, the studies concluded that interrupting or dose alteration of NOACs was not required. FurtherRCTs have to be done to confirm the above mentioned conclusions and to form guidelines for carrying out invasive procedure in dental patients under NOACs.

Keywords: novel oral anticoagulants, NOACs, direct oral anticoagulants, oral anticoagulants and warfarin

INTRODUCTION

Sound oral health is necessary for maintaining good systemic health. Diseases of tooth and associated structures have an impact on quality of life – both local and systemic. Many systemic diseases have their manifestation in oral cavity. Care has to be taken while delivery of oral health in patients with systemic comorbidities. Precautions has to be taken during dental treatment in patients who are on drug therapy for systemic illness **[1]**. One such drug or group of drugs, which require modification in dosing and administration especially during invasive dental treatments, are anticoagulants. Common oral anticoagulants in use are the warfarin and other vitamin K antagonists (VKAs). Warfarin and heparin were used for more than 60 years since their discovery in 1948 and 1920s. VKAs have been extensively researched upon since their introduction. As they were associated with increased risk of bleeding complication and the need for frequent monitoring for dose titration, there was a necessity for newer anticoagulants. Recently, a new group of anticoagulants called direct thrombin inhibitors and factor Xa inhibitors were introduced **[2]**. These groups of drugs were collectively called as novel oral anticoagulants (NOACs). NOACs are also known as Direct oral anticoagulants (DOACs), Newer oral anticoagulants and non – vitamin K antagonists. The novel or newer oral anticoagulants were introduced in the year 2010 and hence have been in use for a various thromboembolic disorders. NOACs, since their approval for human use, are being compared to VKAs to test their efficiency and safety in patients with thromboembolic disorders.

Thromboembolic disorders are the leading cause of death and are estimated to account for about 1 in 4 deaths worldwide. Incidence rates and mortality rates due to of ischemic heart disease is realized to be higher than the other thromboembolic disorders including atrial fibrillation, venous thromboembolism and ischemic stroke **[3]**. Anticoagulants are prescribed to

patients for a variety of thromboembolic disorders are deep vein thrombosis, pulmonary embolism, myocardial infarction, rheumatic heart disease, atrial fibrillation, cerebrovascular disorders, prosthetic heart valves and renal dialysis **[4]**.

One of the most common invasive procedure done in a dental setup is extraction **[5]**. Extractions should be done with caution in patients under anticoagulant therapy as it is associated with escalated chances of profuse bleeding and complications associated with morbidity-mortality **[1]**. Guidelines for management of patients under VKAs for oral surgical procedures has been widely described. A controversy under debate is the discontinuation/ dose alteration of the novel oral anticoagulant drug before the invasive dental procedure. There are no clear guidelines nor large scale clinical trial to answer this question. This study focuses on identification and appraisal of available evidence regarding the bleeding risk in patients on NOACs undergoing invasive dental procedures.

MATERIALS AND METHODS

We searched four databases for relevant studies published till February 2019. The sources included were PubMed - Mesh, Ovid MEDLINE, and Cochrane Central Register for Controlled Trials

Inclusion criteria

This review included studies involving patients over the age of 18 years under anticoagulant drugs for various thromboembolic disorders.

Studies comparing the effect of NOACs and oral anticoagulant drugs on bleeding due to dental extractions were included.

Only studies in English language were included.

Exclusion criteria

Studies that did not compare the effect of NOACs and other oral anticoagulant drugs on invasive dental treatment were excluded.

