TRABAJO DE FIN DE GRADO

Grado en Odontología

Can't Stop this Bleeding: Management of Anticoagulated Patients in Dental Clinics

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Número identificativo 145

Abbreviations

NOAC	New Oral Anti-Coagulant
PT	Prothrombin Time
INR	International Normalized Ratio
UF	Unfractionned heparin
LMWH	Low Molecular Weight Heparin

Resumen

Introducción:

La hemostasia es el proceso de prevenir o detener el sangrado de un vaso sanguíneo para volver a la circulación sanguínea normal. La etiología de los trastornos hemorrágicos parece ser más multifactorial. Un tejido dañado dará lugar a una secuencia de activación fisiológica y molecular que evita una situación hemorrágica. La formación del coágulo de sangre estará respaldada por el proceso regulador. La hemostasia incluye 3 pasos principales: en primer lugar, la constricción del vaso sanguíneo. En segundo lugar, la formación de un tapón plaquetario temporal. Y finalmente, se logrará la activación de la cascada de coagulación y la formación del tapón de fibrina.

Objetivos:

Este trabajo tendrá como principal objetivo evaluar los múltiples riesgos y beneficios que podrían beneficiarse de la interrupción del tratamiento anticoagulante o antiagregante plaquetario antes del tratamiento odontológico. En segundo lugar, se discutirá en profundidad el manejo del sangrado, insistiendo en las distintas terapias existentes y mencionando también la interacción farmacológica. Por último, se destacarán varias situaciones de emergencia con el fin de concienciar al lector de las limitaciones existentes.

Materiales y métodos:

Para llevar a cabo la siguiente revisión de la literatura, se llevó a cabo una investigación exhaustiva utilizando bases de datos científicas confiables como PubMed, Medline y sitios web de ADA que cubren todos los estudios no mayores de 15 años en inglés, francés y español y utilizando las siguientes palabras clave: hemostasia, medicamentos antiplaquetarios, anticoagulantes, manejo, sangrado, anticoagulantes orales directos, cirugía, nuevos anticoagulantes orales.

Resultados, discusión y Conclusión:

Para minimizar el riesgo de hemorragia durante los procedimientos dentales, se han establecido muchos protocolos de manejo junto con una historia clínica completa y pruebas hemostáticas. La mayoría de los autores recomiendan no suspender ni alterar la medicación y prefieren el uso de medidas hemostáticas locales, que son suficientes para controlar las probables dificultades hemorrágicas derivadas de un procedimiento dental.

Abstract

Introduction:

Hemostasis is the process of preventing or stopping bleeding from a blood vessel in order to return to normal blood circulation. The etiology of bleeding disorders seems to be more multifactorial. A damage tissue will lead to a physiologic and molecular activation sequence refraining a hemorrhagic situation. The formation of the blood clot will be supported by the regulatory process. Hemostasis includes 3 main steps: firstly, the constriction of the blood vessel. Secondly, the formation of a temporary platelet plug. And finally, the activation of the coagulation cascade and formation of the fibrin plug will be achieved.

Objectives:

This work will primarily aim in evaluating the multiple risks and benefits that could be benefited from the discontinuation of the anticoagulant or antiplatelet therapy prior to dental treatment. Secondly, the bleeding management will be discussed in depth, thus insisting on the various existing therapies and mentioning as well the pharmacological interaction. Lastly, several emergency situations will be highlighted in order to make the reader aware of the existing limitations.

Materials and methods:

To carry out the following litterature review a thorough research was carried out using reliable scientific data bases such as PubMed, Medline and ADA websites covering all studies not exceeding 15 years in English, french and spanish and using the following keywords : hemostasis, antiplatelet drugs, anticoagulants, management, bleeding, direct oral anticoagulants, surgery, new oral anticoagulants.

Results, discussion and conclusion:

To minimize the bleeding risk during the dental procedures many management protocols have been established together with a complete clinical history and hemostatic tests. Most authors recommend not to stop or alter the medication and prefer the use of local hemostatic measures which is sufficient to control probable bleeding difficulties arising from a dental procedure.

Index

I. Introduction

Hemostasis includes all of the blood phenomena that prevent or stop bleeding from a blood vessel allowing normal blood circulation to return.

Nowadays bleeding disorders mostly come from the use of drugs but they seem to be more multifactorial: deficiency states, hereditary and metabolic alterations, cancer, etc.

In the case of tissue damage a vascular breach is found leading to bleeding and triggering a physiological and molecular activation sequence to avoid hemorrhage. Then the regulatory processes will localize the formation of the blood clot on its active site.

Hemostasis can be described schematically in several steps:

- Constriction of the blood vessel:

Immediately after the vascular breach, the vascular smooth muscle will produce a vasoconstriction of the blood vessel in order to reduce bleeding. This phase being not enough to compensate with the loss of blood, it will trigger the second phase with the formation a temporary platelet plug. This mechanism is particularly effective in arteries, but not in veins.

- Formation of a temporary platelet plug

In this phase the platelets will aggregate, adhere to the sub-endothelial collagen and form a temporary platelet plug of the damaged blood vessel. This mechanism is particularly effective in arteries, but much less in veins.

- Activation of the coagulation cascade and formation of the fibrin plug.

In this phase the temporary platelet plug is consolidated by means of fibrin production. The coagulation cascade is composed of 2 pathways: the intrinsic pathway, that begins with the factor

XII released after contact of the subendothelial tissues and the injured blood vessel, the extrinsic pathway will start when the tissue thromboplastin enters in contact with blood releasing the factor VII.

Both will converge into a common pathway thanks to the factor Xa given by both pathways. The transformation of prothrombin (or factor II) into thrombin (or factor IIa) is achieved. The formation of fibrin from fibrinogen happens after thrombin factor is activated.

The hemostasis process is an essential mechanism in all invasive dental treatments, but it can malfunction in many ways and therefore lead to the development of many pathologies. Knowledge of this process and their drugs allows tailoring of care to our patients.

Many drugs help to control the hemostasis process and thus prevent the formation of blood clots or the occurrence of bleeding. These drugs can act on different phases of the hemostasis. The first phase can be controlled using anti-platelet drugs which by his name inhibit the aggregation of platelet and therefore stopping the formation of the platelet plug. On another the anticoagulant drugs will control the second phases of hemostasis by inhibiting the vitamin K reductase which is essential to convert vitamin K epoxide into its active form. Therefore, the coagulation process is stopped because the formation of the coagulation factors will depend on it (1,2).

Many drugs can be used to control the hemostasis of the patient. Oral anticoagulants drugs like warfarin will interfere with vitamin K activation and are used to reduce patient's thromboembolism. Some interactions with food or other drugs can modify the levels of warfarin therefore there is a need to control the INR levels before any surgical procedure. To counter these side effects new oral anticoagulants are used because of their faster onset, shorter half-life, less drug interactions and no need to monitor the INR. Nowadays the new oral anticoagulants (NOACS) have a selective anticoagulant effect. In fact rivaroxaban for example will act by direct inhibition

of the blood clotting factor X while dabigatran will act by direct inhibition of thrombin and there factor II (1).

LMWH will inhibit the coagulation with the boosting of antithrombin III that will bind to factor Xa and inhibit it at the same time. This inactivation will not produce thrombin and therefore no fibrin will be formed for the formation of the clot.

Nowadays there is a growing number of individuals under anticoagulation or anti-platelet medications, acetylsalicylic acid (ASA) and warfarin therapy is the gold standard in the treatment of venous thromboembolism and the prevention of stroke (3). In fact, in 2011, a study by the Health Insurance Fund on the consumption of anticoagulants showed that 4% of the French population had received at least one reimbursement for anticoagulants. The increased bleeding time and risk of postoperative hemorrhage that Antiplatelet and anticoagulant therapy can produce have long been known(4).

The result remains the same, we must be able to control hemorrhage when it occurs during surgical treatment. For this some recommend stopping, reducing or replacing treatments. Others are against it because of the thromboembolic problems that it can lead.

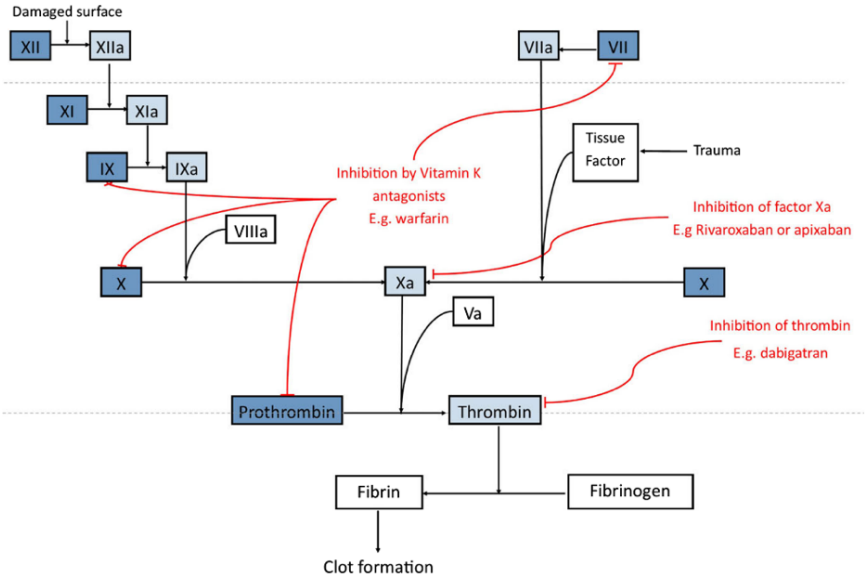

Fig 1: the coagulation cascade and the anticoagulants effects(1).

II. Objectives

Main objective :

- To provide the health care professional with the adequate information and to manage the anticoagulated patients in the dental clinic.

Secondary objectives :

- To understand the physiological mechanism of hemostasis
- To define the different pathological diseases related to hemostasis disfunction
- To determine and understand the mechanisms of the drugs used to control it.

III. Materials and methods

To carry out the following litterature review a thorough research was carried out using reliable scientific data bases such as PubMed, Medline and ADA websites covering all studies using the following keywords : hemostasis, antiplatelet drugs, anticoagulants, management, bleeding, direct oral anticoagulants, surgery, new oral anticoagulants. Combinating the previous keywords allowed us to find some strategies:

- Hemostasis process
- Management of dental patients taking anticoagulants drugs
- Management of dental patients taking antiplatelet drugs
- Management of dental patients taking new oral anticoagulants

Inclusion criteria:

- Articles written in french, english and spanish
- Articles treating new oral anticoagulants
- Articles mostly written in the last 15 years

Exclusion criteria :

- Articles older than 15 years
- Articles not talking about the new oral anticoagulants

IV. Results and Discussion

a) Evaluation of bleeding risk

Dentistry is a medical field in which distinct procedures can be found provoking different bleeding risk in patients taking anticoagulated medication (Figure 1). Nowadays, multiple dental protocoles permit the dental professional to reduce the bleeding risk of their patients. J Lee in 2018 emphazised the concern of dentists towards any hemorrhage complications that could occur even small oral surgeries. It is important to define bleeding complications as it will be frequently observed in the dental practice; it is an extended or abundant bleeding uninhibited by the initial hemostasis (5). The Scottish Dental Clinical Effectiveness Programme (SDCEP) performed a study in which they depicted a classification of dental procedures according to three levels of bleeding risks (6).

Dental procedures that are unlikely to cause bleeding	Dental procedures that are likely to cause bleeding	
	Low bleeding risk procedures	High bleeding risk procedures
• Local anaesthesia by infiltration, intraligamentary or mental nerve block • Local anaesthesia by inferior dental block or other regional nerve blocks • Basic periodontal examination (BPE) • Supragingival removal of plaque, calculus, and stain • Direct or indirect restorations with supragingival margins • Endodontics (orthograde) • Impressions and other prosthetic procedures • Fitting and adjustment of orthodontic appliances	• Simple extractions (1–3, with restricted wound size) • Incision and drainage of intraoral swellings • Detailed six-point full periodontal examination • Root surface instrumentation (RSI) • Direct or indirect restorations with subgingival margins	• Complex extractions, adjacent extractions that will cause a large wound, or more than three extractions at once • Flap raising procedures ○ Elective surgical extractions ○ Periodontal surgery ○ Preprosthetic surgery ○ Periradicular surgery ○ Crown lengthening ○ Dental implant surgery • Gingival recontouring • Biopsies

Fig 2. Bleeding possibilities according to different dental procedures (5-7).

The tendency to bleeding is also influenced by the patient's medical condition. The American Academy of Neurology published evidence-based guidelines. Depending on the patient's individual characterists we are able to weight the risk and benefits. In fact patients will be divided into 2 groups of risks according to their medical condition. For patients presenting ischemic

cerebrovascular disease the medication should'nt be stopped. Patients with ischemic heart disease without coronary stent surgery will be considered as low risk wheres the ones with associated prothestic heart valve and atrial fibrillation will be considered as high risk. An important thing to note is that patients with mechanical prosthetic valve can not benefit the use of NOACS. Moreover the assessment of thromoboembolic risk can be done according to patient's medical condition.

Low thromboembolic risk (<5%)	High thromboembolic risk (≥5%)
Atrial fibrillation with a $CHADS_2$ score[1] of 0-2	Atrial fibrillation with a $CHADS_2$ score[1] of 3-6
Atrial fibrillation with a CHA_2DS_2–VASc score[2] of 0-4	Atrial fibrillation with a CHA_2DS_2–VASc score[2] of 5-9
Prosthetic heart valve without high-risk features[3]	Prosthetic heart valve within 3 months of surgery or with high-risk features[3]
Venous thromboembolism after 3 months of anticoagulation treatment	Venous thromboembolism within the past 3 months
Coronary stents after 1 year of antiplatelet therapy	Coronary stents placement within the past 1 year

[1]$CHADS_2$ score means congestive heart failure, hypertension, age ≥75 years, diabetes, and prior stroke/transient ischemic attack.
[2]Updated version of $CHADS_2$ score.
[3]High-risk features include atrial fibrillation, prior thromboembolism, left ventricular ejection fraction ≤35%, mitral or tricuspid valve placement, ≥2 prosthetic valves, and older aortic ball or tilting disc valves.

Fig 3. Thromboembolic risk stratification (5).

Differenciation should be made regarding the type of medication and the medical disorder that the patient presents. This is the reason why J Armstrong in 2013 stated that patients with ischemic heart disease but who have not undergone coronary stent surgery are considered to be low risk. On the other side, patients presenting both prosthetic heart valve and atrial fibrillation are believed to be high risk (8). Additionally, other authors such as JW. Eikelboom, SJ Connolly and M Brueckmann state that patients with mechanical prosthetic valves cannot be treated with the New Oral Anti Coagulant (9).

SJ Connolly et al highlight that patient taking NOAC have alike or lower risk of hemorrhage compared to patients under warfarin treatment (9–11).

Special care should be taken with patients presenting renal, liver or bone marrow impairement (12). J Lee also cites in his articles that patients should pay attention to aliments such as garlic for instance that could alter the bleeding process (5).

b) Management of bleeding

In the article written by J Lee (5), the author depicts the necessity to follow a strict method in order to reduce bleeding during dental treatments. Dentists should differenciate patients taking medication on a long term compared to newly medicated patients. Thus, the authors explains that in cases with newly medicated patients, the dental procedure can be possibly delayed until the ending of the medication. In patients carrying prosthetic valves such as metallic ones, or even coronary stents, the dentist should offer an interconsultaiton with the patient's cardiologist in order to find an alternative towards the anticoagulation protocole. A special consideration has to be taken towards anti inflammatories as they aggravate bleeding risk. In cases in which the patient is under aspirin only, J Lee (5) underlines the non necessity of stopping it. For instance, the dentist could take precautions to allow a control of the bleeding time by scheduling the patient early on the morning (5). Additionally, it can be analyzed that Y Jimenez et al in 2008 agreed with the study conducted R Sacco et al in 2007 the scheduling of the patients in early morning, thus reducing bleeding problems throughout the daytime (2,13,14).

M Pototski and J Amenábar depict in 2007 the importance of performing procedures at the beginning of the week; therfeore this will allow to retard the re-bleeding. Procedures should also be performed early in the week, allowing for the treatment of delayed re-bleeding outbreaks, which usually take place 24-48 hours after the procedure (4,15). PB Lockhart describe the importance of

using anestesia with vasoconstrictor to reduce the bleeding. This can be applied with two distinct techniques: the infiltrative one or the intraligamentary (12). The total blockage of nerve regions should not be done, nevertheless if no other issue is possible, the use of aspirating seringue is recommended (4). Moreover, the authors underline the possibility to obtain a local vasoconstrictor thanks to the infiltration of local anesthesia nearby the location of the surgery.

NJ McCormick *et al.* state that local mechanical arrest with the use of packaging of the sockets with hemostatic substances and suture is considered as one of the most helpful hemostatic methods (5,16). Consequently, PB Lockhart *et al.* also state the same method; they underline the importance of packing the sockets with absorbable hemostatic materials and then suture it prudently (4,12,15). C Scully *et al.* describe that resorbable sutures are prefered as they capture less plaque (4,15). In case of using non resorbable sutures, the authors consider the necessity to eliminate them after 4-7 days (15). Afterwards, compression should be made on the site with the use of a gauze pad, making the patient bite on the gauze for approximatly an average of 15 to 30 minutes (4). Besides, other authors prefer reabsorbable sutures, they state that they reduce the trauma and decrease the hemorrage as they do not need to be removed (17–19).

Many authors have depicted a similarly strict protocole to follow in order to decrease post-operative complication thus improving bleeding control. For instance, other authors such as A. Mingarro-de-León, B Chaveli López recommend the application of pressure for at least 30-40 minutes (2,4,12,15). The same authors underline the importance of the patients compliance; for instance A Mingarro-de-León depicts that the patient should not perform oral rinses during the first day after his surgery. Moreover, he highlights the necessity to adopt a diet containing soft and cold food. This author emphasizes on the patient's awareness towards the non performance of suctioning movements. The patient should not perfom digital pressure on the region of the tooth, neither with

his tongue (2). Moreoever, Scully and Cawson insist on the same protocole, however they add some instructions. They accentuate the importance of non chewing on the surgical side in order to stabilize the clot (4,15). M Pototski mentions that the patient should importantly contact his dentist if the bleeding persists (4). The professional should make the procedure as least traumatic as possible and bleeding management should be done through local procedures (4).

Multiple authors have different vision regarding the management of bleeding patients; for instance many of them aim on reducing the post operative bleeding controlling it through the use of acceptable hemostatic measure (2). On the other hand, some authors favor the stopping of the patient's therapy in order to reduce post-operative hemorrhage (2,20,21). Therefore it can be understood that there is a lack of agreement between the authors in the management of patients under anticoagulant/antiplatelet treatment. Some recommend to stop or reduce the treatment 2-3 days before any dental procedure that involves bleeding. Nowadays the most useful method is to use local hemostatic procedures like packing of open sockets with hemostatic material and suture after dental procedures rather than stoping the treatment (2). Since 2007, multiple authors have agreed to act towards a more conservative method. GB Ferrieri *et al.* favoured not to act on the patient's anticoagulant or antiplatelet therapy; they would rather regulate hemorrhage using local hemostatic techniques (14,18,22,23). Additionally, Lockhart states that the use of hemostatic measures could avoid the changing of the patient's antiplatelet or anticoagulant therapy (12); some example should be stated such as post operative tranexamic acid rinses in order to consolidate the clot. IL Evans *et al.*, C Mendez *et al.*, DJ Aframian *et al.*, M Pototski *et al.* underline that Amchafibrin® avoids plasminogen activation and therefore fibrinolysis (4,19,24,25). Additionally, it does not seem to present much side effects and is very well tolerated (25). DJ Aframian states that the rinses should be performed at least twice a day during the first 48 hours after the operation

(12,19). On the other hand, other authors favor the use of tranexamic acid embedded gauzes rather than solutions; they argue saying that rinses could produce a dissociation of the clot thus counterbalancing the result of the antifibrinolytic (22,26). It is important to highlight that countries such as Japan do not reflect tranexamic acid as being a local hemostasis (23) or countries that do not offer it to their patients such as the United Kingdom (12).

The patients receiving antiplatelet or anticoagulant treatment are considered as special patients in our clinical practice. In fact two mainly parameters will condition our management: the type of drug taken by the patient and the level of the risk of the dental prodecure.

- Patients under Low Molecular Weight Heparin (LMWH)

R Goel *et al.* highlight that in the early 1930s, medical doctors handled heparin as an anticoagulant (1,27). Nevertheless, they only administer it intravenously and the necessity of an important monitoring is essential. Scully *et al.* assess that heparin is usually used in patients presenting acute thromboembolic situations or for instance in patients necessiting an hospital admission after an important surgery (1,15). In the pharmaceutical area, 2 types of heparin can be found: dalteparin and enoxaparin; authors affirm that their use could be single or twice per day. It is important to understand the way of action of heparin; it's action is done by inhibiting factors IXa, Xa, and thrombin, which will thus avoid the coagulation of blood. In order to do so, it will bind to an antithrombin. Consequently the thrombin fibrinogen reaction is hindered. Notwithstanding their consequences for coagulation, heparin will also avoid thrombin induced platelet activation (28,29). According to Suryanarayan *et al.*, heparin is classified according to two types: the unfractionated heparin (UF) and the low molecular weight heparin (LMWH) (28,29). On one hand the

unfractioned heparin can lasts 6 hours which is short and can produce thrombocytopenia induced due to heparin. On the other hand the low molecular weight heparin lasts longer with higher bioavailibity as it binds less to proteins therefore reducing antiplatelet effects (1,28–30).

It is important to highlight the insufficiency in guidelines concerning the management of dental patients taking heparin oblige patients to have an interconsultation with the doctor prior to dental treatment. Patients presenting chronic renal failure used to be treated with heparin during dialysis (5). That's why a special care to those patients needs to be done: the dental treatment will be delayed on the day after the dialysis.

