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MANAGEMENT OF PATIENTS ON ANTI-COAGULANT THERAPY UNDERGOING DENTAL SURGICAL PROCEDURES. Review Article

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SUMMARY

Dental treatment performed in patients receiving oral anticoagulant drug therapy is becoming increasingly common in dental offices.

The aim of oral anticoagulant therapy is to reduce blood coagulability to an optimal therapeutic range within which the patient is provided some degree of protection from thromboembolic events. This is achieved at the cost of a minor risk of haemorrhage.

Frequently raised questions concern the safety and efficacy of the various anticoagulation regimens and their accompanying thromboembolic and bleeding risks relative to invasive dental procedures.

The aim of this literature review is to evaluate the available evidence on the impact of anticoagulant medications on dental treatment and highlight certain patient management issues closely interrelated to various aspects of dental treatment.

For that purpose literature search in the electronic database of Medscape, Pubmed-Medline, Science Direct, and EBSCO host, in the data base of Medical University Plovdiv and specialised published books in general medicine and dentistry was made.

A total of 33 publications between 1995 and 2013 were identified: 12 review articles, 11 randomized controlled and non-randomised studies, 6 guidelines and practical guides, 1 meta-analysis and 3 specialised books.

Key words: oral anticoagulants, venous or arterial thromboembolism, bleeding risk, INR, oral surgery, tooth extraction, fibrin sealing, local haemostasis.

INTRODUCTION

Four Millions Patients worldwide are taking medications that alter haemostasis and decrease the risk for thromboembolic events. Oral anticoagulant therapy is prescribed for prophylaxis and treatment of pulmonary embolism, venous thromboembolism and deep vein thrombosis, including thromboprophylaxis for the prevention of postoperative venous thromboembolism after orthopaedic surgical procedures as hip fracture and prosthetic total hip or knee joint replacement, thromboembolic complications associated with atrial fibrillation and/or prosthetic replacement of cardiac valves. [1, 2]

Management of these patients with forthcoming dental surgical procedures has changed dramatically nowadays, but there are still differences in the approaches of general dentists, oral and maxillofacial surgeons.

Several protocols for such patients have been proposed and can be summarised as: temporary discontinuation or a reduction in dose of oral anticoagulants to obtain a subtherapeutic international normalised ratio (INR); replacement of oral anticoagulation with heparin or low-molecular weight heparins or no change in the therapy. [3]

The balance between reduction in the drug dose on the one hand, and excessive bleeding during surgery in therapeutically anticoagulated patients on the other, is major problem, particularly with outpatient procedures.

However, the latest recommendations emphasise that the risk of tromboembolic complications outweigh the risk of bleeding and the latter in patients with therapeutic INR is small. It has therefore been suggested that the dose of oral anticoagulant should not be discontinued or changed.

None of these approaches is risk free for the patient, and the surgeon must make a clinical judgment of the risk-benefit ratio between management strategies and adverse complications. [2]

Oral anticoagulant medications

The most frequently used medications for oral anticoagulant therapy are:

1. ***Anticoagulants with indirect action (coumarin derivatives)***

1.1. Acenocoumarol

2 Acenocoumarol is a derivative of coumarin and is vitamin K antagonist. He have role in synthesis of factors II, VII, IX, X. Peak of action with oral intake occurs 12 h after administration. After discontinuation, the action persists for 48 - 72 h.

Indications: atrial fibrillation and mitral stenosis, or a history of embolism; atrial fibrillation and age over 65age; hypertension; diabetes or expressed left ventricular hypertrophy; intramural thrombus of the heart after a heart infarction or aneurysm of the anterior hart wall (3-6 months); artificial heart valves, with a limited left ventricular function. [4, 5]

1.2. Warfarin sodium

19 Warfarin is also coumarin derivate and affects the extrinsic clotting pathway by preventing the reduction of vitamin K into its active form. Its effectiveness in the patient is measured by the INR. Depending on the reason for the anticoagulation (cardiovascular thrombo-embolic risk), the patient's target INR therapeutic ranges will be different. Patients with atrial fibrillation, DVT, or stroke have a target INR of 2.0 to 3.0, whereas after undergoing cardiac valve replacement surgery, patients have a target range of 2.5 to 3.5. [4, 5, 6, 7]

2. Direct thrombin inhibitors

2.1. Dabigatran is a selective, reversible direct thrombin inhibitor currently used in Europe and North America for stroke prevention in nonvalvular AF and in Europe for VTE prophylaxis in orthopedic patients.

