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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Factor V secreted by the a-granules of activated platelets binds to activated factor X to produce prothrombin activator, which in the presence of calcium, catalyzes the formation of thrombin from prothrombin. Thrombin then catalyzes the production of fibrin monomer from fibrinogen, which in the presence of calcium and fibrin stabilizing factor (factor XIII), forms fibrin threads. Thrombin also binds to platelet surface receptors and activates serum factor VIII, which forms complexes with factor IX on the platelet surface. Activated factors VIII and IX participate in the activation of factor X via the intrinsic pathway (4).

The blood clot consists of a fibrin mesh containing the platelet aggregate, as well as entrapped red and white blood cells. Contraction of the platelet actin myosin fibers is responsible for retraction of the clot, which occurs within 20 min to 1 h, further closing the vessel (4).

Historically bleeding time, prothrombin time (PT) and partial thromboplastin time (PTT), have been the standards by which clinicians evaluate anticoagulation levels. Nevertheless, an international normalized ratio (INR) was introduced in 1983 by the World Health Organization Committee on Biological Standards to assess patients receiving anticoagulation therapy more accurately (5).

The INR is calculated from the ratio of the patient's PT and control PT, raised to the power of the international sensitivity index value (ISI). INR = (patient PT/mean normal PT)^{ISI}. It is a more reliable and sensitive value for determining the level of anticoagulation because it depends on the patient's blood and on the sensitivity of the thromboplastin reagent and the assigned ISI value. Therefore, PT may not be the laboratory value of importance when evaluating the level of anticoagulation (5).

A patient with a normal coagulation profile would have an INR of 1.0. It is recommended that a patient undergoing invasive treatment should have a PT within 1.5 to 2.0 times the normal value, and this corresponds to an INR of 1.5 to 2.5 when the ISI is 1.0 (5).

In patients with anticoagulant therapy, an INR between 2.0 and 3.0 is recommended for most indications. Thus, an INR of 2.5 (range, 2.0 to 3.0) minimizes the risk of either hemorrhage or thromboembolism (6).

Antiplatelet therapy

Since platelets provide the initial haemostatic plug at the site of a vascular injury, they are involved in pathological processes and are an important contributor to arterial thrombosis leading to myocardial infarction and ischaemic stroke (7). The most common antiplatelet drugs are acetylsalicylic acid, clopidogrel and dipyridamole.

Acetylsalicylic acid - ASA

ASA is still the only nonsteroidal anti-inflammatory drug (NSAID) used in the treatment and prevention of thromboembolic diseases (3). The antithrombotic action of ASA depends on the irreversible inhibition of arachidonate cyclo-oxygenase activity in platelets, thereby reducing the extent of thromboxane A2 formation that occurs after activation of phospholipase A2 and release of arachidonic acid (3). Thromboxane A2 is a strong platelet agonist, which is an effective inducer of platelet granule secretion as well as platelet aggregation (3). Available evidence suggests that a daily ASA dose of 75-150 mg is recommended for long term prevention of serious vascular events in high risk patients (8). In clinical situations where an immediate antithrombotic effect is required (such as acute myocardial infarction, stroke, or unstable angina), a loading dose of 300 mg is recommended (8).

Clopidogrel

The antiplatelet activity of clopidogrel is greater than that of ASA in the secondary prevention of CVA, myocardial infarction and peripheral arterial insufficiency (9). Despite its growing popularity, clopidogrel is very expensive, so it is used only selectively in patients resistant to treatment with ASA. The antiplatelet effect of clopidogrel is irreversible and lasts for the life of the platelet (7 to 10 days) (9).