- Patients taking oral anticoagulants

Vitamin K antagonists that include warfarin and indaniodine derivatives have been used for more than 50 years; although they presented various adverse effects and interactions with drugs and foods, they were the only available oral anticoagulants at that time (27). These medications allowed us to partly surmount the fact that heparin was only available parenteraly. Therefore, warfarin is the most commonly used vitamin K antagonist (4). Many authors describe the action of Vitamin k as it is useful for the synthesis of the clotting factors II,VII and IX (4,15,28). The production of endogenous anticoagulant protein C and S are also dependent on vitamin K (28). The absence of this vitamin K or the presence of its antagonist will promote a decrease in the rate of factors and protein production consequently leading to anticoagulation (4). Warfarin presents two actions which are an anticoagulant effect and an antithrombotic. When doctors prescribe warfarin in it's therapeutic range, it will subsequently reduce the formation of Vitamin K to a mean range of 30 to 50% (4,31). This will lead to a decrease in the biological activity of the clotting factors and finally the coagulation systeme will be functionally scarce (31). Its absorption is reached through

the gastrointestinal tract and the highest level of plasma concentration is reached around 60-90 minutes after the administration (15,27,28). It works by binding to the vitamin K reductase inhibiting the synthesis of Vitamin K. Warfarin will decrease consequently the thrombin, and factors VII, IX X and protheins C and S (1). The absorbtion is quiet fast, nevertheless the antithrombic effect will begin it's action around approximatelly 8-12h after the administration reaching the peak at 36 hours and the reduction of the coagulation factors will not occur until the 5th day. Therefore, in situations in which a fast anticoagulation effect is needed, heparin will be used (30). Due to the liver metabolism of warfarin and because of its narrow therapeutic range, a close monitoring and adjustment of the dose is needed in order to achieve our therapeutic goal: a balance between anticoagulation and coagulation is need to be achieved (2). Multiple authors such as Dézsi *et al.* (6) highlight that the general consensus about treatments involving Vitamin K antagonist will be not to stop the antithtrombotic therapy before dental procedures (6,32). The guidelines of the American College of Chest Physicians (ACCP) recommend dental surgery without stoping the Vitamin K antagonist treatment but with the additional use of hemostatic measures (33). The british guidelines strenghtens the american guidelines regarding not altering the anticoagulation treatment for most of the patients with the need of dental surgery (6). Patients receiving oral Vitamin K anticoagulants requires a periodic monitoring using the INR rather than the Prothrombin Time because sometimes it can be imprecise and therefore offer contradicting values. If the patient's INR is stable, it will be checked 72 hours prior to the dental procedure. On the contrary if the patient presents an instable, the INR it should be checked 24 hours prior to the intervention (34–36). Stable INR means that the INR is less than 4 during the last 2 months and subsequent delay will be done in dental treatment until the patient is stabilized by means of

anticoagulation treatment (6). It's also recommended to treat the patient in separate visits and limit the treatment when dealing with high bleeding risk procedures (5).

The recommended INR is between 2-3 except for patients with heart valve implants; in that case it will have to be maintained between 2.5 and 3.5. Many articles compared a control group in which the anticoagulant was stopped and another experimental group in which it was maintained (2).

In the five studies performed by Evans *et al.* (24), Méndez *et al.* (25), Al-Mubarack *et al.* (37), Sacco *et al.* (14) and Bajkin *et al.* (38) no considerable differences were observed regarding bleeding in one or another group. These results support the American College of Chest Physicians and the British guidelines on the fact that the suspension or reduction of the treatment is not necessary if the INR is below 3.5 and when dealing with procedures that are unlikely to cause bleeding, for low and high bleeding dental procedures as the use of hemostatic measures are sufficient. If the INR is above 3.5 and when dealing with low and high bleeding dental procedures: they can be delayed until reaching adequate INR level. Two other options are also available : the suspension of anticoagulant treatment 2-3 days before surgery can be done or the replacement of oral anticoagulant by LMWH and the restart of OAC after 12 hours (6).

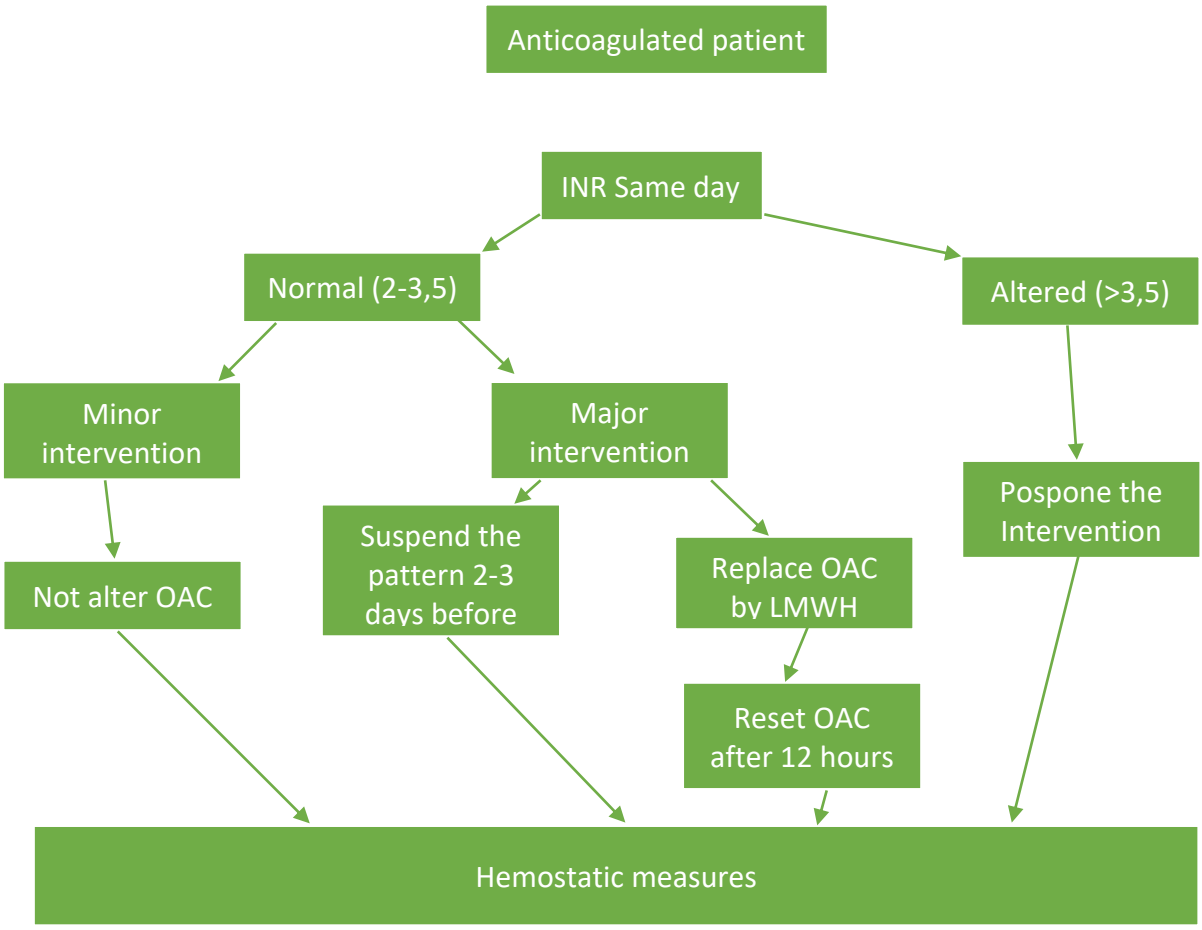

Fig 4. Procedure to follow according to patients INR (2).

- Patients taking new oral anticoagulants

New oral anticoagulant, or also known as direct oral anticoagulant, is an antirhombotic medication which acts directly on a bleeding factor called thrombin (Factor Xa) (30,39). Therefore, the next oral anticoagulant avoid the apparition of thrombin formation, therfore inhibiting the creation of the fibrin meshwork. In order to do so, the NOAC will avoid the transofrmation of fibrinogen into fibrin, thus decreasing the aggregation of the thrombin induced by platelets (40). Previous studies

were conducted in the finding of a direct thrombin inhbitor, nevertheless it presented important hepatitic toxicity, thus in 2006 it was removed from the market (28,30,39). Therefore in 2008, they approved the use of Dabigatran and Rivaroxaban as a diret thrombin inhibitor, their onset is respectively in a range of 30 minutes and 1-4 hours, and can both be administered orally (27,30,41,42).

The direct oral anticoagulants are indicated in the prevention of stroke, systemic embolization in non valvular atrial fibrillation, venous thromboembolism prophylaxis after orthopedic surgery, hospitalized patients and the mangament of acute coronary syndrome. They are also used in the treatment of deep vein thrombosis and pulmonary embolism. Adjustement of the dose in needed in old patients and patients with renal impairement (6).

However, nowadays it is hard to control their action and they are usually irrelevant data when performed Prothrombin time or INR evaluations on patients taking NOAC (43). But, these drugs present a higher stability in anticoagulation compared to Warfarin for example (44). Their onset is faster and their half life is also shorter in comparaison to Warfarin (5). Therefore their rapidity does not need such a drastic checking. Based on early data it would appear that suspension or dose modification of the anticoagulant is not necessary for procedures with normal or low risk of bleeding and without renal impairment . However, for procedures with a high risk of bleeding it is advisable to suspend the anticoagulant 24 hours prior to dental treatment and to resume it 24 hours later (6).

- Patients taking antiplatelets

Antiplatelets are medication that are frequently recommended to patients in order to avoid arteriovenous thrombosis. These patients can usually present numerous pathologies such as ischemic heart disease, heart stents, heart valves. These patients also have the risk to undergo cerebrovascular episodes for instance stroke could be an example (2). Multilple authors state that this antiplatelet medication has been recognized as being an acceptable antithrombotic therapy, as they inhibit platelet function (2,45). M. Pototski *et al.* mention that the mostly prescribed drugs used in pharmaceutics are clopidrogel, dipyridamole and acetylsalicylic (4).

Due to their high risk of producing hemorrhagic consequences, doctors prefer suspending the antiplatelet therapy prior to the surgery, deprieving the thrombotic risk that the patient could present post operatively (2). On the other hand other authors such as Aframmian *et al.* disagree and state that the hemorrhagic risk that could happen due to this medication has been overstated, simultanesouly, undervaluing the chance of a thrombotic phenonemon (19).

Therefore, T Lillis *et al.* (45), GA Madan *et al.* (46) and DJ Aframian *et al.* (19) suggest that the patient should not stop the antiplatelet medication as the chance of producing a thromboembolism is more dangerous than an increase of bleeding.

Nowadays, there is not an adequate measurement method in order to assess the hemorrhagic outcome of the antiplatelet pmedication. Thus, authors such as Lee *et al.* express that patients being under a dual antiplatelet therapy have a higher risk of post up bleeding compared to patients only taking one anti-platelet medication (such as Aspirin for example). Nonetheless, it is recommended for the patient not to interrupt his antiplatelet therapy (5,8,33,47). A special consideration should be taken to patient who have had a coronary stent surgical procedure, therefore their medication should be continued for 12 following months (5).

Treatment planning must be thoroughly performed prior to any surgical procedure; accordingly patients who take Aspirin will be restricted to a single tooth extraction or for example scaling and root planing of a maximum of three dental elements. If further dental interventions are needed with an increased bleeding expectency, the treatment must be divided in multiple steps. Additionally, methods should be taken such as for example local hemostatic preventions with the use of sutures or packing (5).

Currently, patients that are under DAPT are usually taking Aspirin combined with clopidrogel, the hemostasis can appear 60 minutes later, thus a previous restriction protocole, similar to the one mentionned for patients under Aspirin must be undertaken (5).

In patients presenting complicated pathologies such as for example atrial fibrilliation, they might also be developping other pathologies such as ischemic heart pathologies. Thus, in that case, the patients have a high probability of presenting post-operative hemorrhagic episodes. Consequently, the dentist will refer the patient to his physician in order to avoid any non expectant complication.

c) Pharmacological interaction of anti thrombotic drugs with other drugs.

The concomittant prescription of drugs such as antibiotics or analgesics in patients under anti-thrombotic medication is quiet common. Particular precautions regarding the interactions of those drugs with anti thrombotic drugs need to be taken. A table representing the different risks of interactions of anticoagulant or antiplatelet drugs with other drugs is presented (5,7).

Oral anticoagulants	
Warfarin	Amoxicillin
Phenindione	Metronydazole Erythomycin Clarythromycin
Acenocoumarol	Aspirin Ibuprofen Diclofenac Carbamazepine Miconazole Fluconazole
Oral antiplatelets	
Aspirin	Ibuprofen Diclofenac
Clopidrogel	Aspirin Ibuprofen Diclofenac Erythromycin Carbamazepine Fluconazole Omeprazole
Dipyridamole	Aspirin
Presugrel	Aspirin Ibuprofen Diclofenac
Ticagrelor	Aspirin Ibuprofen Diclofenac Carbamazepine
NOACs	

Apixaban	Aspirin Ibuprofen Diclofenac Carbamazepine
Dabigatran	Aspirin Ibuprofen Diclofenac Clarythromycin Carbamazepine
Rivaroxaban	Aspirin Ibuprofen Diclofenac Carbamazepine
Injectable anticoagulant **Dalteparin**	Aspirin Ibuprofen Diclofenac
Enoxaparin	Aspirin Ibuprofen Diclofenac

Fig 5. interactions of anti coagulants medications with most the common prescribed drugs by the dentists (5,7)

In red : the medication that increase the haemorragic possibility

In green : the medication that decrease the haemorragic possibility

d) Emergency situations

Critical circumstances can appear such as for instance in patients presenting an INR higher than 5, in situations necessiting emergency interventions, or for example in patints presenting head wounds. In these cases, the practionner might need to counterbalance the effect of the anticoagulant therapy in order to avoid drastic bleeding (1,27,48–50). Although this sutations are infrequent and occasional, it is important to be conscient of them in order to reduce hemorrhagic episodes (1).

In cases were post-operative hemorrhagic can occur, it is first important to act locally, just as previously mentionned using packed gauzes, sutures etc. Then in a second step the professional will consider the possibility of using reversal products in order to decrease the persistent bleeding (1,39). It is therefore important to state the various reversal agents depending on the antithrombotic therapy that the patient is following. D Suryanaray *et al.*, C Scully *et al.* and A Schlitt *et al.* highlight in their various studies that the use of Vitamin K is very efficient in order to reverse the anticoagulant effect of Warfarin (15,28,49); between 1 to 2 milligrammes of oral or intravenous Vitamin K will be able to bring back the INR to a normal value between 12 to 24 hours (49). In some critical situations, the patient might be presenting an INR higher than 9, therefore in these cases D Suryanaray *et al.* and A. Schlitt *et al.* recommend the use of higher doses of vitamin K (28,49).

Nevertheless it is important to be aware that excessive bleeding can be lethal and fast effect is desired. Therefore, R Goel *et al.*, D Suryanaray *et al.* and C Scully *et al.* insist on using fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) (15,27,28) as they will offer a quick result. New oral anti coagulant therapy do not present a specific reversal medication; tests are still

done in order to achieve it (1). For example, many studies use Factor VII as a reversal agent for dabigatran and rivaroxaban, but discrepancy is still present (27,48,51).

e) Limitations

A lack of standardization can be noticed through the study of the previous articles. For instance, some of them consider patients with various range ages and do not define a specific limitation of it. Additionally, many articles written by authors consider in their studies different number of patients, and this lack of uniformity could therefore promote errors, making us reach different conclusions.

V. Conclusion

Through the redaction of this literature review, it can be understood that multiple protocols are available in order to manage patients with hemorrhagic complications in the dental clinic. Therefore, there is a lack of evidence in order to offer the professional with a gold standard protocole. Additionnally, multiple factors play an significant role such as for example the medication that the patient takes, his systemic pathologies, his associated drugs, the type of intervention that needs to be performed and also his INR and PT, if they are controlled or not. For this reason fluent comunication btween dentists and specialists precribing anticoagulants is warranted or a good management of anticoagulaed patients that need a dental intervention.

Besides, it can be noted that multiple dental treatment do not need a disruption of the anticoagulated or antithrombotic therapy, through the use of local hemostatic measure (sutures or packing with gauzes), bleeding control can be easily preformed. We can also conclude that new oral anticoagulant do not present a specific antidote and specific guideline to counteract their effect in cases needed. It is important to be aware of the pros and the cons; for instance it is true that

hemorrhagic complications can produce apprehension to the patient and the professional, however they are less dangerous than the appearance of thromboembolic complications. Therefore, multiple future scientific studies are desired in order to conclude with an optium therapeutic guideline regarding the management of patients receiving anticoagulant or antithrombotic therapy.

Social responsibility

Nowadays, multiple patients follow diverse anti thrombotic and anti coagulant therapy in order to regulate their bleeding problems. Therefore, the management of anticoagulated patients is highly important due to its high prevalence. Additionally, these patients can often present adverse situations in the dental clinic; these should be more highlithed in the scientific literature.

It is of one's right to be treated accordingly to its pathologies, and clinicians should be highly aware of the evaluation, the management and the multiple drug interactions that could be present in these patients.

On the other hand, some of these patients could potentially come to the dental office due to an emergency situation, thus bringing even more importance over this subject.

Therefore, this thesis brings an important social sustainability as it affects the patient's quality of life.

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VII. Annexes

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Anticoagulant therapy and its impact on dental patients: a review

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ABSTRACT

Several new oral anticoagulants have been studied in the past decade, and have now started to enter the market. These drugs are reported to be as effective as, or more effective than, warfarin. In Australia, the Therapeutic Goods Administration has approved dabigatran, rivaroxaban and apixaban. The use of these newer anticoagulants is likely to increase in time, and it is important for dentists to have a sound understanding of the mechanisms of action, reversal strategies, and management guidelines for patients taking oral anticoagulants. This article discusses the process of coagulation, available anticoagulants and their monitoring and reversal, and provides clinical advice on the management of patients on anticoagulants who require dental treatment.

Keywords: Anticoagulants, bleeding, dabigatran, oral surgery, rivaroxaban.

Abbreviations and acronyms: APC = activated protein; aPTT = activated partial thromboplastin; DVT = deep vein thrombosis; FFP = fresh frozen plasma; ING = international normalized ratio; LMW = low-molecular weight; NOAC = novel oral anticoagulants; PCC = prothombin complex concentrate; PT = prothombin time; TF = tissue factor; TFPI = tissue factor pathway inhibitor; TGA = Therapeutic Goods Administration; UFH = unfractionated heparin; VKA = vitamin K antagonists; VTE = venous thromboembolism.

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INTRODUCTION

The use of anticoagulants is common in the management and prophylaxis of thromboembolic disease. The indications for their use include the prevention and treatment of venous thromboembolism (prior thromboembolism, immobilized patients, patients after major surgery, etc.), and the prevention of embolic stroke (patients with non-valvular atrial fibrillation, prosthetic heart valves).[1–5]

Anticoagulants work by altering the physiological procoagulant and anticoagulant pathways.[6] This is achieved in two ways; by preventing the formation of a clot, and by slowing the progression of an existing clot.[7] The mechanisms of existing anticoagulant agents are based on our understanding of the coagulation cascade, and with an improved understanding of pharmacology and coagulation pathways, there has been a recent trend towards more specific anticoagulant therapy.[4,7] This trend has occurred due to the limitations of older anticoagulants, such as heparins and vitamin K antagonists (VKA), which can have a narrow therapeutic window and an unpredictable effect on coagulation, requiring laboratory monitoring to ensure safety and efficacy.[1,4,6–9]

One of the most commonly encountered anticoagulants in Australia remains warfarin, despite its unpredictable pharmacological nature.[10] The ability of warfarin to be administered orally meant that it remained the first-choice anticoagulant, over parenteral alternatives such as heparin. If warfarin is managed carefully, it is highly effective in the management of thromboembolic disease, but the need for frequent monitoring of a patient's international normalized ratio (INR) is a drawback. Non-compliance with warfarin therapy and INR measurement can result in patients receiving suboptimal anticoagulation, with an increased risk of either thromboembolic events or uncontrolled bleeding.

Due to the problems associated with warfarin's narrow therapeutic range, and its numerous food-drug and drug-drug interactions, alternatives have been developed to provide a convenient, predictable anticoagulant which can be taken orally.[3,7,8,11] A number of these medications, termed novel oral anticoagulants (NOACs), have been approved for use in Australia by the Therapeutic Goods Administration (TGA). The drugs that have been approved by the TGA at this time are dabigatran (Pradaxa®), rivaroxaban (Xarelto®) and apixaban (Eliquis®), and they are

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Dental management of patients receiving anticoagulant and/or antiplatelet treatment

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Abstract

Introduction: Adequate hemostasis is crucial for the success of invasive dental treatment, since bleeding problems can give rise to complications associated with important morbidity-mortality. The dental treatment of patients who tend to an increased risk of bleeding due to the use of anticoagulant and/or antiplatelet drugs raises a challenge in the daily practice of dental professionals. Adequate knowledge of the mechanisms underlying hemostasis, and the optimized management of such patients, are therefore very important issues.

Objectives: A study is made of the anticoagulant / antiplatelet drugs currently available on the market, with evaluation of the risks and benefits of suspending such drugs prior to invasive dental treatment. In addition, a review is made of the current management protocols used in these patients.

Material and Methods: A literature search was made in the PubMed, Cochrane Library and Scopus databases, covering all studies published in the last 5 years in English and Spanish. Studies conducted in humans and with scientific evidence levels 1 and 2 (metaanalyses, systematic reviews, randomized phase 1 and 2 trials, cohort studies and case-control studies) were considered. The keywords used for the search were: tooth extraction, oral surgery, hemostasis, platelet aggregation inhibitors, antiplatelet drugs, anticoagulants, warfarin, acenocoumarol.