Dabigatran etexilate's has comparatively rapid onset of action. It is able to provide stable anticoagulation at a fixed dose without the need for routine laboratory monitoring of INR and associated dosage adjustments. No specific antidote or reversal agent exists to counter the anticoagulant effect of dabigatran. However, owing to dabigatran's short half-life (12-14 hours (14-17 hours in the elderly)), merely discontinuing the administration of the drug is thought to be sufficient to resolve minor bleeding in most circumstances. [1, 5, 7, 8, 9]

2. direct factor Xa inhibitors

2.1. Rivaroxaban is approved in Europe and North America for stroke prevention in nonvalvular AF and VTE prophylaxis. It is a highly selective direct Factor Xa inhibitor with oral bioavailability and rapid onset of action. Rivaroxaban interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin and no effects on platelets have been demonstrated. It also provides stable anticoagulation at a fixed dose without the need for routine INR monitoring. There is no specific reversal agent or antidote for rivaroxaban, but its short half-life means that the discontinuation of the drug is likely be adequate to correct most bleeding problems caused by its use. [1, 5, 6, 7, 8, 9, 10]

2.2. Apixaban is a potent, reversible, highly selective, direct inhibitor of free and prothrombinase-bound factor Xa. It is characterized by > 50% oral bioavailability, peak plasma concentrations 1-3 h after administration, and a 12-h terminal half-life.

It is indicated in the prevention of venous thromboembolism (VTE) after major orthopaedic surgery, treatment of acute VTE, prevention of stroke or systemic embolism in patients with atrial fibrillation and for secondary prevention in ischemic heart disease.

It has low potential for drug-drug interactions and is eliminated through mixed renal and metabolic pathways. [5, 7, 9, 11]

Tests for anticoagulation assesment

The **prothrombin time ratio (PTR)**, defined as the patient's prothrombin time (PT) was used to monitor anticoagulant therapy for many years.

Because of the variability of Prothrombin Time (PT) values from different reagents, a system of standardizing the reporting of anticoagulation activity has been developed by the World Health Organization. [12, 13, 14]

In 1985, the International Committee on Thrombosis and Homeostasis requested that all lots of thromboplastin have an indication of their international sensitivity index (ISI)which allows standardization of the results from different laboratories by the introduction of the **INR**.

$$INR = \left(\frac{PT_{test}}{PT_{normal}}\right)^{ISI}$$

It is now widely used for monitoring anticoagulant therapy and dosage planning. The INR for a healthy patient is 1 and the therapeutic INR for those on anticoagulant therapy typically ranges from 2 to 4, depending on the reason for anticoagulation. [15, 16, 17, 18]

Both **TT** and **ECT** tests are the most sensitive tests for quantifying the anticoagulant effects of dabigatran, but in emergency situations, **aPTT** and/or **TT**, performed 6-12 hours prior surgery, would usually be the most accessible methods for monitoring the anticoagulant effects of dabigatran, because the ECT test (based on snake venom) is not widely available. [9, 12]

FXaIs, rivaroxaban and apixaban, are reported to slightly prolong **PT** and **aPTT**. The test that is reported to be best able to monitor the anticoagulant effect of FXaIs (as well as LMWH) is an anti–factor Xa assay; however, no routine laboratory test monitoring of coagulation should be required for patients receiving rivaroxaban or apixaban, except possibly in special circumstances, such as renal failure, obesity, or severely underweight patients. [1, 10]

Risk of thrombosis on stopping anticoagulation therapy

In the past decade, it has become clear that routine discontinuation of oral anticoagulant therapy for dental

procedures is not supported by the scientific literature, as it may put patients at unnecessary medical risk for thromboembolic events either from the cessation of anticoagulant therapy or because of "rebound phenomenon.". This phenomenon is hypercoagulability owing to increased thrombin production or platelet activation if therapy is abruptly discontinued, which can damaged prosthetic cardiac valves and even cause thrombotic deaths in dental patients. So, unless serious bleeding is anticipated, the therapy should be continued. [19]

The risk of thrombosis associated with temporarily discontinuing anticoagulants prior to dental surgery is small but potentially fatal. In the review of Wahl, 5/493 (1%) patients undergoing 542 dental procedures and in whom anticoagulants were withdrawn specifically for surgery, had serious embolic complications of which four were fatal. The four deaths comprised: a fatal cerebral embolism 17 days after discontinuing warfarin; one fatal myocardial infarction 19 days after interruption of therapy for nine days; one fatal cerebral thromboembolism five days postoperatively and one patient died from a thromboembolism but no other data are available. [20, 21]

Currently, most guidelines indicate that patients with an INR less than 3.5 can undergo minor oral surgery (e.g., simple single extraction) without any adjustment in anticoagulation. Withdrawal or temporary interruption of anticoagulant medication, could lead to thromboembolic events. [12, 16, 20, 22]

Risk of bleeding complications with continuing anticoagulant therapy

Specific consideration must be given to the issue of whether oral anticoagulant treatment should be unaltered, modified, or stopped according to possible bleeding complications.

