

UPDATE OF ORAL SURGERY MANAGEMENT IN ORALLY ANTICOAGULATED PATIENTS

AŽURIRANI ORALNOHIRURŠKI MENADŽMENT BOLESNIKA SA ORALNIM ANTIKOAGULANSIMA

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ABSTRACT

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 anti-coagulants. The aim of operative treatment is to minimize the risk of hemorrhage while continuing to protect the patient against thrombus-embolism 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 thrombus embolism. Thus, this issue is still controversial.

The update management of oral surgery procedures on patients treated with oral 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.

Key words: oral surgery, oral anticoagulant therapy

SAŽETAK

Cilj ovog rada je dati pregled dokaza drugačijeg terapijskog pristupa, da se istaknu područja koja su od velike važnosti, i predložiti određeni oralnohirurški tretman za pacijente na oralnim antikoagulansima. Cilj operativnog liječenja je smanjiti rizik od krvarenja, dok je pacijent sa kontinuiranom zaštitom od tromboembolijske formacije. Obični tretman uključuje prekid antikoagulantne terapije prije oralnohirurških intervencija kako bi se spriječilo krvarenje. Međutim, logično ova praksa može povećati rizik od potencijalno opasne po život tromboembolije. Dakle, ovo pitanje još uvijek je kontroverzno.

Ažurirani menadžment oralnohirurških procedura kod bolesnika liječenih oralnim antikoagulansima trebao bi biti pod utjecajem nekoliko faktora: laboratorijske vrijednosti, opsega i hitnosti intervencije, liječničke preporuke, dostupnih sadržaja, stručnosti stomatologa i oralnog, medicinskog i općeg stanja pacijenta.

Ključne riječi: oralna hirurgija, oralni antikoagulantsna terapija

Introduction

The race for time and money in everyday and ordinary life has implications on human health, which has resulted with increased number of cardiovascular diseases in the young population and with consequences creating socio-economic 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 [1].

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 emboli as the complication 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 others hemorrhagic disorders combined [1].

Antithrombotic agents

The anti-thrombosis medicaments are antiplatelet, anticoagulant and thrombolytic agents. Antiplatelet drugs are used to prevent and / or treat thrombo-embolic disorders, which play a key role in cardiovascular diseases. Given the fact that the anti-aggregate mechanism of action consists in inhibiting the platelet function by preventing aggregation, in the initial phase of hemostasis, usage of these drugs can make patients more susceptible to hemorrhages [2].

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 European countries). These drugs are widely prescribed for preventing arterial thrombo-embolism in patients with atrial fibrillation and/or heart valve prostheses, so as for the treatment and prevention of deep venous thrombosis and pulmonary embolism. Oral anticoagulants (OA) inhibit the enzyme vitamin K epoxide reductase, which converts vitamin K into 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. As 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 [2].

Oral anticoagulants 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 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 γ -carboxylation of terminal glutamic acids on the procoagulant proteins, Factors II, VII, IX, and X [3].

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 surgeons still recommend stopping of antiplatelet and oral anticoagulants at least 3 days before any kind of oral surgery procedure. However, the stopping of these drugs before the interventions expose the patient to vascular problems, and to potential morbidity [3].

The handling of these drugs requires correct monitoring 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 anti-thrombotic action (which can produce thrombosis).

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 continuation

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 thrombus-embolism 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 thrombo-embolism. Thus, this issue is still controversial [4].

Assael said that the hemostasis care of the oral anticoagulated patients is a shared responsibility of 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 thus risking thrombo-embolism or leaving the patient on the oral anticoagulants therapy with risk of uncontrolled bleeding. A common approach to managing patients with a low risk of thrombo-embolism needing surgery is to interrupt oral anticoagulants therapy for several days before and after surgery. Patients with a high risk of thrombo-embolism commonly stop with OA and bridge anticoagulation with infractional heparin (UHF) or low-molecular-weight heparin (LMWH) [4, 5].

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 posterior affected: factor IX prolongs activated partial thromboplastin time (aPTT), while factors X and II prolong both PT and a PTT. 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 [6, 7].

However, patients who interrupt oral anticoagulants therapy are at risk of developing a thrombo-embolism with or without bridging therapy. On the other hand, oral anticoagulants therapy can be continued without interruption for procedures such as dento-alveolar surgeries that rarely cause significant or life-threatening bleeding. Stopping oral anticoagulants is problem creating because of its slow unpredictable reversal effect [8].