Results and Conclusions: Many management protocols have been developed, though in all cases a full clinical history is required, together with complementary hemostatic tests to minimize any risks derived from dental treatment. Many authors consider that patient medication indicated for the treatment of background disease should not be altered or suspended unless so indicated by the prescribing physician. Local hemostatic measures have been shown to suffice for controlling possible bleeding problems resulting from dental treatment.

Key words: *Tooth extraction, oral surgery, hemostasis, platelet aggregation inhibitors, antiplatelet drugs, anticoagulants, warfarin, acenocoumarol.*

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ORIGINAL ARTICLE

Perioperative management of oral anticoagulated patients undergoing an oral, implant, or periodontal procedure: a survey of practices of members of two dental scientific societies, the PRADICO study

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Abstract

Objectives Studies on the perioperative management of patients on direct oral anticoagulants (DOACs) receiving oral invasive procedures are sparse. Moreover, the recommendations of the scientific societies on DOACs are discordant, and the practices are highly variable. We conducted a survey of general and specialized dentists in France to compare their practices concerning the management of patients receiving vitamin K antagonists (VKAs) and DOACs.

Materials and Methods Members of two dental surgical societies were invited to participate in the survey. One hundred forty-one practitioners answered an online questionnaire focusing on the periprocedural management of oral anticoagulated patients (participation rate, 17.8%).

Results Practitioners at hospitals or mixed practices and specialists treated significantly more anticoagulated patients and more frequently performed procedures with high hemorrhagic risk than practitioners with private practice and general dentists. Greater than 90% of practitioners did not modify the treatment for patients on VKAs and controlled the International Normalized Ratio (INR) preoperatively. Regarding DOACs, 62.9% of practitioners did not change the treatment, 70.8% did not prescribe any biological tests, and 13.9% prescribed an INR. Practitioners at hospitals and mixed practices and specialists had better training and knowledge about DOACs.

Conclusions This survey showed that anticoagulated patients were managed mostly by specialists in private or hospital care, notably when requiring oral procedures at high hemorrhagic risk.

Clinical relevance A growing proportion of anticoagulated patients are being treated by dentists in primary care. Consequently, they need training, especially concerning DOACs. Additionally, consensus recommendations are necessary for better coordination of stakeholders and patient safety.

Trial registration on ClinicalTrials.gov: NCT03150303.

Keywords Periprocedural management · Practices · Survey · Oral surgery · Anticoagulants · Vitamin K antagonists · Direct oral anticoagulants

Introduction

Oral anticoagulant therapy is the cornerstone for treating venous thromboembolism and for preventing atrial fibrillation-related stroke. Vitamin K antagonists (VKAs) have been the reference oral anticoagulants for several decennials. In 2011, a study of the Health Insurance Fund on anticoagulant consumption showed that 4% of the French population has received at least one anticoagulant refund [1]. Direct oral anticoagulants (DOACs) have been licensed since 2009 for medical indications. In 2013, they became available in France; since then, their prescription has been increasing dramatically. The majority of patients receiving anticoagulants were on VKAs, but a large number of patients initiated on anticoagulant were started on DOACs (more than 1 million patients on

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Review

Dental management of patients receiving anticoagulation or antiplatelet treatment

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Abstract: Antiplatelet and anticoagulant agents have been extensively researched and developed as potential therapies in the prevention and management of arterial and venous thrombosis. On the other hand, antiplatelet and anticoagulant drugs have also been associated with an increase in the bleeding time and risk of postoperative hemorrhage. Because of this, some dentists still recommend the patient to stop the therapy for at least 3 days before any oral surgical procedure. However, stopping the use of these drugs exposes the patient to vascular problems, with the potential for significant morbidity. This article reviews the main antiplatelet and anticoagulant drugs in use today and explains the dental management of patients on these drugs, when subjected to minor oral surgery procedures. It can be concluded that the optimal INR value for dental surgical procedures is 2.5 because it minimizes the risk of either hemorrhage or thromboembolism. Nevertheless, minor oral surgical procedures, such as biopsies, tooth extraction and periodontal surgery, can safely be done with an INR lower than 4.0. (J. Oral Sci. 49, 253-258, 2007)

Keywords: antiplatelet; anticoagulants; INR; oral surgery; dentistry.

Introduction

Thrombotic and thromboembolic occlusions of blood vessels are the main cause of ischaemic events in heart, lungs and brain (1). Since the observation that thrombi occluding arteries were rich in platelets, antiplatelet agents and anticoagulants have been extensively researched and developed as potential therapies for the prevention and management of arterial thrombosis (1). Platelet activation and aggregation is considered to be central to arterial thrombus production (2). Platelets are the 'major players' in arterial thrombosis and therefore are attractive targets in the prevention and treatment of cardiovascular diseases such as myocardial infarction, cerebral ischemia and peripheral arterial insufficiency (1).

Even though several antiplatelet and anticoagulant agents have been developed in recent years, acetylsalicylic acid (ASA) and warfarin are the standard drugs for preventing vascular diseases (3).

Antiplatelet and anticoagulant therapies have long been associated with an increase in the bleeding time and risk of postoperative hemorrhage. Typically, it is recommended that the patient stops the therapy 3 days before any surgical procedure. This article reviews the main antiplatelet and anticoagulants drugs in use today and explains the dental management of these patients when submitted to oral surgery procedures.

Blood clotting

The blood clotting mechanism is initiated by one of two pathways: intrinsic and extrinsic. In both cases, this is a cascaded reaction sequence in which inactive factors become activated and catalyze the formation of products from precursors, which in turn activate more factors until the final products are formed. The intrinsic pathway is initiated by damage, or alteration, to blood independent of contact with damaged tissue, whereas the extrinsic pathway is initiated by exposure to factors derived from damaged tissue (4).

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INVITED REVIEW ARTICLE

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Dental management of patients on anti-thrombotic agents

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Abstract (J Korean Assoc Oral Maxillofac Surg 2018;44:143-150)

The number of geriatric patients seeking dental service is ever-rising because of increased life expectancy, also with problem of increased chronic medical conditions. One of them are patients on anti-thrombotic medication. Bleeding complication after minor oral surgery by anti-thrombotic agents is of concerns to dentists on dental management of these patients. Risk and benefit of the anti-thrombotic agents must be weighed before initiating dental procedures, which should be established as a treatment guideline. Purpose of the paper is to optimize the management of the dental patients on anti-thrombotic medication via standardization of treatment protocol of such a patient.

Key words: Anti-thrombotic, Anti-coagulant, Anti-platelet, Minor oral surgery

[paper submitted 2018. 7. 10 / accepted 2018. 7. 10]

I. Introduction

Thromboembolism in acute coronary syndrome or atrial fibrillation is largely prevented by anti-thrombotic agents[1,2]. However, bleeding complications related to these agents after minor oral surgery is of concern to dentists for dental management of these patients. Risks and benefits of the anti-thrombotic agents must be weighed before initiating dental procedures, which should be established as treatment guidelines. The purpose of this paper is to optimize the management of dental patients on anti-thrombotic medication via standardized treatment protocols. The target readership of the paper is undergraduate and postgraduate dental students, general dental practitioners, trainees and residents of oral and maxillofacial surgery, and oral and maxillofacial surgeons.

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II. Background

Hemostasis occurs as a result of the interaction of the components of Virchow's triad, namely endothelial cells, blood composition and vascular flow. Interplay of these three factors determines the chance of thrombotic accident. Arterial thrombosis is related to platelet-rich white clots, whereas venous thrombosis is related to fibrin-rich red clots[3]. Anti-thrombotic agents are classified into two categories, anti-platelets and anti-coagulants, which are listed in Table 1[4]. While anti-platelet agents inhibit platelet aggregation, anti-coagulant agents block the coagulation cascade after platelet aggregation. Anti-platelet agents are useful for the prevention and treatment of platelet-rich white clot formation, whereas anti-coagulant agents prevent and treat venous thromboembolism. Currently popular anti-thrombotic agents in Korea will be discussed briefly.

1. Anti-platelet agents

1) Aspirin (Astrix)

Aspirin is an anti-inflammatory drug that inhibits the cyclooxygenase pathway of arachidonic acid, which is mobilized in the inner cellular membrane[5]. In inhibiting this pathway, aspirin also inhibits the production of thromboxane, making it a standard for treatment of ischemic heart diseases. It can be used as a single load or used in combination with clopidogrel

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REVIEW ARTICLE

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Management of dental patients receiving antiplatelet therapy or chronic oral anticoagulation: A review of the latest evidence

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KEY MESSAGES

- Most dental interventions can be safely performed without the alteration of antiplatelet therapy or anticoagulant therapy in patients taking direct oral anticoagulants or vitamin K antagonists.
- Before high bleeding risk procedures, missing one dose of direct oral anticoagulants on the morning of the intervention may be recommended.

ABSTRACT

The perioperative management of patients treated with antithrombotic medications who undergo surgical procedures represents a common clinical problem. Dental interventions are usually associated with a low risk of bleeding; however, the dental implications of new antithrombotic agents are not yet fully understood. The present review is based on the latest evidence and recommendations published on the periprocedural management of dental patients treated with single or dual antiplatelet therapy, vitamin K antagonists, or direct oral anticoagulants for a variety of indications.

Abbreviations: ACCP: American College of Chest Physicians; ACS: acute coronary syndrome; ADP: adenosine diphosphate; BPE: basic periodontal examination; CrCl: creatinine clearance; DAPT: dual antiplatelet therapy; DVT: deep vein thrombosis; DOAC: direct oral anticoagulant; ICD: implantable cardioverter defibrillator; INR: international normalized ratio; NOAC: novel oral anticoagulant; NVAF: non-valvular atrial fibrillation; PCI: percutaneous coronary intervention; PE: pulmonary embolism; RSI: root surface instrumentation; SDCEP: The Scottish Dental Clinical Effectiveness Programme; TURP: transurethral resection of the prostate; VKA: vitamin K antagonist; VTE: venous thromboembolism

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KEYWORDS
Antiplatelet therapy; vitamin K antagonists; direct oral anticoagulant; dental interventions; periprocedural management

Introduction

Most practical recommendations consider dental procedures as minor interventions associated with a low risk of bleeding and self-limited blood loss that can be managed with local haemostatic agents [1–3]. However, certain interventions, such as dental reconstruction surgery, may require the temporary discontinuation of antithrombotic therapy. Therefore, it may not be appropriate to handle dental procedures as a homogeneous group when it comes to assessing the risk of bleeding. The Scottish Dental Clinical Effectiveness Programme (SDCEP) guidance provides a comprehensive classification of dental interventions based on the associated bleeding risks (Table 1) [2].

Due to the increasing life expectancy and the ageing of the population, the periprocedural management of patients receiving oral anticoagulant or antiplatelet therapy for the primary or secondary prevention of cardiovascular disease is an increasingly common clinical problem [4,5]. The management of these patients represents a challenge for physicians as they should carefully balance the risk of bleeding with the risk of thromboembolic complications resulting from the temporary interruption of antithrombotic therapy. Previous

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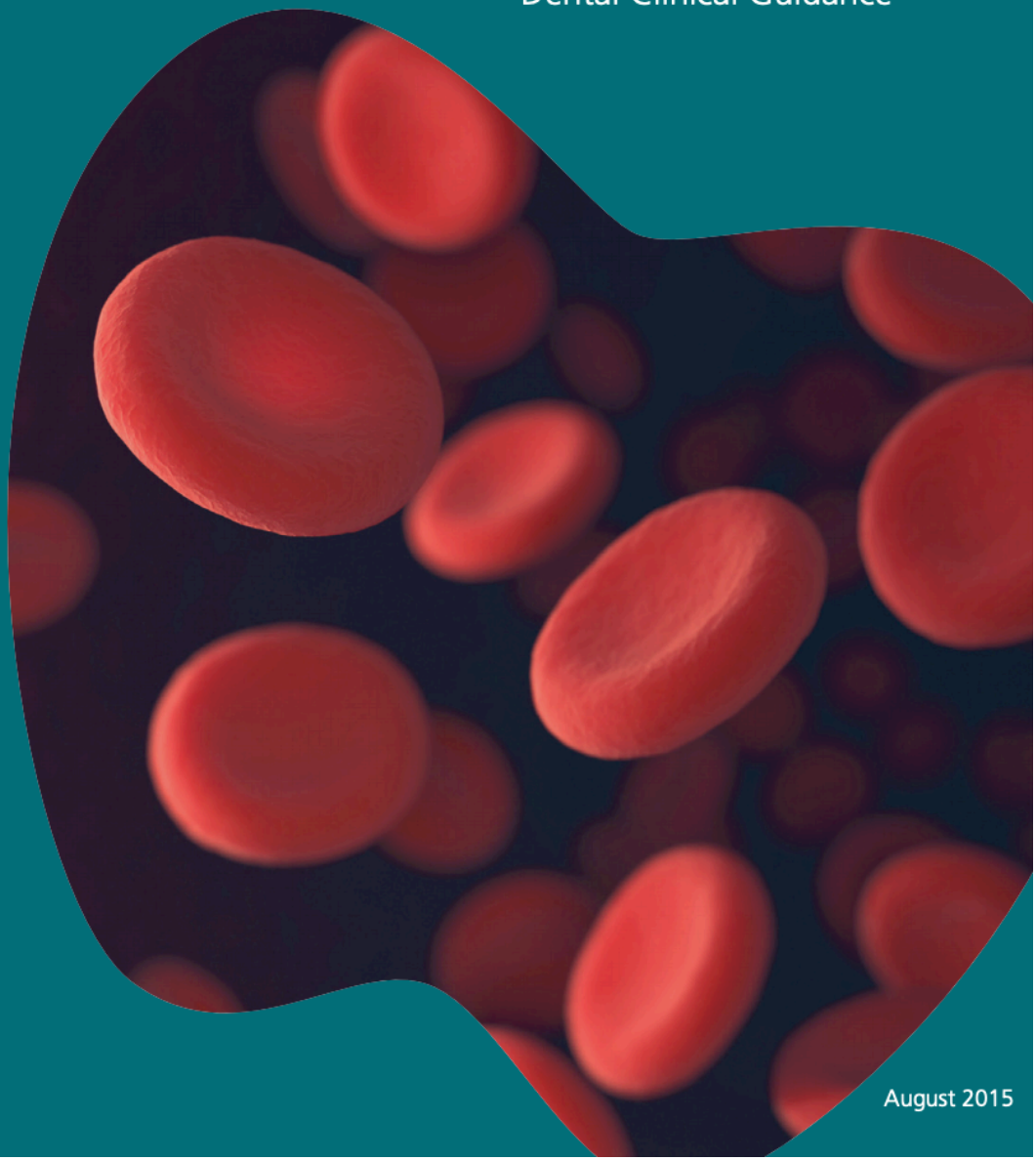
Scottish Dental
Clinical Effectiveness Programme

SDCEP

Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs

Dental Clinical Guidance



August 2015

SPECIAL ARTICLE

Summary of evidence-based guideline: Periprocedural management of antithrombotic medications in patients with ischemic cerebrovascular disease

Report of the Guideline Development Subcommittee of the American Academy of Neurology

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ABSTRACT

Objective: To assess evidence regarding periprocedural management of antithrombotic drugs in patients with ischemic cerebrovascular disease. The complete guideline on which this summary is based is available as an online data supplement to this article.

Methods: Systematic literature review with practice recommendations.

Results and recommendations: Clinicians managing antithrombotic medications periprocedurally must weigh bleeding risks from drug continuation against thromboembolic risks from discontinuation. Stroke patients undergoing dental procedures should routinely continue aspirin (Level A). Stroke patients undergoing invasive ocular anesthesia, cataract surgery, dermatologic procedures, transrectal ultrasound-guided prostate biopsy, spinal/epidural procedures, and carpal tunnel surgery should probably continue aspirin (Level B). Some stroke patients undergoing vitreoretinal surgery, EMG, transbronchial lung biopsy, colonoscopic polypectomy, upper endoscopy and biopsy/sphincterotomy, and abdominal ultrasound-guided biopsies should possibly continue aspirin (Level C). Stroke patients requiring warfarin should routinely continue it when undergoing dental procedures (Level A) and probably continue it for dermatologic procedures (Level B). Some patients undergoing EMG, prostate procedures, inguinal herniorrhaphy, and endothermal ablation of the great saphenous vein should possibly continue warfarin (Level C). Whereas neurologists should counsel that warfarin probably does not increase clinically important bleeding with ocular anesthesia (Level B), other ophthalmologic studies lack the statistical precision to make recommendations (Level U). Neurologists should counsel that warfarin might increase bleeding with colonoscopic polypectomy (Level C). There is insufficient evidence to support or refute periprocedural heparin bridging therapy to reduce thromboembolic events in chronically anticoagulated patients (Level U). Neurologists should counsel that bridging therapy is probably associated with increased bleeding risks as compared with warfarin cessation (Level B). The risk difference as compared with continuing warfarin is unknown (Level U). *Neurology*® 2013;80:2065–2069

GLOSSARY

AC = anticoagulation; **AP** = antiplatelet; **RR** = relative risk; **TE** = thromboembolic.

Neurologists are frequently asked to recommend whether practitioners should temporarily stop anticoagulation (AC) and antiplatelet (AP) agents in patients with prior strokes or TIAs undergoing invasive procedures. The balance of risks of recurrent vascular events with discontinuation of these agents vs increased periprocedural bleeding with continuation is often unclear, leading to variability in care and possibly adverse outcomes.

This article summarizes the findings, conclusions, and recommendations of an evidence-based guideline regarding periprocedural management of patients with a history of ischemic cerebrovascular disease receiving AC or AP agents. The full text of the guideline is available as a data supplement on the *Neurology*® Web site at www.neurology.org. Four questions are addressed:

Supplemental data at www.neurology.org

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The NEW ENGLAND JOURNAL of MEDICINE

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Dabigatran versus Warfarin in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Warfarin reduces the risk of stroke in patients with atrial fibrillation but increases the risk of hemorrhage and is difficult to use. Dabigatran is a new oral direct thrombin inhibitor.

METHODS

In this noninferiority trial, we randomly assigned 18,113 patients who had atrial fibrillation and a risk of stroke to receive, in a blinded fashion, fixed doses of dabigatran — 110 mg or 150 mg twice daily — or, in an unblinded fashion, adjusted-dose warfarin. The median duration of the follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism.

RESULTS

Rates of the primary outcome were 1.69% per year in the warfarin group, as compared with 1.53% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.91; 95% confidence interval [CI], 0.74 to 1.11; P<0.001 for noninferiority) and 1.11% per year in the group that received 150 mg of dabigatran (relative risk, 0.66; 95% CI, 0.53 to 0.82; P<0.001 for superiority). The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group receiving 110 mg of dabigatran (P=0.003) and 3.11% per year in the group receiving 150 mg of dabigatran (P=0.31). The rate of hemorrhagic stroke was 0.38% per year in the warfarin group, as compared with 0.12% per year with 110 mg of dabigatran (P<0.001) and 0.10% per year with 150 mg of dabigatran (P<0.001). The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with 110 mg of dabigatran (P=0.13) and 3.64% per year with 150 mg of dabigatran (P=0.051).

CONCLUSIONS

In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. (ClinicalTrials.gov number, NCT00262600.)

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ORIGINAL ARTICLE

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

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ABSTRACT

BACKGROUND

The use of warfarin reduces the rate of ischemic stroke in patients with atrial fibrillation but requires frequent monitoring and dose adjustment. Rivaroxaban, an oral factor Xa inhibitor, may provide more consistent and predictable anticoagulation than warfarin.

METHODS

In a double-blind trial, we randomly assigned 14,264 patients with nonvalvular atrial fibrillation who were at increased risk for stroke to receive either rivaroxaban (at a daily dose of 20 mg) or dose-adjusted warfarin. The per-protocol, as-treated primary analysis was designed to determine whether rivaroxaban was noninferior to warfarin for the primary end point of stroke or systemic embolism.

RESULTS

In the primary analysis, the primary end point occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) (hazard ratio in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.96; P<0.001 for noninferiority). In the intention-to-treat analysis, the primary end point occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (hazard ratio, 0.88; 95% CI, 0.74 to 1.03; P<0.001 for noninferiority; P=0.12 for superiority). Major and nonmajor clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year) (hazard ratio, 1.03; 95% CI, 0.96 to 1.11; P=0.44), with significant reductions in intracranial hemorrhage (0.5% vs. 0.7%, P=0.02) and fatal bleeding (0.2% vs. 0.5%, P=0.003) in the rivaroxaban group.

CONCLUSIONS

In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. (Funded by Johnson & Johnson and Bayer; ROCKET AF ClinicalTrials.gov number, NCT00403767.)

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*A complete listing of the steering committee members and trial investigators in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) is provided in the Supplementary Appendix, available at NEJM.org.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban versus Warfarin in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Vitamin K antagonists are highly effective in preventing stroke in patients with atrial fibrillation but have several limitations. Apixaban is a novel oral direct factor Xa inhibitor that has been shown to reduce the risk of stroke in a similar population in comparison with aspirin.

METHODS

In this randomized, double-blind trial, we compared apixaban (at a dose of 5 mg twice daily) with warfarin (target international normalized ratio, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. The trial was designed to test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.

RESULTS

The median duration of follow-up was 1.8 years. The rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority; P=0.01 for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; P<0.001), and the rates of death from any cause were 3.52% and 3.94%, respectively (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; P=0.047). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; P<0.001), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (hazard ratio, 0.92; 95% CI, 0.74 to 1.13; P=0.42).

CONCLUSIONS

In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. (Funded by Bristol-Myers Squibb and Pfizer; ARISTOTLE ClinicalTrials.gov number, NCT00412984.)

