Antiplatelet drugs: a review of pharmacology and the perioperative management of patients in oral and maxillofacial surgery

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ABSTRACT

INTRODUCTION An increasing number of patients are taking oral antiplatelet agents. As a result, there is an important patient safety concern in relation to the potential risk of bleeding complications following major oral and maxillofacial surgery. Surgeons are increasingly likely to be faced with a dilemma of either continuing antiplatelet therapy and risking serious haemorrhage or withholding therapy and risking fatal thromboembolic complications. While there are national recommendations for patients taking oral antiplatelet drugs undergoing invasive minor oral surgery, there are still no evidence-based guidelines for the management of these patients undergoing major oral and maxillofacial surgery.

METHODS MEDLINE and EMBASE databases were searched to retrieve all relevant articles published to 31 December 2017.

FINDINGS A brief outline of the commonly used antiplatelet agents including their pharmacology and therapeutic indications is discussed, together with the haemorrhagic and thromboembolic risks of continuing or altering the antiplatelet regimen in the perioperative period. Finally, a protocol for the management of oral and maxillofacial patients on antiplatelet agents is presented.

CONCLUSIONS Most current evidence to guide decision making is based upon non-randomised observational studies, which attempts to provide the safest possible management of patients on antiplatelet therapy. Large randomised clinical trials are lacking.

KEYWORDS

Aspirin – Clopidogrel – Antiplatelets – Perioperative – Haemorrhage – Thrombosis

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Introduction

An increasing number of patients are taking oral antiplatelet agents for primary or secondary prevention of vascular thrombosis. Surgeons are increasingly likely to be faced with the dilemma of continuing or omitting antiplatelet therapy prior to major surgery.¹ The potential risk of continuing therapy could result in severe haemorrhage, whereas the potential risk of omitting therapy may result in fatal thromboembolic complications. Due to the challenges faced when dealing with this cohort of patients, the need for evidence-based guidelines is essential to address this important patient safety concern.

Although there are national guidelines for patients taking antiplatelet drugs undergoing invasive minor oral surgery procedures, these are based on consensus and expert opinions alone.² There are no evidence-based guidelines for the perioperative management of patients on

antiplatelet therapy undergoing major oral and maxillofacial surgery where the risk of bleeding complications is potentially greater.

Methods

MEDLINE and EMBASE databases were searched to retrieve all relevant articles published to 31 December 2017. Linked search terms included ‘oral’, ‘maxillofacial’, ‘surgery’, ‘antiplatelets’ and ‘anticoagulants’, together with generic and brand names for all commonly used antiplatelet agents such as clopidogrel. General consensus was used to agree upon discrepancies in article selection otherwise our second author (IS) made the final decision to resolve any disagreement between the authors. Only articles in English language were included in our review.

Findings

This is the first review to propose recommendations based upon the current literature and scientific evidence. A brief outline of the commonly used antiplatelet agents including their pharmacology and therapeutic indications is discussed along with the haemorrhagic and thromboembolic risks of continuing or altering the antiplatelet regimen in the perioperative period. Finally, a protocol for the management of oral and maxillofacial patients on antiplatelet agents is presented.

Effect of antiplatelet agents on clotting and bleeding time

After a vascular injury, platelets aggregate to plug the defect at the earliest stage of haemostasis. However, they are also fundamental in the pathological process of arterial thrombosis leading to coronary and cerebrovascular events.⁵ Antiplatelet agents reduce the ability of blood to clot or coagulate by reversibly or irreversibly inhibiting platelet activation and aggregation necessary for the initial platelet plug in primary haemostasis. Platelet function is quantified using the cutaneous bleeding time with a normal range of 2–10 minutes,⁵ although there is no reliable correlation between bleeding time and the rate of surgical bleeding complications.⁴

Antiplatelet agents and their therapeutic indications

Antiplatelet agents are prescribed for patients after an acute coronary syndrome or coronary stent placement. Damaged endothelium and stents act as unstable plaques. A bare-metal stent is covered by endothelium within 12 weeks,⁵ whereas a drug-eluting stent has a slower endothelialisation rate of 15% at three months and 56% at three years.⁶ Thus, the recommended duration of antiplatelet therapy for a bare-metal stent is a minimum of 6 weeks and a minimum of 12 months for a drug-eluting stent.⁷