Interruption of Oral Anticoagulant Therapy and Risk of Thrombotic Episode

The risk for thrombo-embolism 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 thrombo-embolism [9].

The goal of managing anticoagulated patients who need surgery is to prevent major or life-threatening bleeding while protecting them against thrombo-embolism. Some procedures such as intra-abdominal, intrathoracic, major cancer surgery, removal of head and neck of tumors, and extra oral open reduction of facial fractures are associated with considerable bleeding [9].

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 monitoring is required, and such control must be more frequent when changes occur in any of the aforementioned aspects. 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 [10].

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 [11].

Thus, $INR = (\text{patient time} / \text{control time})^{ISI}$.

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)[11].

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 [12].

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 sub-therapeutic 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 12 hours before surgery, followed by 12 hours after surgery to be reintroduced to the original treatment, provided there is no bleeding [13].

Bridging Therapy

Life threatening or major bleeding in patients who need high-risk surgery may be 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 as bridging therapy in these high-risk patients who develop arterial thrombo-embolism [13].

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 thrombo-embolism, bridging is not recommended because the efficacy of bridging with UFH and LMWH does not outweigh the risk of postoperative bleeding [14].

Patients with a low risk of thrombo-embolism can stop the oral anticoagulant and restart it after the surgery. Stopping oral anticoagulant and bridging is

Clinical pathology INR	INR
Prophylaxis – venous thrombo-embolism (high risk surgery)	2.0-3.0
Prophylaxis – venous thrombo-embolism (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, bio prostheses, or acute myocardial infarction	2.0-3.0
Valve prostheses, recurrent systemic embolism, recurrent myocardial infarction	2.5-3.5

INR = International Normalized Ratio

Table 1. Therapeutic anticoagulation levels [11]

not recommended for procedures for which major bleeding is not likely to develop.

Depending on the existing thrombo-embolic 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 thrombo-embolic risk. In general, heparins are reintroduced only 12 hours post-surgery, and dosing is postponed for longer periods in the case of evidence of bleeding [15, 16].

Oral Surgery Procedures and management of bleeding

The management of oral surgery procedures on patients treated with anticoagulants is very much 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 antibiotic prophylaxis [17].

Procedures including single and multiple dental extractions, full mouth extractions, and alveolotomies are associated with very few bleeding episodes in patients who continue oral anticoagulants therapy [18].

In Sindet-Pedersen's original article [19], anticoagulant-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 exceeding 4.0, and local measures including antifibrinolytic therapy were instituted [20, 21, 22].

Wahl [23] published a review of peri-operative 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 thrombo-embolic complication, resulting in 4 deaths. He concluded that as long as the surgery was done with INR introduced into 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 [24, 25].

Martinowitz et al. [26] 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.

Recently, some authors have recommended that the 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 for the patients with therapeutic levels higher than 3.0 and this group comprises the highest risk of serious thrombo-embolic events if their anticoagulation is temporarily discontinued or decreased such as in the case of prosthetic mitral valve replacement. A 4.8% tranexamic acid mouthwash is effective in controlling local hemostasis in anti-coagulated patients undergoing dental extractions. Statistically, there appears to be no difference between prescribed two-days vs. a five-day course [27, 28].

The usage of Surgicel, according to 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 hemostatic action depends on the binding of hemoglobin 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 [29].

In 2003, Carter et al. [30] conducted a randomized study in patients under oral anticoagulation and

subject 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 was in turn recommended for the patients having difficulties to perform rinses correctly. Posterior studies reported the same efficacy in controlling hemostasis by applying rinses for two days only. Tranexamic acid has no marketing licenses 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 [30].

Post-extraction bleeding is generally controlled by local measures such as socket curettage, suturing, and local compression, thanks to an easy access to the bleeding zone [31, 32].

Given such measures proved insufficient, and the anticoagulation effect must be suppressed, the solution is in administering vitamin K. In this sense, intravenous administration elicits faster effects than the oral route - the recommended dose being 5-10mg. The use of concentrates of prothrombin complex or fresh frozen plasma is reserved for significant bleeding cases [33, 34, 35].

Based on the evidence that the benefit of preventing thromboembolism outweighs the risk of bleeding, the recommendations of the published clinical studies and the experts' opinions are to keep the OAC dose unchanged, working with therapeutic INR levels, and adopting local hemostatic measures - using 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 [36, 37, 38].