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*The members of the steering committee, as well as other committee members and investigators in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, are listed in the Supplementary Appendix, available at NEJM.org.

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IN BRIEF

- There is little scientific basis for treatment standards for patients with coagulopathies.
- The medical history is critical to the identification of patients at risk for prolonged bleeding.
- Laboratory tests ordered must be specific to the specific bleeding disorder.
- The relationship between oral bleeding and liver, kidney and bone marrow disease is poorly understood.
- There is a need for research on the dental management of patients with coagulopathies.

VERIFIABLE CPD PAPER

Dental management considerations for the patient with an acquired coagulopathy. Part 1: Coagulopathies from systemic disease

P. B. Lockhart[1], J. Gibson[2], S. H. Pond[3] and J. Leitch[4]

Current teaching suggests that many patients are at risk for prolonged bleeding during and following invasive dental procedures, due to an acquired coagulopathy from systemic disease and/or from medications. However, treatment standards for these patients often are the result of long-standing dogma with little or no scientific basis. The medical history is critical for the identification of patients potentially at risk for prolonged bleeding from dental treatment. Some time-honoured laboratory tests have little or no use in community dental practice. Loss of functioning hepatic, renal, or bone marrow tissue predisposes to acquired coagulopathies through different mechanisms, but the relationship to oral haemostasis is poorly understood. Given the lack of established, science-based standards, proper dental management requires an understanding of certain principles of pathophysiology for these medical conditions and a few standard laboratory tests. Making changes in anticoagulant drug regimens are often unwarranted and/or expensive, and can put patients at far greater risk for morbidity and mortality than the unlikely outcome of postoperative bleeding. It should be recognised that prolonged bleeding is a rare event following invasive dental procedures, and therefore the vast majority of patients with suspected acquired coagulopathies are best managed in the community practice setting.

Dental patients often present with a medical history that suggests the potential for clinically significant intraoperative bleeding, which might be defined as blood obscuring the operative site and interfering with carrying out a given procedure, or blood loss sufficient to require transfusion. Several hours of minor postoperative bleeding is of little concern following procedures such as dental extractions, but there is no commonly accepted definition of what constitutes prolonged or clinically significant postoperative bleeding. It could be defined as that which:

1. Continues beyond 12 hours;
2. Causes the patient to call or return to the dental practitioner or to the accident and emergency department;
3. Results in the development of a large haematoma or ecchymosis within the oral soft tissues; or
4. Requires a blood transfusion.

Most episodes cause concern or inconvenience to the patient, and rarely require a return to the dental surgery or local accident and emergency department.

Coagulopathies that predispose to oral bleeding can be divided into two broad categories – inherited and acquired. This two part review covers acquired coagulopathies that arise from disease, or medications, or both. Disease-related bleeding disorders result most often from hepatic, renal, and bone marrow disorders, which have varying effects on the haemostatic process (Table 1). Bleeding problems from medications will be covered in a subsequent paper. An understanding of the basic features of the coagulation cascade is helpful for an appreciation of the common elements of inherited and acquired coagulopathies and how medications and disease affect the coagulation cascade (Fig. 1).[1]

The challenge for the dental practitioner is to:

This work was initiated while Dr. Lockhart was a TC White Visiting Professor at the Royal College of Physicians and Surgeons, and at Glasgow Dental Hospital and School, University of Glasgow, UK

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An update on the management of anticoagulated patients programmed for dental extractions and surgery

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http://www.medicinaoral.com/medoralfree01/v13i3/medoralv13i3p176.pdf

Abstract

Oral anticoagulants (OACs) antagonizing vitamin K - fundamentally sodium warfarin and acenocoumarol - are widely used 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.

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). This is particularly important when patients must be subjected to surgical procedures such as tooth extractions. In this context, a number of management recommendations are available.

The present study offers an update on the recommendations for the management of anticoagulated patients programmed for tooth extractions. In recent years, most studies do not recommend reducing or interrupting anticoagulation, or replacing it with heparin, prior to tooth extraction - provided therapeutic international normalized ration (INR) levels are maintained, with emphasis on the application of local measures such as antifibrinolytic agents, for the control of hemostasia.

Key words: *Oral anticoagulants, extraction, tranexamic acid, warfarin, acenocoumarol, surgery.*

Introduction

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 Spain). 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 (1).

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)(1).

When such patients require surgery (e.g., tooth extractions), increased bleeding risk is postulated if the OAC dose is not lowered. However, reducing the drug levels in turn can increase the risk of thromboembolism. Thus, a series of management guidelines are needed in such situations.

The present study offers an update on OACs and on the recommendations for the management of anticoagulated patients programmed for tooth extractions, based on the results of clinical studies and expert opinions.

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Oral surgery in patients on oral anticoagulant therapy: a randomized comparison of different INR targets

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Patients receiving oral anticoagulant therapy (OAT) are a clinical challenge when therapy has to be interrupted to carry out invasive procedures. Dental procedures represent a particularly common intervention for these patients. A number of reports indicate that in most cases it is not necessary to change the intensity of OAT [1–5]. Nevertheless, there is still a widespread belief among dental practitioners and physicians that OAT must be discontinued to prevent hemorrhagic complications, particularly in case of invasive procedures such as dental extractions or fixture insertions. However, OAT discontinuation may engender the risk of thromboembolism, particularly in patients with atrial fibrillation. With this as the background, we designed a prospective, randomized, open-label study to evaluate the outcome of oral surgery in patients on OAT operated upon conditions of reduced International Normalized Ratio (INR) values, compared with patients maintained in their usual therapeutic ranges.

Eligible cases were individuals of any age on OAT for at least 1 month for any reason. A clinical evaluation, including a general medical evaluation and a surgical and radiological evaluation through orthopantomography, was carried out. Each patient's medical history was evaluated, with special emphasis on the indication for OAT, its dosage, length of treatment and the type of drug prescribed. We included in the study 131 consecutive patients on long-term OAT because of a prosthetic valve (45%), atrial fibrillation (30%), venous

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Oral surgery in patients on anticoagulant therapy

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Objective. Surgery is the main oral healthcare hazard to the patient with a bleeding tendency, which is mostly caused by the use of anticoagulants. The traditional management entails the interruption of anticoagulant therapy for dental surgery to prevent hemorrhage. However, this practice may increase the risk of a potentially life-threatening thromboembolism. Because this issue is still controversial, it is the aim of this paper to review the evidence, to highlight the areas of major concern, and to suggest management regimens for patients on the 3 main types of anticoagulants: coumarins, heparins, and aspirin.
Materials reviewed. The pertinent literature and clinical protocols of hospital dentistry departments have been extensively reviewed and discussed.
Results. 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 methods are used to prevent bleeding; and patients at risk are referred to hospital-based clinics.
Conclusion. The management of oral surgery procedures on patients treated with anticoagulants should be influenced by several factors: extent and urgency of surgery, laboratory values, treating physician's recommendation, available facilities, dentist expertise, and patient's oral, medical, and general condition.
(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;94:57-64)

Hemostasis in the healthy individual involves interaction between 4 biologic systems: the blood vessel wall, the blood platelets, the blood coagulation system, and the fibrinolytic system. Blood vessel constriction is an essential first stage; platelet adhesion and aggregation follow. The hemostatic mechanism is initiated at the site of injury by local activation of surfaces and release of tissue thromboplastin, resulting ultimately in formation and deposition of fibrin. The coagulation process is regulated by physiologic anticoagulants.[1] Activation of fibrinolysis is triggered by the presence of fibrin and tissue-type plasminogen activators at the site of fibrin formation, a process regulated by physiologic inhibitors such as α_2-antiplasmin, histidine-rich glycoprotein, and plasminogen activator inhibitor.[1]

Oral surgery induces changes of fibrinolysis in the oral environment; initially, the fibrinolytic activity of saliva is reduced because of the presence of inhibitors of fibrinolysis originating from the blood and the wound exudates, but when the bleeding and exudation reduce, the fibrinolytic activity of saliva increases. Plasminogen and plasminogen activator are present in the oral environment in physiologic conditions because plasminogen is secreted into the saliva and tissue-type plasminogen activators arise from oral epithelial cells and gingival crevicular fluid. Thus, after surgery, fibrinolysis is triggered.[2]

Some patients have a tendency to bleed excessively after trauma. Surgery is the main oral healthcare hazard to the patient with a bleeding tendency, but regional block local anesthetic injections also may be a hazard because bleeding into the fascial spaces of the neck can threaten airway patency. Most bleeding tendencies are from the use of anticoagulants,[3] usually prescribed to treat a number of cardiac or vascular disorders, including atrial fibrillation, ischemic cardiac disease, cardiac valvular disease, prosthetic cardiac valves, postmyocardial infarction, deep venous thrombosis, pulmonary embolism, cerebrovascular accident, and many others.[4-6]

Concern exists about intraoperative and postoperative bleeding in patients undergoing anticoagulation therapy and the best management for the situation. Many clinicians have recommended interruption of continuous anticoagulant therapy for dental surgery to prevent hemorrhage. However, with review of the available literature, no well-documented cases of serious bleeding problems from dental surgery in patients receiving therapeutic levels of continuous warfarin sodium therapy were identified, but several documented

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Haemostasis Part 1: The Management of Post-Extraction Haemorrhage

Abstract: The management of bleeding complications following a dental extraction is an essential skill for the dental practitioner. Extractions are often carried out on patients with complex medical histories and a long list of medications. This paper aims to help the clinician manage post-extraction haemorrhage. A review of the management of patients on anti-thrombotic medications will be covered in a subsequent paper.

Clinical Relevance: This article reviews the management of haemorrhage following tooth extraction; from the risk assessment of any underlying medical conditions and medications, to the clinical techniques used to control bleeding following an extraction.

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Haemostasis at the site of a dental extraction is considered to be a prerequisite before the patient leaves the clinic. Failure of haemostasis could occur in any patient; however, a number of different medical conditions and medications may interfere with this process.

The most recent Adult Dental Survey (2009) has shown a growing number of our patients are remaining dentate.[1] People are living longer as a result of increasing health awareness and the success of medical treatments. The concept of 'polypharmacy' management requires dental clinicians to have an increased knowledge of the drugs that may affect dental treatment and their potential for drug interactions. Some drug therapies can increase the potential for bleeding post-operatively.

Risk assessment prior to embarking on a tooth extraction can allow the operator to foresee complications such as a haemorrhage. This involves careful planning and a thorough analysis of the medical history.[2] Table 1 shows the haemorrhage risk factors surrounding a dental extraction.

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Overview of haemostasis

A sound knowledge of the physiology of haemostasis is important in understanding how haemorrhage may occur. A full description of the process is outside the remit of this paper; however, several key points are worth noting.

The process of haemostasis involves:

- Vasoconstriction – vascular spasm in smooth muscle in the walls of blood vessels;
- Platelet plug formation – adhesion, interaction and aggregation of platelets;
- Coagulation cascade/network – clotting factors in the extrinsic, intrinsic and common pathways lead to the formation of fibrin.

Clot formation is a dynamic process, involving a balance between the haemostatic and the fibrinolytic systems. The involvement of numerous cells, chemicals and plasma proteins are all required for successful haemostasis. Fibrinolysis occurs when the plasma enzyme plasminogen activates plasmin, which digests the fibrin threads in the clot. In health, this will occur once the site is repaired. Figure 1 outlines the timeline of clot formation.

Consideration of the normal mechanism allows the clinician to interpret which patients may be at high risk of poor haemostasis. This may be the result of underactive clotting or overactive

Dental treatment of patients with coagulation factor alterations: An update

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ABSTRACT

Hemostasia is a defense mechanism that protects vascular integrity, avoids blood loss, and maintains blood fluidity throughout the circulatory system. The biochemical processes leading to blood clot formation are complex, and alterations can appear at any point within the chain of events. While a range of alterations can affect the coagulation factors, some are more common than others in the general population, including congenital (hemophilia A and B, Von Willebrand's disease) and acquired disorders (anticoagulant drugs). Such diseases require special consideration in the context of dental treatment, and therefore must be known to dental professionals. Interconsultation with the hematologist will provide orientation on the characteristics of the disease and on the best approach to treatment, including the need for replacement therapy, the application of local hemostatic measures, the modification of anticoagulant therapy, etc. In any case, the most important concern is the prevention of bleeding complications by compiling a detailed clinical history, with adequate planning of treatment, and taking special care to avoid soft tissue damage during the dental treatment of such patients. The dental surgeon must enhance awareness among patients and their relatives of the importance of correct oral hygiene, which will help avoid the need for invasive dental treatments and will reduce the number of visits to the dentist.

Key words: *Hemostasia, coagulation factors, hemophilia, Von Willebrand's disease, anticoagulant drugs, interconsultation, bleeding accidents, prevention.*

RESUMEN

La hemostasia es un mecanismo de defensa cuya finalidad es conservar la integridad vascular y evitar la pérdida de sangre, a la vez que mantiene la fluidez de la sangre en todo el torrente circulatorio. Los procesos bioquímicos que conducen a la formación de coágulos son complejos y pueden producirse trastornos a cualquier nivel. Las alteraciones que afectan a los factores de la coagulación son múltiples, pero algunas de ellas se presentan con más frecuencia en la población: congénitas (hemofilias A y B, enfermedad de von Willebrand) y adquiridas (fármacos anticoagulantes).Estas patologías requieren consideraciones especiales en el tratamiento dental, por lo que el odontólogo debe conocerlas. La interconsulta con el hematólogo del paciente le informará sobre las características de la enfermedad y las pautas de tratamiento: necesidad de terapia sustitutiva, empleo de medidas hemostáticas locales, alteración de la pauta de tratamiento anticoagulante, etc. En cualquier caso, la medida más importante a tomar es la prevención de complicaciones hemorrágicas mediante la elaboración de una correcta y detallada historia clínica, la planificación adecuada de los tratamientos y prestando especial cuidado de no dañar los tejidos blandos orales durante la terapéutica dental. Es labor del odontólogo concienciar al paciente y a sus familiares de que una correcta higiene oral evitará la necesidad de tratamientos dentales invasivos y reducirá las visitas al odontólogo.

Management of dental extraction in patients undergoing anticoagulant treatment

Results from a large, multicentre, prospective, case-control study

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Summary

Following favourable results from a previous study, a large, multicentre, prospective, case-control study was performed to further assess the incidence of bleeding complications after dental extraction in patients taking oral anticoagulant therapy (OAT). Four hundred fifty-one patients being treated with warfarin who required dental extraction were compared with a control group of 449 non-anticoagulated subjects undergoing the same procedure. In the warfarin-treated group, the oral anticoagulant regimen was maintained unchanged, such that the patients had an International Normalised Ratio ranging between 1.8 and 4, and local haemostatic measures (i.e. fibrin sponges, silk sutures and gauzes saturated with tranexamic acid) were adopted. All the procedures were performed in an outpatient setting. Seven bleeding complications occurred in the OAT group and four in the control group; the difference in the number of bleeding events between the two groups was not statistically significant (OR=1.754; 95% CI 0.510 – 6.034; p=0.3727). No post-operative late bleeds requiring hospitalisation and/or blood transfusions were recorded, and the adjunctive local haemostatic measures were adequate to stop the bleeding. The results of our protocol applied in this large, multicenter study show that dental extractions can be performed easily and safely in anticoagulated outpatients without any modification of the ongoing anticoagulant therapy, thus minimising costs and reducing discomfort for patients.

Keywords

Dental extraction, anticoagulated patients, warfarin therapy, multicenter study

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Introduction

The proper approach to dental extractions in patients on oral anticoagulant therapy (OAT) remains a matter of debate focused on the balance between the risk of thromboembolic events and bleeding complications (1). In fact, three decades of research on this issue have produced conflicting results. Some authors recommend the withdrawal of OAT for several days or prescribe heparin before the dental procedure (2, 3). Other authors recommend a reduction of OAT until an International Normalised Ratio (INR) value of 1.5 is reached (4, 5). More recently, it has been proposed that the OAT regimen could be left unchanged and the patient be treated with several post-procedural local haemostatic measures (e.g. gelatine sponges, oxidized cellulose, fibrin glue, sutures and tranexamic acid) to control the bleeding risk (6–10). In fact, no fatal bleeding complications have been reported in the literature in association with this approach, while some deaths related to OAT withdrawal for dental extractions have occurred (11). Interestingly, already in 1966, McIntyre had suggested maintaining anticoagulant treatment when performing dental extractions (12).

Following recent consistent evidence in favour of the maintenance of OAT when a dental extraction must be performed and suggestions that this might be the gold standard for the management of patients on OAT (13, 14), a specific protocol for the management of such patients was published by our group, drawing on the results of a prospective case-control study conducted in 2003 (20). That study, which compared the incidence of bleeding complications after dental extraction between a group of healthy patients and a group of anticoagulated patients treated without withdrawal of OAT, did not show any statistical difference between groups in the bleeding outcome. The results of the study have already been taken into account by guidelines (15–18), but, in order to further validate our protocol, we performed a large, prospective, multicentre, case-control study.

Management of dental patients taking common hemostasis-altering medications

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Objective. Millions of patients worldwide are taking medications that alter hemostasis and decrease the risk for thromboembolic events. This systematic review is intended to provide recommendations regarding optimal management of such patients undergoing invasive dental procedures. The primary focus of this report is on warfarin therapy, although issues related to heparin and aspirin are briefly discussed because of the frequency with which they are encountered in dental practice.

Study design. The review of literature and development of recommendations was based on the Reference Manual for Management Recommendations for the World Workshop in Oral Medicine IV (WWOM IV). A total of 64 publications were identified for initial review. From these publications, the following types of articles were critically analyzed using WWOM standard forms: randomized controlled trials (RCT), non-RCT studies that assess effects of interventions, and studies that assess modifiable risk factors. Development of recommendations was based on the findings of these reviews as well as expert opinion.

Results. The following evidence-based recommendations were developed: (1) For patients within the therapeutic range of International Normalized Ratio (INR) below or equal to 3.5, warfarin therapy need not be modified or discontinued for simple dental extractions. Nevertheless, the clinician's judgment, experience, training, and accessibility to appropriate bleeding management strategies are all important components in any treatment decision. Patients with INR greater than 3.5 should be referred to their physician for consideration for possible dose adjustment for significantly invasive procedures. (2) A 2-day regimen of postoperative 4.8% tranexamic acid mouthwash is beneficial after oral surgical procedures in patients on warfarin. (3) It is not necessary to interrupt low-dose aspirin therapy (100 mg/day or less) for simple dental extractions.

Conclusion. For most patients undergoing simple single dental extractions, the morbidity of potential thromboembolic events if anticoagulant therapy is discontinued clearly outweighs the risk of prolonged bleeding if anticoagulant therapy is continued. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103(suppl 1):S45.e1-S45.e11)**

The aim of oral anticoagulant therapy (OAT) 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 spontaneous bleeding. When patients on anticoagulant therapy present for an invasive dental procedure expected to cause bleeding, the question arises as to whether the anticoagulant therapy should be continued, modified, or discontinued at some point before dental treatment. In such situations, clinicians must assess the patient's ability to achieve hemostasis following a procedure if anticoagulation is continued versus the risk of thromboembolism if anticoagulant therapy is decreased or discontinued. To avoid these potential complications, several alternative periprocedural anticoagulation strategies have been proposed; however, each of these techniques may be problematic (Fig. 1).

This topic was selected as 1 of 10 to be reviewed at the Fourth World Workshop in Oral Medicine (WWOM IV). Recommendations for the optimal management of patients taking hemostasis-altering medications put forth in this document are based on the results of a systematic review of the published literature as well as the experience of a panel of experts (consultants). Furthermore, review articles from recent years were consulted.[1-15] The primary focus of this report will be on warfarin, given the relative strength of the literature base for this subject. Issues specifically related to heparin and aspirin will only be briefly discussed, in view of the more limited data available from randomized clinical trials (RCTs) regarding use of these agents in patients in the dental setting.

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Dental extractions in patients on warfarin: is alteration of anticoagulant regime necessary?