Dipyridamole

Dipyridamole inhibits adenosine uptake in erythrocytes and endothelial cells. This increases plasma adenosine levels, which means that there is more available for binding to the adenosine receptor on the platelet. Adenosine activates the release of adenylate cyclase, which converts cyclic adenosine triphosphate (cATP) to cyclic adenosine monophosphate (cAMP). Dipyridamole also blocks the enzyme cyclic guanine monophosphate phosphodiesterase (cGMP), thereby inhibiting the breakdown of cGMP (3). However, the antiplatelet activity of dipyridamole is less than that of ASA and ADP receptor blockers. Moreover, its action on phosphodiesterase is wholly reversible and ceases about 24 h after the drug is discontinued (10).

Antiplatelet therapy and oral surgery

When platelets are inhibited, it takes longer time for free blood flow from a cut to stop and for primary haemostasis to occur, as a consequence, the bleeding time is prolonged (1). However, the effect on primary haemostasis is minimal in patients without additional risk factors for impaired clotting. Antiplatelet medications can double the baseline bleeding time, but this may still be within or just outside

the normal range. It has been reported that only 20% to 25% of patients using ASA have an abnormal bleeding time (1). Patients taking antiplatelet medications will have a prolonged bleeding time, but this may not be clinically relevant because postoperative bleeding after dental procedures can mostly be controlled using local haemostatic measures.

Lockhart et al. (11) suggested that postoperative bleeding is considered to be significant if it conforms to the following four criteria: the bleeding continues beyond 12 hours; it causes the patient to call or return to the dental practice or accident and emergency department; results in the development of a large haematoma or ecchymosis within the oral soft tissues; and requires a blood transfusion.

A study investigating stopping versus continuing low-dose ASA prior to dental extraction was done by Ardekian et al. (12). Thirty-nine patients taking ASA 100mg daily were studied. Nineteen continued ASA as normal, while 20 stopped taking ASA seven days before the planned extractions. A bleeding time test was performed one hour prior to the procedure. The mean bleeding time was longer in patients who continued ASA compared to those who stopped (3.1 min vs 1.8 min, $P = 0.004$). Although the difference was statistically significant, none of the patients who continued ASA had a bleeding time outside the normal range in this study (2-10 min). Intraoperative bleeding was controlled in 33 (85%) patients with gauze packing and sutures. Six patients (2 who stopped ASA and 4 who continued ASA) had tranexamic acid added to the local packing. At the end of the study, it was observed that no patient experienced uncontrolled bleeding immediately after the procedure or in the following week.

There are few published studies on the relative risks of perioperative bleeding with clopidogrel and dipyridamole. The pharmacological mechanisms underlying the antiplatelet action of clopidogrel and dipyridamole suggest that patients taking these medications will be at no greater risk of excessive bleeding than those taking ASA (13).

A review of the implications of antithrombotic medications in dentistry concluded that patients on clopidogrel should not have the dose altered prior to dental procedures (13). Based on these reports, it is suggested that these medications should not be discontinued prior to dental surgical procedures. On the other hand, if patients take both ASA and clopidogrel, they should be referred to a dental hospital or hospital based oral/maxillofacial surgeon.

Anticoagulation therapy

The goal of anticoagulant therapy is to prevent clot formation or expansion and Warfarin is the most common drug used in this therapy (6).

Warfarin

Warfarin is an antagonist of vitamin K, an element necessary for synthesis of clotting factors II, VII, IX and X, as well as the naturally occurring endogenous anticoagulant proteins C and S. These factors and proteins are biologically inactive without the carboxylation of certain glutamic acid residues. This carboxylation process requires a reduced vitamin K as a cofactor. Antagonism of vitamin K or a deficiency of this vitamin reduces the rate at which these factors and proteins are produced, thereby creating a state of anticoagulation (6).

Warfarin has two functions: anticoagulant activity and antithrombotic effect. Therapeutic doses of warfarin reduce the production of functional vitamin K dependent clotting factors by approximately 30 to 50 percent. A concomitant reduction in the carboxylation of secreted clotting factors yields a 10 to 40 percent decrease in the biologic activity of the clotting factors. As a result, the coagulation system becomes functionally deficient (6).

