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Review Article

DENTAL MANAGEMENT OF PATIENTS ON ANTIPLATELET THERAPY: LITERATURE UPDATE

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ABSTRACT

Antiplatelet drugs are used in the prevention and management of arterial and venous thrombi. These drugs are associated with an increase in bleeding time and risk of post-operative hemorrhage. Because of this, dental surgeons recommend their patients to stop the therapy before surgical procedures which may in turn cause fatal thromboembolic complications. This article reviews the commonly used antiplatelet drugs, dental management of patients on these drugs when subjected to minor oral surgical procedures. The objective of this article is to review various literature, whether to discontinue or continue antiplatelet therapy during dental surgical procedures, and current consensus and recommendations have been established. It is concluded that antiplatelet monotherapy and even antiplatelet dual therapy can be safely continued on patients during dental surgical procedures, and there is no need for altering or discontinuing the drugs. Post-operative bleeding can be managed by local hemostatic measures.

Keywords: Aspirin, Antiplatelet therapy, Bleeding, Thromboembolism, Dental extraction.

INTRODUCTION

Thrombogenesis (clot formation) includes 2 principal processes: platelet aggregation and coagulation. Platelet aggregation consists of activated platelets attaching to strands of fibrinogen, whereas coagulation is a complex cascade of enzymatic events, leading to the formation of fibrin strands. Antithrombotic drugs include those that inhibit platelet aggregation (antiplatelet drugs), inhibit formation of fibrin strands (anticoagulants), and dissolve existing clots (fibrinolytics) [1].

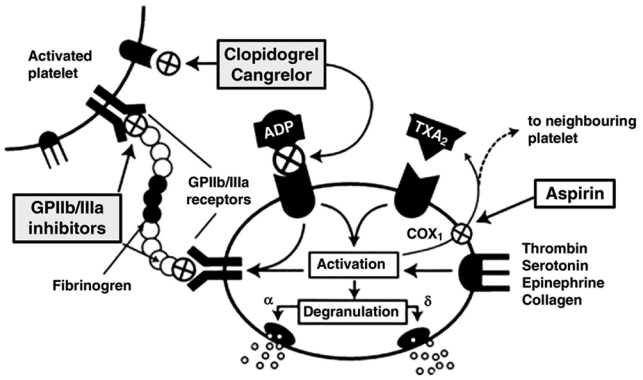
Platelets provide the initial hemostatic plug at the site of vascular injury, and they are involved in pathological processes and are an important contributor to arterial thrombosis, leading to myocardial infarction and ischemic stroke. Antiplatelet agents are widely used in prevention and treatment of various ischemic cardiovascular and cerebrovascular conditions [2], and the common indications for their long-term use are arterial thrombosis, ischemic heart disease, myocardial infarction, both stable and unstable angina, coronary artery bypass and placement of a stent, non-hemorrhagic stroke, transient ischemic attacks (ischemic stroke), peripheral arterial disease, atrial fibrillation.

Despite the benefits of antiplatelet drugs, they are not without the risks of bleeding during oral surgical procedures. Hence, dentists while treating patients on antiplatelet therapy advise them to stop drugs before extractions which may predispose them to thromboembolic complications. Hence, dental surgeons are in a dilemma whether to stop or continue antiplatelet drugs during extractions. Various studies have been conducted worldwide to address this issue. The rationale of this article is to review the present literature on this topic and to obtain the updated and recent consensus and recommendations made while treating patients on antiplatelet therapy undergoing oral surgical procedures.

ANTIPLATELET DRUGS

Drug	Mechanism of action
Aspirin	COX 1 inhibitor
Clopidogrel	ADP receptor inhibitors
Prasugrel	
Ticlopidine	
Dipyridamole	Adenosine reuptake inhibitor and phosphodiesterase inhibitor
Triflusal	COX and phosphodiesterase inhibitor
Abciximab	Glycoprotein IIb/IIIa inhibitor
Eptifibatide Tirofiban	

COX: Cyclooxygenase, ADP: Adenosine diphosphate



Mechanism of action – antiplatelet drugs

ASPIRIN

Aspirin, acetylsalicylic acid (ASA), is a non-steroidal anti-inflammatory drug that exhibits analgesic, antipyretic, anti-inflammatory, and antiplatelet properties. It is the most commonly used drug in the prevention and treatment of thromboembolic diseases because of its antiplatelet action. Aspirin has been shown to be a powerful secondary prevention agent, reducing the risk of myocardial infarction and ischemic stroke by up to 20% in patients diagnosed with cardiovascular disease [3]. Its mechanism of action involves an irreversible inhibition of the activity of cyclooxygenase-1 (COX-1) and a modification of the enzymatic activity of COX-2. COX is an enzyme responsible for the conversion of arachidonic acid to prostaglandins, prostacyclin, and thromboxane. Thromboxane-A2, a strong platelet agonist, is a specific eicosanoid lipid found in platelets important in promoting platelet aggregation over-damaged endothelium in blood vessels. The irreversible nature of the inhibition of COX is unique to aspirin among its counterparts [3,4]. Platelets are affected for the life of the cell, and complete reversal of antiplatelet activity might not occur until

approximately 2 weeks after cessation of therapy. The best screening test to evaluate the effect of aspirin on platelets is the platelet function analyzer-100 which is equally effective and less invasive than the Ivy bleeding time. The prothrombin time, activated partial thromboplastin time, and platelet count are usually normal in patients on aspirin therapy, but the bleeding time may be prolonged. Dosage: 75-150 mg for long-term prevention of thrombo-embolic events and 300 mg as a loading dose for acute clinical conditions (acute myocardial infarction, stroke, unstable angina) was used.

