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MANAGEMENT OF ORAL SURGERY PROCEDURES IN ORALLY ANTICOAGULATED PATIENTS

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Summary

The oral and maxillofacial surgeons are frequently asked to manage patients who are receiving oral anticoagulants. The goal of treatment is to minimize the risk of hemorrhage while continuing to protect the patient against thromboembolism formation. The ordinary treatment includes the interruption of anticoagulant therapy for oral surgery interventions to prevent hemorrhage. However, this practice may logically increase the risk of a potentially life-threatening thromboembolism. Thus, this issue is still controversial.

Aim of this study is to review the evidence of different therapy approach, to highlight the areas of major concern, and to suggest specific oral surgery treatment for patients on oral anticoagulants.

A Medline and an extensive hand search were performed on English-language publications beginning in 1971 till now. The pertinent literature and clinical protocols of hospital dentistry departments have been extensively reviewed, presented and discussed.

Several evolving clinical practices in the last years have been detected:

- anticoagulant use is generally not discontinued;
- oral surgery is performed despite laboratory values showing significant bleeding tendency;
- new effective local haemostatic modalities are used to prevent bleeding;
- patients at risk are referred to hospital-based clinics.

The management of oral surgery procedures on patients treated with anticoagulants should be influenced by several factors: laboratory values, extent and urgency of the intervention, treating physician's recommendation, available facilities, dentist expertise, and patient's oral, medical, and general condition.

Introduction

Thrombosis is the formation, from the components of blood, of an abnormal mass within the vascular system. It involves the interaction of vascular, cellular, and humoral factors within a flowing stream of blood. Thrombosis and the complicating emboli that can result are among the most important causes of sickness and death in developed countries.

Thrombosis is of greater overall clinical importance in terms of morbidity and mortality than all of the hemorrhagic disorders combined.

Excessive activation of coagulation or inhibition of anticoagulant mechanisms may result in hypercoagulability and thrombosis. Injury to the vessel wall, alterations in blood flow, and changes in the composition of blood are major factors leading to thrombosis.

Thrombotic disorders can be caused by an inherited deficiency of antithrombin III, heparin cofactor II,protein C, protein S, thrombomodulin, plasminogen, or tissue plasminogen activator; an activated protein C resistance (factor V Leiden); dysfibrinogenemia; and homocysteinemia.

Most of these disorders have also been reported as acquired conditions.

The rice for time and money in the everyday and ordinary life has implication on the human health, which resulted with increased number of cardiovascular diseases in the young population, and with the effect and consequences as a socio-economical problem.

The scientific literature, the rapid development and the use of new scientific clinical methods of laboratory investigations changed the oral surgery treatment for the patients on oral anticoagulants.

Antithrombotic agents

The antithrombotic medicaments are antiplatelet, anticoagulant and thrombolytic agents.

Antiplatelet drugs are used to prevent and / or treat thromboembolic disorders, which play a key role in cardiovascular diseases. Given the fact that the antiaggregant mechanism of action consists in inhibiting the platelet function by preventing aggregation, the initial phase of haemostasis, use of these drugs

can make patients more susceptible to haemorrhages. This is of vital importance in the daily practice of dentists, particularly when performing surgery, such as dental extractions. Over the last few years the recommendation has been to continue with the antiplatelet therapy during dental extractions. There is little literature referring to dental extractions in patients taking antiplatelet drugs, and the majority of the studies available exclusively, or almost exclusively, refer to the use of aspirin or acetylsalicylic acid it is actually the most used antiplatelet drug.

The term oral anticoagulant (OAC) refers to oral vitamin K antagonists, including mainly sodium warfarin (the most widely used agent in Anglo-Saxon countries) and acenocoumarol (widely used in some countries of Europe). These drugs are widely prescribed for preventing arterial thromboembolism in patients with atrial fibrillation and/or heart valve prostheses, and for the treatment and prevention of deep venous thrombosis and pulmonary embolism Oral anticoagulants (OA) inhibits the enzyme vitamin K epoxide reductase, which converts vitamin K to vitamin K hydroquinone. The vitamin K hydroquinone is needed to gamma carboxylate the glutamic acids at the N-terminal portion of the clotting factors II, VII, IX, and X and endogenous proteins C and S. If the clotting factors are not carboxylated, they are not biologically active. Return of normal clotting after stopping OA requires the elimination of OA followed by the synthesis of new clotting factors. Because the elimination half-life of OA is 40 hours and the clotting factors have different and sometimes long half-lives, it takes days to reverse the effects of OA.