RESULTS

a. General information on selected articles: **(Table 1)**

Chart 01 – Search Flow Chart

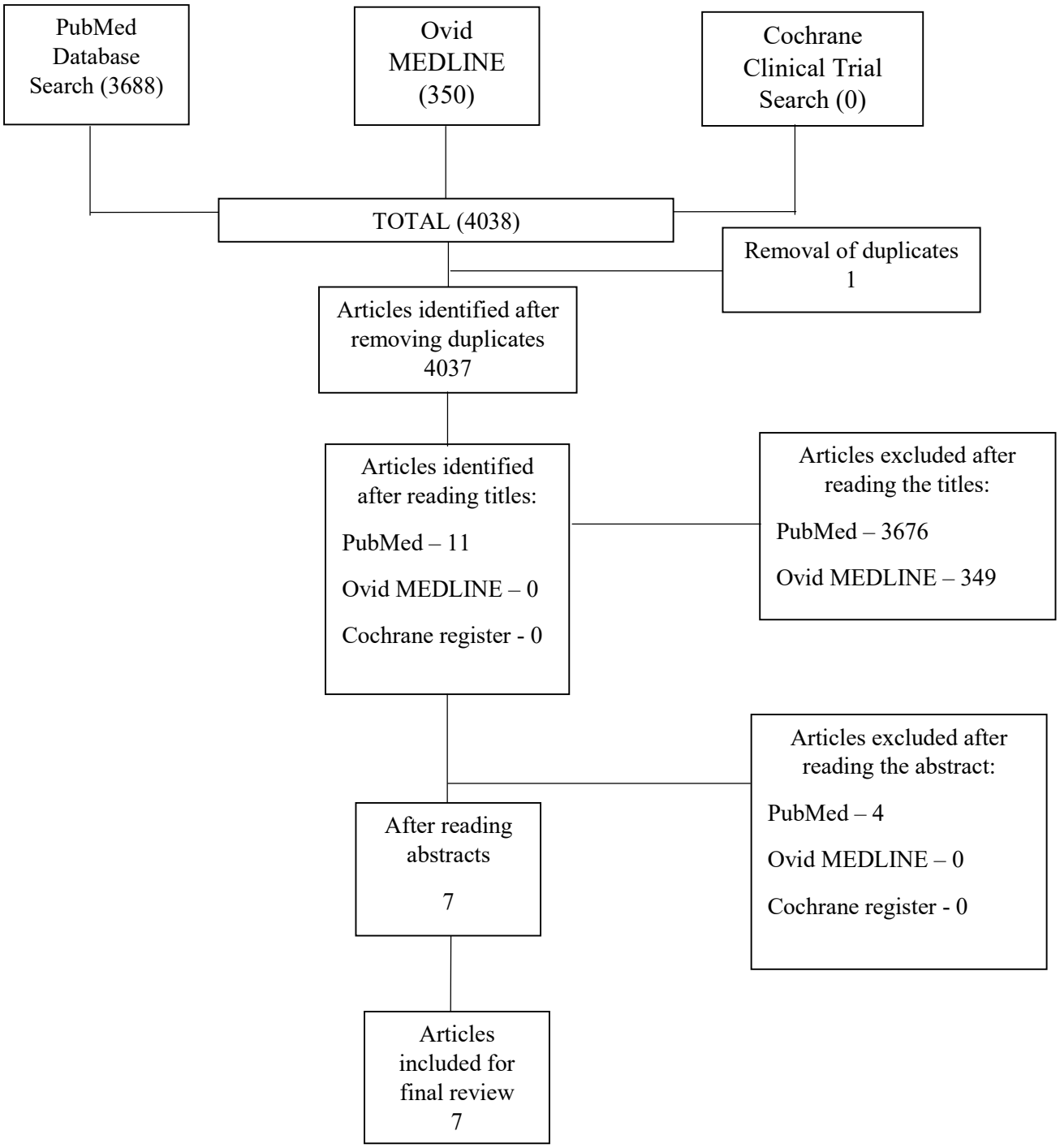

Table 1: Characteristics of included studies

S. No	AUTHORS	PATIENT CONDITION	YEAR	STUDY DESIGN	EXPERIMENTAL GROUP	CONTROL GROUP	MODIFICATION OF ANTICOAGULANT DOSAGE BEFORE SURGERY	MEASUREMENTS	PRIMARY OUTCOME	SECONDARY OUTCOME	CONCLUSION
1	*Berton et al*	Patients under oral anticoagulant therapy	2018	Prospective case control study	65 patients under DOACs for at least 2 months	65 patients under warfarin for at least 2 months	Continuing the usual anticoagulant treatment	Peri- and post – operative bleeding from simple single dental extraction	Post-operative bleeding after single tooth extraction	1.Any complications: ecchymosis, nerve injury, alveolitis 2. Cotton roll imbibition assay	Non - discontinuation of DOACs for simple single tooth extraction
2	*Andrade MVS et al*	Patients with non – valvular AF under dabigatran and warfarin	2018	Prospective, single – centre controlled study	12 patients under Dabigatran	25 patients under warfarin	Continuing the usual anticoagulant treatment	Severity of bleeding from single/ multiple dental extractions	Bleeding time 1 – between beginning of suture and complete hemostasis	Bleeding time 2 – between end of suture and complete hemostasis, bleeding before, during, after 24 hours, 48 hours, 7 days post procedure	There is no significant difference in the intensity of bleeding of patients taking dabigatran and warfarin. Bleeding after 24 hours was less frequent in patients on dabigatran.
3	*Caliskan M et al*	Patients under oral anticoagulants	2017	Prospective, observational study	1.17 Patients under direct thrombin inhibitor 2.21 Patients under factor Xa inhibitor 3.22 Patients under warfarin	24 patients taking no anticoagulants	Continuing the usual anticoagulant treatment	Amount of bleeding and post-operative complications	Amount of bleeding measured from weight of gauze pads, Post extraction bleeding assessment on 2^{nd} and 7^{th} after extraction	PT, INR, platelet count	For simple tooth extractions, DOACs are safe drugs in terms of bleeding and extractions can be carried out without interrupting anticoagulant regimen with the aid of local hemostatic measures.