CLOPIDOGREL

Clopidogrel is an antiplatelet drug with a mechanism of action causing irreversible inhibition of an adenosine diphosphate receptor important in promoting platelet aggregation and cross-linking of platelets by fibrin. It is first activated in the liver by cytochrome P450 enzymes [5]. Clopidogrel is very expensive and is used in patients who are resistant to aspirin. Action starts within 2 hrs of ingestion, and antiplatelet effect lasts for lifetime of the platelets. At present, in dual antiplatelet therapy, clopidogrel is most commonly used with aspirin to prevent thromboembolic events in high-risk patients. It is an alternative drug for persons who require anticoagulation and who are unable to tolerate aspirin therapy. The dosage used is 75-100 mg/day, with a half-life of 8 hrs.

TICLOPIDINE

Ticlopidine also functions as an adenosine diphosphate receptor inhibitor. It is used to treat patients who cannot tolerate aspirin or for whom dual antiplatelet therapy is desirable. Because ticlopidine has been reported to increase the risk of thrombotic thrombocytopenic purpura and neutropenia, it has largely been replaced by clopidogrel which is believed to confer a much lower hematologic risk [6].

DIPYRIDAMOLE

Dipyridamole is a drug that exhibits both antiplatelet and vasodilatory activities. In patients with ischemic cardiomyopathy, it has been shown to increase both myocardial perfusion and left ventricular function and to decrease pulmonary hypertension, used as an adjunct to oral anticoagulation for the prophylaxis of thromboembolism associated with prosthetic heart valves. Its mechanism of action involves the inhibition of the enzyme thromboxane synthase, resulting in lower levels of thromboxane-A2 and decreased platelet aggregation, similar to aspirin. Dipyridamole also impairs platelet aggregation by causing an elevation in the serum levels of cyclic adenosine monophosphate through inhibition of the phosphodiesterase enzymes that break it down [7,8]. Dipyridamole produces vasodilation through its inhibition of the cellular reuptake of adenosine into platelets, red blood cells, and endothelial cells. This results in increase of extracellular adenosine which promotes vasodilation. Its presence also results in reductions in the number of thrombin and platelet endothelial cell adhesion molecule-1 receptors on platelets in patients with stroke. Despite all this activity, dipyridamole has been shown to be less effective than aspirin as an adenosine diphosphate receptor inhibitor, and its action on phosphodiesterase is fully reversed 24 hrs after discontinuation of the drug. Therefore, it has been less commonly prescribed than other antiplatelet medications [7,8].

COMBINATION THERAPY

Low doses of aspirin, clopidogrel, ticlopidine, and dipyridamole are the most common antiplatelet drugs, and they inhibit platelet function by different mechanisms. Aspirin, clopidogrel, ticlopidine, and prasugrel (thienopyridines) affect the activity of platelets during their lifetime (7-10 days). These drugs are given individually as monotherapy or sometimes combined, two drugs as dual therapy because they work in different ways and have synergistic effect [9]. The combination of low-dose aspirin (150 mg) and clopidogrel (75 mg) is mainly used to prevent thrombotic complications after percutaneous insertion of a coronary stent [8]. This combination is used for 4-12 weeks following the insertion of a bare metal stent and for 6-12 months following the insertion of a drug-eluting stent [10]. Sometimes, antiplatelet drugs are combined with anticoagulant drug to achieve the desired anticoagulant activity in high-risk patients. The combination of aspirin plus dipyridamole is used for the prevention of strokes or transient ischemic attacks.

ANTIPLATELET THERAPY AND ORAL SURGERY

Despite the benefits of antiplatelet drugs, they are not without risk in that they can increase the risk of bleeding, particularly gastrointestinal bleeding, hemorrhagic stroke, and post-operative bleeding. In patients who take combinations of antiplatelet drugs, the risk is higher because of their synergistic effect. Although many surgical procedures are done in oral cavity, exodontia is the simplest and commonest procedure done in dentistry. When dental surgeons treat patients on antiplatelet therapy, they are in a dilemma whether or not to suspend aspirin before extraction. Dentists typically advise patients to stop taking aspirin before tooth extraction for fear of excess bleeding. The effect of aspirin starts within 1 hr of ingestion and lasts for 7-10 days, i.e., lifespan of a platelet [10]. Therefore, traditionally, it was recommended to stop aspirin therapy 7-10 days before invasive surgical procedure and was restarted 24-48 hrs after surgery. The idea is to allow 10 days time for regeneration of newer platelets as the platelets replenish approximately at the rate of 10% a day. However, this can result in thromboembolic events (e.g., deep-vein thrombosis and pulmonary embolism) within 10 days of stopping the drugs that are worse for the patient than post-operative bleeding. One has to maintain the balance between risk of increased bleeding and risk of thromboembolic events. On theoretical basis, stopping aspirin decreases the risk of bleeding but increases risk of thromboembolic events, whereas continuing aspirin decreases risk of thromboembolic events but increases risk of bleeding.

Various studies were conducted to determine whether to continue or discontinue antiplatelet medications during dental surgical procedures, and the literature review is presented here to arrive at a conclusion.