Oral anticoagulans act by blocking the ability of Vitamin K to carboxylate the Vitamin K dependent clotting factors, thereby reducing their coagulant activity. OA works by interfering with internal recycling of oxidized Vitamin K to the reduced form. When OA are given, the oxidized form of Vitamin K builds up in the blood leading to a deficiency of reduced Vitamin K and a decrease in carboxylation of prothrombin. OA interferes with g–carboxylation of terminal glutamic acids on the procoagulant proteins, Factors II, VII, IX, and X.

The antiplatelet and anticoagulant agents have been extensively researched and developed as potential therapies for prevention and

management of arterial and venous thrombosis. Also, these drugs have been associated with prolongation of bleeding after oral surgery interventions. Thus, some of the oral surgeon still recommend to stop antiplateled and oral anticoagulants at last 3 days before any kind of oral surgery procedure.

However, stopping these drugs before the interventions expose the patient to vascular problems, and with potential of significant morbidity.

The handling of these drugs requires correct monitorization and dose adjustment to obtain the desired therapeutic effect while minimizing the adverse effects associated both with excessive anticoagulation (which leads to bleeding) and with insufficient antithrombotic action (which can produce thrombosis).

Aim

The aim of this study is to review the evidence of different therapy approach, to highlight the areas of major concern, and to suggest specific oral surgery treatment for patients on oral anticoagulants.

Oral anticoagulants – withdraw or continuing

The oral and maxillofacial surgeons are frequently asked to manage patients who are receiving oral anticoagulants. The goal of treatment is to minimize the risk of hemorrhage while continuing to protect the patient against thromboembolism formation. The ordinary treatment includes the interruption of anticoagulant therapy for oral surgery interventions to prevent hemorrhage. However, this practice may logically increase the risk of a potentially life-threatening thromboembolism. Thus, this issue is still controversial.

Assael said that the haemostasis care of the oral anticoagulated patients is a shared responsibility and oral and maxillofacial surgeons, and the hematology/coagulation team huddle to determine the steps.

The surgeon is faced with the choice of altering or stopping oral anticoagulants and risking thromboembolism or leaving the patient on the oral anticoagulants and risking uncontrolled bleeding. A common approach to managing patients with a low risk of thromboembolism needing surgery is to interrupt oral anticoagulans therapy for several days before and after surgery.

Patients with a high risk of thromboembolism commonly stop OA and bridge anticoagulation with unfractionated heparin (UHF) or low-molecular-weight heparin (LMWH).

The anticoagulant effect in turn depends on the half-life of the inhibited factors. In this sense, the half-lives of factors VII, IX, X and II are 6, 24, 40 and 60 hours, respectively. Blood coagulation factor VII is the first to be affected, prolonging prothrombin time (PT). Factors IX, X and II are posteriorly affected: factor IX prolongs activated partial thromboplastin time (aPTT), while factors X and II prolong both PT and aPTT. These are well tolerated drugs, with rapid absorption via the oral route. The peak plasma concentrations are reached one hour after administration, though the reduction in coagulation factors takes place 48-72 hours after dosing. The half-life of warfarin is 48-72 hours, versus 8-10 hours in the case of acenocoumarol. Thus, the effects of warfarin are longer lasting in terms of both the induction and disappearance of therapeutic action.

However, patients who interrupt oral anticoagulants therapy are at risk of developing a thromboembolism with or without bridging therapy. On the other hand, oral anticoagulants therapy can be continued without interruption for procedures such as dentoalveolar surgeries that rarely cause significant or life-threatening bleeding. Stopping oral anticoagulants is problematic because of its slow unpredictable reversal.

Interruption of Oral Anticoagulant Therapy and Risk of Thrombotic Episode

The risk for thromboembolism depends on several factors, including the clinical indications for anticoagulation. Anticoagulation is required in the management of patients with prosthetic heart valves, chronic atrial fibrillation, hypercoagulable states (ie, protein C deficiency, protein S deficiency, factor V Leiden mutation, antithrombin III deficiency, antiphospholipid-antibody syndrome), venous or arterial thromboembolism, and cerebrovascular disease with strokes. However, patients who require anticoagulation do not have equal risk of developing thromboembolism.

The goal of managing anticoagulated patients who need surgery is to prevent major or life-threatening bleeding while protecting against thromboembolism.

Some procedures such as intra-abdominal, intrathoracic, major cancer surgery, removal of head and neck tumors, and extra oral open reduction of facial fractures are associated with considerable bleeding.

Some patients are particularly sensitive to OACs, and the activity of these drugs moreover can be affected by a range of factors including individual patient response, diet, or the simultaneous administration of other commonly used drugs such as antibiotics, analgesics, or even herbal remedies. As a result, regular monitorization is required, and such control must be more frequent when changes occur in any of the aforementioned aspects (3,5). OAC action is monitored on the basis of the effect of such drugs on prothrombin time (PT), i.e., the time required for the clotting of citrate-treated plasma, after adding calcium and thromboplastin. Thromboplastin is extracted from different tissues with different levels of sensitivity - a fact that complicates the comparison of PT test results. The PT results are usually reported as the ratio patient time / control time. The simple ratio is extremely variable, depending on the sensitivity of the reagent used - thus making it impossible to establish universally applicable therapeutic margins.

