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CLINICAL PRACTICE PERSPECTIVES ON MANAGING PATIENT ON ANTICOAGULANT/ ANTIPLATELET THERAPY DURING DENTAL PROCEDURES: AN UPDATED NARRATIVE REVIEW

[1]Dr. Sweta Singh, [2*]Dr. Shailendra Kumar, DM, [3]Dr. Yudhyavir Singh, MD, [4]Dr. Gaurav Singh Tomar, DM

[1]BDS MDS: Oral and Maxillofacial Surgery, Ex Senior Resident AIIMS, New Delhi
Consultant and Head, Dental Services, Paras Hospital, Ranchi, Jharkhand.
[2]Associate Professor, Department of Anesthesiology, Critical Care and Pain Medicine,
All India Institute of Medical Sciences, New Delhi.
[3]Assistant Professor, Department of Anesthesiology, Critical Care and Pain Medicine,
All India Institute of Medical Sciences, New Delhi.
[4]Assistant Professor, Department of Anesthesiology and Critical Care,
World College of Medical Sciences and Research, Jhajjar, Haryana.

***Corresponding Author: Dr. Shailendra Kumar, DM**
Associate Professor, Department of Anesthesiology, Critical Care and Pain Medicine, All India Institute of Medical Sciences, New Delhi.
Mob. 87450 27472

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INTRODUCTION

Anticoagulant and antiplatelet agents are prescribed for individuals who are at high risk for or who have had thromboembolic events (e.g., blood clots). These include patients who have experienced deep-vein thrombosis (DVT) or pulmonary embolism (PE) or who have nonvalvular atrial fibrillation (NVAF), a cardiac arrhythmia that predisposes patients to clot formation. Anticoagulants include the vitamin K antagonist warfarin (Coumadin®) and the newer direct oral agents, including the direct thrombin inhibitor dabigatran (Pradaxa®) and the factor Xa inhibitors apixaban (Eliquis®), rivaroxaban (Xarelto®), and edoxaban (Savaysa® [Lixiana® in the European Union, Japan, and others]).[1-6] Antiplatelet agents include clopidogrel (Plavix®), ticlopidine (Ticlid®), prasugrel (Effient®), ticagrelor (Brilinta®), and/or aspirin[7] (Table 1). Adverse effects associated with these drugs can include prolonged bleeding or bruising.

There is a significant number of individuals prescribed anticoagulation or antiplatelet therapy, as well as medications for their respective diseases. There is strong evidence for the older medications (i.e., warfarin, antiplatelet agents), as well as limited evidence for the newer direct-acting oral anticoagulants medications that, for most patients, it is not necessary to alter anticoagulation or antiplatelet therapy prior to dental intervention.

While performing dental procedures on patients on anticoagulation, the major concern is when it is safe to perform surgery without increasing the risk of haemorrhage or increasing the risk of thromboembolism (e.g, venous, arterial) after discontinuing treatment. In treating patients on long-term warfarin perioperatively, consider the risks of haemorrhage or thromboembolism versus the benefit from the operation. When considering dental surgery, these factors and the need to weigh the risk of haemorrhage against that of thromboembolism must be analyzed on an individual patient basis.

Table 1: Commonly used Anticoagulant and Antiplatelet Medications. [* Strong evidence; ** Limited evidence]

Drug Class	Drug Names
Anticoagulant*	• Warfarin (Coumadin®)
Antiplatelet agents*	• Clopidogrel (Plavix®) • Ticlopidine (Ticlid®) • Prasugrel (Effient®) • Ticagrelor (Brilinta®) • Aspirin
Direct-acting oral anticoagulants**	• Dabigatran (Pradaxa®) • Rivaroxaban (Xarelto®) • Apixaban (Eliquis®) • Edoxaban (Savaysa®)

Without the anticoagulant/antiplatelet medications, these patients are at higher risk for blood clot development, which could result in thromboembolism, stroke, or myocardial infarction (MI). The serious risks of stopping or reducing these medication regimens need to be balanced against the potential consequences of prolonged bleeding,[8-10] which can be controlled with local measures such as mechanical pressure, hemostatic agents

(e.g., Gelfoam® or Surgicel®), suturing, and tranexamic acid mouthwash.[11-13] The objective of this review is to discuss the evidence-based practice guidelines based on available literature to manage patients with anti-coagulants therapy seeking invasive dental procedures.