Studies recommending discontinuation of antiplatelet therapy

Lemkin *et al*. [11] in 1974 explained bleeding after oral surgery with aspirin therapy which required platelet transfusion for correction. McGaul [12] and Daniel *et al*. [13] stated that continuing aspirin caused post-operative bleeding and advised discontinuation for 7-10 days before surgical procedures. This was recommended on the basis of surgical studies which showed rise in both intra- and post-operative bleedings. Some authors advised that stopping of antiplatelets only for 3 days will be sufficient. Studies by Conti [14], Speechley and Rugman [15], Scher [16], Scully and Wolf [17], Little *et al*. [18], and Burger *et al.* [19] recommended stoppage of antiplatelets to avoid the risks of post-operative bleeding.

Thomason *et al.* [20] in their study found bleeding after gingival surgery with aspirin therapy and advised to discontinue aspirin before surgery. Elad *et al.* [21] reported a case of severe bleeding episode, following nonsurgical periodontal treatment in a patient taking dual antiplatelet therapy (aspirin 100 mg plus clopidogrel 75 mg/day). Severe life-threatening hemorrhage occurred post-operatively leading to hemorrhagic shock. Schrodi *et al.* [22] found increased bleeding on probing in patients who consumed aspirin in a dose of 325 mg/day for 7 days. A case was reported by Foulke in which bleeding episode occurred after oral prophylaxis with ultrasonic scaler [23]. Several studies have documented the risk of bleeding in patients on antiplatelet therapy undergoing cardiac surgeries [24-26].

Risks of withdrawal of antiplatelet therapy

However, scientific evidence showed that stopping antiplatelet therapy is associated with a progressive recovery of platelet function and with a potential risk of rebound of thromboembolic vascular events due to excessive thromboxane-A2 activity and decreased fibrinolytic activity [27,28]. Ferrari *et al.* [29] and Chassot *et al.* [30] suspected the existence of a biological platelet rebound phenomenon on interruption

of aspirin therapy, thus creating a prothrombotic state which may ultimately cause fatal thromboembolic events. Other studies showed potential risk of fatal thromboembolic events such as myocardial infarction and stroke on stopping aspirin therapy [31-35]. One study pointed out that suspending aspirin therapy resulted in a 3-fold increase in the incidence of cerebral infarction and major cardiovascular events compared with continuation of the therapy [36]. Discontinuation of antiplatelet therapy in high-risk patients has been shown to increase the risk of cardiac complications and death. Wahl and Howell [37] were one of the first groups of authors to conclude that the risk of hemorrhage after dental surgery may be greatly outweighed by the risk of thromboembolism after withdrawal of anti-thrombotic therapy.

A systemic review and meta-analysis on the potential risks and health hazards of stopping aspirin by Biondi-Zoccai *et al.* confirmed the major detrimental impact of withdrawal across a greater number of individuals (50,279) at risk for coronary artery disease [38]. Ferrari *et al.* [29] in his study have evaluated the role of aspirin withdrawal in a cohort of 1236 patients hospitalized for acute coronary syndrome. A total of 51 (4.1%) of these patients discontinued aspirin within 1 month of the acute coronary syndrome. Thirteen of these acute coronary syndrome cases were withdrawn from aspirin before a dental procedure. The mean delay between aspirin withdrawal and acute coronary event was between 4 and 17 days, and the risk of thromboembolic events increases between 4 and 30 days of withdrawal of antiplatelet therapy [29]. Collet *et al.* performed retrospective analysis of 475 patients admitted to the hospital with the diagnosis of myocardial infarction. Eleven patients stopped aspirin therapy within 15 days before general surgical procedure. Another nine patients stopped aspirin 3 days before elective surgical procedures, one of which was a dental surgical procedure. This dental patient was stable and asymptomatic for 10 years with continued use of aspirin. Unfortunately, myocardial infarction occurred 10 days after stopping aspirin therapy [39,40].

Studies recommending continuation of antiplatelet therapy

Bajkin *et al.* [41] in their study concluded that patients taking single or dual antiplatelet drugs may have teeth extracted safely without interruption of treatment using only local hemostatic measures to control post-operative bleeding. Verma *et al*. [42] in their prospective study concluded that there is no need to stop the antiplatelet dose of aspirin prior to simple tooth extraction as there was 0% incidence of post-operative bleeding in their patients. Olmos-Carrasco *et al.* [43], in their prospective study on 181 patients who underwent dental extractions observed regarding hemorrhagic complications, concluded the safety of dental extraction without withdrawal of double antiplatelet therapy. The American College of Chest Physicians recommends continuing the antiplatelet drugs perioperatively in patients who require operation within 6 weeks of placement of a metal stent or 6 months of placement of a drug-eluting stent. Acute myocardial infarction has followed in such patients after withdrawal of antiplatelet therapy [44,45].

Girotra *et al.* [46] from their prospective study concluded that there was no necessity to stop antiplatelet therapy, and higher levels of bleeding measures are necessary in patients with dual antiplatelet therapy. According to a study by Hanken *et al.* [47], continued aspirin therapy in patients undergoing dental osteotomies has no effect on the incidence of post-operative bleeding and should not be interrupted. Nooh [48] in his study concluded that subjects who received 81 mg ASA daily could undergo dental extraction without bleeding risks. van Diermen *et al.* [49] in their literature review suggest not to interrupt oral antithrombotic medication, not even dual antiplatelet therapy, in simple dental procedures. Broekema *et al*. [50] from their prospective study concluded that dentoalveolar surgery is safe in patients being treated with anticoagulants.