Conclusions

The evidence from clinical trials and focused reviews support the continuation of 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 dento-alveolar surgery is not supported by clinical evidence. The risk of developing life-threatening bleeding or uncontrolled bleeding using local measures following dental extractions, alveoloplasties, or dental implants is so low not needing stopping of warfarin.

Local hemostasis will control the bleeding in the few patients who develop post-surgical bleeding. The risk of uncontrolled life threatening bleeding following dento-alveolar surgery is so low not necessarily leading towards the stopping of anticoagulation even for a short interval and risk thrombo-embolism in patients being on oral anticoagulants.

References

1. Bloom AL, Thomas DP. Hemostasis and Thrombosis. Churchill Livingstone, 1 Ed., Edinburgh - London - Melbourne - New York, 1981
2. Ratnoff O, Forbes Ch. Disorders of Hemostasis. 2nd ed. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo, 1991.
3. Rogerson KC. Haemostasis for dental surgery. Dent Clin N Amer 1995; 39 (3): 649 - 662.
4. Hirsh J, Warkentin T, Shaughnessy S, Anand S, Halperin J, Raschke R, Granger C, Ohman M, Dalen JE. Heparin And Low-Molecular-Weight Heparin Mechanisms of Action, Pharmacokinetics, Dosing, Monitoring, Efficacy, and Safety. Chest 2001;119:64- 94.
5. Barrowcliffe TW, Thomas DP. Antithrombin III and Heparin. Eds: Hemostasis and Thrombosis, 3rd ed. Philadelphia: JB Lippincott, 1994: 712 - 724.
6. Assael LA. Hemostasis is a Shared Responsibility. J Oral Maxillofac Surg. 2003; 61: 1377 - 1378.
7. Balderston RH. Warfarin and extraction. Br Dent J. 2003; 194 (8): 408 - 9.
8. Bauersachs R, Breddin HK. Moderne Antikoagulation. Probleme des Bewährten, Hoffnung auf das Neue. Internist. 2004; 45: 717 - 726.