DISCUSSION

Direct-Acting Oral Anticoagulants

Four newer direct-acting oral anticoagulants have been approved by regulatory agencies for use in patients to prevent or treat DVT and PE, or reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF). These are dabigatran (Pradaxa®), apixaban (Eliquis®), rivaroxaban (Xarelto®), and edoxaban (Savaysa® or Lixiana®).[1-4] These agents differ from traditional oral anticoagulant therapy (i.e., warfarin) in that they are targeted in action; are given as fixed doses; have more predictable pharmacokinetics and shorter half-lives; require little to no routine monitoring; and have fewer drug or food interactions.[14]

There is no direct evidence from prospective trials comparing different periprocedural management strategies for patients receiving the target-specific anticoagulants and evaluating effects on patient outcomes. A 2015 consensus guideline from the European Heart Rhythm Association[15,16] (updating a 2013 guideline[17]) suggests that interventions not necessarily requiring discontinuation of the newer anticoagulants include extraction of 1 to 3 teeth; periodontal surgery; abscess incision; or implant positioning.

A 2018 systematic review[18] focussed on how to safely manage direct-acting oral anticoagulants in patients requiring dental procedures with low-to-moderate risk of bleeding. Procedures that were defined as being low risk were administration of local anesthetic, simple restorations, supragingival scaling, and single tooth extraction; procedures considered moderate risk were extractions of 2 to 4 teeth and local gingival surgery of 5 or fewer teeth. Five papers were included in the review of evidence. Among patients receiving the direct-acting anticoagulants and undergoing dental procedures associated with low-to-moderate bleeding risk, bleeding rates were low whether the anticoagulant was continued or held peri-procedurally. Bleeding that was documented was generally mild and controlled by local hemostatic measures.

A 2015 narrative review by Elad et al.[19] specifically addressed the currently marketed direct-acting oral anticoagulants, providing a general overview and potential management strategies for dental practitioners. The authors evaluated bleeding complication rates reported in 18 randomized, controlled trials comparing the new agents with conventional anticoagulants or placebo and also reviewed prior narrative reviews[20] and case reports[21,22] of patients undergoing dental interventions while receiving the newer anticoagulant therapy. After consideration of factors such as patient comorbidity and the risk of bleeding from the procedure, and in addition to usual local measures to control bleeding (e.g., sutures, absorbable gelatin), the authors recommended the following options for drug management: Either continue regular dose administration of the anticoagulant or, postpone the timing of the daily dose of the anticoagulant (time the daily dose after the dental treatment or skip one daily dose); or time the dental intervention as late as possible after last dose of anticoagulant; or temporarily interrupt drug therapy for 24 to 48 hours.

According to the authors,[19] "Based on the current reported dental literature, limited dental surgery may benefit from the first 2 conservative options.

Another 2015 dental-specific narrative review by Thean and Alberghini[11] offered similar advice regarding dental patient management, balancing the risks of perioperative bleeding against the risk of thrombosis. They also recommend that consideration be given to other supplements or drugs (e.g., fish oil, antiplatelet agents) patients may be taking or comorbid conditions patients may have that increase bleeding risk. The authors state that in conjunction with appropriate local measures to control bleeding, low-risk procedures such as scaling and/or root planing, restorative or endodontic treatment, simple extractions, or surgery lasting less than 45 minutes do not appear to require suspension of therapy with the new anticoagulants (Table 2). For procedures associated with increased risk of bleeding, such as surgical extractions, multiple extractions, more complex oral surgery, or head and neck cancer surgery, the authors recommend a multidisciplinary preoperative approach that includes consultation with the patient's physician regarding potentially stopping anticoagulant medications 2 to 5 days before surgery (Table 3).