Many other studies have recommended that dental extractions can be carried out safely without discontinuation of antiplatelet therapy [51-59]. Studies related to general and cardiovascular surgery also did not show any significance increase in bleeding in patients on antiplatelet drugs [60,61]. Zhao *et al.* [62] from their meta-analysis stated that they could not conclude that bleeding time or the extent of hemorrhage in dental extraction is prolonged when patients are on long-term aspirin therapy and recommend not to stop antiplatelet drugs before tooth extraction and that the hemostasis method is enhanced. Napenas *et al.* [63] conducted a retrospective analysis to evaluate the risk of bleeding complications in patients on single or dual antiplatelet therapy, undergoing invasive oral surgical procedures including dental extractions. They concluded that risk of stopping antiplatelet therapy and predisposing the patient to thromboembolic events far overweighed the negligible risk of bleeding from dental procedures.

Krishnan *et al*. concluded that patient continuing aspirin therapy can undergo routine dental extractions without increased risk of excessive or prolonged bleeding [56]. Bajkin *et al.* conducted a prospective study to evaluate the post-extraction bleeding in patients on aspirin monotherapy, oral anticoagulant therapy, and dual therapy with aspirin + oral anticoagulant (71 patients in each group). None of the patients on aspirin monotherapy had post-operative bleeding [51]. Lillis *et al.* performed a prospective study to compare the incidence of bleeding complications among patients taking aspirin monotherapy, clopidogrel monotherapy, and dual therapy with both aspirin and clopidogrel and patients not taking aspirin at all. The results showed that greater number of patients on dual antiplatelet therapy showed prolonged immediate bleeding when compared to control healthy patient group, and the difference was statistically significant. Although there is greater incidence of prolonged immediate bleeding in dual antiplatelet therapy group, hemostasis is achieved easily by local hemostatic measures. Therefore, they concluded that the patient should not be predisposed to risk of thromboembolism by stopping either antiplatelet monotherapy or dual therapy [64]. Madan *et al.* concluded that most minor oral surgical procedures can be carried out safely without interrupting long-term low-dose aspirin therapy [58].

According to Scully and Wolf for uncomplicated forceps extraction of 1 to 3 teeth, there is no need to interfere the aspirin dose. In patients taking 100 mg of aspirin a day, bleeding can be controlled by suturing and local hemostatic measures. In patients taking higher dose of aspirin, if the current value of bleeding time is more than 20 minutes, then surgical treatment should be postponed [17]. Little *et al.* [18], Gaspar *et al.* [65], and Sonksen *et al.* [66] claimed that there are no significant intra- and post-operative bleedings after dental extractions as long as prolongation in bleeding time remains within acceptable limit (bleeding time up to 20 minutes) preoperatively. The study of Blinder *et al.* [67] concluded that dental extraction could be performed without interruption in patients' treatment with oral anticoagulants. Another recent study stated that there was no need to discontinue either the anticoagulant or aspirin in the patients taking the combined oral anticoagulant-aspirin regimen who required dental extraction [51].

Napeñas *et al.* [53] and Morimoto *et al.* [52] from their studies suggest that the risk for post-operative bleeding complications is greater with warfarin, either alone or in combination with antiplatelet medications, than antiplatelet medications alone. The results of their review suggest that there is no indication to alter or discontinue antiplatelet therapy before invasive dental procedures and post-operative bleeding can be managed by local hemostatic measures. Ardekian *et al.* [68] concluded that dental extractions can be performed in patients on continued antiplatelet therapy. A recent survey of vascular surgeons showed that most did not stop the administration of antiplatelet drugs pre-operatively [69]. One might assume that the risk of bleeding complications would be much greater with vascular procedures (i.e., carotid endarterectomy or infrainguinal bypass) than with routine exodontia.

In a study by Cañigral *et al.* [70], 4 of the 9 patients (44.4%) receiving dual therapy had moderate hemorrhage that was defined as hemorrhage lasting more than 10 minutes and was stopped using local hemostatic

measures in less than 60 minutes in all cases. A study by Park *et al.* [71] with all dental extractions included 100 patients with double and triple antiplatelet therapy; only 2 cases of excessive hemorrhage (lasting 4 and 5 hrs) were found. According to Bassand *et al.*, dual antiplatelet therapy was found to increase major bleeding events by 1% as compared to aspirin monotherapy, but no life-threatening complications were reported and no transfusions were required [72]. Morimoto *et al.* in their study reported post-operative bleeding of 1.4% for single or dual antiplatelet therapy, 4.1% for warfarin, and 8.2% for combined warfarin and antiplatelet therapy after teeth extractions [52]. The same group performed a similar study involving periodontal therapy (e.g. scaling and root planing, periodontal surgery), with post-operative bleeding occurrences of 0%, 1.4%, and 3.4% for antiplatelet therapy, warfarin, and combined warfarin and antiplatelet therapy, respectively [73] but were managed by local hemostatic measures. Duygu *et al.* [74], and Medeiros *et al.* [75] have assessed the bleeding risk in patients on antiplatelet therapy during dental invasive procedures and have concluded to be safe to continue the drugs.

ORAL SURGERY CONSIDERATIONS

Minor surgical procedures such as simple extraction of up to three teeth, gingival surgery, crown and bridge procedures, supragingival scaling, and surgical removal of teeth can be safely carried out without altering the antiplatelet medication dose. If more than three 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. Scaling and gingival surgery should initially be restricted to a limited area to assess if bleeding is problematic.