4	***Yagyuu et al***	**Patients under DOACs, VKAs**	**2017**	**Retrospective, cohort study**	**1. 72 patients under DOACs 2. 100 patients under VKAs**	**67 patients taking no anticoagulants**	**Continuing the usual anticoagulant treatment**	**Incidence of post extraction bleeding**	**Occurrence of post extraction bleeding**	**HAS – BLED, ATRIA, ORBIT values**	**Similar risks of post extraction bleeding in pts under DOACs and VKAs. HAS – BLED, ATRIA, ORBIT scores had low, moderate and moderate ability to predict post extraction bleeding among patients.**
5	***Mauprivez et al***	**Patients under DOACs and warfarin**	**2016**	**Prospective, observational study**	**31 patients under DOACs for non valvular Atrial fibrillation**	**20 patients under VKAs**	**Continuing the usual anticoagulant treatment**	**Postoperative bleeding**	**Incidence of post -operative bleeding after tooth extractions**	**Risk factors of postoperative bleeding after tooth extraction survey**	**Application of local hemostatic measures is enough to control bleeding. DOACs therapy can be continued in patients undergoing tooth extractions**
6	***Muller et al***	**Patients under DOAC, phenprocoumon and without anticoagulation undergoing tooth extraction**	**2018**	**Retrospective study**	**1. 16 patients under DOAC 2. 21 patients under Phenprocoumon**	**27 patients without anticoagulants**	**Continuing the usual anticoagulant treatment**	**Characteristics of bleeding, treatment and outcome**	**Time point of bleeding and number and location of extracted teeth**	**Need for hospital admission and length of hospital and ED stay**	**No difference in delayed bleeding between DOAC and phenprocoumon could be demonstrated**
7	***Yoshikawa et al***	**Patients under DOACs and warfarin**	**2019**	**Prospective, observational study**	**119 patients under DOAC**	**248 patients under warfarin**	**Continuing the usual anticoagulant treatment**	**Postoperative bleeding**	**Incidence of post -operative bleeding after tooth extraction**	**Risk of post – operative bleeding using APTT, PT**	**Interrupting DOAC therapy is not necessary for tooth extraction**

Table 2: Sample size of included studies

STUDY	No. OF PATIENTS UNDER NOACs	No. OF PATIENTS UNDER OTHER ORAL ANTICOAGULANTS
Berton et al (2018)	65	65
Andrade et al (2018)	12	25
Caliskan et al (2017)	38	22
Yagyuu et al (2017)	72	100
Mauprivez et al (2016)	31	20
Muller et al (2018)	16	21
Yoshikawa et al (2019)	119	248

