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Management of oral surgery patients undergoing hemostasis modifying therapy: a literature review

Manejo do paciente sob terapia modificadora da hemostasia submetido à cirurgia oral: uma revisão de literatura

Liliane Maria Dantas Lira[1*], **Luiz Carlos Ferreira da Silva**[2]

[1]Doctor of Dental Surgery, Oral and maxillofacial surgery department, Federal University of Sergipe, Aracaju, Sergipe, Brazil. [2]Associate Professor of Oral and Maxillofacial Surgery, Federal University of Sergipe, Aracaju, Sergipe, Brazil. *Author for correspondence. E-mail: lila-lira@hotmail.com

Abstract: Introduction: Hemostasis is the balance of the flow of blood within the vessel without overflow or coagulate. In some situations, this balance can be changed, among these the continued use of anticoagulants and antiplatelet agents for the prevention of thromboembolic events. Traditionally withdrew the previously therapy oral surgery to prevent possible bleeding during and after surgery. The objective of this work was to seek scientific evidence that gives support for decision-making as the interruption or not modifying therapy hemostasis in oral surgery. Methods: We performed a literature in clinical trials and review articles for databases Medline / PubMed, academic Google and periodicals Capes. Conclusion: it can be concluded that current evidence suggests that minor oral surgery can be performed safely in patients using modifiers hemostasis drug, subject to compliance with the appropriate level of INR hemostasis and local measures are taken.

Keywords: aspirin, surgery oral, tooth extraction, hemostasis, warfarin.

Resumo: Introdução: A hemostasia consiste no equilíbrio da fluidez do sangue dentro do vaso, sem extravasar nem coagular. Em algumas situações esse equilíbrio pode ser alterado, dentre essas o uso contínuo de medicamentos anticoagulantes e antiagregantes plaquetários para prevenção de eventos tromboembólicos. Tradicionalmente retirava-se a terapia previamente a cirurgia oral para se evitar possíveis sangramentos trans e pós-operatório. O objetivo deste trabalho foi buscar evidências científicas que deem suporte para a tomada de decisão quanto a interrupção ou não da terapia modificadora da hemostasia em cirurgia oral. Materiais e métodos: foi realizado um levantamento bibliográfico em estudos clínicos e artigos de revisão pelas bases de dados Medline/PubMed, google acadêmico e periódicos do Capes. Conclusão: pode-se concluir que a evidência atual sugere que cirurgia oral menor pode ser realizada com segurança em pacientes em uso de medicamentos modificadores da hemostasia, desde que seja observado o nível adequado de INR e medidas locais de hemostasia sejam adotadas.

Palavras-chaves: aspirina, cirurgia bucal, extração dentária, hemostasia, varfarina.

Introduction

Hemostasis is the physiological process of maintaining blood flow after a vascular injury, ensuring the balance of the circulatory system through various mechanisms. Blood should remain liquid within the vasculature and, even then, coagulate rapidly when exposed to subendothelial surfaces at sites of vascular injury (Goodman & Gilman, 2012). Certain conditions may alter this balance by predisposing the individual to excessive bleeding, including the continued use of hemostasis modifying drugs as anticoagulants or antiplatelet agents commonly used by medicine to prevent thromboembolic events.

In dentistry, the practice of discontinuing anticoagulant therapy prior to minor oral surgery procedures has been admitted for years to avoid probable bleeding in the trans and/or postoperative period. However, this behavior began to be questioned so that the preoperative management of the patient on hemostasis-modifying drugs should balance the risk of bleeding if they are continued and the risk of thromboembolism if they are not. The objective of this study was to demonstrate, through clinical studies, scientific subsidies that support decision-making regarding the need or otherwise of stopping anticoagulant therapy before minor oral surgery.

Revisão

The components of the hemostatic system include platelets, vessels, blood coagulation proteins, natural anticoagulants, and the fibrinolysis system (Franco, 2001). The sequence of events that encompass hemostasis consists of (1) transient vasoconstriction and platelet aggregation to form a platelet buffer at the injury site, (2) coagulation to form a fibrin mesh through the activation of intrinsic factors, (3) fibrinolysis for the removal of platelets and fibrin buffer as illustrated in figure 1. Soon after the process of tissue repair of the lesion site begins.

