



Implant Considerations in the Anticoagulated Patient: A Review

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Abstract: Oral anticoagulation therapy is one of the most prevalent forms of treatment used in contemporary medicine. It is estimated that more than 50 million Americans adhere to some type of anticoagulation regimen. With an increase in implants and implant related surgical procedures done in the dental office, dentists should be well versed in the management and potential complications that can arise from patients undergoing anticoagulation therapy. The purpose of this article is to review contemporary oral anticoagulation therapy and offer literature based recommendations on the perioperative management of these patients in the practice of implant dentistry.

Key-words: dental implants, pharmacologic protocol, oral medicine, implant complications

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BACKGROUND

Oral anticoagulation therapy is one of the most prevalent forms of treatment used in contemporary medicine. It is estimated that more than 50 million Americans adhere to a low dose daily aspirin protocol and other anticoagulants such as warfarin sodium (Coumadin®, Bristol-Myers Squibb 345 Park Ave., New York, NY 10154) and Clopidogrel bisulfate (Plavix®, Bristol-Myers Squibb), which routinely rank among the top 50 medications prescribed in the United States.^{1,2} As the make up of the American population

ages with the majority of "baby boomers" now reaching retirement age, trends of increased oral anticoagulant use are expected to continue. Perioperative management of these patients for dental procedures has been a controversial issue for quite some time with debates regarding the risk of uncontrolled bleeding, if medication is continued, versus the possibility of thromboembolic complications, if the medication is discontinued. Since the late '50s, a menagerie of different recommendations have been issued with protocols that often contradict one

another. With implant surgery becoming the standard of care to replace the missing tooth, dental practices are increasing their exposure to surgical ramification. With the increasing age of the population, it is inevitable that the dentist will be faced with treating the anticoagulated patient within the implant setting. Dentists should be well versed in the management of the anticoagulated patient and the potential complications. The purpose of this article is to review contemporary oral anticoagulation therapy and offer literature-based recommendations on the perioperative management of these patients in the practice of implant dentistry.

ANTICOAGULATION RATIONALE

Improved understanding of cardiovascular physiology and advances in the management and treatment of cardiovascular disease have rendered oral anticoagulation therapy, a mainstay of modern medicine. Reduction in the occurrence of thromboembolism is often the goal of oral anticoagulation therapy for patients with a history of various conditions including, but not limited to; angina, atherosclerosis, atrial fibrillation, cerebrovascular occlusion, coronary stents, deep vein thrombosis, ischemic heart disease, myocardial infarction, prosthetic heart valves, and pulmonary embolism.³⁻⁶

In order to understand the manner in which oral anticoagulants treat these conditions, a basic understanding of hemostasis is necessary (Fig. 1). Briefly, hemostasis is a three part mechanism consisting of vascular spasm, platelet plug formation, and coagulation.⁷ Traumatic blood vessel injury induces protective vasoconstriction via neural reflexes and myogenic spasm.⁸ As the vessels contract, resulting in a narrowed lumen diameter, newly exposed collagen fibers activate nearby platelets causing them to morph

their shape, express multiple pseudopodia, and release stored granules. Platelet secretion of adenosine diphosphate and prostaglandins leads to further platelet recruitment and eventual formation of a platelet plug that occludes the narrowed vessel lumen. The final coagulation cascade is initiated by exposed subendothelial collagen and extravasated thromboplastin which respectively activate the intrinsic and extrinsic coagulation pathways. The ensuing interaction of multiple coagulation factors ultimately triggers activation of the common coagulation cascade. Subsequent interactions of Factor X and Factor V form a prothrombin activator complex that promotes cleavage of prothrombin to thrombin. Thrombin interacts with fibrinogen to form fibrin monomers that ultimately crosslink and occlude the narrowed vessel lumen with entrapped vascular components such as platelets, blood cells, and plasma.

Lab Evaluation of the Anticoagulated Patient

Bleeding problems can be screened by various lab tests which include the platelet count, bleeding time, prothrombin time, partial thromboplastin time, and International Normalized Ratio (INR).