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SUMMARY. **Various clinical protocols for the management of warfarinised patients needing dental extractions have been suggested. This study was designed to compare two approaches in the management of these patients. A control group of 32 patients had their warfarin treatment stopped for 2–3 days prior to having dental extractions, resulting in a reduction in the average preoperative international normalised ratio (INR) from 2.6 to 1.6. The study group of 33 patients did not have their anticoagulant treatment altered before extractions, and had an average preoperative INR of 2.7. All patients were treated under local analgesia on an outpatient basis, and local measures—consisting of Surgicel® pack and sutures—were used in all cases to control postoperative bleeding from extraction sockets. None of the patients had any immediate postoperative bleeding, and only 1 patient from each group had mild delayed haemorrhage, which was easily controlled with local measures. It is proposed that, provided the INR is within the therapeutic range of 2.0 to 4.0 and local measures are used to control postoperative bleeding, there is no justification in altering warfarin treatment prior to dental extractions in these patients, and thereby exposing them to the risk of thromboembolism.**

INTRODUCTION

The management of patients on oral anticoagulant therapy who need dental extractions is controversial. There has been some debate as to whether, prior to minor oral surgery, anticoagulant treatment should be altered or not; the risk of serious postoperative haemorrhage has to be balanced against the potential for life-threatening thromboembolism.[1–3]

Warfarin, which belongs to the coumarin group of drugs, is the most commonly used oral anticoagulant.[4] It is a competitive inhibitor of vitamin K, which is required for the carboxylation of glutamic acid residues on clotting factors II, VII, IX, X, and protein C in the liver. This inhibition results in the failure of formation of gamma carboxyglutamic acid, and the production of functionally inert coagulation proteins.[5]

There are several currently recognised indications for the use of warfarin. These include deep vein thrombosis, pulmonary embolism, vascular thromboembolism, transient cerebral ischaemic attacks, and stroke. In addition, cardiac indications include myocardial infarction, dilated cardiomyopathy, arrhythmias including atrial fibrillation and paroxysmal supraventricular tachycardia, established atrial or ventricular mural thrombus formation, rheumatic heart disease, valvular disorders, prosthetic heart valves, and following coronary artery by-pass graft surgery.[4–6]

Warfarin dosages are adjusted to achieve an optimum level of anticoagulation.[7] This is done by monitoring the prothrombin time—expressed as the international normalised ratio (INR)—with the therapeutic range generally accepted as between 2.0 and 4.0, depending on the primary indication for anticoagulation (Table I).[8] Daily maintenance doses usually range from 3 mg to 9 mg. The anticoagulant effect of the drug is delayed in onset by 2–3 days after starting treatment, and likewise persists for about the same length of time on cessation, both because of the nature of drug action on protein synthesis and because coumarins are strongly bound to plasma proteins.[5]

Haemorrhage is the principal adverse effect of oral anticoagulants, and regular monitoring of the INR in these patients is mandatory. Spontaneous airway-threatening bleeding has been reported in the

Table 1 – Indications and optimum levels for warfarin anticoagulation

Indication	Ideal INR	No. of patients
Deep vein thrombosis (DVT)	2.0–3.0	8
Pulmonary embolism (PE)	2.0–3.0	4
Recurrent DVT or PE	3.0–4.5	5
Vascular thromboembolism	3.0–4.5	2
Transient cerebral ischaemic attacks (TCIAs)	2.0–3.0	3
Stroke (CVA)	2.0–3.0	5
Myocardial infarction (MI)	3.0–4.5	2
Dilated cardiomyopathy	2.0–3.0	3
Arrhythmias (including AF and SVT)	1.4–2.8	12
Valvular disorders	2.0–4.5	16
Prosthetic valve replacement	3.0–4.5	1
Coronary artery by-pass graft (CABG)	3.0–4.5	4
Total		65

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Simple and Safe Method to Prepare Patients With Prosthetic Heart Valves for Surgical Dental Procedures

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Summary: Temporary discontinuation of high-intensity oral anticoagulant treatment is not recommended in patients undergoing dental surgery. This policy is not based on solid data from randomized clinical trials but on expert consensus. The alternative, i.e., to continue treatment and treat patients with tranexamic acid mouthwash, often is not applicable. A prospective cohort study was carried out to evaluate bleeding and thromboembolic complications in patients bearing prosthetic heart valves and registering International Normalized Ratio (INR) values between 2.0 and 4.5, who underwent dental procedures after a 2-day suspension of warfarin treatment. One hundred four consecutive patients receiving high-intensity anticoagulation underwent 123 dental procedures after 2 days' warfarin withdrawal. No major bleeding complications occurred in the week after the procedure; minor bleeding requiring local measures occurred in two patients. No thromboembolic events and no cases of bacterial endocarditis were recorded in the 3 months after the procedure. A mean decrease in INR by approximately 1.0 U (from 2.95 ± 0,59 to 1.87 ± 0,46) occurred after 2 days' warfarin suspension. Seven days after reinitiation of warfarin, INR values returned to the therapeutic range in 90% of cases. The calculated average time spent at INR less than 2.0 (critical value) was 28 hours. Two days' warfarin suspension is a simple and safe policy for patients with prosthetic heart valves undergoing dental surgery. **Key Words:** Prosthetic heart valves—Dental surgical procedures.

Long-term oral anticoagulant (OA) treatment to prevent cerebral and systemic embolism is recommended in patients bearing prosthetic heart valves (1). Although a medium-intensity treatment comparable to that suggested for other indications has recently been suggested for low-risk patients with prosthetic valves in the aortic position (2), patients with mechanical heart valves are usually kept on a medium-high intensity regimen with an International Normalized Ratio (INR) target value (≥3.0 (1,3,4). Because bleeding complications are related to the intensity of OA treatment (5), bleeding after surgical procedures might be relevant (6–8); however, withdrawal of OA treatment before surgery generally is not recommended in these patients (1,3,4). The use of tranexamic acid mouthwash has been shown to exert a beneficial hemostatic effect without systemic complications (7), and thus represents a possible alternative to withdrawal of OA in patients who must undergo dental surgery. Nevertheless, suspension of OA treatment for several days or even substitution of OA with heparin in patients at very high risk of thromboembolism is recommended by some authors (1,9–11).

The policy to continue medium-high intensity treatment in patients with prosthetic heart valves undergoing oral surgery is not based on solid data and does not take into account two practical aspects. First, the personal dentist outside the hospital is often reluctant to operate under conditions of full anticoagulation; and second, the method for rinsing with tranexamic acid mouthwash is rather complicated and often not applicable to all patients.

Because short-term suspension of OA is considered safe (12), in the past few years we decided to adopt a scheme of fixed suspension and early resumption of usual treatment in patients with prosthetic heart valves undergoing dental procedures.

MATERIALS AND METHODS

Starting in January 1994, patients with prosthetic heart valves treated with warfarin and monitored at our Thrombosis Centre at the University of Padova were asked to follow a fixed 2-day withdrawal regimen on the occasion of surgical dental procedures. Only patients un-

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Oral Surgery in Patients on Anticoagulant Treatment Without Therapy Interruption

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Purpose

Conflicting opinions exist in literature concerning the management of oral surgery in patients on oral anticoagulants because no consensus on perioperative protocols is available, including precise guidelines regarding the need for therapy modification or withdrawal. The aim of this study was to evaluate bleeding complications associated with oral surgery performed on patients on oral anticoagulants without therapy modification or withdrawal but following a standardized comprehensive perioperative management protocol.

Patients and Methods

Patients on oral anticoagulant therapy with warfarin and in need of oral surgery underwent a thorough general and oral clinical evaluation to assess thromboembolic and bleeding risk; 255 subjects who, on the morning of surgery, had INR values ≤5.5 were included in the study. An atraumatic surgical technique was carried out and all patients received postoperative careful instructions.

Results

Five cases (1.96%) of bleeding complication were observed in patients with moderate to high thromboembolic and bleeding risk.

Conclusion

The findings from this study suggest that a comprehensive perioperative management protocol for oral surgery in patients on oral anticoagulants including *1*) thromboembolic and bleeding risk assessment, *2*) an atraumatic surgical technique, and *3*) postoperative careful instructions, can lead to safe and successful results with minimal complications.

On the use of prothrombin complex concentrate in patients with coagulopathy requiring tooth extraction

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In patients on high-level anticoagulant therapy (prothrombin time–international normalized ratio [PT-INR] ≥ 4.5), surgical procedures can be carried out with bridging therapy using heparin. However, surgical treatment options are severely limited in patients on high-level anticoagulant therapy and who have heparin-induced thrombocytopenia (HIT), as heparin use is contraindicated.

We performed tooth extraction using prothrombin complex concentrate (PCC) in 2 HIT patients on high-level anticoagulation therapy (PT-INR ≥ 4.5). Five hundred units of PCC were administered intravenously, and after 15 minutes, it was confirmed that PT-INR was less than 2.0. Tooth extraction was then performed and sufficient local hemostasis was achieved. At 3 hours after tooth extraction, PT-INR was 2.0 or higher and later increased to 4.0 or higher, but postoperative bleeding was mostly absent.

When performing tooth extraction in HIT patients on high-level anticoagulant therapy, favorable hemostatic management was achieved through sufficient local hemostasis and transient warfarin reversal using PCC. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:e7-e10)**

In patients on oral anticoagulant therapy (prothrombin time–international normalized ratio [PT-INR] < 3.5), continuous administration of a maintenance dose of warfarin is recommended when performing tooth extraction.[1,2] However, invasive procedures should be delayed when PT-INR is 3.5 or higher.[1,2]

Mechanical circulatory support (MCS), such as the left-ventricular assist system (LVAS), is used in the treatment of unresponsive severe heart failure. As thrombogenesis at the blood-contacting surface inside the device is likely with MCS, high-level anticoagulant therapy (PT-INR ≥ 4.0) is necessary in some patients,[3] and hemostatic management during oral surgery becomes difficult. Thus, surgical procedures are carried out with bridging therapy using heparin (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]).[1,3,4] However, surgical treatment options are severely limited for patients on high-level anticoagulant therapy and with heparin-induced thrombocytopenia (HIT), as heparin use is contraindicated.[5-7]

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Recent studies have demonstrated the efficacy of prothrombin complex concentrate (PCC) to quickly reverse the anticoagulation effects of warfarin in patients on warfarin therapy having severe hemorrhagic complications, such as cerebral bleeding.[8-11]

Here we performed tooth extraction using PCC in 2 HIT patients on high-level anticoagulation therapy (target PT-INR: 4.5) for LVAS, and hemostatic management was favorable.

CASE REPORTS

Patient 1

The patient was a 38-year-old woman with dilated cardiomyopathy (DCM), and because of severe heart failure, circulation was maintained using LVAS. Tooth extraction was scheduled because of persistent pus discharge owing to #37 periapical periodontitis. Antithrombotic therapy comprised 100 mg/d aspirin and 2.0 to 4.0 mg/d warfarin, and the target PT-INR value was set at 4.5 (range: 4.0-5.0). Because of HIT, UFH and LMWH could not be used for tooth extraction; thus, PCC was used to transiently reverse the effects of warfarin, and warfarin therapy was resumed after bleeding was stopped.

At 30 minutes before tooth extraction, 500 U of PCC (PPSB-HT NICHIYAKU, Japan Pharmaceutical Company, Tokyo, Japan) was administered intravenously. After 15 minutes, PT-INR had decreased from 4.94 to 1.43, and #37 tooth extraction and curettage were performed. Electrocautery was used for coagulating gingival bleeding points, oxidized cellulose (Surgicel; Ethicon, Inc. Somerville, NJ) was inserted into the tooth extraction wound, and gingiva was sutured using 4-0 silk. A splint was then placed using periodontal packs. During the procedure, excessive bleeding was not observed (Fig. 1).

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Can warfarin be continued during dental extraction? Results of a randomized controlled trial

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SUMMARY. **A randomized controlled trial was set up to investigate whether patients who were taking warfarin and had an International Normalised Ratio (INR) within the normal therapeutic range require cessation of their anticoagulation drugs before dental extractions. Of 109 patients who completed the trial, 52 were allocated to the control group (warfarin stopped 2 days before extraction) and 57 patients were allocated to the intervention group (warfarin continued). The incidence of bleeding complications in the intervention group was higher (15/57, 26%) than in the control group (7/52, 14%) but this difference was not significant. Two patients in the study required hospital review for bleeding and all other episodes of bleeding were controlled by patients at home. Continuing warfarin when the INR is <4.1 may lead to an increase in minor post-extraction bleeding after dental extractions but we found no evidence of an increase in clinically important bleeding. As there are risks associated with stopping warfarin, the practice of routinely discontinuing it before dental extractions should be reconsidered.**

INTRODUCTION

Warfarin is the most commonly prescribed oral anticoagulant. At present over 300,000 people in the UK are taking oral anticoagulants[1] and the treatment is underused in some conditions.[2] With an ageing population in the UK and a greater proportion of this population retaining their teeth, the number of patients taking warfarin who require dental extractions is likely to increase.

Therapeutic levels of warfarin are measured by the International Normalised Ratio (INR). The British Society of Haemotology has published guidelines on anticoagulant control which recommend a maximum target INR of 3.5, with a range of 3–4.[3] For dental extractions, patients who have been taking warfarin are at an increased risk of perioperative thromboembolism if the drug is stopped but may be at an increased risk of bleeding if it is continued.[4] Patients may bleed from extraction sockets and may also bleed into the medial pterygoid muscle if an inferior dental nerve block is given. A small bleed can produce trismus but a large bleed could embarrass the airway.[5] On the other hand, discontinuing warfarin can cause serious embolic complications[6] and may lead to a rebound hypercoagulable state.[7–10] In addition, several antibiotics that are prescribed as prophylaxis during dental extraction against bacterial endocarditis may increase the effects of warfarin and the risk of bleeding. Indeed, several case reports have been published of antibiotic-induced bleeding in patients who were taking warfarin after dental procedures.[11]

Customary practice in the UK has been to stop warfarin treatment 2 days before extractions, to do an INR on the day of operation and to proceed if the INR is <2.1. Warfarin is started again later the same day.[12] Several authors have suggested that the anticoagulant regimen does not require alteration for dental extractions if the INR is <4.0.[1,12–16] Additional measures that can be taken to ensure haemostasis include packing sockets with oxidized cellulose gauze and suturing all sockets.[1,12] Tranexamic acid has been used as a mouth rinse to reduce haemorrhage further postoperatively.[15,17] Because of the risks associated with either stopping or continuing warfarin for dental extraction, general dental and medical practitioners routinely refer patients who are taking warfarin to maxillofacial units for this procedure. If patients could be treated without altering their anticoagulant regimen, then it is possible that most dental extractions could be done in general dental practice on the same day as regular INR blood monitoring. This would often be more convenient and quicker for the patient, cost-effective and would help to reduce hospital waiting lists.

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ARTÍCULO ORIGINAL

Control del sangrado postoperatorio en pacientes anticoagulados empleando colutorios de ácido tranexámico. Implicancias de la periodontitis

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Control of the posoperative bleeding in patients using anticoagulants mouthwash with tranexamic acid. Implicans of the periodontitis

Resumen

Se analizó el efecto hemostático clínico del colutorio de ácido tranexámico frente al tratamiento convencional en pacientes tratados con anticoagulantes orales. Los procedimientos quirúrgicos (exodoncias) se llevaron a cabo después de suspender la medicación anticoagulante tres días, en 10 pacientes quienes fueron sometidos a 10 procedimientos (grupo control) y sin modificar el tratamiento anticoagulante, en 15 pacientes en quienes se realizaron 20 procedimientos empleando además colutorios de ácido tranexámico (grupo casos). En este último grupo, antes de suturar, el campo operatorio fue irrigado con la solución de ácido tranexámico (agente antifibrinolítico) al 5%. Posteriormente, los pacientes del grupo casos fueron instruidos para emplear 10ml del colutorio por dos minutos, cuatro veces al día por siete días. La única diferencia estadísticamente significativa (p<0,05) entre los dos grupo de tratamiento, al inicio del estudio, fue el nivel de anticoagulación. El INR promedio para el grupo casos y control fue de 2,53 y 1,13 respectivamente. No hubo diferencias significativas entre los dos grupos de tratamiento en la incidencia de sangrado postoperatorio. Los resultados demostraron que el ácido tranexámico es eficaz para controlar el sangrado postoperatorio y que el estado periodontal, particularmente la periodontitis aguda, está más asociado con los eventos de sangrado que el nivel de anticoagulación terapéutico.

Palabras clave: *anticoagulación, INR, ácido tranexámico, periodontitis, sangrado postoperatorio.*

Abstract

This study analysed the hemostatic clinical effect of the tranexamic acid mouthwash against the conventional treatment in patients treated with oral anticoagulants. After suspending the anticoagulant medication for three days, ten surgical procedures were carried out in ten patients(control group), and without modifying or altering the anticoagulant treatment, 20 procedures were carried out using tranexamic acid in 15 patients(case group). In this last group, before suturing the surgical field was irrigated with tranexamic acid solution at 5%. After that, patients of case group were instructed to use 10 ml of the mouthwash for two minutes, four times a day per seven days. The only statisticaly significative difference (p 0,05) between both groups at the beginning of this research, was the level of the anticoagulation. The average of the INR for case and control group was 2,53 and 1,13 respectively. There weren't significative differences between both groups with the incidence of postoperatory bleeding . The results of this research have shown that tranexamic acid is effective to control the postoperatory bleeding and the periodontal state is more related to the events of bleeding rather than the therapeutic anticoagulation level.

Key words: *anticoagulation, INR, tranexamic acid, periodontitis, postoperatory bleeding.*

Introducción

Actualmente se ha incrementado en la consulta odontológica de centros hospitalarios la atención de pacientes con una gran diversidad de enfermedades sistémicas, que antes tenían una baja expectativa de vida. Esta situación demanda un amplio conocimiento de medicina estomatológica, por parte del profesional que ejerce en los nosocomios ya que de ellos depende la continuación de un estado de salud estable, de los diferentes pacientes de riesgo, entre ellos se encuentran los pacientes bajo tratamiento con anticoagulantes orales, cuyos motivos de anticoagulación más comunes son: reemplazo de válvula cardiaca, fibrilación auricular y tromboembolismo venoso.

La modalidad de tratamiento en el paciente anticoagulado que requiere procedimientos quirúrgicos se ha basado en estudios realizados hace mucho tiempo, mediados del siglo pasado, a partir de una serie de casos que presentaron sangrado profuso luego de intervenciones quirúrgicas como la exodoncia donde las medidas hemostáticas locales de aquel entonces eran insuficientes para controlar la hemorragia por lo que se debía administrar vitamina K o plasma fresco para detener la hemorra-

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Bleeding after dental extractions in patients taking warfarin

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Abstract

Objective: To assess the incidence of bleeding after dental extractions in subjects taking warfarin continuously before and after extractions whose International Normalised Ratio (INR) was below 4.0 at the time of extraction.
Methods: This was a case series study of 150 patients without controls who required extraction of at least one tooth under local anaesthetic. All sockets were subsequently packed with absorbable oxycellulose and sutured.
Results: A total of 58 women and 92 men were included (mean age 66 years); their ages were similar. The mean INR (S.D.) was 2.5 (0.56), although most patients had an INR less than 2.5 ($n = 101$). Ten patients (7%) bled after extraction, enough to require a return to hospital. Five patients of 101 with an INR ≤ 2.5, and 5 with an INR > 2.5 out of 49 bled after extraction ($p = 0.29$). Bleeding after extraction was not associated with operative antibiotics. All patients who bled were managed conservatively and none was admitted to hospital.
Conclusion: Patients taking warfarin whose INR is up to 4.0 and who have dental extractions in hospital do not have clinically significant bleeds post-operatively.

Keywords: Warfarin; INR; Dental extractions; Post-operative bleeding

Introduction

Warfarin is one of the coumarin group of drugs and is prescribed for various conditions (Table 1). It blocks the formation of prothrombin and factors II, VII, IX, and X, which are involved in both the extrinsic and common coagulation pathways, and prevents the metabolism of vitamin K to its active form that is needed for the synthesis of these factors. Other vitamin K-dependent proteins inhibited by warfarin include proteins C and S, which are involved in the fibrinolytic system. Because coumarins bind strongly to plasma proteins, warfarin has a half-life of 36 h and acts slowly. Conversely, its discontinuation results in a prolonged latent effect, which explains advice to discontinue its use 2–3 days before dental extractions.[1]

The activity of warfarin is expressed as the International Normalised Ratio (INR),[2] which is the standard introduced by the World Health Organization 20 years ago. It is a prothrombin ratio obtained by dividing the prothrombin time by the laboratory control prothrombin time. The therapeutic range is the value of INR or degree of anticoagulation that is required to prevent the development of serious thromboembolism and it is normally maintained between 2.0 and 4.0.[3] The desirable range for the INR depends on the condition being treated (Table 1), and the risk of bleeding increases as the INR rises.[2]

The management of patients who take warfarin has varied, and included stopping 2 days before an operation, reduction in the dose, no change in the dose provided the INR was <4.0, and changing from the normal regular dose of warfarin to one of low molecular weight heparin preoperatively.[1] The risk of operative or postoperative bleeding must be balanced against the risk of thromboembolism in patients in

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Newer Oral Anticoagulant Agents: A New Era in Medicine

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Abstract: After a gap of almost 60 years following the development of warfarin, 2 new categories of oral anticoagulant agents have been approved for clinical use – the direct thrombin inhibitors and factor Xa inhibitors. These agents promise to be more convenient to administer with fixed dosing but still have equivalent efficacy and improved bleeding risk compared to warfarin. The clinical community is looking forward to the widespread usage of these agents but there is also some apprehension regarding bleeding risks, non-availability of specific reversal strategies and lack of specific monitoring parameters. This review article will attempt to educate the reader about three representative drugs from these classes: Dabigatran, Rivaroxaban and Apixaban. We will discuss the historical perspective to the development of these drugs, available research data and pharmacology of these agents. The best strategies for monitoring and reversal of these drugs in special situations will also be touched upon.

Keywords: Acute coronary syndrome, apixaban, atrial fibrillation, dabigatran, deep venous thrombosis, pulmonary embolism, rivaroxaban, venous thromboembolism.

INTRODUCTION AND HISTORICAL PERSPECTIVE

Therapeutic anticoagulation is widely used to treat and prevent thromboembolic disorders. Anticoagulant agents not only prevent new clot formation but also facilitate intrinsic mechanisms of clot lysis by retarding existing clot progression.

Effective anticoagulation has formed the basis of treatment for acute venous thromboembolic (VTE) events (deep venous thrombosis and pulmonary embolism) for a long time and reduces the mortality rate in this condition from 30% to 3-8% [1, 2]. Anticoagulants are administered in a preventative role to reduce clot formation in inherited and acquired hypercoagulable states. Anticoagulation is also used to prevent clot formation related to atrial fibrillation (left atrial appendage) and those caused by foreign bodies in contact with blood stream (artificial valves, catheters and cardiac devices). Anticoagulation reduces the incidence of stroke in atrial fibrillation by 60% [3-5]. Anticoagulation for deep venous thrombosis (DVT) prophylaxis in hospitalized medical patients decreases the incidence of DVT by up to 67% [5].