Anticoagulation therapy and oral surgery

If warfarin therapy is stopped, it would take about four days for INR to reach 1.5 in almost all patients and with this INR, any surgery can be safely performed (14). After warfarin therapy is restarted, approximately three days will be needed for the INR to reach 2.0. Therefore, if warfarin is withheld for four days before surgery and treatment is restarted as soon as possible after surgery, patients would have a sub-therapeutic INR for approximately two days before surgery, and two days after surgery increasing the risk of thromboembolism (15).

Besides this, independent of the intensity of anti-coagulation, the perioperative risk of thromboembolism may be increased due to other factors, in particular a rebound hypercoagulable state caused by the discontinuation of warfarin and the prothrombotic effect of the surgery itself (16). Consequently, for patients whose INR returns to normal shortly after stopping warfarin therapy, it can be assumed that the risk of preoperative arterial thromboembolism, postoperative arterial thromboembolism, and preoperative venous thromboembolism will be similar to that which is expected in the absence of anticoagulation (7).

Wahl (17) studied the impact of stopping the anti-coagulation therapy in dentistry by reviewing 542 documented cases involving 493 patients, who had anticoagulation therapy withdrawn prior to a variety of dental procedures. He reported that four patients experienced fatal thromboembolic events (2 cerebral

thromboses, 1 myocardial infarction, 1 embolus - type not specified); one patient experienced two non-fatal thromboembolic complications (1 cerebral embolus, 1 brachial artery embolus) and the majority of patients had no adverse effects. The incidence of serious thrombo-embolic complications was 1%. These findings have been criticized as the duration that the anticoagulant was stopped was either longer than normal practice (range 5-19 days) or unknown (18). Although, it cannot be assumed that stopping the anticoagulant therapy caused the thromboembolic events, there is a risk associated with the perioperative withdrawal of oral anticoagulants. For minor procedures such as dental surgery, the risk appears to vary from 0.02% to 1%.

In another study, Wahl (19) also estimated the incidence of serious bleeding problems in 950 patients receiving anticoagulation therapy undergoing 2400 individual dental procedures. Only 12 patients (< 1.3%) experienced bleeding uncontrolled by local measures and none of the patients were reported to have experienced serious harm. Of these 12 patients, seven had higher than recommended anticoagulation levels; three were given a course of postoperative antibiotics, which may have interacted with the warfarin and two were using a placebo mouthwash four times a day immediately after the procedure, which is contrary to standard advice to avoid rinsing for the first 24 h.

Bleeding complication vs thromboembolic complication

Even though continuing the antiplatelet or the anticoagulation therapy during dental surgical procedures will increase the risk of postoperative bleeding requiring intervention, stopping them does not guarantee that the risk of postoperative bleeding requiring intervention will be eliminated as serious bleeding can occur in non-anticoagulated patients (19). Most cases of postoperative bleeding can be managed by pressure or repacking and re-suturing the sockets. The incidence of postoperative bleeding which could not be controlled by local measures varied from 0% to 3.5% (19,20).

Bleeding complications, while inconvenient, do not carry the same risks as thromboembolic complications. Patients are more at risk of permanent disability or death if they stop antiplatelet or anticoagulation medications prior to a surgical procedure than if they continue it.

Thromboembolic events, including fatalities, have been reported after antiplatelet or anticoagulation withdrawal. Although the risk is low, the outcome is serious. This must be balanced against the fact that there is no single report of uncontrollable bleeding when dental procedures have been carried out without stopping antiplatelet or anticoagulation medications (21).

It is important to consider the consequences of venous and arterial thromboembolism, and of bleeding, in addition to the rates at which these outcomes occur. Six percent of recurrent episodes of venous thromboembolism are expected to be fatal (22). A small group of patients with recurrent events, perhaps 2%, will have serious permanent disability, though the majority will recover well. The consequences of arterial thromboembolism are much more serious; approximately 20 percent of these episodes are fatal, and 40 percent result in serious permanent disability (23).