Low-dose aspirin

Aspirin (75–300 mg daily) is primarily used for secondary prevention of thromboembolic cardiovascular and cerebrovascular disease. Patients also self-prescribe aspirin based upon professional recommendation or a belief it will offer cardiovascular protection. It irreversibly acetylates cyclooxygenase-1 to inhibit thromboxane-A₂ production and reduces platelet aggregation.⁸

Clopidogrel

Clopidogrel offers greater thromboembolic protection than aspirin in the secondary prevention of myocardial infarction, cerebrovascular and peripheral vascular disease.⁹ Clopidogrel irreversibly inhibits the adenosine diphosphate (ADP) receptors on platelet membranes to reduce platelet aggregation.²

Aspirin and clopidogrel dual-therapy

Dual therapy with low-dose aspirin and clopidogrel is used for patients with non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction

who have been medically treated and eligible for thrombolytic therapy. This combination is also licensed following insertion of drug-eluting and bare-metal stents.¹⁰ Aspirin and clopidogrel block complementary pathways in platelet aggregation and therefore have synergistic effects when used in combination.¹¹

Dipyridamole

Dipyridamole is used in combination with oral anticoagulation for prophylaxis of prosthetic heart valve thromboembolic events.¹² It inhibits cellular adenosine uptake leading to its greater availability for binding to the adenosine receptor on platelets. It also inhibits the enzyme cyclic guanine monophosphate phosphodiesterase.⁸ Dipyridamole has less antiplatelet activity compared with aspirin and ADP receptor blockers and its action on phosphodiesterase ceases to exist within 24 hours of stopping the drug.¹³

Aspirin and dipyridamole

Aspirin and dipyridamole as a combined drug is licensed for secondary prevention of cerebrovascular disease and transient ischaemic attacks but does not appear to increase the incidence of adverse bleeding events compared with individual antiplatelet agents.¹⁴

Prasugrel and ticagrelor

Prasugrel and ticagrelor are new generation anti-platelet drugs. They are currently only licensed for use in combination with aspirin for the secondary prevention of cardiovascular and cerebrovascular disease.^{15,16}

Prasugrel has irreversible antiplatelet activity by binding to P2Y₁₂ ADP receptors.¹⁵ It is more effective than clopidogrel in preventing stent thrombosis but has an increased rate of serious bleeding (1.4% vs 0.9% in the clopidogrel group) and fatal bleeding (0.4% vs 0.1%).¹⁶

Ticagrelor is an allosteric antagonist which reversibly blocks ADP receptors of subtype P2Y₁₂. Unlike clopidogrel and prasugrel, ticagrelor is not a prodrug and does not require metabolic activation for antiplatelet activity.¹⁶

Vorapaxor

Vorapaxar is a novel antiplatelet agent which was granted by the European Union marketing authorisation in June 2015 for secondary prevention of thrombotic cardiovascular events in patients with a history of myocardial infarction or peripheral arterial disease.² It is a tricyclic himbacine-derived selective inhibitor of protease-activated receptor-1, a thrombin receptor expressed on platelets. By inhibiting protease-activated receptor-1, vorapaxar prevents thrombin-related platelet aggregation.

Antiplatelet agent therapy cessation and thromboembolism risk

Stopping antiplatelet therapy in the perioperative period is particularly hazardous due to increased platelet aggregation. Thromboembolic events associated with the

interruption of antiplatelet therapy are well recognised and although the risk is low the consequences are serious. Recurrent venous thromboembolism has a mortality of 6%. Arterial thromboembolism is more serious with a mortality of 20%.¹⁷

Aspirin cessation

A meta-analysis of 14,981 patients comparing the perioperative continuation with discontinuation of low-dose aspirin revealed that 93 (0.6%) patients who discontinued aspirin presented with acute vascular events with 14 (15.1%) of these discontinuing aspirin due to dental surgery.¹⁸ Furthermore, a review and meta-analysis of 50,279 patients revealed that aspirin discontinuation had a detrimental effect regardless of its indication.¹⁹ It is therefore not advised to alter aspirin therapy prior to surgery, particularly when it is prescribed for secondary prevention after cerebrovascular accident, acute coronary syndrome, myocardial infarction or coronary revascularisation.

