GUIDELINES FOR DENTAL PATIENTS ON ORAL ANTICOAGULANTS AND ANTIPLATELET DRUGS - A LITERATURE REVIEW

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ABSTRACT
Patients reporting to the maxillofacial surgery department for minor surgical procedures suffer from problems related to cardiovascular system, cerebrovascular diseases and other systemic diseases requiring anticoagulants and antiplatelet drugs. These drugs interfere with clotting mechanism and does not form blood clot which results in excess loss of blood during surgical procedures. To prevent complications certain guidelines and preventive measures should be followed which is discussed with review of literature.

KEYWORDS: anticoagulants, antiplatelet drugs, guidelines for dental procedures.

INTRODUCTION
Patients are treated with oral anticoagulants and antiplatelet drugs who suffer from cerebral ischaemia, cerebrovascular accidents, thrombocytopenic purpura, arterial and venous thrombosis, cardiovascular disorders and patients with pacemakers, which reduces blood coagulability to an optimal therapeutic range within which the patient is provided some degree of protection from thromboembolic events. when these patients report for an invasive dental procedure which can cause bleeding, now the question arises as to whether the anticoagulant therapy should be continued, modified, or discontinued before dental treatment but sudden withdrawal of oral anticoagulants may lead to emboli formation which block the blood vessels thereby depriving blood supply to the organs leading to necrosis of the organs. To avoid these potential complications, certain guidelines should be followed. The clinicians must assess the patient’s ability to achieve hemostasis, before minor maxillofacial surgical procedures. If anticoagulation is to be continued considering the risk of thromboembolism, or the anticoagulant therapy to be decreased or discontinued and weather any preoperative investigations required before the procedure are discussed in detail in this review article.

Mechanism of action
They act by interfering the action of clotting factors in the blood and vitamin k leading to decreased availability of the clotting factors. Most commonly used oral anticoagulants are Warfarin - vitamin K antagonist, Coumarin, and Newer oral anticoagulant drugs – dabigatran, apixaban, rivoroxiban.

Warfarin
Warfarin is an antagonist of vitamin k which is necessary for synthesis of clotting factors II, VII, IX, X and endogenous anticoagulant proteins C&S. [3]

Warfarin, a 4-hydroxycoumarin derivative, is one of the most commonly used oral anticoagulants worldwide. It is a vitamin K antagonist, which acts by inhibiting the posttranslational carboxylation of glutamic acid residues that are found at several sites at the N-terminal end of coagulation factors II, VII, IX, and X. Warfarin also inhibits glutamate carboxylation on the amino terminus of the proteins C and S. Warfarin is rapidly and completely absorbed and peak plasma concentrations can be seen within 1 hour of ingestion. Its half-life is approximately 37 hours. Circulating warfarin is almost completely bound to albumin. It is metabolized in the liver into inactive compounds excreted primarily in urine. The measured anticoagulant effect of warfarin results predominantly from reduction in factor II (prothrombin) rather than a cumulative effect of lowering all 4 vitamin K-dependent factors. Prothrombin has a considerably longer half-life, 96 hours, than do the other vitamin K-dependent factors. [4] Dosage: 2to5mg orally
or intravenously once a day followed by a maintenance dose of 2 to 10 mg orally.

Therapeutic doses of warfarin reduces vitamin K dependent clotting factors by 30% to 50%. If warfarin therapy is stopped it takes around four days for the INR to reach 1.5.

**Coumarin derivatives**

**Acenocoumarol or nicumarone:** The half-life of this drug is quite short (8-10 hours). It is prescribed as a single daily dose.\(^3\)

**Ethyl biscumacetate:** This drug is not commonly used, due to its short lasting action.

**Phenprocoumon:** This drug is longer acting than acenocoumarol.

**Fluindione**

**Indandione derivatives**

These are very toxic synthetic drugs which is associated particularly to hypersensitivity reactions.\(^4\)

**New generation drugs**

**Dabigatran etexilate:** This recently marketed drug is a potent inhibitor of free thrombin, thrombin bound to fibrin, and platelet aggregation induced by thrombin—thereby preventing thrombus formation. Mostly indicated in elective total hip or knee replacement surgery & for prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. It requires no monitoring. The drug is administered via the oral route in the form of two daily doses of 110 mg. Therapy is started 1-4 hours after surgery and is maintained for up to 10 days post surgery. Plasma peak concentrations are reached between 30 minutes and two hours after administration. The bioavailability is 5-6%, and the half-life after single and multiple dosing is 8 and 17 hours, respectively. Most of the drug (80%) is excreted in urine.\(^4\)