The introduction of heparin in the 1930s was a major breakthrough and provided the first widely available anticoagulant agent [6]. The major limitation was its limited mode of administration as a parenteral only agent which required close monitoring. This was partially overcome by another drug of historical importance which was also was the first oral anticoagulant agent – warfarin. It was first synthesized in 1940 and named after the Wisconsin Alumni Research Foundation [7]. Warfarin and its congeners were the only available oral anticoagulant agents until recently. Even though it has immense efficacy as an anticoagulant, warfarin is universally acknowledged as a cumbersome agent to use. It has a delayed onset of action, unpredictable efficacy affected by genetics, co-administered drugs & diet, body weight and age of the patient. It requires periodic monitoring to ensure therapeutic levels and despite careful follow up, only about 50% of the patients are able to achieve therapeutic level as defined by international normalized ratio (INR) [8]. The fact that heparin and warfarin are in wide use, some 80 and 60 years after their respective discoveries, is a testament to the relative efficacy and safety of these drugs. On the other hand, it indicates a failure to develop more effective and improved anticoagulant agents. The ideal anticoagulant agent needs to be efficacious, safe, convenient to use and easy to administer (preferably be oral).

Our improved knowledge of pharmacology and coagulation pathways has allowed us to develop newer anticoagulants which have shown significant promise. Beginning in the 1980s the low molecular weight heparins, enoxaparin and dalteparin being the principal agents, and then selective indirect factor Xa inhibitors like fondaparinux have been introduced [9]. These agents are parenteral and have their own limitations but nonetheless are seen as increasingly viable options to heparin. Danaparoid is another heparinoid with a mechanism of action similar to heparin, is an artificially formulated mixture of non-heparin glycosaminoglycans. This agent had been used extensively in patients with HIT after approval in 1996, but has not been available for use in the United States since 2002 after withdrawal by the manufacturer. Perhaps, their use primarily for HIT was being supplanted by emerging agents. Parenteral direct thrombin inhibitors like bivalirudin and argatroban were both approved in 2000 for unstable angina and heparin-induced thrombocytopenia respectively, are now being approved for expanding indications.

Newer oral anticoagulant agents have begun to emerge only recently and promise significant advantages over war-

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1 Basic principles underlying coagulation

Dougald M. Monroe

This chapter will discuss coagulation in the context of a hemostatic response to a break in the vasculature. *Coagulation* is the process that leads to fibrin formation; this process involves controlled interactions between protein coagulation factors. *Hemostasis* is coagulation that occurs in a physiological (as opposed to pathological) setting and results in sealing a break in the vasculature. This process has a number of components, including adhesion and activation of platelets coupled with ordered reactions of the protein coagulation factors. Hemostasis is essential to protect the integrity of the vasculature. *Thrombosis* is coagulation in a pathological (as opposed to physiological) setting that leads to localized intravascular clotting and potentially occlusion of a vessel. There is an overlap between the components involved in hemostasis and thrombosis, but there is also evidence to suggest that the processes of hemostasis and thrombosis have significant differences. There are also data to suggest that different vascular settings (arterial, venous, tumor microcirculation) may proceed to thrombosis by different mechanisms. Exploitation of these differences could lead to therapeutic agents that selectively target thrombosis without interfering significantly with hemostasis. Other chapters of this book will discuss some of the mechanisms behind thrombosis.

Healthy vasculature

Intact vasculature has a number of active mechanisms to maintain coagulation in a quiescent state. Healthy endothelium expresses ecto-ADPase (CD39) and produces prostacyclin (PGI_2) and nitric oxide (NO); all of these tend to block platelet adhesion to and activation by healthy endothelium [1]. Healthy endothelium also has active anticoagulant mechanisms, some of which will be discussed below. There is evidence that the vasculature is not identical through all parts of the body [2]. Further, it appears that there can be alterations in the vasculature in response to changes in the extracellular environment. These changes can locally alter the ability of endothelium to maintain a quiescent state.

Even though healthy vasculature maintains a quiescent state, there is evidence to support the idea that there is ongoing, low-level activation of coagulation factors [3]. This ongoing activation of coagulation factors is sometimes termed "idling" and may play a role in preparing for a rapid coagulation response to injury. Part of the evidence for idling comes from the observation that the activation peptides of factors IX and X can be detected in the plasma of healthy individuals. Because levels of the factor X activation peptide are significantly reduced in factor VII deficiency but unchanged in hemophilia, the factor VIIa complex with tissue factor is implicated as the key player in this idling process.

Tissue factor is present in a number of tissues throughout the body [4]. Immunohistochemical studies show that tissue factor is present at high levels in the brain, lung, and heart. Only low levels of tissue factor are detected in skeletal muscle, joints, spleen, and liver. In addition to being distributed in tissues, tissue factor is expressed on vascular smooth muscle cells and on the pericytes that surround blood vessels. This concentration of tissue factor around the vasculature has been referred to as a hemostatic envelope. Endothelial cells in vivo do not express tissue factor, except possibly during invasion by cancer cells. Also, there is evidence to suggest that tissue factor may be present on microparticles in the circulation. The nature and function of this circulating tissue factor is being actively researched by a number of groups. The information to date suggests that this tissue factor

Emergence of new oral antithrombotics: a critical appraisal of their clinical potential

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Abstract: In Western countries, venous thromboembolism (VTE) is a widespread and serious disorder, with hospital admission rates that appear to be increasing. Current anticoagulant therapies available for the prevention and treatment of VTE have several drawbacks that make them either difficult to manage effectively, due to a need for careful monitoring to control coagulation, or, in the case of parenterally administered agents, inconvenient for long-term use. To address some of these issues, new anticoagulants are in clinical development that can be orally administered and directly target specific factors in the coagulation cascade. This article reviews the rationale behind development of these novel agents and provides a critical appraisal of their clinical potential. In addition, the impact that the introduction of such agents into clinical practice would have is discussed from the patient perspective.

Keywords: antithrombotic agents, venous thromboembolism, Factor Xa, thrombin

The history of antithrombotics

Anticoagulants are recommended for the prevention and treatment of venous thromboembolism (VTE), and the prevention of thromboembolic events in patients with chronic conditions such as atrial fibrillation (AF) (Buller et al 2004; Geerts et al 2008), or in patients with mechanical heart valves. For the prevention of VTE, the American College of Chest Physician (ACCP) guidelines recommend that extended thromboprophylaxis should be given to patients for up to 35 days (grade 1A) following total hip replacement (THR) and for at least 10 days after total knee replacement (TKR) (grade 1A) (Geerts et al 2008). Currently available anticoagulants comprise the heparins – unfractionated heparin (UFH) and the low molecular weight heparins (LMWHs), eg enoxaparin, tinzaparin, dalteparin – the vitamin K antagonists (VKAs), including warfarin, and the synthetic pentasaccharide fondaparinux. Although effective, these agents have significant limitations (Table 1).

UFH, developed more than 60 years ago (Hirsh et al 2007), requires parenteral administration, making it inconvenient for use outside the hospital setting. It also requires coagulation monitoring and is associated with heparin-induced thrombocytopenia (HIT) and osteopenia (Hirsh et al 2001). The LMWHs, developed in the 1980s, overcame some of the drawbacks associated with UFH: they do not require monitoring and have a substantially lower risk of HIT compared with UFH (Warkentin et al 1995). However, LMWHs are administered by subcutaneous injection, and accumulation can occur in patients with renal impairment (Hirsh et al 2004).

VKAs have been in use in humans for more than 50 years and are currently the only oral anticoagulants available. The utility of VKAs is limited by the difficulty of managing them, the requirement of frequent monitoring and the necessity for dose adjustment to limit the adverse consequences of a narrow therapeutic window, multiple food and drug interactions, and variable pharmacology. These qualities, in addition to

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Oral Anticoagulants: Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutic Range

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Abbreviations: AFASAK = Atrial Fibrillation, Aspirin, Anticoagulation; AMI = acute myocardial infarction; AF = atrial fibrillation; CARS = Coumadin Aspirin Reinfarction Study; CI = confidence interval; DVT = deep vein thrombosis; INR = international normalized ratio; IRP = international reference preparation; ISI = international sensitivity index; MI = myocardial infarction; PE = pulmonary embolism; PT = prothrombin time; SPAF = Stroke Prevention in Atrial Fibrillation; WHO = World Health Organization

(CHEST 2001; 119:8S–21S)

The optimal therapeutic range for oral anticoagulant therapy was reviewed by the Committee on Antithrombotic Therapy of the American College of Chest Physicians and the National Heart, Lung, and Blood Institute in 1986, 1989, 1992, 1995, and again in 1998. The validity of the recommendation made at the earlier conferences, that the intensity of warfarin treatment should be reduced for many indications, continues to be upheld. Thus, whenever a more intense international normalized ratio (INR) is compared directly in a randomized trial, with an INR of 2.0 to 3.0, the less intense INR is as effective and safer. The recommendations for the optimal therapeutic range for the various indications remains unchanged (Table 1).

A recommendation of an INR of 2.0 to 3.0 is made for most indications. The exceptions are some types of mechanical prosthetic heart valves (see chapter on Antithrombotic Therapy in Patients With Mechanical and Biological Prosthetic Heart Valves). In addition, certain patients with thrombosis and the antiphospholipid syndrome may require a higher targeted INR than 2.0 to 3.0. Results of studies in atrial fibrillation (AF) support the earlier findings that the effectiveness of warfarin is reduced when the INR falls to < 2.0 and is essentially lost when the INR falls to < 1.5.[145,145a] The Coumadin Aspirin Reinfarction Study (CARS)[144] and recently reported CHAMP (*c*ombined *h*emotherapy and *m*ortalitly *p*revention) study[144a] also showed that the addition of low-dose warfarin (mean INR 1.3 and 1.9, respectively) did not improve the efficacy of aspirin in the secondary prevention of acute myocardial infarction (AMI). In contrast, the Thrombosis Prevention Trial,[119] a primary prevention study in men free of ischemic heart disease at entry, reported that warfarin is effective in reducing myocardial ischemic events (including fatal events) when used at a targeted INR of 1.3 to 1.8 (mean warfarin dose of 4.1 mg). The addition of low-dose aspirin to warfarin therapy resulted in a further small benefit but at a risk of increased bleeding.

In summary, the results of studies (1) do not support the use of fixed low-dose warfarin therapy for the treatment of patients with AMI or AF[144,145]; (2) indicate that the effectiveness of warfarin is reduced when the INR is < 2.0[144,145,145a]; (3) indicate that adjusted-dose warfarin therapy produces some benefit at an INR of 1.3 to 2.0 when used for primary prevention, and that an INR of > 1.5 confers some benefit in patients with AF, although the benefit is clearly less than that which occurs with an INR of > 2.0[45a]; and (4) two studies evaluating the long-term treatment of deep vein thrombosis (DVT) reported that recurrences are prevented completely at an INR of 2.0 to 3.0[137,138]; the small number of events in the warfarin group occurred when the patients discontinued treatment. These findings suggest that it might be possible to lower the INR range to < 2.0, a hypothesis that is being tested in a number of randomized trials.

Mechanism of Action of Coumarin Anticoagulant Drugs

Coumarins are vitamin K antagonists that produce their anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide). Vitamin K is a cofactor for the posttranslational carboxylation of glutamate residues to γ-carboxyglutamates on the N-terminal regions of vitamin K-dependent proteins (Fig 1).[1–6] These coagulation factors (factors II, VII, IX, and X) require γ-carboxylation for their biological activity. Coumarins produce their anticoagulant effect by inhibiting the vitamin K conversion cycle, thereby causing hepatic production of partially carboxylated and decarboxylated proteins with reduced procoagulant activity.[7,8] In addition to their anticoagulant effect, the vitamin K antagonists inhibit carboxylation of the regulatory anticoagulant proteins C and S and therefore have the potential to exert a procoagulant effect.

In the presence of calcium ions, carboxylation causes a conformational change in coagulation proteins[9–11] that promotes binding to cofactors on phospholipid surfaces. The carboxylation reaction requires the reduced form of vitamin K (vitamin KH_2), molecular oxygen, and carbon dioxide, and is linked to the oxidation of vitamin KH_2 to vitamin K epoxide. Vitamin K epoxide is then recycled to vitamin KH_2 through two reductase steps. The first, which is sensitive to vitamin K antagonists,[1–3] reduces vitamin K epoxide to vitamin K_1 (the natural food form of vitamin K_1), while the second, which is relatively insensitive to vitamin K antagonists, reduces vitamin K_1 to vitamin KH_2. Treatment with vitamin K antagonists leads to the depletion of vitamin KH_2, thereby limiting the γ-carboxylation of the vitamin K-dependent coagulant proteins. The effect of coumarins can be counteracted by vitamin K_1 (either ingested in food or administered therapeutically) because the second reductase step is relatively insensitive to vitamin K antagonists (Fig 1). Patients treated with a large dose of vitamin K_1 can also become warfarin resistant for

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Clinical
PRACTICE

Dental Surgery for Patients on Anticoagulant Therapy with Warfarin: A Systematic Review and Meta-analysis

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ABSTRACT

Purpose: To evaluate the effect of continuing warfarin therapy on the bleeding risk of patients undergoing elective dental surgical procedures.

Methods: Data sources were the MEDLINE and EMBASE databases, the Cochrane Central Register of Controlled Trials, a manual citation review of the relevant literature, content experts and relevant abstracts from the proceedings of the International Association for Dental Research. Study selection was carried out independently by 2 reviewers, as was quality assessment. Data extraction was done by 3 reviewers. Differences were resolved by consensus. Eligible studies were randomized controlled trials that compared the effects of continuing the regular dose of warfarin therapy with the effects of discontinuing or modifying the dose on the incidence of bleeding in patients undergoing dental procedures.

Results: Five trials (a total of 553 patients) met the inclusion criteria. Compared with interrupting warfarin therapy (either partial or complete), perioperative continuation of warfarin with patients' usual dose was not associated with an increased risk for clinically significant nonmajor bleeding (relative risk [RR], 0.71; 95% confidence interval [CI]: 0.39–1.28; $p = 0.65$; $I^2 = 0\%$) or an increased risk for minor bleeding (RR, 1.19; 95% CI: 0.90–1.58; $p = 0.22$; $I^2 = 0\%$).

Conclusions: Continuing the regular dose of warfarin therapy does not seem to confer an increased risk of bleeding compared with discontinuing or modifying the warfarin dose for patients undergoing minor dental procedures.

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Warfarin therapy is used by more than 4 million patients in North America for conditions such as atrial fibrillation, mechanical heart valve and venous thromboembolism.[1] Warfarin therapy reduces the risk of arterial thromboembolic events such as stroke by 70%[2,3] and the risk of recurrent venous thromboembolism by 90%.[4] Given these therapeutic benefits, the management of patients on anticoagulant therapy who require surgery or another invasive procedure is a problem because clinicians must weigh the risk of thromboembolism caused by a temporary interruption of warfarin therapy against the risk of perioperative bleeding if the therapy is continued.

In clinical practice, the management of patients on anticoagulant therapy who require

CHEST Supplement
ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Perioperative Management of Antithrombotic Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: **This guideline addresses the management of patients who are receiving anticoagulant or antiplatelet therapy and require an elective surgery or procedure.**
Methods: **The methods herein follow those discussed in the Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines article of this supplement.**
Results: **In patients requiring vitamin K antagonist (VKA) interruption before surgery, we recommend stopping VKAs 5 days before surgery instead of a shorter time before surgery (Grade 1B). In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, we suggest bridging anticoagulation instead of no bridging during VKA interruption (Grade 2C); in patients at low risk, we suggest no bridging instead of bridging (Grade 2C). In patients who require a dental procedure, we suggest continuing VKAs with an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure instead of alternative strategies (Grade 2C). In moderate- to high-risk patients who are receiving acetylsalicylic acid (ASA) and require noncardiac surgery, we suggest continuing ASA around the time of surgery instead of stopping ASA 7 to 10 days before surgery (Grade 2C). In patients with a coronary stent who require surgery, we recommend deferring surgery > 6 weeks after bare-metal stent placement and >6 months after drug-eluting stent placement instead of undertaking surgery within these time periods (Grade 1C); in patients requiring surgery within 6 weeks of bare-metal stent placement or within 6 months of drug-eluting stent placement, we suggest continuing antiplatelet therapy perioperatively instead of stopping therapy 7 to 10 days before surgery (Grade 2C).**
Conclusions: **Perioperative antithrombotic management is based on risk assessment for thromboembolism and bleeding, and recommended approaches aim to simplify patient management and minimize adverse clinical outcomes.** ***CHEST 2012; 141(2)(Suppl):e326S–e350S***

Abbreviations: aPTT = activated partial thromboplastin time; ASA = acetylsalicylic acid; AT8 = Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition); AT9 = Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; ATE = arterial thromboembolism; CABG = coronary artery bypass graft; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack; INR = international normalized ratio; LMWH = low-molecular-weight heparin; PICO = population, intervention, comparator, and outcome; SC = subcutaneous; UFH = unfractionated heparin; VKA = vitamin K antagonist

Summary of Recommendations

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

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ORIGINAL RESEARCH

Dental extraction in patients on warfarin treatment

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Background: Warfarin is one of the most common oral anticoagulants used to prevent thromboembolic episodes. The benefits of discontinuation of this drug before simple surgical procedures are not clear and this approach could be associated with complications. The aim of this study was to evaluate the risk of bleeding in a series of 35 patients (in cases where the international normalized ratio [INR] is less than 4) following simple tooth extraction without modification of the warfarin dose given to patients.

Methods: Thirty-five patients taking warfarin who had been referred to the Oral and Maxillofacial Department, College of Dentistry, King Saud University, for dental extractions were included in the study. Exclusion criteria included patients with an INR of ≥4 or with a history of liver disease or coagulopathies. No alteration was made in warfarin dose, and the CoaguChek System was used to identify the INR on the same day of dental extraction. Bleeding from the extraction site was evaluated and recorded immediately after extraction until the second day.

Results: A total of 35 patients (16 women and 19 men) aged between 38 and 57 years (mean =48.7) were included in the present study. All patients underwent simple one-tooth extraction while undergoing warfarin treatment. Oozing, considered mild bleeding and which did not need intervention was seen in 88.6% of patients. Moderate bleeding occurred in 11.4% of all cases. The INR of the patients ranged from 2.00 to 3.50, with 77.2% of patients having INR between 2.0 and 2.5 on the day of extraction. No severe bleeding which needed hospital management was encountered after any of the extractions. The patients who suffered moderate bleeding were returned to the clinic where they received local treatment measures to control bleeding. Moderate bleeding occurred only in four patients, where three had INR between 3.1 and 3.5, and one with INR less than 3.

Conclusion: In the present study, we have shown that simple tooth extraction in patients on warfarin treatment can be performed safely without high risk of bleeding, providing that the INR is equal or less than 3.5 on the day of extraction. A close follow-up and monitoring of patients taking warfarin is mandatory after dental extraction.

Keywords: tooth extraction, bleeding, INR

Introduction

Warfarin, which acts by antagonizing the effect of vitamin K, is one of the most commonly used oral anticoagulants. The drug can be absorbed completely and reaches its peak in 1 hour after ingestion.[1] Albumin is bound to circulating warfarin, and the half-life of warfarin is approximately 36 hours.[2] The liver metabolizes warfarin into inactive compounds, which are then excreted, mainly into the urine. Warfarin has been used to decrease the thromboembolism in millions of patients worldwide. Its effect is measured by international normalized ratio (INR), which is a measure of patient's

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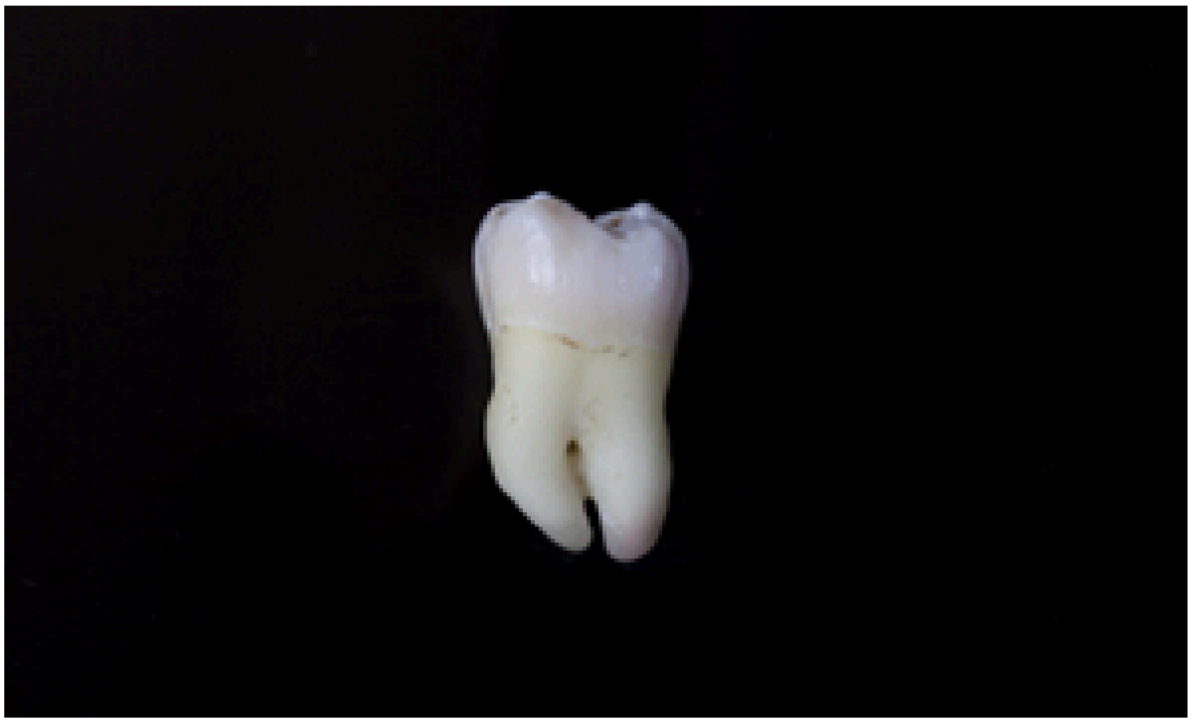
Management of Dental Extractions in Patients taking Warfarin as Anticoagulant Treatment: A Systematic Review



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October 13, 2015

A gyógyszer indukálta vérzékeny betegek fogorvosi, szájsebészeti ellátása: a 2015-ös hazai szakmai ajánlás alkalmazása és értékelése

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Bevezetés: A Magyar Arc-, Állcsont- és Szájsebészeti Társaság és a Magyar Fogorvosok Implantológiai Társasága által 2015-ben elfogadásra került „A gyógyszer indukálta vérzékeny betegek fogorvosi ellátása" szakmai ajánlás. *Célkitűzés:* A szerzők célja volt az ajánlásban leírt lokális vérzéscsillapítási módszerek hatékonyságának, megbízhatóságának ellenőrzése. *Módszer:* Az orális antithromboticus kezelésben részesülő betegeiknél vizsgálták a fogorvosi, szájsebészeti ellátásukat követő utóvérzések előfordulását, retrospektív módon. *Eredmények:* 263, vérzéssel járó beavatkozás történt (186 betegnél), amelyből 138 K-vitamin-antagonista, 97 thrombocytaaggregáció-gátló és 6, úgynevezett új típusú orális antikoaguláns kezelésben részesülő betegeknél. Összesen 6 (2,3%) esetben tapasztaltak utóvérzést az egyórás kontrollnál, míg ügyeletbe 1 beteg jött vissza utóvérzés miatt (0,5%). Ezzel szemben 86-an jelentkeztek ügyeletükön, akiknél az ajánlást nem vették figyelembe, közülük K-vitamin-antagonista gyógyszert szedett 3 beteg, alacsony molekulasúlyú heparinkezelésben részesült 24 beteg, thrombocytaaggregáció-gátló szert szedett 30 beteg és új típusú orális antikoaguláns kezelésben részesült 1 beteg. *Következtetések:* A hazai szakmai ajánlás az ambuláns gyakorlatban biztonságosan alkalmazható az antithromboticus terápiában részesülő páciensek vérzéssel járó fogorvosi/szájsebészeti beavatkozásakor, habár a körzetes fogorvos ellátók sok esetben nincsenek ilyen jellegű ellátásra felkészülve. Orv. Hetil., 2016, *157*(43), 1722–1728.