Hong C. et al. reported a study with 122 patients who had a total of 240 dental extractions. 35 patients (29%) were on concomitant medications thought to potentate bleeding. Seven patients were on multiple antithrombotic medications (excluding warfarin); 2 were taking a combination of aspirin, cilastazol, and nonsteroidal analgesic medication; 3 were on a combination of aspirin and clopidogrel; and 2 were on a combination of aspirin and enoxaparin. Ten (8%) patients had medical history which could potentially affect their risk for bleeding.

The average INR value was 2.4 ±1.2. Multiple extractions were performed in 41 cases. Local haemostatic measures with gelatine compressed sponges and sutures were used.

The results of this retrospective study suggest that the overall prevalence of persistent bleeding after dental procedures in patients on warfarin therapy is low (2%).

Additionally, most complications experienced were controlled with local hemostatic measures. [16]

Pereira C. end al. conducted a study with 108 patients. 215 extractions were performed in which only one case of postoperative bleeding occurred. Warfarin was used by 98 patients; Warfarin associated with salicylic acetic acid by 9 patients and salicylic acetic acid in only 1 patient. INR ranged from 0.8 to 4.9, with a mean of 3.15. They concluded that extractions in patients on oral anticoagulants must be performed in the least traumatic manner possible. It is not necessary to stop anticoagulant therapy prior teeth extractions. Local hemostasis techniques, such as sutures alone are sufficient to prevent hemorrhagic complications. [23]

Perini et al. published a study with 400 patients that have been treated with warfarin for at least six months submitted to dental extractions without modifying the anticoagulant therapy. All patients have been treated with suture, positioning of oxidized cellulose and topic tranexamic acid. The level of INR appraised immediately before surgery, ranged from 1.8 to 4. There were 7 cases of late bleeding which have been treated with socket toilette and a new suture, in no case more than local hemostatic measures were needed. [24]

Sacco R. end al. presented a study with 131 patients on OAT which were randomized to reduced anticoagulation or to full anticoagulation. 511 teeth were extracted by the same surgeon. Mild bleeding, but excessive enough to warrant adoption of supplementary local haemostatic measures, was observed in 10 cases (15.1%) in the reduced dosage group and in 6 cases (9.2%) in the unmodified dosage group, which wasn't significant difference. This randomized study shows that, using simple measures for local haemostasis, it is not necessary to reduce OAT in patients undergoing routine dental extractions. [25]

Salam S. et al. presented a study of 150 anticoagulated patients who required extraction of at least one tooth. The INR ranged from 0.9 to 4.2. All sockets were subsequently packed with absorbable oxycellulose and sutured.

Ten patients (7%) bled after extraction, enough to require a return to hospital.

Five patients of 101 with an INR $\leq$ 2.5, and 5 with an INR > 2.5 out of 49 bled after extraction. All patients who bled were managed conservatively and none was admitted to hospital.

The authors concluded that the risk of thrombo-embolism outweighed the risk of postoperative bleeding and patients whose INR is up to 4.0 do not have clinically significant bleeds post-operatively. [26, 27]

Sanz M. et al. investigated INR level in patients on warfarin therapy. They concluded that most of the anticoagulated patients do not have INR within the therapeutic range when attending a dental practice, which might increase the risk of bleeding or a thromboembolic event as a consequence of the dental intervention. INR

testing should, therefore, be incorporated into any dental practice in which invasive procedures are performed. [6, 28]

Local haemostasis

French Association of Oral Surgery and Medicine does not recommend the use of block anaesthetic techniques, including Inferior alveolar nerve block, in patients taking oral anticoagulants, whereas the British Committee for Standards in Haematology mentions the safety of inferior alveolar nerve block only if the INR is less than 3. Without doubt it is advisable to use intraligamentary or intraseptal techniques of local anaesthesia in these patients, as they are safer and less likely to provoke haemorrhagic complications. [13, 29, 30, 31]

Local haemostasis after single or multiple teeth extractions can be achieved through: - - Local pressure (biting on gauze); site packing with **gelatine sponges; absorbable oxycellulose; microcrystalline; collagen;** additional suturing**; Electrocauterization; topical thrombin powder.**

- **Fibrin sealants** induce clot formation at the site of the surgical wound. It mimics the last phase of blood clotting by conversion of fibrinogen to fibrin. The system has 2 components. The first consists mainly of fibrinogen and plasma proteins, and the second consists of thrombin and calcium chloride. When the 2 components are mixed, thrombin converts fibrinogen into fibrin so that clotting is initiated and the mixture is solidified. Fibrin sealants for oral surgery in patients on oral anticoagulant therapy can be used to reduce postoperative haemorrhage in the therapeutic INR range of 1 to 5 in patients with a wide range of degrees of surgical trauma. [12, 13, 15, 32]