**Rivaroxaban and apixaban:** These are selective factor Xa inhibitors administered via the oral route and with an absorption of near 100%. The available clinical data are still limited, and the existing information on their metabolism and possible drug interactions comes mainly from nonclinical studies. The same way as dabigatran, these drugs do not require routine monitoring. Patients treated with oral anti-vitamin K anticoagulants require periodic monitoring, based on the prothrombin time (PT). Since this parameter is somewhat 2.5-3.5.\(^4\)

**Antiplatelet drugs**

These are agents that act on platelets and prevent them from aggregation of platelets to form a platelet plug. Antiplatelet drugs are generally prescribed for the prevention of arterial and venous thrombosis in patients with ischemic heart disease, heart valve implants and stents, and in people at risk of suffering cerebrovascular events such as stroke. Since these drugs act by inhibiting platelet function, they have been accepted as adequate antithrombotic treatment.

The main antiplatelet drugs are Acetyl salicylic acid, Clopidogrel bisulfate, Dipyridamole, Triflusal.

Mechanism of action of acetylsalicylic acid.

Acetylsalicylic acid (ASA) blocks thromboxane A2 production, thereby inhibiting cyclooxygenase activity and consequently platelet aggregation. The effect of this drug upon the platelets is irreversible, and therefore lasts for the full length of platelet life (7-10 days). Low doses (75-100 mg) are generally indicated in cases of chest pain, ischemia, transient ischemic accidents, and during the postoperative period (post-angioplasty/angiography).

Various evidence based studies recommended aspirin in the range of 75–100 mg/day for the prophylaxis against serious vascular events in high risk patients. However, recent randomized clinical trial indicates that 160 mg/day is the optimal dose of aspirin to prevent myocardial infarction and stroke. In clinical situations where immediate antithrombotic effect is required (such as unstable angina, acute myocardial infarction, or stroke), a loading dose of 300 mg is recommended.\(^4\)

Most frequently recommended doses of aspirin for prevention of myocardial infarction and stroke are 81, 160, and 325 mg/day in the United States, whereas, in Europe and other countries, these doses are 75, 150, and 300 mg/day.

Clopidogrel bisulfate inhibits platelet aggregation by blocking ADP binding to its platelet receptor and subsequent activation of the GPIIb-IIIa complex mediated by ADP.

Ticlopidine hydrochloride inhibits platelet binding to ADP-fibrinogen, along with posterior platelet-platelet binding (aggregation).\(^3\)

Dipyridamole blocks adenosine transport in platelets, erythrocytes and endothelial cells. The resulting increase in the local extracellular concentrations of adenosine acts directly upon the platelet A2-receptors, increasing the platelet cyclic adenosine monophosphate (cAMP) levels and consequently blocking platelet aggregation.

**Potential Risk of Continuing Aspirin drug Therapy prior to Surgery**

When platelets activity is altered, a longer time period is required to stop bleeding from a cut surface because of alteration in primary hemostasis mediated by platelet plug formation.
Literature review

Because of their potential bleeding effect, antiplatelet drugs are often interrupted during the perioperative period, without adequately evaluating the increased thrombotic risk of this decision. More recent publications suggest that the increase in bleeding risk induced by antiplatelet drugs has been exaggerated, while at the same time the increased thrombotic risk associated with treatment interruption has been underestimated. Consequently, although each invasive dental procedure implies a risk of oral bleeding, it is not advisable to interrupt antiplatelet therapy, since the increased risk of thromboembolism could outweigh the risk of bleeding.

Dental surgery in anticoagulated patients is common and historically their management has been controversial following early reports of major bleeding in such individuals. Many of the early reports of haemorrhage associated with dental surgery during this period predated the standardisation of oral anticoagulant control by means of the INR.

In 1954, the American Heart Association recommended a therapeutic range for oral anticoagulant therapy of a prothrombin time ratio (PTR) of 2 – 2.5 using human brain reagents. Later, the use of less sensitive commercial thromboplastins was not accompanied by a change in the target PTR ratio.

Clinicians, therefore, administered larger doses of oral anticoagulants to achieve the target ratio, resulting in an increased incidence of haemorrhage. The development and introduction of the INR did not take place until 1983.

The risks of bleeding associated with dental extraction in individuals not receiving oral anticoagulants is approximately 1%. In a review of 10 studies of patients undergoing dental surgery and in whom oral anticoagulants were continued, 9% (89/990) had delayed postoperative bleeding and in 3.5% of cases this was classified as ‘serious’ i.e. not controlled by local measures. Other studies have reported the incidence of minor bleeding as higher and in some cases up to 50%.