Table 3: Indication for anticoagulation therapy with NOACs

STUDY	VENOUS THROMBOEMBOLIC DISORDER UNDER TREATMENT WITH NOACS
Berton et al (2018)	AF, VTE, Stroke, PE, combination
Andrade et al (2018)	Non valvular AF
Caliskan et al (2017)	AF, PE/DVT, MI, CVA, ACS, prosthetic cardiac valve
Yagyuu et al (2017)	Not specified
Mauprivez et al (2016)	AF, VTE, Stroke, Acute coronary syndrome
Muller et al (2018)	AF, PE, AF+PE, Valve replacement
Yoshikawa et al (2019)	Nonvalvular AF, valvular heart disease, prosthetic cardiac valves, MI

(AF – Atrial fibrillation, PE – Pulmonary embolism, VTE – Venous thromboembolism, DVT – Deep vein thrombosis, MI – Myocardial infarction, CVS – Cerebrovascular disorders, ACS - Acute coronary syndrome)

Table 4: Number of days follow-up for assessment of post-operative bleeding

STUDY	NO.OF DAYS FOLLOW – UP FOR POST OPERATIVE BLEEDING
Berton et al (2018)	Immediate post-operative assessment – within 30 minutes and late post – operative assessment – within a week after surgery
Andrade et al (2018)	24,48 hours and 7 days after extraction
Caliskan et al (2017)	2nd and 7th day postoperatively
Yagyuu et al (2017)	Between 30 minutes and 7 days postoperatively
Mauprivez et al (2016)	3rd and 7th day post extraction
Muller et al (2018)	Within 24 hours - Early bleeding and After 24 hours – late bleeding event
Yoshikawa et al (2019)	7th day postoperatively

Table 5: Methods of assessment of bleeding used

STUDY	METHODS OF BLEEDING ASSESSMENT USED
Berton et al (2018)	Pre – operative – HAS –BLED, CHA2DS2VASC scales Intraoperative - Cotton roll imbibition test Postoperatively – Classification of Iwabuchi et al
Andrade et al (2018)	Intraoperative - differences in weights of gauze pads –AOB (Amount of Bleeding) Postoperatively – No, Mild, moderate and severe bleeding based on how hemostasis was achieved
Caliskan et al (2017)	Bleeding time 1, between the beginning of suture and complete hemostasis Bleeding time 2 - between the end of suture and complete hemostasis Bleeding before dental extraction, bleeding during dental extraction, and bleeding 24 hours, 48 hours and 7 days after the procedure using classification of Iwabuchi et al
Yagyuu et al (2017)	Postoperative – HAS –BLED, ATRIA, ORBIT scales
Mauprivez et al (2016)	Survey to assess the incidence and severity of bleeding events
Muller et al (2018)	Need for hospital admission and length of hospital and ED stay
Yoshikawa et al (2019)	Postoperatively – Bleeding risk assessment by APTT, PT

The number of selected patients for the included studies is summarized in **Table 2**.

The most common indication for anticoagulant therapy observed in the included studies was atrial fibrillation **(Table 3)**. In all the included studies, the prescription oral anticoagulant drug dosage was not altered.

Table 4 shows the number of days of post-operative follow-up done for bleeding events in patients under NOACs and other oral anticoagulants. Early bleeding was reported as bleeding events within 24 hours of extraction and delayed bleeding was observed as bleeding in the extraction site after 24 hours. Except for study done by Muller et al, all other included studies show follow up examination after one week post operatively.

Table 5 shows the various methods of bleeding assessment done in the included studies.

Berton *et al***[6]**showed that in patients under anticoagulation therapy using VKAs and DOACs undergoing dental extractions, about 69.3% and 81.6% patients did not report of a bleeding event postoperatively. Most post-operative bleeding events were managed by local haemostatic measures in both groups. Only one of 65 patients in the VKAs group required surgical intervention. Andrade et al**[7]**, on comparing bleeding intensity in patients under dabigatran and warfarin showed that patients on dabigatran showed no bleeding after 24 hours and after 48 hours postoperatively. There was no significant difference in delayed bleeding, during and after suture removal.