9. Anavi Y, Sharon A, Gutman D, Laufer D. Dental extractions during anticoagulant therapy. *Refuat Hapeh Vehashinayim*. 1981 Apr;28 (4): 9 - 12.
10. Blinder D, Manor Y, Martinowitz U, Taicher S. Dental extractions in patients maintained on oral anticoagulant therapy: Comparison of INR value with occurrence of postoperative bleeding. *Int J Oral Maxillofac Surg*. 2001 Dec; 30 (6): 518 - 521.
11. Hirsh J, Poller L. The International Normalized Ratio. A Guide to Understand and Correcting Its Problems. *Arch Intern Med*. 1994; 154 (3): 282 - 288.
12. Sulejmanagic N, Haracic M, Basic V, Rizanvebegovic R. Effects of High-Impact Dose of amoxicillin on the Laboratory Value of the INR: Oral-Surgery Impact. *Balk J Stom*. 2005; 9: 102 - 106.
13. Heit JA. Low-Molecular-Weight Heparin. *Biochemistry, Pharmacology, and Concurrent Drug Precautions*. *Reg Anest Pain Med*. 1998; 23 (6)Suppl 2:135-139.
14. Jeske W, Messmore HL, Fareed J: Pharmacology of Heparin and Oral Anticoagulants. In Loscalzo J, Schafer AI, eds: *Thrombosis and Hemorrhage*, 2nd ed. Baltimore: Williams & Wilkins, 1998: 1193 - 1213.
15. Johnson Leong C, Rada RE. The use of low-molecular-weight heparins in outpatient oral surgery for patients receiving anticoagulation therapy. *J Am Dent Assoc*. 2002 Aug; 133 (8): 1083 - 1087.
16. Aguilar D, Goldhaber SZ. Clinical Uses of Low-Molecular-Weight Heparins. *Chest*. 1999; 115:1418-1423.
17. Beirne OR. Anticoagulation and Minor Oral Surgery: Should the Anticoagulation Regimen Be Altered? *J Oral Maxillofac Surg*. 2000; 58: 135 - 136. Carter G, Goss AN, Lloyd J, Tocchetti R. Current concepts of the management of dental extractions for patients taking warfarin. *Aust Dent J* 2003; 48 (2): 89 - 96; quiz 138.
18. Beirne OR. Evidence to Continue Oral Anticoagulant Therapy for Ambulatory Oral Surgery. *J Oral Maxillofac Surg*. 2005; 63: 540 - 545
19. Sindet-Pedersen S. Haemostasis in oral surgery - the possible pathogenetic implications of oral fibrinolysis on bleeding. Experimental and clinical studies of the haemostatic balance in the oral cavity, with particular reference to patients with acquired and congenital defects of the coagulation system. *Dan Med Bull* 1991; 38(6): 427 - 43.
20. Okamoto T, Alves-Rezende MCR, Cláudio CC, Rodrigues TS, Okamoto R. Effects Of Tissucol And Epsilon Aminocaproic Acid In The Healing Process Following Dental Extraction In Dehydrated Rats. *Braz Oral Res* 2006; 20 (1): 33 - 39.
21. Dimova C, Andonovska B, Kovacevska I, Popovska L, Georgiev Z. Contemporary concept of oral surgical treatment of prosthetic heart valves patients. *Apolonia* 2009; 21: 57-70.
22. Plaza-Costa A, Garcia-Romero P, Poveda-Roda R, Bagan JV, Silvestre-Donat FJ, Cervero JA. A comparative study between INR and the determination of prothrombin time with the CoaguChek(r) portable coagulometer in the dental treatment of anticoagulated patients. *Med Oral*. 2002 Mar - Apr; 7 (2): 130 - 135.
23. Wahl MJ. Myths of dental surgery in patients receiving anticoagulant therapy. *J Am Dent Assoc*. 2000 Jan; 131 (1): 77 - 81.
24. Wahl MJ. Dental surgery in anticoagulated patients. *Arch Intern Med*. 1998; 158 (15): 1610-16.
25. Wahl MJ, Howell J. Altering Anticoagulant Therapy: A Survey of physicians. *JADA*. 1996; 127: 625 - 638.
26. Martinowitz U, Schulman S. Fibrin sealant in surgery of patients with a hemorrhagic diathesis. *Thromb-Haemost*. 1995 Jul; 74(1): 486 - 492.
27. Carter G, Goss A, Lloyd J, Tocchetti R. Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. *J Oral Maxillofac Surg*. 2003 Dec; 61 (12): 1432 - 1435.
28. Lieblich S. Tranexamic Acid Rinses in Anticoagulated Patients. *J Oral Maxillofac Surg*. 1996; 54: 657.
29. Halfpenny W, Fraser JS, Adlam DM. Comparison of 2 hemostatic agents for the prevention of postextraction hemorrhage in patients on anticoagulants. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2001 Sep; 92 (3): 257 - 259.

30. Carter G, Goss A. Tranexamic acid mouthwash - a prospective randomized study of a 2-day regimen vs. 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. *Int J Oral Maxillofac Surg.* 2003 Oct; 32 (5): 504 - 507.
31. Al-Mubarak S, Rass MA, Alsuwyed A, Alabdulaaly A, Ciancio S. Thromboembolic risk and bleeding in patients maintaining or stopping oral anticoagulant therapy during dental extraction. *J Thromb Haemost.* 2006 Mar; 4 (3): 689 - 91.
32. Barrero MV, Knezevic M, Martin MT, Llorente AV, Valverde JCO, Jimenez FG, Perez OL, Sarmiento SD, Cremades JMD, Reyes JC. Oral surgery in patients undergoing oral anticoagulant therapy. *Med Oral.* 2002 Jan-Feb; 7(1): 63 - 6, 67 - 70.
33. Little JW, Miller CS, Henry RG, McIntosh BA. Antithrombotic agents: Implications in dentistry. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2002; 93: 544 - 551.
34. Aldous JA, Olson CJ. Managing patients on warfarin therapy: a case report. *Spec Care Dentist.* 2001 May-Jun; 21 (3): 109 - 112.
35. Blomgren J, Eriksson H, Sjoberg WA. New routines make tooth extraction possible during warfarin treatment. *Lakartidningen.* 2004 Jun; 101 (25): 2168 - 2170.
36. Bridbord JW. Another view on the anticoagulated patient. *J Oral Maxillofac Surg.* 2002 Mar; 60(3): 342.
37. Dios PD, Feijoo JF. Tooth removal and anticoagulant therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2001 Sep; 92 (3): 248 - 249.
38. Dodson TB. Strategies for managing anticoagulated patients requiring dental extractions: an exercise in evidence-based clinical practice. *J Mass Dent Soc.* 2002; 50 (4): 44 - 50.