However, the interpretation and comparison of bleeding rates in patients undergoing oral surgery is difficult as rates for different procedures are not analysed separately, the definitions used to describe serious bleeding vary and surgery can involve the use of differing treatments to secure haemostasis.

Studies recommending discontinuation of antiplatelet therapy

Lemkin et al. In 1974 explained bleeding after oral surgery with aspirin therapy which required platelet transfusion for correction. McGaul and Daniel et al stated that continuing aspirin caused post-operative bleeding and advised discontinuation for 7-10 days before surgical procedures. This was recommended on the basis of surgical studies which showed rise in both intra- and post-operative bleedings. Some authors advised that stopping of antiplatelets only for 3 days will be sufficient. Studies by Conti, Speechley and Rugman, Scher, Scully and Wolf, Little et al., and Burger et al. Recommended stoppage of antiplatelets to avoid the risks of post-operative bleeding. Thomason et al in their study found bleeding after gingival surgery with aspirin therapy and advised to discontinue aspirin before surgery. Elad et al reported a case of severe bleeding episode, following nonsurgical periodontal treatment in a patient taking dual antiplatelet therapy (aspirin 100 mg plus clopidogrel 75 mg/day). Severe life-threatening hemorrhage occurred post-operatively leading to hemorrhagic shock. Schrdi et al found increased bleeding on probing in patients who consumed aspirin in a dose of 325 mg/day for 7 days. A case was reported by Foulke in which bleeding episode occurred after oral prophylaxis with ultrasonic scaler. Several studies have documented the risk of bleeding in patients on antiplatelet therapy undergoing cardiac surgeries. Krishnan et al. concluded that patient continuing aspirin therapy can undergo routine dental extractions without increased risk of excessive or prolonged bleeding.

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). The consensus opinion states that healthcare providers who perform invasive or surgical procedures (e.g., dentists) and are concerned about peri procedural and post procedural 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. 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. 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.

Management of patients on anticoagulant drugs

GENERAL GUIDANCE

Morning appointments, earlier in the week allow any post operational bleeding to be dealt with in the working day and before the weekend.
Local anaesthetic solutions containing a vasoconstrictor should be used unless rarely contraindicated on other medical grounds. An aspirating syringe must be used for all local anaesthetic injections.

For sub-gingival scaling, a small area should be scaled first, to assess the amount of bleeding, before instrumentation of larger areas is carried out. It may be necessary to complete a full mouth scaling over several visits.

Extractions should be restricted to a maximum of three to four teeth per visit in a maximum of two quadrants.

All extractions should be completed as atraumatically as possible (using luxators/periotomes) Sockets should be gently packed with a haemostat and sutured with resorbable sutures at the time of the extraction.52

MANAGEMENT OF WARFARINISED PATIENTS
The vast majority of patients on Warfarin will have an INR of 2.0 to 3.0 and should be able to undergo routine dental extractions/minor oral surgery without stopping their warfarin. Extractions should be able to be safely carried out in the following circumstances. Where the INR is less than 4

If local haemostatic measures are taken (packing, sutures). Warfarin should not be stopped but the INR should be checked within 24 hours of the planned procedure (patients can usually co-ordinate this themselves with either their doctor or anti-coagulant clinic).

Patients should be referred if other coagulopathies co-exist or if the INR is maintained at greater than 4.52

NEW ORAL ANTI-COAGULANTS (NOAC)
The main drugs in this classification that you will come across include.
DABIGATRAN Direct thrombin inhibitor (factor IIa) BD
RIVAROXABAN Direct Factor Xa inhibitor OD
APIXABAN Direct Factory Xa inhibitor BD
Their primary use is for the treatment of atrial fibrillation (AF) or because of recent or recurrent pulmonary embolus (PE). Occasionally used for 2 to 6 weeks.53

DENTAL MANAGEMENT FOR PATIENTS ON NEW ORAL ANTI-COAGULANTS
For patients on short courses of anti-coagulant, delay elective treatment until patient is recovered.
If additional concerns exist for any patient e.g. social or medical, consider referral even if treatment seems straightforward.52

LOW RISK
Less than or equal to 3 - 4 simple extractions in up to 2 quadrants / simple oral surgery (e.g. incision of abscess, periodontal surgery, positioning of implants, simple oral surgery). Do not stop the new oral anti-coagulant drugs.