Table 2: Low-risk dental procedures not requiring anticoagulation therapy interruption **(Keep INR within therapeutic range for patients on Vit. K antagonist therapy)*.

Low-risk dental procedures *
Dental scaling
Dental restorations that involve soft-tissue manipulation
Dental extractions that are not surgically complex
Fewer than 3 teeth
Soft-tissue biopsy
Endodontic procedures
Implant placement
Prosthodontic procedures
Fixed and removable dentures
Crowns
Bridges

Table 3: High-risk dental procedures requiring anticoagulation therapy interruption.

High-risk dental procedures
1. Complex extractions, adjacent extractions that will cause a large wound, or more than three extractions at once.
2. Flap raising procedures
a. Elective surgical extractions
b. Periodontal surgery
c. Preprosthetic surgery
d. Periradicular surgery
e. Crown lengthening
f. Dental implant surgery
3. Gingival recontouring
4. Biopsies

A 2013 systematic review[23] by van Diermen et al. (updating a prior 2009 review[24]) provided management recommendations for invasive dental treatment in patients using oral antithrombotic medication, including the target-specific oral anticoagulants. The authors acknowledged that no clinical studies or guidelines had been published to directly address the periprocedural management of dental patients receiving the newer anticoagulants. It appears that the authors' proposed recommendations regarding the target-specific anticoagulants were derived from published reports[20,25,26] available at the time and extrapolation from evidence for other traditional anticoagulants (e.g., warfarin). This systematic review proposed that in patients undergoing "simple dental treatment" (e.g., single or multiple dental extractions [up to 3 teeth], up to 3 dental implants, scaling and root planing, probing, flap surgery, apex resection, alveoloplasty), therapy with the new anticoagulants should not be interrupted. They also recommended that patients be advised to not take their medication 1 to 3 hours immediately before dental treatment.

Warfarin and Antiplatelet Agents

Warfarin or antiplatelet agents such as clopidogrel (Plavix®), ticlopidine (Ticlid®), prasugrel (Effient®), ticagrelor (Brilinta®) and/or aspirin are commonly used in patients who have experienced a DVT or PE, patients who have had an MI and/or who have undergone cardiac stent placement, or in patients with NVAF.

There is general agreement that treatment regimens with these older anticoagulants /antiplatelet agents should not be altered before dental procedures.[8,12,13,23,24,27-33] A 2009 systematic review and meta-analysis found no increased risk of bleeding associated with continuing regular doses of warfarin in comparison with discontinuing or modifying the dose for patients undergoing single and multiple tooth extraction.[27] A 2013 systematic review found no clinically significant increased risk of postoperative bleeding complications from invasive dental procedures in patients on either single or dual antiplatelet therapy.[12] In a 2013 statement, the American Academy of Neurology recommended that patients taking aspirin or warfarin for stroke prevention and undergoing dental procedures continue taking their medications.[29] A 2015 systematic review of management of dental extractions in patients receiving warfarin determined that patients whose International Normalized Ratio (INR; a measure of warfarin's therapeutic index) was in therapeutic range (i.e., 3.0 or less) could continue their regular warfarin regimen prior to the procedure.[33]

In February 2007, the American Heart Association, the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, the American College of Surgeons, and the American Dental Association published their consensus opinion about drug-eluting stents and antiplatelet therapy (e.g., aspirin, clopidogrel, ticlopidine).[9,10] The consensus opinion states that healthcare providers who perform invasive or surgical procedures (e.g., dentists) and are concerned about periprocedural and postprocedural bleeding should contact the patient's cardiologist regarding the patient's antiplatelet regimen and discuss optimal patient management, before discontinuing the antiplatelet medications. Given the importance of antiplatelet medications post-stent implantation in minimizing the risk of stent thrombosis, the medications should not be discontinued prematurely.[9,10]