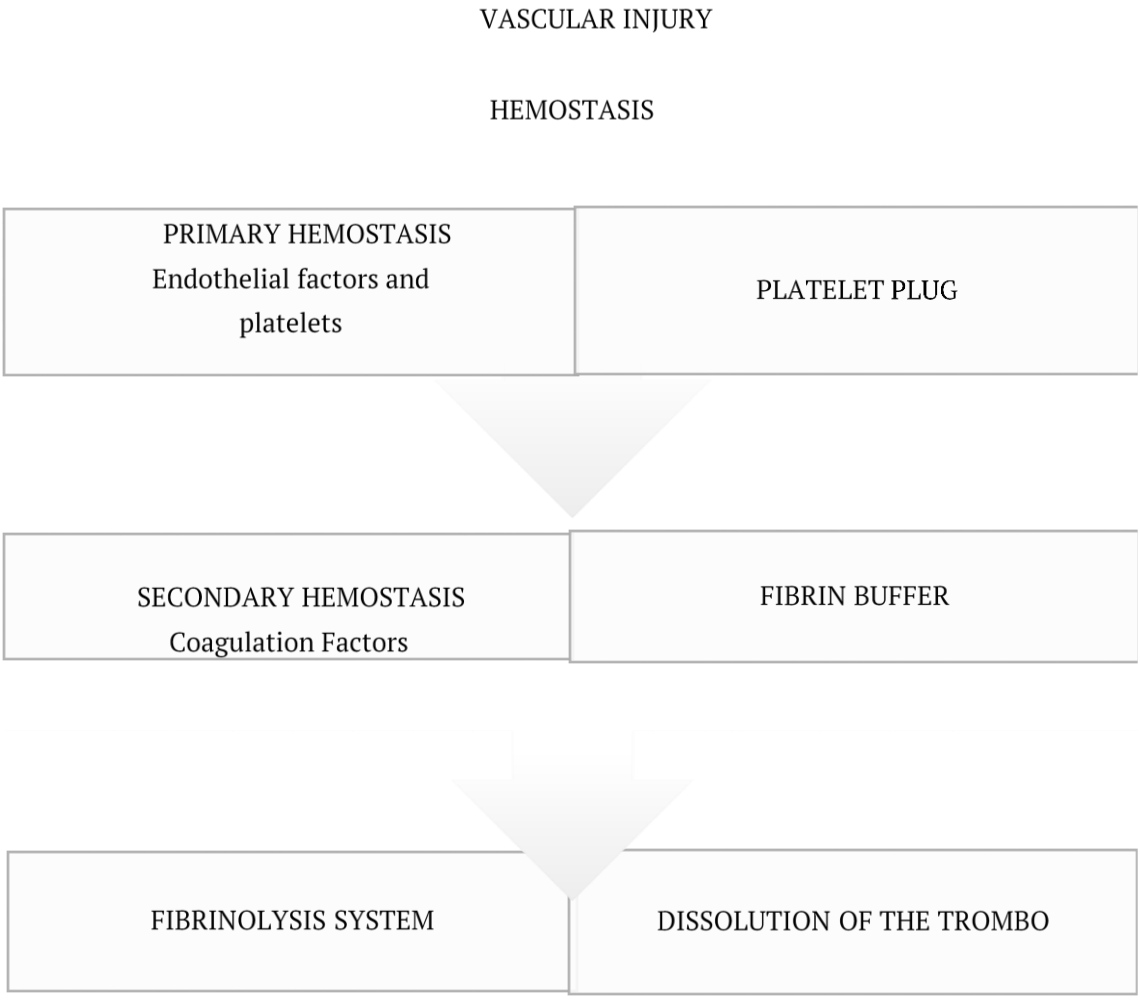

Figure 1. Blood clotting cascade flowchart.

In situations where any component of these mechanisms is altered, hemostasis is compromised and the result may be both thrombosis and bleeding (Davie et al., 1991).

Main hemostasis modifying drugs

Oral anticoagulants

The most frequent indications for chronic anticoagulation are cardiac valvular prostheses, ventricular fibrillation, prevention and treatment of venous thromboembolism, and the prevention and treatment of ischemic strokes. Oral anticoagulants are vitamin K antagonists, which inhibit the synthesis of coagulation factors II, VII, IX and X and C and S anticoagulant proteins (Franco, 2001).

WARFARIN is the most commonly used vitamin K antagonist oral anticoagulant in the world. It is metabolized in the liver to inactive compounds and excreted mainly in the urine. The half-life varies (25-60 h), with an average of 40 hours and the duration of action is 2-5 days. The anticoagulant effect of warfarin results predominantly from decreased factor II (prothrombin) rather than the decrease of all four dependent factors of vitamin K and peak plasma concentrations can be measured after one hour of ingestion (Osswald & Guimarães, 2001).