No cases of permanent disability or death, reported as a consequence of postoperative bleeding associated with a dental surgical procedure in which the patient continued oral anticoagulation, were found. The majority of publications that have considered the risks of stopping versus continuing anticoagulation or antiplatelet therapy for dental procedures have concluded that most dental patients can undergo procedures without stopping their therapies provided that local haemostatic measures are used to control bleeding (11,17,21,24,25).

Oral surgery considerations

The activity of anticoagulants is expressed using the international normalized ratio (INR). For an individual not taking anticoagulant or antiplatelet drugs, the normal coagulation profile is an INR of 1.0. The INR must be measured prior to dental procedures, ideally this should be done within 24 h before the procedure (21,25-27), but, for patients who have a stable INR, an INR measured within 72 h before the procedure is acceptable.

Scientific literature has advocated that minor dental surgical procedures can safely be carried out with the INR within the therapeutic range (2.0-4.0) when local haemostatic measures are used to control bleeding (13,17-20,24,26,27). However, patients who have an INR greater than 4.0 should not undergo any form of surgical procedure, including dental, without consultation with the clinician who is responsible for maintaining their anticoagulation.

Minor surgical procedures, such as simple extraction of up to three teeth, gingival surgery, crown and bridge procedures, supragingival scaling and the surgical removal of teeth (11,28), can be safely carried out without altering the anticoagulation or antiplatelet medication dose. If more than 3 teeth need to be extracted then multiple visits will be required and the extractions may be planned to remove 2-3 teeth at a time, by quadrant, or one at a time in separate visits (24). Scaling and gingival surgery should initially be restricted to a limited area to assess if bleeding

is problematic.

Management of bleeding

According to Scully and Wolff (26), oral procedures must be done at the beginning of the day because this allows more time to deal with immediate re-bleeding problems. Also the procedures must be performed early in the week, allowing delayed re-bleeding episodes, usually occurring after 24-48 h, to be dealt with during the working weekdays.

Local anesthetic containing a vasoconstrictor should be administered by infiltration or by intraligamentary injection wherever practical (11,26). Regional nerve blocks should be avoided when possible. However, if there is no alternative, local anesthetic should be administered cautiously using an aspirating syringe (30). Local vasoconstriction may be encouraged by infiltrating a small amount of local anesthetic containing adrenaline (epinephrine) close to the site of surgery.

Sockets should be gently packed with an absorbable haemostatic dressing (11,26) and then carefully sutured. Resorbable sutures are preferable as they attract less plaque (26). If non-resorbable sutures are used they should be removed after 4-7 days (26). Following closure, pressure should be applied to the socket using a gauze pad that the patient bites down on for 15 to 30 min. Efforts should be made to make the procedure as atraumatic as possible and any bleeding should be managed using local measures.

Scully and Cawson (30) also developed the following list of instructions that should be given to the patients for management of the clot in the postoperative period: to look after the initial clot by resting while the local anesthetic wears off and the clot fully forms (2-3 h); to avoid rinsing the mouth for 24 h; not to suck hard or disturb the socket with the tongue or any foreign object; to avoid hot liquids and hard foods for the rest of the day; to avoid chewing on the affected side until it is clear that a stable clot has formed; if bleeding continues or restarts, to apply pressure over the socket using a folded clean handkerchief or gauze pad for 20 min; if bleeding does not stop, the dentist should be contacted.

Anticoagulants and antiplatelet drugs used in the prevention of thromboembolic diseases can cause intra-operative and postoperative hemorrhagic complications. However, stopping these drugs before a procedure exposes the patient to vascular problems with the potential for significant morbidity.

The optimal INR value for dental surgical procedures is 2.5 because it minimizes the risk of either hemorrhage or thromboembolism. Nevertheless, minor dental surgical procedures can safely be done with the INR between 2.0 and 4.0, being aware that local haemostatic measures may be needed to control bleeding.

Patients who have an INR greater than 4.0 should not undergo dental surgical procedures, and they must be referred to the clinician who is responsible for maintaining their anticoagulation.

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