For this reason, in 1978 the World Health Organization (WHO) recommended PT standardization, and in 1983 it introduced the INR (international normalized ratio), which is calculated by raising the simple ratio to the international sensitivity index (ISI) of the thromboplastin used.

Thus, INR = (patient time / control time) ISI.

This is the formula used to standardize PT, allowing comparison regardless of the thromboplastin used by the different laboratories, and ensuring increased reliability in monitoring OAC treatment. At the same time, the different international societies established recommendations regarding the therapeutic anticoagulation levels to be maintained according to the existing patient pathology - the corresponding INR value ranging from 2 to 3.5. Because of that

there is a strong correlation between INR and bleeding risk - the latter increasing when INR >4 (Table 1).

Table 1. Therapeutic anticoagulation levels

Clinical pathology INR	**INR**
- Prophylaxis – venous thromboembolism (high risk surgery)	2.0-3.0
- Prophylaxis – venous thromboembolism (hip surgery)	2.0-3.0
- Treatment of deep venous thrombosis or pulmonary embolism	2.0-3.0
- Prevention of systemic embolism in patients with atrial fibrillation, heart valve disease, bioprostheses, or acute myocardial infarction	2.0-3.0
- Valve prostheses, recurrent systemic embolism, recurrent myocardial infarction	2.5-3.5

INR = international normalized ratio

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The recommendations vary according to the bleeding risk of the surgical intervention and the indication of anticoagulation therapy (i.e., the thromboembolic risk of the patient). Thus, for example, treatment to prevent venous thromboembolism is not the same as treatment for dealing with an acute thrombotic episode.

Although consensus is lacking, the expert groups do establish a series of recommendations:

1. For patients at low risk of bleeding after the operation, anticoagulation can be maintained at the lower limit of the therapeutic range (INR = 2.0).

2. For patients at high bleeding risk, anticoagulation should be maintained at subtherapeutic levels (INR = 1.5). Accordingly, acenocoumarol should be suspended 3-4 days before surgery (4-5 days in the case of warfarin). On day -3, low molecular weight heparin (LMWH) should be provided at therapeutic, medium or prophylactic doses, depending on whether the thrombotic risk of the patient is high, moderate or low, respectively. This is to be maintained until 12 hours before surgery, followed 12 hours after surgery be reintroduction of the original treatment, provided there is no bleeding.

Bridging Therapy

Life threatening or major bleeding in patients who need high-risk surgery is avoided by stopping oral anticoagulants with or without bridging therapy. The

Food and Drug Administration has not approved bridging therapy with LMWH in patients with prosthetic heart valves, and UFH is frequently recommended for bridging therapy in these high-risk patients who develop arterial thromboembolism.

Bridging with UFH or LMWH is done to shorten the interval of sub therapeutic anticoagulation while waiting for the reversal of oral anticoagulation. For patients with a low risk of thromboembolism, bridging is not recommended because the efficacy of bridging with UFH and LMWH does not outweigh the risk of postoperative bleeding.

Patients with a low risk of thromboembolism can stop the oral anticoagulant and restart it after the surgery. Stopping oral anticoagulant and bridging is not recommended for procedures for which major bleeding is not likely to develop.

Depending on the existing thromboembolic risk, the American Heart Association / American College of Cardiology Foundation Guide to Warfarin Therapy recommends different heparin management regimens for the patients with moderate, high and low thromboembolic risk. In general, heparins are not reintroduced before 12 hours post surgery, and dosing is postponed for longer periods in the case of evidence of bleeding.

Oral Surgery Procedures and management of bleeding

The management of oral surgery procedures on patients treated with anticoagulants should be influenced by several factors: laboratory values, extent and urgency of the intervention, treating physician's recommendation, available facilities, dentist expertise, and patient's oral, medical, and general condition and atibiotic profilaxis.

Procedures including single and multiple dental extractions, full mouth extractions, and alveolectomies are associated with very few bleeding episodes in patients who continue oral anticoagulans therapy.

Wahl published a review of perioperative management of patients receiving oral anticoagulants in 1998. He summarized the outcome of 2,014

dental surgical procedures in patients who continued oral anticoagulation. Serious bleeding occurred in only 12 of the procedures, and 5 of the 12 bleeds were associated with INRs above therapeutic levels. Wahl also examined reports including 493 patients who discontinued warfarin; 5 of these patients developed serious thromboembolic complication, resulting in 4 deaths. He concluded that as long as the surgery was done when the INR was within therapeutic range, 2.0 to 4.0, the chance of serious bleeding following dentoalveolar surgery was low in patients who continue their oral anticoagulation therapy.