The platelet count provides a quantitative evaluation of platelet function. A normal platelet count should be 100,000-400,000 cells/mm³. A platelet count of less than 100,000 cells/mm³ is called thrombocytopenia and is often associated with major postoperative bleeding. The average lifespan of a platelet ranges from 7 to 12 days.

The bleeding time provides an assessment of adequacy of platelet count and function. The test measures how long it takes a standardized skin incision to stop bleeding by the formation of a temporary hemostatic plug. The normal range of bleeding time depends on the

way the test is performed, but is usually between 1-6 minutes. The bleeding time is prolonged in patients with platelet abnormalities, or taking medications which affect platelet function. This test assesses platelet function.

The prothrombin time (PT) measures the effectiveness of the extrinsic pathway to mediate fibrin clot formation. It is performed by measuring the time it takes to form a clot when calcium and tissue factor are added to plasma. A normal prothrombin time indicates normal levels of Factor VII and those factors common to both the intrinsic and extrinsic pathways (V, X, prothrombin, and fibrinogen). A normal prothrombin time is usually between 10-15 seconds. Prothrombin time is most often used by physicians to monitor oral anticoagulant therapy such as warfarin.

The partial thromboplastin time (PTT) measures the effectiveness of the intrinsic pathway to mediate fibrin clot formation. It tests for all factors with the exception of Factor VII. The test is performed by measuring the time it takes to form a clot after the addition of kaolin, a surface activating factor; and cephalin, a substitute for platelet factor; to the patient's plasma. A normal partial thromboplastin time is usually 25-35 seconds. Partial thromboplastin time is most often used by physicians to monitor heparin therapy.

The INR was designed for patients on chronic anticoagulant therapy. It allows comparisons from one hospital to another. A patient with normal coagulation parameters has an INR of 1.0. The therapeutic range for a patient on anticoagulant therapy is between 2.0-3.5.

ANTICOAGULATION MEDICATIONS

In the United States, contemporary anticoagulation therapy (Table 1) commonly utilizes one, or a combination of the following medications:

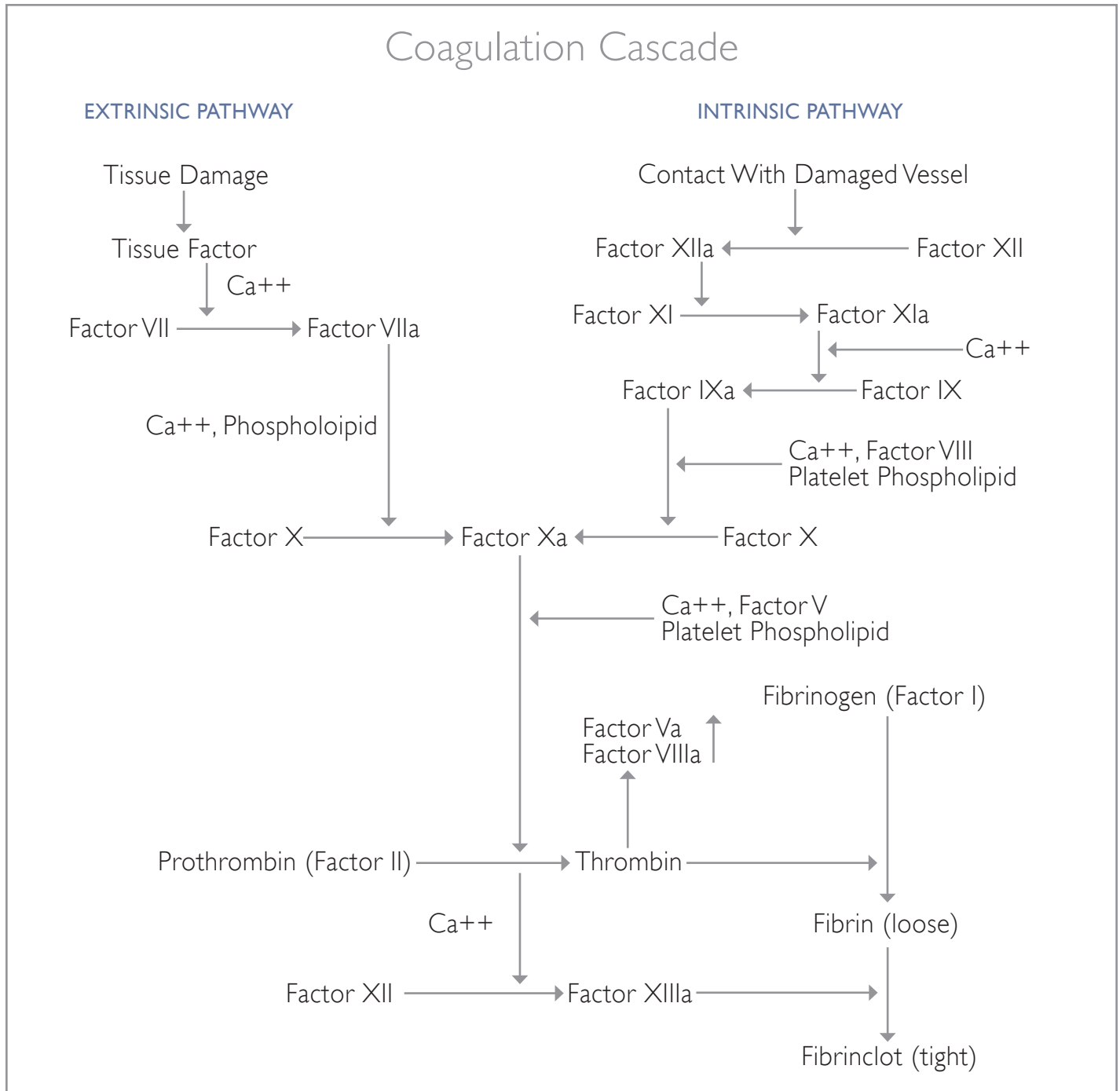


Figure 1: Intrinsic and extrinsic pathways of the coagulation cascade.

Acetylsalicylic Acid (Aspirin)

Aspirin is the most widely utilized oral anticoagulant with use by more than one third of the United States population. Among patients with known cardiovascular disease, the prevalence of aspirin-based oral anticoagulant therapy exceeds 80%.¹

When used as an oral anticoagulant, aspirin is typically prescribed in an 81mg or 325mg once-daily dosing. Aspirin affects platelets through the inhibition of cyclooxygenase I (COX-1). With inhibition of COX-1, platelet production of thromboxane A2 (TXA2), a potent vasoconstrictor,

platelet activator, and platelet aggregator, is impaired. Aspirin's effects on platelet function are irreversible and span the 8-10 day lifecycle of the platelet. Due to platelet turnover, approximately 10% of platelets with normal COX-1 activity are recovered daily following cessation of low dose aspirin

therapy.⁹ As such, it may take up to 10 days to fully recover COX-I activity, although full COX-I activity may not be required for adequate hemostasis.

Clopidogrel Sulfate

Clopidogrel sulfate (Plavix[®], Bristol-Myers Squibb/Sanofi Aventis, 345 Park Ave., New York, NY 10154) is an oral anticoagulant used in the prevention of atherosclerotic events for patients with medical histories similar to those treated with low dose daily aspirin therapy.¹⁰ In fact, clopidogrel sulfate is often prescribed as a dual therapy with aspirin as the combination has proven more effective than aspirin alone in the treatment of certain cardiovascular conditions.¹¹ Clopidogrel sulfate prevents platelet aggregation by selectively inhibiting the binding of adenosine diphosphate to platelet receptors.¹² Like aspirin, the effects of Clopidogrel sulfate on platelet function are irreversible and last for the life span of the platelet. Platelet aggregation and bleeding time typically return to baseline levels five days after the Clopidogrel sulfate cessation.

Warfarin Sodium (Coumadin[®] , Bristol-Myers Squibb, 345 Park Ave., New York, NY 10154)

Warfarin sodium acts by inhibiting vitamin-K dependent clotting factors II, VII, IX, X and the anticoagulant proteins C and S.⁸ Warfarin sodium half-life is approximately 36 hours and the duration of action for a single dose may last anywhere from 2 to 5 days.¹³ As such, this medication is often utilized for long term anticoagulation therapy on patients with a history of the following: atrial fibrillation, cardiac valve replacement, cerebrovascular accident, coronary stent, deep venous thrombosis, myocardial infarction, and pulmonary embolism.¹⁴ Patients treated with warfarin sodium are generally considered higher risk, both in terms of overall health and risk for bleeding, than patients taking oral antiplatelet therapy.¹⁵

