■ ASPECTS OF CURRENT MANAGEMENT

A review of the use of common antiplatelet agents in orthopaedic practice

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Antiplatelet agents are widely prescribed for the primary and secondary prevention of cardiovascular events. A common clinical problem facing orthopaedic and trauma surgeons is how to manage patients receiving these agents who require surgery, either electively or following trauma. The dilemma is to balance the risk of increased blood loss if the antiplatelet agents are continued peri-operatively against the risk of coronary artery/stent thrombosis and/or other vascular event if the drugs are stopped. The traditional approach of stopping these medications up to two weeks before surgery appears to pose significant danger to patients and may require review.

This paper covers the important aspects regarding the two most commonly prescribed antiplatelet agents, aspirin and clopidogrel.

Antiplatelet agents are widely prescribed for the prevention of cardiovascular events. An unstable atheromatous plaque with superimposed thrombus formation is the main aetiological factor associated with these events.^{1,2} More than two-thirds of sudden cardiac events such as acute coronary syndrome or sudden cardiac death,^{1,3} and half of post-operative myocardial infarctions⁴⁻⁶ are due to the disruption and thrombosis of unstable plaques. Multiple cellular, humoral and neuro-vegetative triggers (psychological or emotional factors playing a role in acute coronary syndromes via the autonomic nervous system) may destabilise these plaques and lead to the development of an occluding thrombus.⁷ The acute coronary syndrome is linked with pro-inflammatory and prothrombotic conditions that involve an increase in fibrinogen, CRP and plasminogen activator inhibitor.⁸ After operation the risk of acute coronary syndrome is further aggravated by the augmented release of endogenous catecholamines, increased platelet adhesiveness and reduced fibrinolysis, which are characteristic of the acute-phase reaction.^{6,9,10} It is therefore understandable that antiplatelet agents can be helpful in situations of increased thrombogenic risk.

About two million patients undergo percutaneous coronary intervention (PCI) each year in western countries, and more than 90% involve the placement of intracoronary stents.¹¹ This procedure then requires long-term treatment with antiplatelet agents, which

are mandatory for the success of the stents. About 5% of patients who have undergone PCI will undergo non-cardiac surgery within the first year after stenting.¹²

A common clinical problem facing orthopaedic and trauma surgeons, therefore, is how to manage patients on these antiplatelet agents who require surgery.

It is necessary to balance the risk of increased blood loss if the antiplatelet agents are continued peri-operatively against the risk of coronary artery/stent thrombosis if they are stopped. It appears that the traditional approach of stopping such medication up to two weeks before surgery poses significant danger to the patient and may require review.¹³ A recent audit among orthopaedic surgeons in Scotland has shown wide variations in practice regarding the continuation or cessation of clopidogrel peri-operatively.¹⁴

Pharmacology of common antiplatelet agents

There are three types of antiplatelet agents: acetylsalicylic acid (aspirin), thienopyridines and platelet glycoprotein (GP) IIB/IIIa receptor antagonists. This review focuses on the two most commonly encountered agents in routine orthopaedic practice, aspirin and clopidogrel (Plavix), as the GPIIb/IIIa receptor antagonists are intravenous agents used mainly in the cardiac catheterisation laboratory during PCL.

Acetylsalicylic acid. Aspirin irreversibly blocks the formation of thromboxane A₂ in platelets

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Fig. 1

Recommendations of the European Society for Cardiology for timing of non-cardiac surgery (PCI, percutaneous coronary intervention). Reprinted with permission from: Poldermans D, Bax JJ, Bosersma E, et al. Guidelines for pre-operative cardiac risk assessment and peri-operative cardiac management in non-cardiac surgery. *European Heart Journal* 2009;30:2769-812.

and inhibits platelet aggregation through inhibition of the cyclo-oxygenase (COX)-1 enzyme.¹⁵ This effect is achieved at the usual daily dose of 50 mg to 150 mg. For a normal adult, a daily dose beyond 150 mg increases the risk of haemorrhage without increasing protection,¹⁶ but the dose may be increased to 325 mg per day in individuals who are overweight. The ability of platelets to aggregate is partially restored within four to five days after stopping the use of aspirin.¹⁷ Platelet COX activity recovers by ~10% per day as a function of platelet turnover. Although it may take ten days for the total platelet population to be renewed and restore normal COX activity, it has been shown that if as little as 20% of platelets have normal activity, haemostasis may be normal.¹⁸

Thienopyridine. These are a class of adenosine diphosphate (ADP) receptor/P2Y₁₂ inhibitors used for their antiplatelet activities. Clopidogrel bisulphate (Plavix) is the only such agent in common use clinically, having largely replaced ticlopidine owing to concerns regarding the side effects of the latter and the faster onset of action of clopidogrel.^{19,20} Clopidogrel is an inhibitor of ADP-induced platelet aggregation, acting by direct inhibition of ADP binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. This action is irreversible. Consequently, platelets exposed to clopidogrel's active metabolite are affected for the remainder of their lifespan of seven to ten days. According to information from the Food and Drug Administration, platelet aggregation and the bleeding time gradually return to baseline values after treatment is discontinued, generally within five days.