Kulcsszavak: antithromboticus kezelés, K-vitamin-antagonista, thrombocytaaggregáció-gátló, új típusú orális antikoaguláns, utóvérzés, fogorvosi-szájsebészeti ellátás

Dental and oral surgical treatment of medication-induced bleeding patients: Audit of the national guideline in Hungary

Introduction: In 2015 a new Hungarian guideline was published regarding dental treatment and management of anticoagulated patients in agreement of the Hungarian Association of Oral and Maxillofacial Surgeons and the Dental Implantology Association of Hungarian Dentists. *Aim:* The aim of the authors was to evaluate the efficiency and safety of local hemostatic measures recommended by the guideline in anticoagulated patients. *Method:* In these patients, postoperative bleeding episodes were examined after dental and oral surgical treatments, retrospectively. *Results:* Overall 263 bleeding risk cases were treated; 138 patients with vitamin K antagonists, 97 patients with antiplatelet therapy and 6 patients with novel oral anticoagulants. Six patients (2.3%) had minor postoperative bleeding after the "one hour control", while one patient needed a night duty support (0.5%). In contrast, 86 patients who were treated in rural practices neglecting the guideline attended the night duty with postoperative bleeding (3 patients treated with vitamin K antagonists, 24 patients taking low molecular weight heparin, 30 patients receiving antiplatelet therapy and one patient on novel oral anticoagulant therapy. *Conclusions:* The Hungarian guideline can be applied safely, without increasing the risk of postoperative bleeding, however, rural dental practices are frequently unprepared for these treatments.

IN BRIEF

- Dental extractions can be safely performed on patients receiving warfarin therapy without stopping or altering the dose of anticoagulant.
- The chances of a thromboembolic attack may be significantly higher than the chance of postoperative bleeding when anticoagulant medication is temporarily stopped.
- Mechanical pressure may be very important and beneficial in stopping postoperative bleeding compared with other alternatives.

Evaluation of dental extractions, suturing and INR on postoperative bleeding of patients maintained on oral anticoagulant therapy

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Objective To examine the consequences of temporary withdrawal of warfarin and/or suturing on bleeding and healing pattern following dental extractions.

Methods Two hundred and fourteen patients on long-term oral anticoagulation (warfarin) therapy scheduled for dental extraction were randomly divided into four groups: no suturing and discontinued (group 1) or continued warfarin (group 2), and suturing and discontinued (group 3) or continued warfarin (group 4). International normalised ratio (INR) was determined at different time points (baseline, days 1, 3 and 7).

Results Discontinuing warfarin reduced INR level significantly at day 1, which subsequently reached <1.5 in 96 out of 104 patients (group 1 and 3). Statistical comparisons among the different treatment groups did not reveal any significant difference regarding bleeding status or healing pattern. Interestingly, patients who received sutures showed higher but insignificant incidence of bleeding postoperatively compared to their respective controls.

Conclusion Dental extractions may be safely performed for patients on anticoagulation therapy provided the INR level is kept ≤ 3.0 and effective measures of local haemostasis are administered. The decision to suture should be made on case-by-case basis, as the trauma associated with soft tissue handling might outweigh its advantages in certain situations like simple extractions.

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INTRODUCTION

Oral anticoagulants are one of the most effective prophylactic/therapeutic medications to combat life-threatening thromboembolic events.[1,2] The principal adverse effect of oral anticoagulants is haemorrhage that may cause related complications for some patients.[3-5] Warfarin, a competitive inhibitor of vitamin K, is a commonly prescribed oral anticoagulant to reduce the risk of thromboembolism in patients with mechanical heart valves, deep vein thrombosis and other hypercoagulable states.[6]

The use of the international normalised ratio (INR) has been recommended for monitoring patients' oral anticoagulant therapy. This recommendation is supported by the American College of Chest Physicians, the National Heart, Lung and Blood Institute and the British Society for Haematology.[7] The INR was developed to incorporate the international sensitivity index (ISI) values and attempt to make prothrombin time (PT) results uniformly useable. The working reference has been calibrated against internationally accepted standard reference preparations which have an ISI value of 1.0.[8] By definition, those more sensitive to thromboplastin have an ISI of less than 1.0 and those less sensitive are greater than 1.0. The ISI value is critical for calculation of the INR, because the ISI value is the exponent in the formula. Consequently, small errors in the ISI assignment may affect the calculated INR substantially.[9]

Most patients on oral anticoagulant therapy belong to the age group where high prevalence of periodontitis and other dental ailments may necessitate surgical intervention[10-13] and hence the evaluation of risk of bleeding (with anticoagulation) or thromboembolism (without anticoagulation) is essential. The dilemma of anticoagulant therapy administration before, during and/or after oral surgery continues to prevail, as there are

BASIC AND PATIENT-ORIENTED RESEARCH | VOLUME 67, ISSUE 5, P990-995, MAY 01, 2009

Randomized, Prospective Trial Comparing Bridging Therapy Using Low-Molecular-Weight Heparin With Maintenance of Oral Anticoagulation During Extraction of Teeth

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DOI: https://doi.org/10.1016/j.joms.2008.12.027

Purpose

To evaluate postoperative bleeding and thromboembolic complications during dental extractions in anticoagulated patients, using 2 different protocols.

Patients and Methods

In total, 214 anticoagulated patients in need of simple dental extractions were randomized into 2 groups. Group A consisted of 109 patients on continuous oral anticoagulation therapy (OAT), with a mean international normalized ratio (INR) of 2.45 ± 0.54. Local hemostasis in these patients was achieved with resorbable collagen sponges, without wound suturing. Group B consisted of 105 patients on bridging therapy with low-molecular-weight heparin (nadroparin-calcium), with a mean INR of 1.26 ± 0.11 on the day of the procedure. Neither local hemostatic agents nor suturing of the wound was used in these patients.

Results

Eight (7.34%) patients in group A and 5 (4.76%) patients in group B manifested postextractional bleeding, without statistical significance (χ^2, Yates' = 0.253, $P > .05$). All cases of hemorrhage were mild and easily controlled using local hemostatic measures. None of the participants in either group experienced thromboembolic complications.

Conclusions

In patients receiving OAT with an INR ≤4.0, simple dental extractions can be performed safely without interruption or modification of OAT, using local hemostatic measures. Suturing of the wound should be reserved for cases with a greater extent of surgical trauma, and when primary hemostasis is insufficient. There is no need for bridging therapy with low-molecular-weight heparin in patients undergoing minor dentoalveolar procedures, although this approach can be used in patients with major oral surgical interventions.

David Brieger
Jenny Curnow

Anticoagulation: a GP primer on the new oral anticoagulants

Background
The acceptability of warfarin has been limited by mandatory laboratory monitoring. A number of new orally active anticoagulants (NOACs), which can be used as alternatives to warfarin, are now available.

Objective
We review the clinical indications and considerations associated with the use of the NOACs.

Discussion
The NOACs currently approved in Australia are dabigatran, rivaroxaban and apixaban. Indications include thromboprophylaxis in non-valvular atrial fibrillation and following hip and knee replacement surgery. Rivaroxaban is also approved for treatment and secondary prevention of deep venous thrombosis (DVT) and pulmonary embolus (PE). The NOACs differ from warfarin in that they do not require laboratory monitoring. They need to be used cautiously in patients with renal impairment and are contraindicated in patients with renal failure. Bleeding may require blood product replacement aided by haematological advice and specialist investigations. Antidotes to the NOACS are undergoing clinical trials.

Keywords
general practice; anticoagulants

Warfarin was orginally developed as a pesticide against rodents but has been used for the treatment of thromboembolic conditions since the 1950s. It is the most commonly used anticoagulant worldwide. Warfarin requires routine coagulation monitoring and dose adjustments to compensate for the many food–drug and drug–drug interactions that interfere with its effects. This complicates treatment and is the stimulus for the development of alternative anticoagulants.

Ximelagatran, the first of the alternative agents to be developled, is a direct thrombin inhibitor. It showed clinical efficacy in non-valvular atrial fibrillation and venous thromboembolic disease in studies conducted in 2000–2005. It was approved for both indications in a range of countries throughout Europe but it was associated with an unacceptable incidence of liver toxicity and was withdrawn from the market in 2006. Ximelagatran was never approved for use in Australia.

A number of new oral anticoagulants (NOACs) with properties that overcome the practical limitations of warfarin have recently become available. These agents have a more stable pharmacokinetic profile, have no significant food–drug interactions and fewer drug–drug interactions, and can be administered in a standard dose without the need for routine monitoring.

The NOACs have been evaluated for use in venous thromboembolic disease, non-valvular atrial fibrillation and several other cardiac indications. Three NOACs now have Therapeutic Goods Administration (TGA) approval for use in Australia and are listed on the Pharmaceutical Benefits Scheme (PBS) for subsidy. The purpose of this article is to provide a simple overview of the different agents and some rational guidance on their integration into our clinical practice.

Pharmacology of the NOACs

The NOACs fall into two broad categories: direct thrombin inhibitors and the factor Xa inhibitors (*Figure 1*). The direct thrombin

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REVIEW

New anticoagulants: beyond heparin, low-molecular-weight heparin and warfarin

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The limitations of traditional anticoagulants, heparin and warfarin, have prompted the development of new anticoagulant drugs for prevention and treatment of both venous and arterial thromboembolism. After a brief review of thrombogenesis and its regulation, this paper focuses on new anticoagulant agents in more advanced stages of clinical testing.
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Keywords: Anticoagulant; antithrombotic; venous thromboembolism; arterial thromboembolism; direct thrombin inhibitor; pentasaccharide

Abbreviations: ADP, adenosine diphosphate; EPCR, endothelial protein C receptor; Factor VIIa, activated factor VII; Factor VIIai, active site-blocked factor VIIa; GP, glycoprotein; INR, international normalized ratio; NAPc2, nematode anticoagulant peptide; PF4, platelet factor 4; TAP, tick anticoagulant peptide; TF, tissue factor; TFPI, tissue factor pathway inhibitor; t-PA, tissue plasminogen activator; u-PA, urokinase plasminogen activator

Thrombogenesis and its regulation

Hemostasis, the physiologic response to vascular injury, results in the formation of a haemostatic plug that prevents blood loss. Under normal conditions, factors that promote blood coagulation are balanced by those that inhibit it. Pathologic thrombosis occurs when procoagulant stimuli overwhelm natural anticoagulant and fibrinolytic systems (Friedman, 1987).

Venous thrombi, which form under low flow conditions, are predominantly composed of fibrin and red cells. Thrombi may develop anywhere within the venous system, but most commonly arise in the deep veins of the leg (Lensing *et al*., 1999), through an interplay among venous stasis, hypercoagulability, and vessel wall damage (Lensing *et al*., 1999). Delayed emptying of the veins retard clearance of activated clotting factors. Hypoxemia caused by stasis results in activation of the endothelial cells lining the avascular valve cusps, a process exacerbated by inflammatory cytokines generated postoperatively or in medical illness. Leukocytes tethered to activated endothelial cells express tissue factor (TF), whereas platelets become activated and aggregate. Congenital or acquired disorders associated with hypercoagulability promote coagulation at these sites, thereby increasing the risk of thrombosis. Direct damage to the veins helps to explain the propensity to deep vein thrombosis after major orthopaedic surgery. Signs and symptoms develop when there is obstruction to venous outflow and inflammation of the vessel wall and perivascular tissue. Symptoms of pulmonary embolism can arise if segments of thrombus detach and embolize to the pulmonary circulation.

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Arterial thrombosis usually is initiated by spontaneous or mechanical rupture of atherosclerotic plaque, a process that exposes thrombogenic material in the lipid-rich core of the plaque to the blood (Fuster, 1996). These thrombi form under high shear conditions and are composed primarily of platelet aggregates held together by fibrin strands. Obstruction of anterograde arterial flow leads to ischemia, which manifests as unstable angina or myocardial infarction in the case of coronary arteries, or stroke if cerebral vessels are involved (Fuster, 1996).

Blood constituents normally do not interact with intact endothelium. After damage to the endothelial lining of veins or arteries, platelets adhere to newly exposed subendothelial matrix components, particularly collagen and von Willebrand factor, *via* constitutively expressed receptors. Adherent platelets become activated, and recruit additional platelets by synthesizing thromboxane A_2 and releasing adenosine diphosphate (ADP) (Davie, 1995). Platelet activation induces conformational changes in glycoprotein (GP) IIb/IIIa, one of the most abundant receptors on the platelet surface. By binding fibrinogen or, under high shear conditions, von Willebrand factor, conformationally activated GPIIb/IIIa crosslinks adjacent platelets (Davie, 1995), resulting in platelet aggregation.

With damage to the vascular wall, TF-expressing cells are exposed to blood (Davie, 1995). This initiates coagulation in both the arteries and veins (Figure 1). TF binds activated factor VII (factor VIIa), which is found in small amounts in plasma, thereby forming factor VIIa/TF complex. This complex, also known as extrinsic tenase, activates factors IX and X, although factor X activation is more efficient (Davie, 1995). Factor Xa then converts small amounts of prothrombin to thrombin. This low concentration of thrombin is sufficient

AMBULATORY ANESTHESIA: EDITED BY THOMAS FUCHS-BUDER

New antithrombotic agents in the ambulatory setting

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Abstract

Purpose of review

Many patients presenting for surgical or other procedures in an ambulatory setting are taking new antiplatelet or anticoagulant agents. This review assesses how the novel features of these new agents affect the management of antithrombotic therapy in the ambulatory setting.

Recent findings

There have been very few studies investigating the relative risks of continuing or ceasing new antithrombotic agents. Recent reviews indicate that the new antithrombotic agents offer greater efficacy or ease of administration but are more difficult to monitor or reverse. They emphasize the importance of assessing the bleeding risk of the procedure, the thrombotic risk if the agent is ceased, and patient factors that increase the likelihood of bleeding. The timing of cessation of the agent, if required, depends on its pharmacokinetics and patients' bleeding risks. Patients at high risk of thrombotic complications may require bridging therapy. Once agreed upon, the perioperative plan should be made clear to all involved.

Summary

As there are few clinical studies to guide management, clinicians must make rational decisions in relation to continuing or ceasing new antithrombotic agents. This requires knowledge of their pharmacokinetics, and a careful multidisciplinary assessment of the relative thrombotic and bleeding risks in individual patients.

New oral anticoagulant drugs – mechanisms of action

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Summary

In 2008, two new oral anticoagulant drugs were registered in Australia for the prevention of venous thrombosis after elective knee or hip replacement. Rivaroxaban is a direct reversible competitive antagonist of activated factor X. Dabigatran etexilate is a direct reversible competitive antagonist of thrombin. Both drugs are effective anticoagulants which offer potential advantages over heparin and warfarin.

Key words: dabigatran etexilate, rivaroxaban.

(Aust Prescr 2010;33:38–41)

Introduction

Since the 1960s warfarin has been the only oral anticoagulant drug in regular use for treating patients with thromboembolic disease. In November 2008 the Therapeutic Goods Administration approved two new oral anticoagulant drugs – rivaroxaban and dabigatran etexilate – for the prevention of venous thrombosis in patients having elective knee or hip replacement.

Mechanisms of action

Rivaroxaban and dabigatran etexilate have low molecular weights. They have specific and restricted anticoagulant activities (Fig. 1). Although their mechanisms of action are different, the specificity of activity has no known clinical relevance and both drugs are effective anticoagulants.

Rivaroxaban is a competitive reversible antagonist of activated factor X (Xa). Factor Xa is the active component of the prothrombinase complex that catalyses conversion of prothrombin (factor II) to thrombin (factor IIa).

Dabigatran etexilate is a competitive reversible non-peptide antagonist of thrombin. Thrombin is a multifunctional enzyme which converts fibrinogen to fibrin, cross-linking fibrin monomers via activation of factor XIII and augmenting further thrombin production via the activation of factors V and VIII. It also activates platelets, generates anticoagulant activity via activation of protein C and initiates numerous cellular processes including wound healing. Most of the actions of thrombin are inhibited *in vitro* by dabigatran etexilate.

Pharmacokinetics

The essential properties of the new anticoagulants are compared to warfarin in Table 1. Their main advantages are a rapid onset of anticoagulant effect, more predictable pharmacokinetics, and a lower potential for clinically important interactions with food, lifestyle and other drugs. There is no requirement for routine monitoring and dose adjustment as required with warfarin.

Rivaroxaban

Rivaroxaban[1] 10 mg tablets are well absorbed (80% bioavailability) with no effect of food on absorption or pharmacokinetic parameters. Plasma concentrations peak at 2.5–4 hours. The plasma elimination half-life is 5–9 hours in young adults and 11–13 hours in older people due to the age-related decline in renal function. This permits once- or twice-daily dosing.

Rivaroxaban is metabolised by liver enzymes, principally cytochrome P450 3A4, and also by cytochrome-independent mechanisms. There are no known active metabolites. Rivaroxaban has a dual mechanism of excretion. Approximately 66% of the dose is excreted via the kidneys, in roughly equal proportions of rivaroxaban and inactive metabolites. The remainder is excreted by the faecal-biliary route. Intestinal excretion of rivaroxaban appears to be mediated, at least in part, by P-glycoprotein, a transport protein, because potent P-glycoprotein inhibitors will increase plasma concentrations of rivaroxaban.

Dabigatran

Dabigatran is a hydrophilic polarised membrane-impermeable molecule which is not absorbed after oral dosing. The oral formulation, dabigatran etexilate,[2] is a prodrug with low bioavailability (approximately 6.5%) and its absorption in the stomach and small intestine is dependent on an acid

Review

The new oral anticoagulants and the future of haemostasis laboratory testing

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Abstract

The tests currently employed within most haemostasis laboratories to monitor anticoagulant therapy largely comprise the prothrombin time (PT)/International Normalised Ratio (INR) and the activated partial thromboplastin time (APTT). These are respectively used to monitor Vitamin K antagonists (VKAs) such as warfarin, and unfractionated heparin. Additional tests that laboratories may also employ for assessing or monitoring unfractionated heparin include thrombin time (TT) and the anti-Xa assay, which can also be used to monitor low molecular weight heparin. Several new anti-thrombotic agents have recently emerged, or are in the final process of clinical evaluation. These novel drugs that include Dabigatran etexilate and Rivaroxaban would not theoretically require monitoring; however, testing is useful in specific situations. The tests currently used to monitor VKAs and heparin are typically either too sensitive or too insensitive to the new drugs to be used as 'typically performed in laboratories', and may thus require some methodological adjustments to increase or decrease their sensitivity. Alternately, different tests may be better employed in these assessments. Whatever the case, laboratories may soon be performing a reduced or possibly increased number of tests, the same kind of tests but perhaps differently, or conceivably different assay panels. Specific laboratory guidance on the choice of the appropriate test to be ordered according to the drug being administered, as well as on appropriate interpretation of test results, will also be necessary. The current report reviews the current state of play and provides a glimpse to the possible future of the coagulation laboratory.

Key words: haemostasis; coagulation; laboratory tests; anticoagulants; anti-thrombotics, Dabigatran, Rivaroxaban.