Caliskan *et al***[8]**reported the amount of bleeding (AOB) in patients receiving anticoagulant therapy undergoing extraction measured using the differences of weights of gauze pad before and after tamponade. The mean AOB was significantly higher in warfarin group when compared to dabigatran and rivaroxaban. The number of patients reporting with mild and moderate bleeding on the 2nd day postoperatively was higher in the warfarin group. In a study done by Yagyuu *et al***[9]**, incidence of postoperative bleeding was observed in 10.4% of patients under DOACs and 12.0% of patients under VKAs.

Five patients under DOACs reported 7 bleeding episodes and four patients under VKAs had five episodes, but no statistically significant difference was observed in the prospective study by Mauprivez *et al*. **[10]**11 out of 12 bleeding events were managed by haemostatic measures and only one required revision of the wound, placement of fibrin gel and resuturing. No bleeding event was reported after 3 days post extraction. In a study done by Muller *et al***[11]** most patients under phenprocoumon, after undergoing extraction reported to the emergency

department with early (within 24 hours) and delayed bleeding (after 24 hours). Occurrence of postoperative bleeding in 3.1% of extraction in DOACs group and 8.8% of extractions in the warfarin group. The risk of bleeding was also significantly higher in warfarin group than in the DOACs group was reported by Yoshikawa *et al***[12]**.

Assessment of risk of bias done using Tool to Assess Risk of Bias in Case Control Studies (Developed by the CLARITY group) showed that all studies have a low risk of bias in assessment of exposure (extraction), outcome of interest (bleeding events) and selection of cases and controls. All studies showed high risk of bias in matching of cases and controls except for study done by Yagyuu *et al***[9]** as cases and controls were age and sex matched.

DISCUSSION

After the discovery of warfarin and approval for human use in 1954, it was used as an anticoagulant in patients with deep vein thrombosis, pulmonary embolism, prevent strokes in patients with atrial fibrillation, valvular heart diseases and prosthetic heart valves. The mechanism of action of warfarin by inhibition of vitamin K epoxide reductase enzyme was discovered by John. W. Suttie in 1974 **[13]**. Hence, they are collectively referred to as Vitamin K antagonists (VKAs). Over the last 70 years of extensive use of warfarin, it has been associated with extreme clinical problems include bleeding, multiple visits to the emergency department, multiple INR tests and variability in responses. The main advantage of warfarin is the high oral availability and high water solubility. The major disadvantage is the longer time needed for the onset of therapeutic effect **[14]**.

In the late 1950s, many trials were conducted to compare the effectiveness of the combination of heparin and dicoumarol to no anticoagulant therapy in patients with pulmonary embolism. A trial by Barritt and Jordan **[15]** showed that patients receiving anticoagulant therapy had significantly better outcome than untreated patients (none of the patients died from pulmonary embolism and only one patient had non-fatal recurrence of pulmonary embolism). This study preceded a number of randomized studies that recommended the use of this therapeutic strategy – the combination of heparin and VKAs as a treatment and prophylaxis of venous thromboembolism, saving countless number of lives over the next 50 years **[16]**. Although heparin was used in the prevention of venous thromboembolism, it was usually followed by long – term anticoagulant therapy using warfarin. The major pitfall of warfarin use is the higher risk of bleeding complications. In 1979, Hull *et al*, compared the efficacy of

warfarin and low dose heparin for secondary prevention of thromboembolic events in patients with Deep vein thrombosis. The results showed that there were recurrent episodes of venous thromboembolism in the low dose subcutaneous heparin group. This study was followed by comparison of dose adjusted high dose heparin and warfarin in patients with DVT **[17]**. Subcutaneous high dose heparin showed lesser instances of major bleeding when compared to warfarin. This regimen remained as a standard treatment for secondary prevention of thromboembolism until the development of alternative anticoagulants **[18]**.

The need for frequent INR monitoring, dose alteration and administration of LMWH in the hospital substantiated the need for improved anticoagulants. In 2002, a new class of synthetic anticoagulant which specifically targets factor Xa was shown by Turpie *et al***[19]**. Fondaparinux belonged to the synthetic anticoagulants which without direct action on thrombin, binds to antithrombin and inhibits factor Xa. In orthopedic patients, the risk of venous thromboembolism is significantly high and fondaparinux significantly reduced this risk. Fondaparinus showed increased efficacy when compared to heparin in patients with PE, DVT and acute coronary syndromes **[20]**.