Heparin

Heparin is a short acting, highly sulfated glycosaminoglycan that is naturally produced by basophils and mast cells.¹⁶ Heparin complexes with antithrombin III to facilitate the removal of circulating thrombin and ultimately leads to reduced

fibrin formation. Unlike other anticoagulants, heparin is traditionally administered by continuous intravenous infusion for short-term inpatient use due to a narrow therapeutic window.⁷ Newly developed low molecular weight heparin, however, is reported to have improved pharmacokinetics that may allow the drug to be utilized on an outpatient basis.¹⁷

PERIOPERATIVE MANAGEMENT

The decision to interrupt oral anticoagulation therapy prior to Implant procedures is multifactorial. In the perioperative management of these patients, factors to consider include: the overall health of the patient, the type of oral anticoagulant therapy utilized, anticipated blood loss associated with the planned procedure, and a contingency plan for excessive or uncontrolled bleeding.

Patients receiving oral anticoagulation therapy can have widely disparate medical histories. Consider the following pair of patients: a 40-year-old male with mild hypertension and early atherosclerosis versus a 60-year-old male with a history of myocardial infarction and coronary stent placement. Certainly, the ASA classifications

TABLE 1: COMMON ANTICOAGULATION MEDICATIONS

Medication	Type	Action	Comment
Acetylsalicylic Acid (Aspirin)	Oral antiplatelet anticoagulant	Inhibition of cyclooxygenase-I (COX-I)	Irreversibly affects platelets
Clopidogrel sulfate (Plavix [®])	Oral antiplatelet anticoagulant	Inhibits binding of adenosine diphosphate to platelet receptors	Irreversibly affects platelets
Warfarin sodium (Coumadin [®])	Oral coagulation cascade anticoagulant	Inhibition of vitamin-K dependent clotting factors II, VII, IX, X and anticoagulant proteins C and S	Half-life ~36 hours. Single dose duration of action may last 2-5 days depending on the patient
Heparin	Intravenous coagulation cascade anticoagulant	Complexes with antithrombin III to reduce circulating thrombin and reduce fibrin formation	Half-life ~1 hour. Typically given intravenously in an inpatient treatment setting.

of these patients differ markedly as should the decisions on how to treat and manage them. When treating these patients, it is important to keep an eye on the “big picture” by considering the patient’s overall health, and not solely focusing on their dental needs.¹⁸ As such, it is important to consult with the patient’s medical treatment provider regarding any questions about his or her medical status.

While the underlying goal of oral anticoagulation therapy is universal, the mechanisms of action by which medications achieve this goal vary. As such, it is important for practitioners to distinguish between antiplatelet anticoagulants and anticoagulants that interfere with the coagulation cascade.¹² Studies examining the hemorrhagic effects of antiplatelet anticoagulants on dental procedures have

found negligible increases in intraoperative and postoperative bleeding.¹⁹⁻²¹ Likewise, similar studies evaluating coagulation cascade anticoagulants have generally found no increased risk of intraoperative or postoperative bleeding that could not be controlled with local measures when International Normal Ratio (INR) values were within therapeutic levels.²²⁻²⁵

INR measures the extrinsic pathway of coagulation and commonly ranges between 0.8–1.2 in healthy adults. Therapeutic INR values differ for various cardiovascular conditions, but typically range between 2.0–3.0.²⁶ For mechanical cardiac valves, higher INR values up to 4.0 are recommended.²⁷ INR values are not typically verified preoperatively for patients treated with antiplatelet anticoagulants. For patients treated with coagulation cas-

cade anticoagulants, however, numerous authors obtain preoperative INR values on the day of surgery.²⁸⁻³⁰ Depending on the extent and complexity of the planned dental procedure, INR values of 3.0 or less are typically recommended for patients treated with coagulation cascade anticoagulants.³¹ If a tranexamic acid rinse protocol is utilized, patients with INR values up to 4.5 have been safely treated without complication.³¹⁻³⁴

When making decisions on the management of anticoagulated patients, anticipated blood loss from the planned procedure must be considered. Expectant blood loss from a restorative procedure such as a dental amalgam will be considerably different from that of a surgical procedure such as a connective tissue graft or impacted third molar extraction.