MANAGEMENT OF POST-OPERATIVE BLEEDING

Post-operative bleeding has more serious consequences for surgeries of the abdomen or thoracic cavity, which have compartment spaces where, after wound closure, post-operative bleeding is invisible. In contrast, the consequences of possible hemorrhage in non-compartment surgeries are greatly outweighed by the risk associated with cessation of antiplatelet therapy, which can result in acute coronary syndrome in serious cases [76,77]. Dental surgery is a non-compartment procedure, and bleeding in the oral cavity is immediately visible and can therefore be treated without delay [78].

All patients receiving antiplatelet medications must be considered to have drug-induced altered platelet function. There will be an increased bleeding tendency if two antiplatelet agents are used in combination than with monotherapy. Several studies were conducted to assess the risk of post-operative bleeding in patients on antiplatelet drugs undergoing dental surgical procedures, and it was found to be safe to continue the drugs during dental treatment [74,75]. Morimoto *et al.* [52], Scully and Wolff [17], and Lillis *et al.* [64] have reported acute inflammation in the form of gingivitis and periodontitis as the aggravating factor of hemorrhage post-extraction in patients on antithrombotic therapy. Other factors which increase the risk of post-operative bleeding are extraction time, surgical tooth extraction, and 3-root extractions [43]. Granulation tissue in extraction sockets should be removed before placement of hemostatic agents as it is a frequent source of post-extraction bleeding.

Aspirin can double the baseline bleeding time, but this may still be within or just outside the normal range. Clopidogrel is considered a more potent antiplatelet agent and can prolong the bleeding time by 1.5-3 times normal. Sensitivity to antiplatelet agents varies from one person to another. According to Thomas *et al.* [79], Brennan *et al.* [55], and Ardekian *et al.* [68], cutaneous bleeding time as a screening procedure to predict post-operative oral bleeding cannot be accepted. The platelet aggregation test is said to be more acceptable test in assessing platelet function.

Patients taking antiplatelet medications will have prolonged bleeding time, but this may not be clinically relevant because post-operative bleeding after dental procedures can mostly be controlled using local hemostatic measures. Lockhart *et al.* [80] suggested post-operative bleeding as clinically significant if it fulfills any of the following four criteria:

1. Bleeding that continued >12 hrs of surgical procedure,
2. Bleeding that makes the patient report back for management,
3. Bleeding that results in large hematoma formation or ecchymosis,
4. Bleeding that required blood transfusion.

LOCAL HEMOSTATIC MEASURES

Surgeons most often apply pressure (biting firmly on gauze for 30 minutes), use a hemostatic matrix such as oxidized regenerated cellulose, absorbable gelatin sponge, or collagen with figure of eight sutures applied to the extraction socket. The hemostatic properties of these agents are based on their ability to activate the coagulation cascade locally. They have no intrinsic coagulation factors or activities but are designed to stimulate clot formation by providing a 3-dimensional scaffold used for clot organization. Others include topical thrombin, bone wax (ostene), 4.8% tranexamic acid mouthwash [81,82], HemCon Dental Dressing (chitosan-based agent), hemostatic solutions (aluminum solution), tannic acid, and fibrin glue. Newer local hemostatic agents under consideration include zeolite (QuikClot), chitosan-based agents (N-acetyl glucosamine polymer), and poly-*N*-acetyl glucosamine agents. Patients are strictly advised to follow the post-operative instructions for the maintenance of the blood clot.

SUMMARY

Patients must be treated based on the following protocol:

1. Assessing status of their medical condition,
2. Proper laboratory assessment of their coagulation profile before surgery,
3. Accurate categorization of their thromboembolic profile,
4. Appropriate surgical risk stratification and effective local control,
5. Close extended post-operative monitoring.

Dual antiplatelet therapy is given for high-risk patients, especially those with coronary stents. Hence, premature withdrawal of these drugs can result in myocardial infarction and death. The American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Physicians, American College of Surgeons, American Dental Association, National Health Service, and numerous authors recommend either maintaining double antiplatelet therapy in dental interventions and applying the necessary local hemostatic measures to control the hemorrhage or delaying the intervention until the dual therapy can be withdrawn without risk [44,45].

A review of the literature showed the risk of bleeding under continued aspirin use to increase by 1.5-fold, but that this can be controlled with local hemostatic measures with no life-threatening bleeding. Dual antiplatelet therapy was found to increase major bleeding events by 1% as compared to aspirin monotherapy, but no life-threatening complications were reported and no transfusions were required and can be managed by local hemostatic measures. An increased rate of surgical bleeding has also been reported with the use of clopidogrel, but this was found not to influence patient morbidity and mortality. Hence, there is no need to expose the patient to the risk of thromboembolism, cerebrovascular accidents, or myocardial or renal infarction by discontinuing antiplatelet therapy before minor oral surgical procedures, which could cost the patient's life [83].

CONCLUSION

1. Antiplatelet monotherapy or even antiplatelet dual therapy need not be altered or stopped before minor oral surgical procedures.
2. Most of the post-operative bleeding can be easily controlled by local hemostatic measures.
3. However, patients on combined anticoagulant and antiplatelet

therapy or dual antiplatelet therapy appear to be at increased risk for post-operative bleeding complications, when major oral surgical procedures are performed and their management warrants added consideration (higher levels of hemostatic measures and appropriate consultation with the physician are necessary).