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Background

Anticoagulant therapy monitoring represents the main purpose of most routine coagulation laboratories, along with preoperative screening. Anticoagulants are alternatively referred to as 'antithrombotics', given their intended clinical therapeutic efficacy. The main current anticoagulant armamentarium comprises heparin and vitamin K antagonists (VKAs) (also known as coumarins) such as warfarin or acenocoumarol. The main new anticoagulant agents include, but do not exclusively comprise, Dabigatran etexilate, Rivaroxaban and Apixaban. VKAs and heparin are typically monitored because they exhibit a narrow therapeutic window, and largely unpredictable behavior in treated individuals. In contrast, the newer agents have been clinically developed and evaluated as requiring little to null laboratory monitoring. Laboratory testing of these agents will, however, be required in select cases, and laboratories should become proactive in recognizing the *in-vitro* behavior of these agents, developing appropriate strategies for any required testing, as well as establishing appropriate policies for post-test counseling on test results and expected outcomes.

Haemostasis, thrombosis and anticoagulant/antithrombotic therapy

Haemostasis represents the mechanism whereby the body maintains circulatory flow. It can be represented by Vichow's triad or - more commonly - as a balance of procoagulant and anticoagulant mechanisms or pathways, inclusive of fibrinolysis (1,2). We have recently reviewed this in the context of the changing landscape of coagulation testing (3), and so shall only briefly reiterate the main aspects here. In brief, an injury to the vascular en-

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New Oral Anticoagulants: Comparative Pharmacology with Vitamin K Antagonists

Francesco Scaglione

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Abstract

New oral anticoagulants (OACs) that directly inhibit Factor Xa (FXa) or thrombin have been developed for the long-term prevention of thromboembolic disorders. These novel agents provide numerous benefits over older vitamin K antagonists (VKAs) due to major pharmacological differences. VKAs are economical and very well characterized, but have important limitations that can outweigh these advantages, such as slow onset of action, narrow therapeutic window and unpredictable anticoagulant effect. VKA-associated dietary precautions, monitoring and dosing adjustments to maintain international normalized ratio (INR) within therapeutic range, and bridging therapy, are inconvenient for patients, expensive, and may result in inappropriate use of VKA therapy. This may lead to increased bleeding risk or reduced anticoagulation and increased risk of thrombotic events. The new OACs have rapid onset of action, low potential for food and drug interactions, and predictable anticoagulant effect that removes the need for routine monitoring. FXa inhibitors, e.g. rivaroxaban and apixaban, are potent, oral direct inhibitors of prothrombinase-bound, clot-associated or free FXa. Both agents have a rapid onset of action, a wide therapeutic window, little or no interaction with food and other drugs, minimal inter-patient variability, and display similar pharmacokinetics in different patient populations. Since both are substrates, co-administration of rivaroxaban and apixaban with strong cytochrome P450 (CYP) 3A4 and permeability glycoprotein (P-gp) inhibitors and inducers can result in substantial changes in plasma concentrations due to altered clearance rates; consequently, their concomitant use is contraindicated and caution is required when used concomitantly with strong CYP3A4 and P-gp inducers. Although parenteral oral direct thrombin inhibitors (DTIs), such as argatroban and bivalirudin, have been on the market for years, DTIs such as dabigatran are novel synthetic thrombin antagonists. Dabigatran etexilate is a low-molecular-weight non-active pro-drug that is administered orally and converted rapidly to its active form, dabigatran—a potent, competitive and reversible DTI. Dabigatran has an advantage over the indirect thrombin inhibitors, unfractionated heparin and low-molecular-weight heparin, in that it inhibits free and fibrin-bound thrombin. The reversible binding of dabigatran may provide safer and more predictable anticoagulant treatment than seen with irreversible, non-covalent thrombin inhibitors, e.g. hirudin. Dabigatran shows a very low potential for drug–drug interactions. However, co-administration of dabigatran etexilate with other anticoagulants and antiplatelet agents can increase the bleeding risk. Although the new agents are pharmacologically better than VKAs—particularly in terms of fixed dosing, rapid onset of action, no INR monitoring and lower risk of drug interactions—there are some differences between them: the bioavailability of dabigatran is lower than rivaroxaban and apixaban, and so the dabigatran dosage required is higher; lower protein binding of dabigatran reduces the variability related to albuminaemia. The risk of metabolic drug–drug interactions also appears to differ between OACs: VKAs > rivaroxaban > apixaban > dabigatran. The convenience of the new OACs has translated into improvements in efficacy and safety as shown in phase III randomized trials. The new anticoagulants so far offer the greatest promise and opportunity for the replacement of VKAs.

Safety of Dental Extractions During Uninterrupted Single or Dual Antiplatelet Treatment

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Optimal dental management in patients on long-term antiplatelet treatment is not clearly defined. Antiplatelet discontinuation increases the risk of thrombotic complications, whereas uninterrupted antiplatelet therapy, which is the currently recommended approach, is assumed to increase the bleeding hazard after dental procedures. We sought to prospectively compare the risk of immediate and late postextraction bleeding in patients receiving uninterrupted single or dual antiplatelet therapy. We recruited 643 consecutive patients referred for dental extractions. In total 111 (17.3%) were on clinically indicated antiplatelet therapy: aspirin (n = 42), clopidogrel (n = 36), and aspirin and clopidogrel (n = 33). Controls (n = 532, 82.7%) were not on antiplatelet treatment. Immediate and late bleeding complications were recorded. Compared to controls the risk of prolonged immediate bleeding was higher in patients on dual antiplatelet therapy (relative risk [RR] 177.3, 95% confidence interval [CI] 43.5 to 722, p <0.001) but not in patients on aspirin alone (RR = 6.3, 95% CI 0.6 to 68.4, p = 0.2) or clopidogrel alone (RR = 7.4, 95% CI 0.7 to 79.5, p = 0.18); however, all immediate bleeding complications in all treatment groups were successfully managed with local hemostatic measures. No patient developed any late hemorrhage. In conclusion, dental extractions may be safely performed in patients receiving single or dual antiplatelet therapy when appropriate local hemostatic measures are taken, thus averting thrombotic risk of temporary antiplatelet discontinuation. **(Am J Cardiol 2011;108:964–967)**

The purpose of this study was to prospectively assess the risk of immediate and late-onset bleeding complications during uninterrupted single or dual antiplatelet therapy in patients undergoing dental extractions.

Methods

The study was conducted from October 2009 through April 2010 at the Aristotle University Dental School, Thessaloniki, Greece. All consecutive patients referred for dental extractions were prospectively screened for study participation. We excluded patients with hematologic, renal, or liver disease; bone marrow disorders; alcoholism; or any concurrent medication affecting hemostasis such as oral or parenteric anticoagulants or anti-inflammatory drugs. Patients who needed extractions of deciduous teeth, surgical extractions, extractions in deferent quadrants, or multiple extractions (>3 teeth) were excluded based on previous studies assessing the bleeding risk of multiple extractions in orally anticoagulated patients.[1] Based on their medications, study participants were categorized as a treatment group receiving uninterrupted aspirin and/or clopidogrel and a control group receiving no antiplatelets. The study protocol was approved by the institutional ethical committee, and all study participants provided informed consent.

All patients were treated in morning sessions. Maxillary and anterior mandibular teeth were extracted under local anesthetic infiltration in the buccal and palatal or lingual aspect of the teeth. Posterior mandibular teeth were extracted under a combination of inferior alveolar nerve block anesthesia and anesthesia infiltration buccally and lingually. Each extraction site was infiltrated with lidocaine solution 2% 1.8 ml with epinephrine 1:80,000 to ensure similar local hemostatic effects of epinephrine.

Wound management included removal of granulation tissue, sharp bony edges, or foreign bodies. After extractions patients were instructed to bite on a pressure pack for 30 minutes. If bleeding was still present, it was by our definition considered prolonged postextraction bleeding. In these cases, a piece of oxidized cellulose gauze (Surgicel; Ethicon Inc, Somerville, New Jersy) was sutured over the inlet of the postextraction socket (3-0 silk sutures); patients then bit on a pressure pack for 30 minutes for a second time and were evaluated before leaving the clinic. All patients were given appropriate postoperative instructions and were advised to immediately report any hemorrhagic complication. Patients were interviewed by telephone at the end of the day of extraction, and complaints of bleeding were recorded. Sutures, if placed, were removed at 6 days.

Postextraction bleeding complications were categorized according to time of occurrence as immediate, occurring during the extraction session at the clinic, or late, occurring any time thereafter. Prolonged immediate bleeding was de-

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Minor Oral Surgery Without Stopping Daily Low-Dose Aspirin Therapy: A Study of 51 Patients

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Purpose: The risk of excessive bleeding prompts physicians to stop low-dose long-term aspirin regimens before surgery, which puts the patient at risk from adverse thrombotic events. We hypothesize that most minor oral surgical procedures can be carried out safely without stopping low-dose aspirin.

Patients and Methods: All minor oral surgery patients at our hospital (Madan Dental Hospital, Ahmedabad, India) from May 2002 to May 2003, who were also on long-term low-dose aspirin therapy regimens (acetylsalicylic acid 75 mg to 100 mg/day), were included. Investigation of bleeding time and platelet count was performed. If within normal limits, aspirin was not stopped before surgery. Patients were operated under local anesthesia on an outpatient basis. All wounds were sutured and followed up at 24, 48, and 72 hours, 1 week, and 2 weeks after the procedure.

Results: The study included 51 patients (32 males, 19 females), ranging in age from 45 to 70 years. Preoperative values were within normal limits for all patients. Aspirin was not stopped for a single patient. There was no excessive intraoperative bleeding in all cases except 1; there was no postoperative bleeding in all cases.

Conclusion: We conclude that most minor oral surgery procedures can be carried out safely without stopping long-term low-dose aspirin regimen.

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Acetylsalicylic acid (ASA) is widely used for its antiplatelet effects.[1] Low-dose aspirin (75 mg to 100 mg) is generally indicated in cases of angina, ischemic heart disease, post-myocardial infarction, post-bypass surgery, post-angiography/angioplasty, stroke, and transient ischemic attacks.[2] But the fear of uncontrolled bleeding prompts physicians to stop aspirin intake before surgical procedures, including oral surgery.[3,4] This puts the patients at risk of developing thromboembolism, myocardial infarction, or cardiovascular accident.[5]

We conducted a study of 51 consecutive patients on long-term low-dose aspirin therapy scheduled for oral surgery. We did not stop aspirin for a single patient and did not face any untoward sequelae. We present our results and observations and propose that most minor oral surgical procedures can be carried out safely without stopping low-dose aspirin therapy.

Materials and Methods

Only those patients who fulfilled all the inclusion criteria given below were included in this study:

1. Patients on long-term low-dose aspirin regimens (75 to 100 mg)
2. Patient requiring minor oral surgery procedures that could be performed on an outpatient basis
3. Patients who were not on any concurrent therapy such as birth control pills, hormone replacement therapy, other anticoagulation; or any drug such as NSAIDs that could interact with the aspirin
4. Patients who presented to our hospital between May 2002 and May 2003

Received from Madan Dental Hospital, Ahmedabad, India.

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Review of postoperative bleeding risk in dental patients on antiplatelet therapy

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Objective. We conducted a review of the literature to assess risk for oral bleeding complications after dental procedures in patients on antiplatelet therapy.

Study Design. We conducted a search in Medline, Embase, and National Guideline Clearinghouse databases for studies involving patients on single and dual antiplatelet therapy that had invasive dental procedures or manipulations that induce oral bleeding.

Results. The literature search yielded 15 studies that met inclusion criteria. There is a trend toward increased occurrence of immediate postoperative bleeding for dual antiplatelet therapy, but there is no increase in the occurrence of intra- or late postoperative bleeding complications.

Conclusions. We found no clinically significant increased risk of postoperative bleeding complications from invasive dental procedures in patients on either single or dual antiplatelet therapy. These findings support the recommendation that there is no indication to alter or stop these drugs, and that local hemostatic measures are sufficient to control bleeding. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:491-499)

Antithrombotics can be divided into 2 entirely different groups of drugs: those that affect platelet aggregation (e.g., acetylsalicylic acid [ASA] and clopidogrel), and those that affect clot formation and maintenance (e.g., coumarin derivatives). Antiplatelet agents are used for the secondary prevention of cardiac and cerebrovascular diseases, specifically for the prevention of arterial and venous thrombosis in patients with conditions such as ischemic heart disease, prosthetic heart valves, and coronary artery stents and those at risk for ischemic cerebrovascular accidents.

Antiplatelet agents can be classified by their mode of action in prevention of platelet activation and aggregation. ASA and triflusal work through inactivation of the enzyme cyclooxygenase, which converts arachidonic acid to the prostaglandin thromboxane A2, a key factor in platelet activation and aggregation. Inhibiting thromboxane A2 prevents clot formation for the lifetime of the platelet, which is 9-11 days.[1,2] Thienopyridines (e.g., clopidogrel, ticlopidine, and prasugrel) irreversibly inhibit adenosine diphosphate, which is necessary for the activation of the receptor GPIIb/IIIa complex in platelet aggregation.[3] Drugs targeted directly to the GPIIb/IIIa complex include tirofiban, eptibatide, and abciximab. Dipyridamole and cilostazol are phosphodiesterase inhibitors that decrease platelet aggregability. In addition, α-tocopherol (vitamin E) has been shown to inhibit platelet adhesion to the adhesive proteins collagen, fibrinogen, and fibronectin.[4]

Of concern to dental practitioners is the risk of excessive oral bleeding during or after invasive dental procedures. Although there is an abundance of literature pertaining to the effects of coumarin derivatives on patients having invasive dental procedures,[5] there is far less information on antiplatelet drugs. Although there have been strong warnings from some authors and organizations[6] that the risks from altering dosage of or stopping antiplatelet drugs far outweigh any benefit[6] there remains a prevailing practice of stopping these drugs before invasive dental procedures. There is no

Statement of Clinical Relevance

This literature review on the postoperative bleeding risk in dental patients on antiplatelet therapy shows that there is no indication to discontinue these drugs and that, in the event of postoperative bleeding, local hemostatic measures are sufficient.

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REVIEW

CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will manage bleeding complications in patients on the new oral anticoagulants

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Practical management of bleeding due to the anticoagulants dabigatran, rivaroxaban, and apixaban

ABSTRACT

The new oral anticoagulants dabigatran etexilate (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis) have predictable pharmacokinetic and pharmacodynamic profiles and are alternatives to warfarin. However, many physicians are wary of these drugs, since there is limited evidence on how to manage bleeding in patients taking them, and since no specific antidote is known to reverse their anticoagulant effect. Management requires careful adherence to first principles of bleeding care. Unapproved and untested reversal strategies may be required in patients with life-threatening bleeding.

KEY POINTS

Thromboprophylaxis with anticoagulants is an important aspect of managing patients at risk of systemic or pulmonary embolization.

Dabigatran is a direct inhibitor of thrombin (factor IIa); rivaroxaban and apixaban inhibit factor Xa.

Monitoring of coagulation function is not routinely necessary with the new drugs but may be useful in emergencies.

Nonspecific hemostatic agents that have been suggested for off-label use in reversing excessive bleeding in patients taking the new oral anticoagulants include recombinant factor VIIa, three-factor and four-factor prothrombin complex concentrate, and activated prothrombin complex concentrate.

*Dr. Crowther has disclosed consulting, teaching, and speaking for Baxter, Bayer, Boerhinger-Ingelheim, Bristol-Myers Squibb, CSL Behring, and Pfizer.

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In the past several years, three new oral anticoagulants—dabigatran etexilate (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis)—have been approved for use in the United States. These long-awaited agents are appealing because they are easy to use, do not require laboratory monitoring, and have demonstrated equivalence, or in some cases, superiority to warfarin in preventing stroke or systemic embolism in at-risk populations.[1–4] However, unlike warfarin, they have no specific reversal agents. How then should one manage spontaneous bleeding problems and those due to drug overdose, and how can we quickly reverse anticoagulation if emergency surgery is needed?

For these reasons, physicians and patients have been wary of these agents. However, with a systematic approach based on an understanding of the properties of these drugs, the appropriate use and interpretation of coagulation tests, and awareness of available therapeutic strategies, physicians can more confidently provide care for patients who require urgent reversal of anticoagulant effects.

Here, we review the available literature and suggest practical strategies for management based on an understanding of the pharmacokinetic and pharmacodynamic effects of these drugs and our current knowledge of the coagulation tests.

NEED FOR ANTICOAGULANTS

Anticoagulants are important in preventing systemic embolization in patients with atrial fibrillation and preventing pulmonary embolism in patients with venous thromboembolism.

Review article

The Perioperative Management of Treatment With Anticoagulants and Platelet Aggregation Inhibitors

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Background: When giving anticoagulants and inhibitors of platelet aggregation either prophylactically or therapeutically, physicians face the challenge of protecting patients from thromboembolic events without inducing harmful bleeding. Especially in the perioperative period, the use of these drugs requires a carefully balanced evaluation of their risks and benefits. Moreover, the choice of drug is difficult, because many different substances have been approved for clinical use.

Method: We selectively searched for relevant publications that appeared from 2003 to February 2013, with particular consideration of the guidelines of the European Society of Cardiology, the Association of Scientific Medical Societies in Germany (AWMF), the American College of Cardiology, and the American Heart Association.

Results: Vitamin K antagonists (VKA), low molecular weight heparins, and fondaparinux are the established anticoagulants. The past few years have seen the introduction of orally administered selective inhibitors of the clotting factors IIa (dabigatran) and Xa (rivaroxaban, apixaban). The timing of perioperative interruption of anticoagulation is based on pharmacokinetic considerations rather than on evidence from clinical trials. Recent studies have shown that substituting short-acting anticoagulants for VKA before a procedure increases the risk of bleeding without lowering the risk of periprocedural thromboembolic events. The therapeutic spectrum of acetylsalicylic acid and clopidogrel has been broadened by the newer platelet aggregation inhibitors prasugrel and ticagrelor. Patients with drug eluting stents should be treated with dual platelet inhibition for 12 months because of the risk of in-stent thrombosis.

Conclusion: Anticoagulants and platelet aggregation inhibitors are commonly used drugs, but the evidence for their perioperative management is limited. The risks of thrombosis and of hemorrhage must be balanced against each other in the individual case. Anticoagulation need not be stopped for minor procedures.

A practice tool for the new oral anticoagulants

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Although warfarin has been the "king" of oral anticoagulation for the past few decades, its reign is now jeopardized by the recent marketing in Canada of 3 new oral anticoagulants: dabigatran (Pradaxa*), rivaroxaban (Xarelto) and apixaban (Eliquis).[1-3] The recent availability of these 3 new oral anticoagulants is challenging for health professionals, as they differ in many ways from warfarin and each other, including in their mechanism of action, pharmacokinetics, drug interaction profile, monitoring and dosage adjustment requirements. Despite their widespread use in the community and hospitals, many practising clinicians remain unfamiliar with how to use these medications safely.[4]

This article provides a practice tool to assist health professionals to effectively use these medications and monitor their patients. For ease of use and retrieval of the specific characteristics of these new anticoagulants, the information has been summarized and presented in tables. A total of 5 comparative tables are featured: 1) pharmacology and pharmacokinetic properties, 2) indications and dosages, 3) significant drug interactions, 4) recommendations for switching anticoagulants and 5) management in the perioperative setting. A brief discussion on laboratory monitoring and reversing the activity of these drugs is also included.

To build these tables, the product monographs of the new oral anticoagulants were reviewed thoroughly and Drugdex (from Micromedex), LexiComp and Lexi-Interact databases were consulted. A literature search was conducted using OVID MEDLINE and an internal citation database of pharmacy journals (AskSam) to identify related articles. The following search terms (Medical Subject Headings and key words) were used: *apixaban*, *dabigatran*, *rivaroxaban*, *review*, *switching*, *perioperative care*, *perioperative setting* and *hemorrhage*. The literature search did not include randomized clinical trials and should not be viewed as a systematic review, as the goal was to collect key and practical prescribing information about the new oral anticoagulants, rather than assess them for their comparative efficacy and safety.

Pharmacology and pharmacokinetic properties

The new oral anticoagulants differ in their pharmacology and pharmacokinetics (Table 1). Although their onset of action and half-life are quite similar, other properties such as their respective mechanism of action, bioavailability, metabolism and clearance are different. Clinicians should be aware of these differences to ensure that each drug is used properly.

Indications and dosages

Table 2 features all indications and dosages approved by Health Canada, extracted from the most recent product monographs available at the time this article was prepared. Currently, rivaroxaban is the only new oral anticoagulant approved for the treatment of deep vein thrombosis and pulmonary embolism. However, this may change in the future, as many trials are currently being conducted for the above indication as well as others, which may lead to further approved indications from Health Canada.

With its low renal elimination, apixaban can be considered the preferred agent for elderly

*Pradaxa was originally named Pradax in Canada: the name was recently changed to align the product name with the United States and European countries (personal communication with Boehringer Ingelheim, October 3, 2012).

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9

Bleeding and antidotes in new oral anticoagulants

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In the past decade, several new oral anticoagulants (NOACs) have been studied and approved for the prophylaxis and treatment of arterial and venous thromboembolism. These agents were shown to be as effective as or better than warfarin and resulted in comparable or lower bleeding rates than warfarin. Specific antidotes for the reversal of the anticoagulant effect of these drugs, such as monoclonal antibodies against the direct thrombin inhibitor dabigatran or recombinant Xa-analog in the case of factor Xa inhibitors, are still being investigated in early clinical trials. In certain situations, as in case of emergency surgery or life-threatening major bleeding, a rapid reversal strategy is needed. Several non-specific prohemostatic agents or coagulation factor concentrates have been suggested as potential candidates for the reversal of NOACs, but the evidence supporting these agents was mainly derived from small animal studies, or is based on partial or complete correction of laboratory parameters in healthy volunteers treated with these agents. Activated prothrombin complex concentrate seems promising for the reversal of dabigatran, while non-activated prothrombin complex concentrates have potential for the reversal of anti-factor Xa. The risk of thromboembolic complications requires careful evaluation. In this article, the evidence- or the lack of it – supporting the use of the different prohemostatic agents for the management of bleeding and for reversal of the different classes of NOACs is discussed.

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