Clopidogrel cessation

Patients with coronary stents are at high risk of thromboembolic complications. This is particularly important for the first 6–12 months after insertion of a drug-eluting stent and 6–12 weeks after insertion of a bare-metal stent.⁷ The most important independent risk factor for drug-eluting stent thrombosis within the first 18 months of placement is cessation of clopidogrel therapy.²⁰ In one prospective study of 192 patients who underwent non-cardiac surgery within two years of commencing dual antiplatelet therapy after PCI, 5 of 91 (5.5%) patients who had their antiplatelet agents withheld experienced an adverse cardiac event. No patients who continued antiplatelet therapy experienced a cardiac complication. Clopidogrel should be continued at the correct dose prior to minor oral surgical procedures,²² but can be stopped seven days before surgery in patients without stents who are at low risk of cardiac events and recommenced the morning after surgery once haemostasis is achieved.²³

Dual-therapy cessation

A Science Advisory Summary issued jointly by the American Dental Association, American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Intervention and American College of Surgeons emphasised the importance of continuing dual antiplatelet therapy in patients with coronary artery stents.²² Stopping aspirin and clopidogrel dual therapy in patients with coronary stents is associated with a five- to tenfold increased risk of a myocardial infarction and mortality. The risk is inversely proportional to the time of revascularisation and surgery.²⁴

Overall, the risk of coronary thrombosis is greater than that of surgical haemorrhage, so perioperative cessation of aspirin and clopidogrel dual therapy should be avoided if possible.²³ Patients on dual antiplatelet therapy should be managed in an oral and maxillofacial surgery unit.²⁴

Antiplatelet agent continuation and haemorrhagic risk

Aspirin continuation

The nature of surgery will dictate the possible clinical consequences of bleeding. A meta-analysis of 474 studies including 49,590 patients reviewed the thromboembolic risks in discontinuing aspirin compared with the haemorrhagic risks with its continuation in the perioperative period in a variety of non-cardiac surgical procedures including ophthalmic, dental, visceral, minor general surgical and endoscopic procedures. It found that surgeons who were blinded to patient aspirin status could not differentiate between the two groups according to intraoperative bleeding. Although quantitative bleeding was greater in the aspirin cohort, there was no change in mortality and the bleeding complications could be managed using identical measures as without the influence of aspirin and without compromising the surgery. However, discontinuing low-dose aspirin resulted in thromboembolic complications, including death.¹⁸ For dentoalveolar surgery, several small prospective observational studies investigated possible bleeding consequences in continuing perioperative aspirin. Compared with those not taking aspirin, there were no significant differences in mean intraoperative blood loss, bleeding duration or intraoperative bleeding complications that could not be controlled with local measures.²⁵

Clopidogrel or dipyridamole continuation

There are few published studies on the relative risks of perioperative bleeding with clopidogrel or dipyridamole monotherapy. The pharmacological mechanisms underlying the antiplatelet action of these agents suggests patients taking these medications will be at no greater risk of excessive bleeding compared with those taking aspirin alone.²²

Dual therapy continuation

For invasive oral procedures, there is little evidence available on haemorrhagic complications in patients taking aspirin and clopidogrel. The TRITON-TIMI 38 trial collected data on 158 patients who were on dual antiplatelet therapy for acute coronary syndrome (prasugrel and aspirin: 78 patients, clopidogrel and aspirin: 80 patients) who received oral surgery. There were no bleeding complications during the oral surgery procedures but there was one minor bleeding event reported within seven days in both groups.¹⁶

The management of antiplatelet agents depends upon taking account of both the haemorrhagic and thromboembolic risks. The vast majority of oral and maxillofacial procedures are of minor or moderate haemorrhage risk. A summary of recommendations is outlined in Table 1.

Conclusions

Oral and maxillofacial surgeons will be involved in the perioperative management of patients taking antiplatelet

Table 1 Suggested perioperative management of the oral and maxillofacial patient on antiplatelet agents according to cardiac and bleeding risk levels.