4. The risk of hemorrhage after dental surgery may be greatly outweighed by the risk of thromboembolism after withdrawal of anti-thrombotic therapy.

REFERENCES

1. Becker DE. Antithrombotic drugs: Pharmacology and implications for dental practice. Anesth Prog 2013;60(2):72-9.
2. Robless P, Mikhailidis DP, Stansby G. Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with peripheral vascular disease. Br J Surg 2001;88(6):787-800.
3. Lewis HD Jr, Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE rd, *et al.* Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. N Engl J Med 1983;309(7):396-403.
4. Sear JW, Higham H. Issues in the perioperative management of the elderly patient with cardiovascular disease. Drugs Aging 2002;19(6):429-51.
5. Harder S, Klinkhardt U, Alvarez JM. Avoidance of bleeding during surgery in patients receiving anticoagulant and/or antiplatelet therapy: Pharmacokinetic and pharmacodynamic considerations. Clin Pharmacokinet 2004;43(14):963-81.
6. Bennett CL, Davidson CJ, Raisch DW, Weinberg PD, Bennett RH, Feldman MD. Thrombotic thrombocytopenic purpura associated with ticlopidine in the setting of coronary artery stents and stroke prevention. Arch Intern Med 1999;159(21):2524-8.
7. Weber R, Weimar C, Diener HC. Antiplatelet agents in stroke prevention: Acute and long-term treatment strategies. Hamostaseologie 2009;29(4):326-33.
8. De Schryver E, Algra A, Van Gijn J, Weinberg PD, Bennett RH,. Dipyridamole for preventing stroke and other vascular vents in patients with vascular disease. Stroke 2008;39:1397.
9. Payne DA, Hayes PD, Jones CI, Belham P, Naylor AR, Goodall AH. Combined therapy with clopidogrel and aspirin significantly increases the bleeding time through a synergistic antiplatelet action. J Vasc Surg 2002;35(6):1204-9.
10. Randall C. Surgical Management of the Primary Care Dental Patient on Antiplatelet Medication. Available from: http://www.ukmi.nhs.uk/activities/specialistServices/.
11. Lemkin SR, Billesdon JE, Davee JS, Leake DL, Kattlove HE. Aspirin-induced oral bleeding: Correction with platelet transfusion. A reminder. Oral Surg Oral Med Oral Pathol 1974;37(4):498-501.
12. McGaul T. Postoperative bleeding caused by aspirin. J Dent 1978;6(3):207-9.
13. Daniel NG, Goulet J, Bergeron M, Paquin R, Landry PE. Antiplatelet drugs: Is there a surgical risk? J Can Dent Assoc 2002;68(11):683-7.
14. Conti CR. Aspirin and elective surgical procedures. Clin Cardiol 1992;15(10):709-10.
15. Speechley JA, Rugman FP. Some problems with anticoagulants in dental surgery. Dent Update 1992;19(5):204-6.
16. Scher KS. Unplanned reoperation for bleeding. Am Surg 1996;62(1):52-5.
17. Scully C, Wolff A. Oral surgery in patients on anticoagulant therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;94(1):57-64.
18. Little JW, Miller CS, Henry RG, McIntosh BA. Antithrombotic agents: Implications in dentistry. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;93(5):544-51.
19. Burger W, Chemnitius JM, Kneissl GD, Rücker G. Low-dose aspirin for secondary cardiovascular prevention - cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation - Review and meta-analysis. J Intern Med 2005;257(5):399-414.
20. Thomason JM, Seymour RA, Murphy P, Brigham KM, Jones P. Aspirin-induced post-gingivectomy haemorrhage: A timely reminder. J Clin Periodontol 1997;24:136-8.
21. Elad S, Chackartchi T, Shapira L, Findler M. A critically severe gingival bleeding following non-surgical periodontal treatment in patients medicated with anti-platelet. J Clin Periodontol 2008;35(4):342-5.
22. Schrodi J, Recio L, Fiorellini J, Howell H, Goodson M, Karimbux N. The effect of aspirin on the periodontal parameter bleeding on probing. J Periodontol 2002;73(8):871-6.
23. Foulke CN. Gingival hemorrhage related to aspirin ingestion. A case report. J Periodontol 1976;47(6):355-7.