TABLE 2: LOCAL HEMOSTATIC AIDS

Product or Action	Composition	Action
Positive Pressure	N/A	Manual occlusive aid to clot formation
Vasoconstrictor	1:100,000 Epinephrine	Activation of α adrenergic receptors
Gelfoam®	Porcine derived gelatin sponge	Occlusive matrix; activation of intrinsic pathway
Surgicel®	Plant derived α -cellulose	Occlusive matrix; activation of intrinsic pathway; antibacterial properties
CollaCote®, CollaPlug® CollaTape®, UltraFoam™ UltraWrap™	Bovine derived collagen	Occlusive matrix; activation of intrinsic pathway
HemCon®	Crustacean derived chitosan	Positively charged chitosan attracts negatively charged red blood cells; antibacterial properties
4.8% Tranexamic Acid Mouth Rinse	Tranexamic acid	Binds to lysine receptor sites on plasmin and plasminogen inhibiting fibrin binding and fibrinolysis
Topical Thrombin	Bovine derived thrombin	Enhances conversion of fibrinogen to fibrin
Electrocautery	N/A	High frequency electric current cauterizes tissue and induces blood coagulation

Studies evaluating blood loss from restorative procedures have reported minimal hemorrhagic complications, while those evaluating surgical operations such as flap-osseous procedures have found up to 592 ml of blood loss from a single surgical site.^{35,36} Blood loss from surgical procedures is also influenced by the experience level of the provider. Surgeries performed by less experienced providers have been shown to take up to three times longer and may result in nearly twice as much blood loss as those performed by more experienced practitioners.³⁶ In general, however, most studies have found that blood loss from dental procedures is under 200 ml and even less when the duration of the procedure does not exceed two hours.³⁶⁻³⁹ When you consider that a pint of blood, the amount generally taken during blood donation, is 473 ml, the amount of blood lost during dental procedures is well within the limits of safety.

HEMORRHAGE MANAGEMENT

This risk of moderate to severe bleeding induced by dental procedures is less than 1% for the average patient.⁴⁰ While this risk increases with the anticoagulated patient, nearly all scenarios of excessive bleeding can be adequately managed with relatively simple local measures (Table 2) such as:

Positive Pressure

Positive pressure to intraoral wounds is typically accomplished by compressing moistened gauze on the site of hemorrhaging (i.e. bone or socket) or compression of the flap itself. Suturing wound margins another method in which compressive force may be applied to bleeding areas.⁷ Positive pressure aids hemostasis by promoting occlusion of the site of injury and providing mechanical aid to clot formation.⁴¹ Minor hemorrhaging is often

controlled with positive pressure alone and may not require further intervention.

Oxidized Regenerated Cellulose

Oxidized regenerated cellulose based products such as Surgicel® (Ethicon, Johnson & Johnson, One Johnson & Johnson Plaza New Brunswick, NJ 08933) are derived from plant based alpha-cellulose and function hemostatically in a manner similar to absorbable gelatin sponges.⁴⁴ A unique property this product has is relatively low pH. The low pH has an antibacterial effect. A broad range of gram negative, gram positive, and antibiotic-resistant bacteria have proven to be locally susceptible to oxidized regenerated cellulose.⁴⁵ When used for oral applications, this product typically resorbs within 7-14 days.

Vasoconstrictor

Dental anesthetics contain vasoconstrictor primarily to increase their duration of action and minimize the risk of local anesthetic toxicity.⁴² Epinephrine, the most commonly utilized vasoconstrictor in dental local anesthetics, is a catecholamine that facilitates vasoconstriction, which when injected into the site in question will help slow the bleeding and aid in coagulation.

Absorbable Collagen Products

Absorbable collagen products such as CollaPlug®, CollaTape®, and CollaCote® (Integra Life Sciences Corp, 311 Enterprise Dr., Plainsboro, NJ 08536) are derived from bovine deep flexor tendons and typically resorb completely within 14 days. Additional bovine derived products such as Avitene® (Traatek, Inc., 3848 SW 30th Ave., Fort Lauderdale, FL 33312) have similar properties. These products aid in coagulation by either acting as a simple occlusive matrix, or promote hemostasis by their collagen content which activates the intrinsic coagulation cascade.