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Recently, a new category of oral anticoagulants has been incorporated for the treatment of thromboembolism which are the direct inhibitors of thrombin and can be represented by DABIGATRAN. Its onset occurs 2 hours after administration and its half-life is 12-17 h. Since 80% of its excretion is renal, it is, therefore, contraindicated for chronic kidney disease (Goodman & Gilman, 2012). In the randomized study by Schulman et al.; Compared with warfarin, warfarin (single daily dose) and dabigatran (150 mg twice daily) were compared in a total of 2,866 patients, dabigatran was effective and associated with a lower rate of clinical bleeding.

Antiplatelet agents

These drugs oppose the platelet activation necessary to form the hemostatic plug (thrombus white) that generates thrombosis. ACETYLSALICYLIC ACID has been commercially available since 1899 and is used for its antipyretic, anti-inflammatory, and antiplatelet activity. It irreversibly acetylates cyclooxygenase, inhibiting the production of thromboxane A2. As platelets do not synthesize new proteins, the action of acetylsalicylic acid on the COX-1 platelet is permanent and persists throughout the platelet life (7-10 days). Thus, the use of repeated doses of acetylsalicylic acid causes a cumulative effect on the platelet function (Goodman & Gilman, 2012). This results in decreased platelet aggregation by adenosine diphosphate (ADP) and collagen (Merritt et al., 2002).

Laboratory evaluation of hemostasis

In 1983, the World Health Organization introduced the INR (International Normalized Ratio), a value calculated from the relationship between the prothrombin time of the patient and the mean of the normal coagulation interval. Araújo et al., 2010. For an INR = 1 normal value In 1992, the American College of Chest Physicians determined that the recommended therapeutic window for continuous oral anticoagulant use is an INR between 2.0 and 3.0 for all conditions except heart valves for which the acceptable INR is between 2.5 and 3.5.

Campanili and Ayoub 2008 reported that the INR can be changed by some factors such as making oral anticoagulant use for more than a year, consuming more than one type of green food per day, self-medication, not ingesting warfarin according to medical prescription, and difficulties in understanding the therapy. The study judged as INR therapy window between 2 and 3. Lourenço et al., 1997 observed 100 patients for an average time of 7.6 months and considered that 53% were adequately anticoagulated with INR between 2 and 4.

Approach to the patient under hemostasis modifier therapy submitted to oral surgery

In a study of 150 patients who used warfarin and required the extraction of at least one tooth, Salam et al., 2007 observed postoperative bleeding in 10 patients (7%). Five patients of 101 with INR ⩽ 2.5 and 5 of 49 with an INR> 2.5. These results allowed the authors to conclude that patients who use warfarin whose INR is up to 4 can undergo dental extractions without risk of significant bleeding in the postoperative period.

Krishnan et all.; 2008 conducted a study with 82 patients who underwent dental extractions, in which 57 of them were on antiplatelet therapy (Aspirin). Patients were divided into 3 groups. Group 1 consisted of patients in whom antiplatelet therapy was discontinued (n 25), group 2 consisted of those who continued medication (n 32), and group 3 consisted of healthy patients not treated with antiplatelet therapy (n 25). No patient in any group had any prolonged or significant bleeding episodes. The authors were able to conclude that dental extractions can be performed safely in patients receiving antiplatelet therapy.

Morimoto, Niwa, and Minematsu, 2008 admitted a sample of 270 patients. 134 using warfarin only, 49 receiving warfarin associated with antiplatelet drugs, and the remaining 87 receiving antiplatelet drugs only. The patients who received warfarin alone had an INR of 1.5-1.99 in 67 patients, 2.0-2.49 in 42, 2.5-2.99 in 21, and 3.0 to 3.7 in 4. All teeth were extracted without reducing the usual antithrombotic therapy. Postoperative bleeding occurred in 7 patients on the warfarin monotherapy and 2 on the combined therapy with warfarin and antiplatelet agents with INR between 1.50 and 2.49. The remaining 2 patients who suffered bleeding were undergoing therapy with antiplatelet drugs alone. Therefore, sufficient hemostasis can be obtained in most cases of dental extraction under anticoagulant therapy with warfarin (INR 3.0) and antiplatelet agents.