- **5% tranexamic acid** mouthwashes used 4 times a day for 2 days (10ml in mouth for 2min) was reported to be effective in patients on anticoagulant therapy. This treatment modality is an attempt to reduce the amount of lysed fibrin and consequently the incidence of postoperative bleeding. It is conceivable that the mouthwash may have an effect only on the superficial clot and not on bleeding from the depth of the socket, an area not accessible to the mouthwash. [15, 29, 32]

Pain control

Generally paracetamol is considered a safe analgesic drug for patients taking anticoagulant medications and it may be taken in normal doses if pain control is needed and no contraindication exists.

Recommendations of the British Committee for Standards in Haematology: Patients taking warfarin should not be prescribed nonselective NSAIDs as analgesics following dental surgery. These drugs inhibit platelet aggregation and may cause GI bleeding and peptic ulceration and/or perforation. Increased bleeding may occur during concomitant NSAID therapy with warfarin independently of an increase in INR. [20, 22]

Patients taking Acenocoumarol should not be prescribed nonselective NSAIDs as analgesics following dental surgery, which potentate bleeding. [4, 5]

Association of new oral anticoagulants with other anticoagulants, platelet inhibitors

(Aspirin, Clopidogrel, Ticlodipine, Prasugrel, Ticagrelor, and others), and non-steroidal anti-inflammatory drugs (NSAID) increases the bleeding risk. [34]

COX-2 inhibitors are unlikely to increase bleeding time following invasive dental procedures, although there are no prospective studies in humans. [18]

Interactions with drugs frequently used or prescribed in dentistry

Macrolide antibiotics (i.e., erythromycin, clarithromycin, and possibly azithromycin) and sulphonamides have been implicated in causing significant episodes of bleeding in patients taking warfarin or acenocoumarol. [4, 5]

Other drugs that may enhance the hypoprothrombinemic effect of anticoagulant drugs include **tetracyclines** (especially doxycycline or tetracycline), and in particular the second and third generation cephalosporins, and levofloxacin. Postulated mechanisms include an antibiotic-induced reduction in prothrombin activity (hypoprothrombinemia) and a reduction in gastrointestinal bacteria flora essential for vitamin K production which is subsequently used to produce various clotting factors. [18]

Dabigatran and rivaroxaban are reported to have comparatively few drug-drug interactions.

The concomitant use of systemic **azoleantimycotics** (ketoconazole, itraconazole, voriconazole, and posaconazole) as well as **HIV protease inhibitors** is not recommended in patients being treated with rivaroxaban.

Fluconazole is expected to have less effect on rivaroxaban exposure and can be coadministered with caution.

Although platelet aggregation was reported to be unaffected, concomitant use of some NSAIDs and rivaroxaban significantly increased bleeding time compared with rivaroxaban alone. [1, 14]

CONCLUSIONS

INR values should be obtained within 24 hours before the dental procedure. For patients with INR in the therapeutic range 2-4 or below, therapy need not be modified or discontinued for simple single dental extractions. More complicated and invasive oral surgical procedures for patients with an INR on the high end of the scale or greater than 3.5 should be referred to physician for dose adjustment or therapy alteration before invasive dental procedures. [13, 16, 28]

The risk of bleeding may be minimised by: use of oxidised cellulose or collagen sponges, fibrin sealants and Tranexamic acid mouthwashes used four times a day for 2

days.

Co morbid conditions as liver disease, bone marrow disorders, biliary tract obstruction, malabsorption, renal disease, and cancers such as leukaemia may potentate an existing bleeding problem. Increased inflammation of the oral tissues in patients on OAT can contribute to excessive bleeding even with minor procedures.

These patients should NOT have a surgical dental procedure and should be referred to a dental hospital or hospital-based oral and maxillofacial surgery department.

The use of concomitant medications, including antibiotics, antifungals, nonsteroidal anti-inflammatory drugs (NSAIDs), and other platelet aggregation inhibitors may affect a patient's ability to achieve adequate haemostasis after a routine dental procedure.

For patients being treated with one of these new oral anticoagulants, the amount of "real-world" data and experience regarding the management of patients undergoing dental procedures that are likely to involve significant bleeding is currently lacking.

Clearly, clinical studies are needed to determine the effects that the new oral DTIs and FXaIs have on bleeding and haemostasis after tooth extractions and other surgical dental procedures.

At this time patients taking dabigatran, rivaroxaban or apixaban should be consulted with the treating physician prior dental surgical procedures. [1]

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