Martinowitz et al. followed 40 patients having 63 teeth removed without altering the oral anticoagulation. Local hemostasis was obtained using a biological adhesive after placing thrombin soaked gauze into the socket for 3 minutes. The INRs on the day of surgery ranged from 2.5 to 4.0. There were no incidences of prolonged or excessive bleeding. One patient had hemorrhage on the third postoperative day that was controlled by biting on gauze.

In Sindet–Pedersen's original article, anti-coagulant-treated patients undergoing oral surgery, were prescribed a 4.8% aqueous solution of tranexamic acid for seven days post-surgery to prevent re-bleeding secondary to fibrinolysis of the wound clot.

The results of the most scientific studies confirm that anticoagulation treatment with warfarin need not be withdrawn prior to dental extractions, provided that the patients do not have a preoperative INR value greater than 4.0, and local measures including antifibrinolytic therapy is instituted.

Recently, some authors have recommended that most anticoagulated patients are capable of withstanding routine, limited, oral surgery procedures without additional medical intervention such as an antifibrinolytic mouthwash provided a good surgical technique is employed. However, they limit acceptable INR values for this proposal to 3.0 or less when clearly there are patients with therapeutic levels higher than 3.0 and this group tends to comprise those most at risk of serious thromboembolic events if their anticoagulation is temporarily discontinued or decreased such as prosthetic mitral valve replacement. A 4.8% tranexamic acid mouthwash is effective in controlling local haemostasis in

anticoagulated patients undergoing dental extractions. Statistically there appears to be no difference between a prescribed two-day *vs* a five-day course.

The usage of Surgicel in the scientific studies is very common, because it is widely available, easy to handle, inexpensive and acts as a good delivery vehicle for the tranexamic acid deep into the base of the tooth sockets and subsequent blood clot after surgery. Surgicel is an oxidized regenerated cellulose preparation whose local haemostatic action depends on the binding of haemoglobin to oxycellulose, allowing the dressing to expand into a gelatinous mass, which in turn acts both as scaffolding for clot formation and a clot stabilizer. The material is completely absorbable and does not interfere with healing or bone regeneration.

In 2003, Carter et al. conducted a randomized study in patients under oral anticoagulation and subjected to extractions without modifying the OAC regimen, and applying two types of hemostatic agents (4.8% tranexamic acid and autologous fibrin adhesive). The authors concluded that both approaches are effective and safe in controlling post-extraction bleeding.

Autologous fibrin adhesive applied to the socket walls in turn was recommended when the patient has difficulties performing rinses correctly. Posterior studies reported the same efficacy in controlling hemostasis by applying rinses for only two days (17). Tranexamic acid has no marketing license in some countries, and fibrin adhesives are not recommended by all authors, due to the risk of disease transmission - though such systems are subjected to viral inactivation processes - and their high cost.

Post-extraction bleeding is generally controlled by local measures such as socket curettage, suturing, and local compression, thanks to easy access to the bleeding zone.

When such measures prove insufficient, and the anticoagulation effect must be suppressed, this can be done by administering vitamin K. In this sense, intravenous administration elicits faster effects than the oral route – the recommended dose being 5-10 mg. The use of concentrates of prothrombin complex or fresh frozen plasma is reserved for cases of important bleeding.

Based on the evidence that the benefit of preventing thromboembolism outweighs the risk of bleeding, the recommendations of the published clinical studies and the expert opinions are to keep the OAC dose unchanged, working with therapeutic INR levels, and adopting local hemostatic measures - with the use of antifibrinolytic agents such as tranexamic acid, in dental extractions. More invasive oral surgery with an increased bleeding risk may constitute an exception to these guidelines, requiring due evaluation in coordination with the hematologist.

Recommendations and conclusions

The evidence from clinical trials and focused reviews supports continuing oral anticoagulation for patients needing dentoalveolar surgery. As long as the INR is within the therapeutic range and local hemostatic measures are taken following the surgery, these patients will have little chance of developing uncontrolled bleeding following the surgery.

Stopping warfarin with or without bridging for dentoalveolar surgery is not supported by clinical evidence. The risk of developing life-threatening bleeding or bleeding that cannot be controlled using local measures following dental extractions, alveoloplasties, or dental implants is so low that there is no need to stop warfarin.

Local hemostasis will control the bleeding in the few patients who develop postsurgical bleeding. The risk of uncontrolled life threatening bleeding following dentoalveolar surgery is so low that it is not necessary to stop anticoagulation even for a short interval and risk thromboembolism in patients on oral anticoagulants.

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