In the review by Wahl, 2015, 5431 patients undergoing more than 11,381 surgical procedures, only 31 (0.6%) required more than local hemostasis to control bleeding. In at least 2673 patients whose warfarin dose was reduced or withdrawn by at least 2775 dental procedures, 22 embolisms (0.8%) occurred including 6 fatal events (0.2%). The author concludes that the risk of an embolic event in patients whose anticoagulation is interrupted for dental surgery exceeds that of significant hemorrhagic complications. Yanamoto et al., 2016 evaluated the bleeding index in dental extractions in 264 patients receiving single or double anticoagulant

therapy and obtained a result of 17.4% of well-controlled hemorrhages. Iwabuchi et al., 2014 reported bleeding events in 35 of the 496 teeth (7.1%) of the group that continued to receive warfarin and 49 of 2321 teeth (2.1%) in the group that discontinued therapy. These main data are summarized in table 1.

Table 1. Illustrative frame of the main results of some studies in which patients' therapy was not interrupted.

	Drug	Sample	RNI	Bleeding
Pereira *et al.;* (2011)	Warfarin: 98 Warfarin associated with acetylsalicylic acid: 9 Acetylsalicylic acid: 1	108	0.8 a 4.9	
Madan *et al.*; (2005)	Acetylsalicylic acid (75 a 100 mg/dia)	51		1 (1,96%)
Cardona-Tortajada *et al.; (*2009)	Acetylsalicylic acid: 118 Clopidogrel: 20 Ticlopidine: 2 Triflusal: 15	155		1 (0,64%)
Sánchez-Palomino *et al.;* (2015)		32		0%
Cabrera *et al.*; (2011)	Warfarin	1194		83(6,94%)
Bakathir (2009)	Warfarin	124	⩽ 3,5	8 (6,5%),
Eichhorn *et al.*; (2012)		637	2,44	47 a (7,4%),
Wahl (2000)	Warfarin a	493	2,0 a 4,0	5(1,01%) e 4 óbitos(0,81%)

Discussion

The organism uses hemostasis as a defense mechanism so that in the face of a vascular injury the loss of blood does not mean a threat to life. According to Rodrigues et all.; 2012 the endothelium undergoes a biochemical reprogramming in the face of a vascular lesion that induces the production of a potent vasoconstrictor (endothelin 1) and the formation of a procoagulant surface.

The benefits of oral anticoagulation with warfarin, acetylsalicylic acid, and other hemostasis modifying drugs are ensured by medicine in the treatment or prevention of cardiovascular pathologies that may culminate in thrombosis. Wahl, 2000 agrees that continuous anticoagulant therapy can save lives, but emphasizes that patients may be at increased risk of bleeding after dental surgery. Questions arise as to the safety of discontinuation of these drugs before oral surgery. Still for Wahl, 2000 the decision to withdraw continuous anticoagulant therapy does not seem to be based on scientific evidence. Given the risk of developing thromboembolic events upon discontinuation of anticoagulant therapy, Aframian et al; 2007 states that there is evidence that suggests a rebound effect of hypercoagulability due to platelet activation by thrombin production if warfarin is abruptly discontinued.

Kreisner, 2003 reinforces that patients are exposed to the development of thromboembolism, myocardial infarction, and cerebrovascular accidents following discontinuation of oral anticoagulants.

In Michael's study, 1970, 7 patients died due to thromboembolism after discontinuation of anticoagulant therapy in 169 patients and thromboembolic events occurred in 22% of patients. The INR is used as a laboratory parameter to support the hypothesis that it would be wise to continue with the therapy, Pereira, 2011 recommends for simple extractions or when the expected bleeding is minimal, an INR of less than 4.0. For cases of moderate bleeding such as impacted third molar surgeries, or multiple extractions, the INR should be smaller. In cases where greater bleeding is expected an INR of less than 3 is indicated. They should be suspended when greater than 5. Blinder et al; 1999 advocate oral surgeries with INR less than 3.5 in agreement with Sacco, 2007. Aldridge and Cunningham, 2010 assert that patients with an INR of less than 4 can undergo extractions in the outpatient setting without discontinuation of their anticoagulant therapy. In fact, in a study conducted by Carter et al; 2003 the two patients who presented postoperative bleeding had slightly elevated INRs (5.9 and 7.6), and warfarin dosage adjustment was necessary after consultation with their physician. In the classic study by Wahl, 1998 the summary of the results of 2,014 dental surgical procedures in patients who

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continued oral anticoagulation was presented. Severe hemorrhage occurred in only 12 of the procedures, and 5 of 12 bleeding occurrences were associated with INRs above therapeutic levels. The relevance of the complementary laboratory examination is shown.