24. Bashein G, Nessly ML, Rice AL, Counts RB, Misbach GA. Preoperative aspirin therapy and reoperation for bleeding after coronary artery bypass surgery. Arch Intern Med 1991;151(1):89-93.
25. Ferraris VA, Ferraris SP, Lough FC, Berry WR. Preoperative aspirin ingestion increases operative blood loss after coronary artery bypass grafting. Ann Thorac Surg 1988;45(1):71-4.
26. Toyoda K, Yasaka M, Iwade K, Nagata K, Koretsune Y, Sakamoto T, *et al.* Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: A prospective, multicenter, observational study. Stroke 2008;39(6):1740-5.
27. Dogne JM, de Leval X, Benoit P, Delarge J, Masereel B, David JL. Recent advances in antiplatelet agents. Curr Med Chem 2002;9(5):577-89.
28. Lordkipanidzé M, Diodati JG, Pharand C. Possibility of a rebound phenomenon following antiplatelet therapy withdrawal: A look at the clinical and pharmacological evidence. Pharmacol Ther 2009;123(2):178-86.
29. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: A special risk for late stent thrombosis. J Am Coll Cardiol 2005;45(3):456-9.
30. Chassot PG, Delabays A, Spahn DR. Perioperative antiplatelet therapy: The case for continuing therapy in patients at risk of myocardial infarction. Br J Anaesth 2007;99(3):316-28.
31. Anderson CS, Jamrozik KD, Broadhurst RJ, Stewart-Wynne EG. Predicting survival for 1 year among different subtypes of stroke: Results from the Perth community stroke study. Stroke 1994;25(10):1935-44.
32. Sibon I, Orgogozo JM. Antiplatelet drug discontinuation is a risk factor for ischemic stroke. Neurology 2004;62(7):1187-9.
33. Kovich O, Otley CC. Thrombotic complications related to discontinuation of warfarin and aspirin therapy peri-operatively for cutaneous operation. J Am Acad Dermatol 2003;48(2):233-7.
34. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, *et al.* Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364(9444):1519-21.
35. Maulaz AB, Bezerra DC, Michel P, Bogousslavsky J. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. Arch Neurol 2005;62(8):1217-20.
36. Vaclavik J, Taborsky M. Antiplatelet therapy in perioperative period. Eur J Intern Med 2011;22:26-32.
37. Wahl MJ, Howell J. Altering anticoagulation therapy: A survey of physicians. J Am Dent Assoc 1996;127(5):625-6.
38. Biondi-Zoccai GG, Lotrionte M, Agostoni P, Abbate A, Fusaro M, Burzotta F, *et al.* A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. Eur Heart J 2006;27(22):2667-74.
39. Collet JP, Himbet F, Steg PG. Myocardial infarction after aspirin cessation in stable coronary artery disease patients. Int J Cardiol 2000;76(2-3):257-8.
40. Collet JP, Montalescot G, Blanchet B, Tanguy ML, Golmard JL, Choussat R, *et al.* Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. Circulation 2004;110(16):2361-7.
41. Bajkin BV, Urosevic IM, Stankov KM, Petrovic BB, Bajkin IA. Dental extractions and risk of bleeding in patients taking single and dual antiplatelet treatment. Br J Oral Maxillofac Surg 2015;53(1):39-43.
42. Verma G, Tiwari AK, Chopra S. Aspirin and exodontia: A comparative study of bleeding complications with aspirin therapy. Int J Dent Sci Res 2013;1:50-3.
43. Olmos-Carrasco O, Pastor-Ramos V, Espinilla-Blanco R, Ortiz-Zárate A, García-Avila I, Rodríguez-Alonso E, *et al.* Hemorrhagic complications of dental extractions in 181 patients undergoing double antiplatelet therapy. J Oral Maxillofac Surg 2015;73(2):203-10.
44. Grines CL, Bonow RO, Casey DE Jr., Gardner TJ, Lockhart PB, Moliterno DJ, *et al*. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: A science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. Circulation 2007;115(6):813-8.
45. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed. American College of

Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141 2 Suppl:7S-47.
46. Girotra C, Padhye M, Mandlik G, Dabir A, Gite M, Dhonnar R, *et al.* Assessment of the risk of haemorrhage and its control following minor oral surgical procedures in patients on anti-platelet therapy: A prospective study. Int J Oral Maxillofac Surg 2014;43(1):99-106.
47. Hanken H, Tieck F, Kluwe L, Smeets R, Heiland M, Precht C, *et al.* Lack of evidence for increased postoperative bleeding risk for dental osteotomy with continued aspirin therapy. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119(1):17-9.
48. Nooh N. The effect of aspirin on bleeding after extraction of teeth. Saudi Dent J 2009;21(2):57-61.
49. van Diermen DE, van der Waal I, Hoogstraten J. Management recommendations for invasive dental treatment in patients using oral antithrombotic medication, including novel oral anticoagulants. Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116(6):709-16.
50. Broekema FI, van Minnen B, Jansma J, Bos RR. Risk of bleeding after dentoalveolar surgery in patients taking anticoagulants. Br J Oral Maxillofac Surg 2014;52(3):e15-9.
51. Bajkin BV, Bajkin IA, Petrovic BB. The effects of combined oral anticoagulant-aspirin therapy in patients undergoing tooth extractions: A prospective study. J Am Dent Assoc 2012;143(7):771-6.
52. Morimoto Y, Niwa H, Minematsu K. Risk factors affecting postoperative hemorrhage after tooth extraction in patients receiving oral antithrombotic therapy. J Oral Maxillofac Surg 2011;69(6):1550-6.
53. Napeñas JJ, Oost FC, DeGroot A, Loven B, Hong CH, Brennan MT, *et al.* Review of postoperative bleeding risk in dental patients on antiplatelet therapy. Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115(4):491-9.
54. Brennan MT, Valerin MA, Noll JL, Napeñas JJ, Kent ML, Fox PC, *et al.* Aspirin use and post-operative bleeding from dental extractions. J Dent Res 2008;87(8):740-4.
55. Brennan MT, Wynn RL, Miller CS. Aspirin and bleeding in dentistry: An update and recommendations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104(3):316-23.
56. Krishnan B, Shenoy NA, Alexander M. Exodontia and antiplatelet therapy. J Oral Maxillofac Surg 2008;66(10):2063-6.
57. Partridge CG, Campbell JH, Alvarado F. The effect of platelet-altering medications on bleeding from minor oral surgery procedures. J Oral Maxillofac Surg 2008;66(1):93-7.
58. Madan GA, Madan SG, Madan G, Madan AD. Minor oral surgery without stopping daily low-dose aspirin therapy: A study of 51 patients. J Oral Maxillofac Surg 2005;63(9):1262-5.
59. Brennan MT, Shariff G, Kent ML, Fox PC, Lockhart PB. Relationship between bleeding time test and postextraction bleeding in a healthy control population. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;94(4):439-43.
60. Ferraris VA, Swanson E. Aspirin usage and perioperative blood loss in patients undergoing unexpected operations. Surg Gynecol Obstet 1983;156(4):439-42.
61. Rajah SM, Salter MC, Donaldson DR, Subba Rao R, Boyle RM, Partridge JB, *et al.* Acetylsalicylic acid and dipyridamole improve the early patency of aorta-coronary bypass grafts. A double-blind, placebo-controlled, randomized trial. J Thorac Cardiovasc Surg 1985;90(3):373-7.
62. Zhao B, Wang P, Dong Y, Zhu Y, Zhao H. Should aspirin be stopped before tooth extraction? A meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119(5):522-30.
63. Napenas JJ, Hong CH, Brennan MT, Furney SL, Fox PC, Lockhart PB. The frequency of bleeding complications after invasive dental treatment in patients receiving single and dual antiplatelet therapy. J Am Dent Assoc 2009;140(6):690-9.
64. Lillis T, Ziakas A, Koskinas K, Tsirlis A, Giannoglou G. Safety of dental extractions during uninterrupted single or dual antiplatelet treatment. Am J Cardiol 2011;108(7):964-7.
65. Gaspar R, Ardekian L, Brenner B, Peled M, Laufer D. Ambulatory oral procedures in patients on low-dose aspirin. Harefuah 1999;136(2):108-10, 175.
66. Sonksen JR, Kong KL, Holder R. Magnitude and time course of impaired primary haemostasis after stopping chronic low and medium dose aspirin in healthy volunteers. Br J Anaesth 1999;82(3):360-5.
67. Blinder D, Manor Y, Martinowitz U, Taicher S, Hashomer T. Dental extractions in patients maintained on continued oral anticoagulant: Comparison of local hemostatic modalities. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;88(2):137-40.
68. Ardekian L, Gaspar R, Peled M, Brener B, Laufer D. Does low-dose aspirin therapy complicate oral surgical procedures? J Am Dent Assoc 2000;131(3):331-5.
69. Smout J, Stansby G. Current practice in the use of antiplatelet agents in the peri-operative period by UK vascular surgeons. Ann R Coll Surg Engl 2003;85(2):97-101.
70. Cañigral A, Silvestre FJ, Cañigral G, Alós M, Garcia-Herraiz A, Plaza A. Evaluation of bleeding risk and measurement methods in dental patients. Med Oral Patol Oral Cir Bucal 2010;15(6):e863-8.
71. Park MW, Her SH, Kwon JB, Lee JB, Choi MS, Cho JS, *et al.* Safety of dental extractions in coronary drug-eluting stenting patients without stopping multiple antiplatelet agents. Clin Cardiol 2012;35(4):225-30.
72. Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology, Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, *et al.* Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28(13):1598-660.
73. Morimoto Y, Niwa H, Minematsu K. Hemostatic management for periodontal treatments in patients on oral antithrombotic therapy: A retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108(6):889-96.
74. Duygu G, Ozcakir-Tomruk C, Guler N, Sencift K. Assessment of effects of antiplatelet drugs on bleeding risk after teeth extractions. Biotechnol Biotechnol Equip 2010;24:2040-3.
75. Medeiros FB, de Andrade AC, Angelis GA, Conrado VC, Timerman L, Farsky P, *et al.* Bleeding evaluation during single tooth extraction in patients with coronary artery disease and acetylsalicylic acid therapy suspension: A prospective, double-blinded, and randomized study. J Oral Maxillofac Surg 2011;69(12):2949-55.
76. Eichhorn W, Burkert J, Vorwig O, Blessmann M, Cachovan G, Zeuch J, *et al.* Bleeding incidence after oral surgery with continued oral anticoagulation. Clin Oral Investig 2012;16(5):1371-6.
77. Sahebally SM, Healy D, Coffey JC, Walsh SR. Should patients taking aspirin for secondary prevention continue or discontinue the medication prior to elective, abdominal surgery? Best evidence topic (BET). Int J Surg 2014;12(5):16-21.
78. Wahl MJ. Dental surgery and antiplatelet agents: Bleed or die. Am J Med 2014;127(4):260-7.
79. Thomas S, Katbab H, abu Fanas SH. Do preoperative cutaneous bleeding time tests predict the outcome of intraoral surgical bleeding? Int Dent J 2010;60(4):305-10.
80. Lockhart PB, Gibson J, Pond SH, Leitch J. Dental management considerations for the patient with an acquired coagulopathy. Part 1: Coagulopathies from systemic disease. Br Dent J 2003;195(8):439-45.
81. Borea G, Montebugnoli L, Capuzzi P, Magelli C. Tranexamic acid as a mouthwash in anticoagulant-treated patients undergoing oral surgery. An alternative method to discontinuing anticoagulant therapy. Oral Surg Oral Med Oral Pathol 1993;75(1):29-31.
82. Sindet-Pedersen S, Ramström G, Bernvil S, Blombäck M. Hemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. N Engl J Med 1989;320(13):840-3.
83. Pototski M, Amenábar JM. Dental management of patients receiving anticoagulation or antiplatelet treatment. J Oral Sci 2007;49(4):253-8.