Surgical bleeding risk level	Cardiac risk level		
	Low ^a	Intermediate ^b	High ^c
Low (dentoalveolar, soft tissue, salivary gland, minor trauma surgeries; transfusion not required)	Maintain aspirin and/or clopidogrel	Maintain aspirin and/or clopidogrel	Elective surgery: Postpone Urgent surgery: proceed and maintain aspirin and/or clopidogrel
Intermediate (oncological resection ± reconstructive, orthognathic, vascular, major trauma surgeries; transfusion may be required)	Maintain aspirin and/or clopidogrel	Elective surgery: proceed according to risk balance Urgent surgery: proceed and maintain aspirin and/or clopidogrel	Elective surgery: Postpone Urgent surgery: proceed and maintain aspirin and/or clopidogrel
High (surgery in closed spaces: intracranial neurosurgery, posterior eye chamber; craniofacial surgery; transfusion required)	Maintain aspirin Consider stopping clopidogrel 7 days before surgery and recommence 24 hours postoperatively after haemostasis achieved	Elective surgery: postpone Urgent surgery: proceed and maintain aspirin. If necessary, consider stopping clopidogrel 7 days before surgery and recommence 24 hours postoperatively after haemostasis achieved. Do not alter dual antiplatelet regime without seeking advice from a cardiologist	Elective surgery: postpone Urgent surgery: proceed and maintain aspirin. If necessary, consider stopping clopidogrel 7 days before surgery. Do not alter dual antiplatelet regime without seeking advice from a cardiologist
^a > 3 months after percutaneous coronary intervention, bare-metal stenting or coronary artery bypass grafting; > 6 months after acute coronary syndrome or myocardial infarction; > 12 months after drug-eluting stenting. ^b 6–12 weeks after percutaneous coronary intervention, bare-metal stenting or coronary artery bypass grafting; 6–24 weeks after acute coronary syndrome or myocardial infarction; > 12 months after high-risk drug-eluting stenting. ^c < 6 weeks after percutaneous coronary intervention, bare-metal stenting, coronary artery bypass grafting, acute coronary syndrome or myocardial infarction (< 3 months if complications); < 12 months after drug-eluting stenting (may be longer in high-risk drug-eluting stenting). These delays can be modified according to the amount of myocardium at risk, the instability of the coronary situation or the risk of spontaneous haemorrhage. The same recommendations apply to newer second-generation drug-eluting stents.			

agents for primary or secondary prevention of vascular thrombosis. The surgeon must balance risking primary or recurrent arterial thromboembolism if antiplatelet therapy is altered against potentially troublesome or catastrophic haemorrhage if therapy is continued. Troublesome haemorrhagic complications do not carry the same weight of risk as thromboembolic complications. Overall, patients are at greater risk of permanent disability or death if antiplatelet therapy is altered before a surgical procedure than if it is continued.

There has been no single report of uncontrollable haemorrhage in patients receiving oral surgical procedures and taking dual anti-platelet therapy. Therefore, there is no indication to interrupt antiplatelet medication in such cases. Bleeding can usually be controlled with local measures.

It is considered safe to continue aspirin throughout the oral and maxillofacial perioperative period. Aspirin therapy should not be altered or stopped for surgery when it is prescribed for secondary prevention after cerebrovascular accident, acute coronary syndrome, myocardial infarction or coronary revascularisation.

Clopidogrel or dipyridamole monotherapy should not be stopped or altered prior to oral surgical procedures. Clopidogrel should be continued at the correct dose prior to minor oral surgical procedure,²² but can be stopped seven days before surgery in non-stented patients who are at low risk of cardiac events and recommenced the morning after surgery once haemostasis is achieved.²⁵

Current guidance for patients who have received coronary stents recommends that all elective operations are postponed beyond the recommended time patients are

receiving dual antiplatelet therapy. In such cases, only vital surgery should be undertaken without interrupting dual anti-platelet therapy. This is particularly important for patients who have undergone percutaneous coronary intervention with a bare-metal stent fitted within one month or a drug-eluting stent fitted within six months, because of the increased risk of fatal coronary stent thrombosis. Aspirin should be continued if clopidogrel therapy is stopped.²⁵ Patients on dual antiplatelet therapy should be managed in an oral and maxillofacial surgery unit.²² A 2018 systematic review highlighted the importance of weighing individual risks for coronary stent thrombosis with those of fatal surgical haemorrhage to inform clinical decisions. The review also emphasised the need to adopt a collaborative multidisciplinary approach through liaison with an interventional cardiologist, haematologist, anaesthetist and surgeon to enable specific tailored dual antiplatelet therapy management.²⁶

Coronary stent thrombosis is a platelet-induced phenomenon so heparin has no useful role as bridging therapy due to its lack of antiplatelet therapy. Short-acting platelet glycoprotein IIb/IIIa inhibitors (for example eptifibatide or tirofiban) are used as a substitute for clopidogrel while aspirin is being maintained but this has not been proven by any randomised controlled trials.

Most of the current evidence to guide decision making is based upon non-randomised observational studies, which attempts to provide the safest possible management of patients on antiplatelet therapy. Large randomised clinical trials are lacking.

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