On the other hand, studies that justify the discontinuation of the therapy or modification of the dose to prevent important bleeding are considered of low clinical relevance and the reduced amount available in the literature. In studies by Lemkin et al; 1974 on postoperative bleeding from dental extraction, it was concluded that there is increased bleeding after tooth extraction and the authors recommend interrupting aspirin, but the study does not specify the INR index of the patients as well as the surgical management. Thomason et al; 1997 reported a case of hemorrhage following gingival surgery, but we can emphasize that the patient was under the use of multiple antithrombotic drugs.

Although the possibility of bleeding is low, hemostatic measures such as an absorbable gelatin sponge, fibrin glue, or a mouthwash with tranexamic acid are adopted in the literature. Carter et al; 2003 examined the efficacy of 2 different local hemostasis measures in patients taking oral anticoagulants who required dental extractions. A group of 49 patients with 152 extractions was divided into 2 groups. Group A: mouthwash was requested with 10 ml of 4.8% tranexamic acid solution, 4 times daily for 7 days postoperatively. Group B received autologous fibrin glue in the trans-operative. The INRs on the day of surgery ranged from 2 to 4. None of the patients in the tranexamic acid group had postoperative bleeding, and 2 patients in the fibrin glue group had small bleeding which occurred 2 days postoperatively. The bleeding was controlled with local compression and additional fibrin glue. In 2018, Wahl reappraised several arguments regarding the discontinuation of anticoagulant therapy in oral surgeries and considered them a myth, reaffirming the increased risks of thromboembolic events.

It is possible to verify large-scale studies on the use of hemostasis modifiers in oral surgery, which empowers and increases the reliability of the research, such as that conducted by Clemm et al., 2016, who did not only focus on the extractions and also analyzed the rate of bleeding in patients submitted to autogenous implants and grafts in platelet or anticoagulant antiplatelet therapy. Only seven cases of postoperative bleeding were observed (1.2% in 564 patients). In the meta-analysis of five studies with reduced sampling Yang et al., 2016 did not observe statistical differences in postoperative bleeding in patients who continued to receive anticoagulant therapy and those who discontinued. The authors reinforced that controlled clinical trials with large sampling and well-defined exclusion criteria are required. In a pilot study coordinated by Mauprivez et al., 2016 post-discharge bleeding was observed in five patients receiving direct oral anticoagulants and in four receiving vitamin K antagonists from a total of 31 and 20 respectively. The authors uphold the safety of minor oral surgery in patients using hemostasis modifiers. Results that reinforce the maintenance of anticoagulant therapy were also found in cross-tests with patients submitted to the installation of dental implants. Tabrizi et al; 2018 did not observe a significant difference between the indices of postoperative bleeding in the group that interrupted the therapy and what is maintained.

Final considerations

After analyzing the results of available clinical research, it was concluded that current scientific evidence suggests that minor oral surgery can safely be performed in patients undergoing hemostasis modifying drugs. Initial careful evaluation associated with a therapeutic index of INR and local hemostasis measures is the fundamental element for adequate management of the dental surgical patient under hemostasis modifying therapy.

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Minicurrículo

Liliane Maria Dantas Lira. Cirurgiã dentista graduada pela Universidade Federal de Sergipe (2016) com experiência em cirurgia oral menor. Atualmente é residente no programa de cirurgia e traumatologia bucomaxilofacial do Hospital Santa Casa de Misericórdia de Piracicaba - SP.

Luiz Carlos Ferreira da Silva. Possui graduação em Odontologia pela Universidade Federal de Sergipe (1989), Mestrado em Patologia Oral pela Universidade Federal do Rio Grande do Norte (2000), Doutorado em Cirurgia Buco-Maxilo-Facial pela Universidade de Pernambuco (2006) e Fellow em Cirurgia Maxilo-Facial pela Duke University (USA). É Professor Associado de Cirurgia Buco-Maxilo-Facial da Universidade Federal de Sergipe, Coordenador do Serviço de Cirurgia Buco-Maxilo-Facial do Hospital Primavera e atende em clínica privada (Sorcise) e no Hospital da Polícia Militar. Tem prática exclusiva em Cirurgia Buco-Maxilo-Facial, atuando principalmente nos seguintes temas: patologia oral, terceiros molares, cirurgia ortognática e implantes.

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