Ximelagatron was the first DTI to be developed. Initial clinical testing showed it was efficacious and was indicated for the prevention of VTE in patients after orthopedic surgery, stroke and myocardial infarction. However, elevated liver enzymes in patients through unknown mechanism lead to the withdrawal of ximelagatron from the market. The development of ximelagatron laid the groundwork for the development of NOACs **[21]**.

NOACs specifically target thrombin and factor Xa in the coagulation cascade. Till now, four NOACs have been approved and used for the prevention of thromboembolic disorders. They are Dabigatranetexilate, rivaroxaban, apixaban and edoxaban**[14]**.

The advantages of NOACs are predictable pharmacokinetics, wide therapeutic window which offers greater potential for safety, fixed dosing without the need for constant monitoring for dose titration and shorter duration of onset of action.

The major disadvantages of NOACs is the lack of antidotes and monitoring. Prothrombin complex concentrate (PCC), recombinant factor VIIa and plasma derived and recombinant factor Xa were investigated as potential antidotes for NOACs **[22]**. Currently, three other NOAC antidotes are investigated – Idarucizumab, andexanetalfa and ciraparantag. Idarucizumab, a monoclonal antibody

fragment is approved by FDA as an antidote for dabigatran. Andexanetalfa, an antidote to factor Xa inhibitors is under FDA review. Ciraparantag, antidote to both DTIs and factor Xa inhibitors, is in phase II trials **[23]**.

NOACs are known to affect coagulation parameters, the changes have not been correlated, measured and standardized to the risk of bleeding. The lack of monitoring has also impaired the physician's ability to assess and monitor patient progress and adherence to the therapy. The daily dosage of NOACs can also lead to steep decline in the effect of anticoagulation when a dose is missed.

There are no specific guidelines for the dental patients under NOACs **[24]**. Various studies done to compare the amount of intra – operative and postoperative bleeding in patients receiving NOACs and other oral anticoagulants are considered in this systematic review **[6-12]**.

The results of the included studies shows that bleeding due to invasive dental procedures was less in patients under NOACs when compared to other oral anticoagulants such as the VKAs and invasive dental procedures like simple dental extractions can be performed for patients with thromboembolic disorders under NOACs without dose alteration/ discontinuation of the drugs. It can also be inferred that local hemostatic measure can be sufficiently used to arrest the bleeding induced by dental extractions. In most of the included studies, only simple dental extractions were performed. However, the same result cannot be applied when other invasive procedures like transalveolar extractions, flap surgery and alveoloplasty are performed in patients under NOACs.

The changes in coagulability of blood was not adequately assessed in patients under NOACs in the included studies. The amount of bleeding was measured using varied methods. These parameters were not standardized in all the included studies. If standardized, the amount and the time of bleeding expected in patients under NOACs and other oral anticoagulants can be accurately quantified and adequate measures can be taken for invasive procedures where bleeding complications are expected.

Quality of evidence of the included studies show that all the studies are case – control studies which are grouped under level 3b.Hence there is limited quality of patient oriented evidence. Even though the included studies do not provide a reliable answer, these studies can be considered as the first step towards an individual randomized control trials with higher number of samples. The risk of bias in the included studies were found to be very high in the included studies as they were not

adequately randomized and blinded as in RCTs.

CONCLUSION

From this systematic review, we can conclude that,

1. Novel oral anticoagulants are associated with less risk of post extraction bleeding when compared to other oral anticoagulants.
2. Adequate use of local hemostatic agents is sufficient to control post extraction bleeding of simple dental extractions in patients under anticoagulation therapy with NOACs.
3. It is not required to alter/ discontinue anticoagulation therapy with NOACs for simple dental extractions.

However, none of the included studied are randomized control trials. As the level of evidence of the included studies is lower compared to systematic reviews of RCTs, the reliability of this systematic review is comparatively lower than systematic reviews of RCTs. Hence, further RCTs have to be done to confirm the above mentioned conclusions and to form guidelines for carrying out invasive procedure in dental patients under NOACs.

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