Some patients who are taking one of these or multiple anticoagulant medications may have additional medical conditions that can increase the risk of prolonged bleeding after dental treatment, including liver impairment or alcoholism; kidney failure; thrombocytopenia, hemophilia, or other hematologic disorders; or may be currently receiving a course of cytotoxic medication (e.g., cancer chemotherapy). In these situations, dental practitioners may wish to consult the patient's physician to determine whether care can safely be delivered in a primary care office.[30,31] Any suggested modification to the medication regimen prior to dental surgery should be done in consultation with and on advice of the patient's physician.[11,23,34]

Haemostasis measure

It was found that bleeding after dental surgery when anticoagulation is continued is rarely or never life threatening. However, the intra-operative bleeding control is particularly important in the endodontic surgery because of its delicate and sensitive procedures.

Mingarro-de-León A. et al. (2014), showed that Local hemostatic measures are suffice for controlling possible bleeding problems resulting from dental treatment.[35] A study by Queiroz SIML, Silvestre VD et al. (2018), emphasized the use of a local haemostatic agent such as a tranexamic acid (TA) after dental extraction in patients on warfarin therapy. Therefore, it was found that this method of the local haemostatic agent in Topical form with cotton gauze compression and irrigation was relatively more effective in reducing the time to attain

immediate haemostasis and in preventing intermediate haemorrhage.[36]

Another study by Ambrogio RI, Levine MH., et al. (2018), supported that Tranexamic Acid (TA) is a safe surgical site haemostatic agent, aiding to improve intraoperative visibility and postoperative haemostasis.[37]

Therefore, we recommend that in a general patient with normal risk, there is no need to discontinue medication; use local measures (local compression, irrigation, tranexamic acid in doses of 10-15mg/kg slow IV infusion) to control bleeding if reported. However, in patients with higher risk of bleeding, there should be a suggested justified modification to the medication regimen prior to dental procedure after consultation and on advice of the patient's physician.

SUMMARY

There is general agreement that in most cases, treatment regimens with older anticoagulants (e.g., warfarin) and antiplatelet agents (e.g., clopidogrel, ticlopidine, prasugrel, ticagrelor, and/or aspirin) should not be altered before dental procedures. The risks of stopping or reducing these medication regimens (i.e., thromboembolism, stroke, MI) far outweigh the consequences of prolonged bleeding, which can be controlled with local measures. In patients with comorbid medical conditions that can increase the risk of prolonged bleeding after dental treatment or who are receiving other therapy that can increase bleeding risk, dental practitioners may wish to consult the patient's physician to determine whether care can safely be delivered in a primary care office. Any suggested modification to the medication regimen prior to dental surgery should be done in consultation and on advice of the patient's physician.

On the basis of limited evidence, general consensus appears to be that in most patients who are receiving the newer direct-acting oral anticoagulants (i.e., dabigatran, rivaroxaban, apixaban, or edoxaban) and undergoing dental interventions (in conjunction with usual local measures to control bleeding), no change to the anticoagulant regimen is required. In patients deemed to be at higher risk of bleeding (e.g., patients with comorbid conditions or undergoing more extensive procedures associated with higher bleeding risk), consideration may be given, in consultation with and on advice of the patient's physician, to postponing the timing of the daily dose of the anticoagulant until after the procedure; timing the dental intervention as late as possible after last dose of anticoagulant; or temporarily interrupting drug therapy for 24 to 48 hours. Moreover, local haemostatic measures are effective in achieving haemostasis and should be taken into considerations whenever feasible and applicable. Further research is needed to definitively establish perioperative management strategies for these patients, especially those considered to be at high risk of bleeding.

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