Carry out procedure with least possible trauma.
Treat with local haemostatic measures (example oxidised cellulose or collagen sponges and sutures).
Allow patient to leave only when bleeding has stopped.52

HIGHER RISK
Greater than 3 - 4 teeth in more than 2 quadrants/difficult oral surgery - Refer to secondary care.52

GUIDE LINES FOR PATIENTS ON ANTI-PLATELET THERAPY
Management of patients taking Clopidogrel plus Aspirin. Clopidogrel is given for a number of reasons but most commonly after PCI (percutaneous coronary intervention, coronary stent placement or to patients who have recently had a MI). There has been some evidence to suggest that Clopidogrel should be stopped prior to surgery if patients are also taking Aspirin as well.

If however there is a stent in situ the risk of stopping Clopidogrel and Aspirin are very high and therefore the drug should continue for six weeks after a bare metal stent and twelve months after a drug alluting stent.52

Stopping anti-platelet therapy increases the risk of a stroke or myocardial infarction occurring – patients are more at risk of permanent disability or death if they stop anti-platelet medication prior to a surgical procedure than if they continue it. Bleeding complications while inconvenient do not carry the same risk as thromboembolic complications. It is therefore advisable to continue an anti-platelet drug and to take appropriate haemostatic measures. There is unfortunately very little evidence published regarding the risk of bleeding associated with dual anti-platelet drugs (Clopidogrel + Aspirin) but it seems sensible to follow the above NOAC guidelines.52

POST OPERATIVE MANAGEMENT/CARE INSTRUCTIONS FOR EXTRACTIONS AND SURGERY
The patient should be advised to rest for four hours post operatively, should avoid eating and drinking for that time to allow the clot to stabilise and local anaesthetic to wear off. The patient should be given the standard postoperative advice verbally and in writing. Appropriate telephone contact details should be issued to the patient in writing and the patient should know how to obtain advice and/or help both in and out of hours if bleeding occurs.

In addition the following advice regarding analgesics should be given.

For post-operative pain control paracetamol is the safest pain killer. Non-steroidal anti-inflammatory drugs such as aspirin, ibuprofen, and voltarol should be avoided.

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If paracetamol alone is not sufficient to manage pain, dihydrocodeine may be an appropriate alternative if not contraindicated. Otherwise, the patient should consult their doctor for advice on pain relief.[5]

**Management of bleeding**

Local anaesthesia with vasoconstrictor in by infiltration or intraligamental injection at the extracted socket site or close to the area of surgical site. Socket is placed with haemostatic dressing and then carefully sutured. After closure of site pressure is applied at the site. Procedures should beatraumatic as possible.

Postoperative instructions like donot rinse the mouth for 24 hours, do not suck hard or disturb the socket. Optimum INR for dental surgical procedures 2.5. The use of 4.8% tranexamic acid and 25% epsilon amino caproic acid mouthwashes has also been recommended to reduce the risk of bleeding.[1]

**PATIENTS UNSUITABLE FOR DENTAL MANAGEMENT IN PRIMARY CARE**

Patients who have an INR greater than 4 or who have a very erratic INR should not undergo any form of dental procedure other than those from the safe list previously mentioned without consultation with the clinician who is responsible for maintaining their anti-coagulation. The anti-coagulant dose may be adjusted prior to the procedure at the discretion of the clinician or elective dental procedures which are at risk of significant bleeding may need to be referred.

The following medical problems may affect coagulation and clotting.

Liver impairment and/or alcoholism.

Renal failure.

Thrombocytopenia, haemophilia or other disorder of haemostasis.[4]

**Summary of Guidelines recommended For Management of Dental patients undergoing anticoagulant and antiplatelet drugs**

1. The risk of significant bleeding in patients on oral anticoagulants and with a stable INR in the therapeutic range 2-4 (i.e. <4) is very small and the risk of thrombosis may be increased in patients in whom oral anticoagulants are temporarily discontinued. Oral anticoagulants should not be discontinued in the majority of patients requiring out-patient dental surgery including dental extraction.

2. For patients stably anticoagulated on warfarin (INR 2-4) and who are prescribed a single dose of antibiotics as prophylaxis against endocarditis, there is no necessity to alter their anticoagulant regimen.[6]

3. The risk of bleeding may be minimised by the use of oxidised cellulose (Surgicel) or collagen sponges and sutures.

4. 5% tranexamic acid mouthwashes used four times a day for 2days. Tranexamic acid is not readily available in most primary care dental practices.

5. For patients who are stably anticoagulated on warfarin, a check INR is recommended 72 hours prior to dental surgery.

6. Patients taking warfarin should not be prescribed non-selective NSAIDs and COX-2 inhibitors as analgesia following dental surgery. The risk of bleeding in anticoagulated patients undergoing oral surgery

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