Absorbable Gelatin Sponge

Gelfoam® (Pfizer Inc., 235 E. 42nd St., New York, NY 10017) is a resorbable gelatin sponge of porcine origin that is capable of absorbing up to 45 times its weight in whole blood.⁴³ Absorbable collagen sponges aid in hemostasis by providing a simple occlusive matrix and additionally through contact activation of the intrinsic pathway.⁴⁴ The gelatin sponge is usually resorbed within 2-5 days.

Chitosan Derived Products

Chitosan derived products such as HemCon® (HemCon Medical Technologies, Inc., 10575 SW Cascade Ave., Ste. 130, Portland, OR 97223) are extremely effective at promoting hemostasis and have recently been used by United States military medical personnel for treatment of battlefield injuries. Chitosan is a naturally occurring polysaccharide that is commercially produced via the deacetylation of crustacean chitin. Positively charged chitosan molecules readily attract negatively charged red blood cells and the two form an extremely strong seal that acts as a primary occlusive barrier for hemorrhagic sites. With hemorrhaging limited and/or stopped by this initial seal, the natural coagulation cascade ensues. Like oxidized regenerated cellulose, chitosan derived products have locally active antibacterial properties.⁴⁶ Chitosan derived products also have antibacterial properties which it achieves via active cell wall disruption.⁴⁷

Tranexamic Acid

Tranexamic acid is an anticoagulant oral rinse that binds to lysine receptor sites on plasmin and plasminogen, and which results in inhibiting fibrin binding and fibrinolysis.⁴⁸ Rinsing with tranexamic acid solution results in therapeutic levels (>100mg/ml) within the saliva for 2-3 hours. Wounds healing in the presence

of tranexamic acid have demonstrated increased tensile strength, thus making the clot more resistant to mechanical disruption.⁵⁰ Tranexamic acid is supplied as a 4.8% solution and patients may be instructed to rinse with 10 ml, four times daily for seven days following surgery.⁴⁹

Topical Thrombin

Topical thrombin facilitates clot stabilization by enhancing the conversion of fibrinogen to fibrin for the initial platelet plug. Medical grade topical thrombin is often bovine derived and is typically supplied as a freeze dried sterile powder that must be reconstituted with sterile saline. For general use in dental applications, a topical thrombin solution of 100 International Units/ml and is delivered via pump/syringe spray or combined with a carrier such as a hemostatic gelatin sponge.

Electrocautery

Electrocautery involves the application of a high-frequency electric current to cauterize tissue and induce blood coagulation and is useful in severe hemorrhaging scenarios.

CONCLUSION

Although most patients experience no problems when their oral anticoagulation therapy is interrupted for dental procedures, complications ranging from nonfatal cerebral emboli to death can occur. Typically, these complications were associated with prolonged discontinuation of anticoagulants that interfere with the coagulation cascade such as warfarin sodium. While there are currently no reports of fatal complications associated with the discontinuation of oral antiplatelet medications prior to dental treatment, such action places these patients at risk of developing thromboembolic complications.^{12,15}

If patients are instructed to continue their oral anticoagulation therapy prior to dental treatment in an effort to avoid thromboembolic complications, do they pose a risk for unmanageable hemorrhaging? According to dental literature, the answer is a resounding "No." Multiple studies have demonstrated that most dental procedures can be safely performed without interrupting oral antiplatelet therapy.^{12,19-21} Likewise, a number of studies have demonstrated that patients taking coagulation cascade anticoagulants can be safely treated as long as INR values are within therapeutic ranges.²⁹⁻³⁴ In nearly all patients involved with these studies, hemorrhaging was easily controlled with local measures.

DISCLAIMER

Although specific, commercially-available products are mentioned in this article, this does not constitute an endorsement of the United States Government, Department of Defense, or Navy Medicine. The opinions and assertions contained in this article are the private ones of the authors and are not to be construed as official or reflecting the views of the Department of the Navy, Department of Defense, or the United States Government.

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