Monitoring the effect of antiplatelet agents

The standard tests of coagulation, the prothrombin time and activated partial thromboplastin time (APTT), do not assess platelet function. The 'bleeding time' is the

traditional clinical test of platelet function and the effect of antiplatelet agents, but it is not the most practical test and has not been shown to correlate well with peri-operative bleeding. The concentrations in the plasma of both aspirin and clopidogrel do not correlate closely with their pharmacodynamic effects, because of irreversible binding of the drugs to the target.¹⁷

There are a variety of tests that can be used for measurement of platelet function which are generally only available in specialist laboratories. Optical light transmission aggregometry is the most widely accepted technique used to assess platelet function, but is laboratory based and time consuming. Point-of-care techniques for assessing platelet function, coagulation and fibrinolysis, such as platelet-mapping and thromboelastography, are in development but appear to have varying accuracy, and none have yet entered common clinical usage, although they are gaining popularity in cardiothoracic and hepatic surgery.²¹

Percutaneous coronary intervention

Percutaneous coronary intervention began in 1977 with balloon angioplasty. This involved the advancement of a balloon-tipped catheter into an area of coronary narrowing, inflation of the balloon and the subsequent removal of the catheter after balloon deflation. In more than 90% of PCIs it is now combined with the insertion of a stent.²² Consequently, there is an increasing sub-group of patients with coronary artery disease with an implanted coronary artery stent who may subsequently require non-cardiac surgery.

Different types of coronary artery stent. There are two major types of coronary stents: bare metal (BMS) and drug-eluting (DES). The latter were introduced in the late 1990s in response to the high incidence of late stent re-stenosis with the former. Re-stenosis is a side effect of normal

healing by neo-intimal hyperplasia, which can, in some cases, lead to occlusion of the coronary lumen.

Thrombosis can occur in both BMS and DES, but because of the delayed re-endothelialisation of the stent struts in DES, they are particularly prone to late thrombosis in those patients who have discontinued thienopyridine therapy prematurely.²³⁻²⁵ Overall, the risk of thrombosis is around 1% to 3% over the first three years after stent implantation.²⁶

Although rare, stent thrombosis is a potentially devastating complication and is associated with an incidence of acute myocardial infarction of 50% and a mortality rate of 20%. Consequently, the prevention of such thrombosis is of paramount importance.²⁷ Premature cessation of antiplatelet therapy has been shown to be the strongest predictor of subsequent thrombosis of the stent.^{28,29}

The European Society of Cardiology, endorsed by the European Society of Anaesthesiology, issued guidelines in 2009 recommending a minimum of six weeks, and optimally more than three months, between the placement of a BMS and non-urgent surgery, and at least 12 months between placement of a DES and non-urgent surgery, irrespective of the type of DES.³⁰ Aspirin should be continued peri-operatively except in very limited circumstances, such as spinal surgery in the medullary canal, intra-cranial neurosurgery, and surgery on the posterior chamber of the eye. Currently, the American College of Cardiology, the American Heart Association and the Society for Cardiovascular Angiography and Interventions recommend that, ideally, patients should be treated with both aspirin and clopidogrel for up to 12 months following insertion of stent (Fig. 1).³¹

Risk of peri-operative haemorrhage. Studies on the risk of intra-operative haemorrhage secondary to antiplatelet therapy are usually statistically underpowered, and there are few large prospective randomised studies.¹³

Patients receiving aspirin

A large review and meta-analysis of 474 studies on the impact of low-dose aspirin on intra-operative blood loss showed that patients on aspirin alone have an increased risk by a factor of 1.5, without an increase in surgical mortality or morbidity.³² In a series of 89 consecutive patients presenting with fractures of the neck of the femur, 32 of whom were taking aspirin on admission, it was shown that pre-operative ingestion of aspirin did not significantly affect the peri-operative blood loss assessed by the change in haemoglobin concentration on the haematocrit.³³ Likewise, a review of 244 adult patients undergoing spinal instrumentation and fusion failed to show that aspirin significantly influenced the need for peri-operative blood transfusion.³⁴ However, a study by Nuttall et al³⁵ of 299 consecutive patients undergoing primary or revision arthroplasty of the hip found the use of aspirin to be a significant indicator for allogeneic red cell transfusion.

Patients receiving clopidogrel

Johansen, White and Turk³⁶ reviewed 17 patients with fractures of the hip who were taking clopidogrel on admission to hospital and demonstrated that the drop between pre- and post-operative haemoglobin levels was 1.3 g/dl less when surgery was delayed for five days, compared to when undertaken within five days of admission, the preference of the surgeon for operating on patients while on clopidogrel being the only factor influencing the timing of surgery. However, patients whose surgery was delayed showed a significant increase in thromboembolic events, which could be attributed to the delay. At the annual meeting of the Orthopedic Trauma Association in 2008 two presentations indicated that early surgery is safe for patients taking clopidogrel. Nydick et al³⁷ examined a case-matched series of 57 patients requiring non-elective orthopaedic surgery, of whom 25 were receiving clopidogrel and 37 age- and injury-matched controls who were not. There was no difference in the rates of transfusion, wound drainage or overall complications between the two groups.³⁷ Collinge et al³⁸ reviewed 447 patients over 60 years of age who had surgery for fracture of the hip. Of these, 38 were taking clopidogrel, 79 were taking aspirin, and 330 were not taking any antiplatelet agent. In no patient was surgery delayed, and there were no differences between the groups with regard to any bleeding parameter or the rate of complications after surgery.³⁸

Patients receiving dual therapy (aspirin and clopidogrel)

The addition of a second antiplatelet agent would be expected to increase surgical haemorrhage, and this has been shown in studies involving patients undergoing coronary artery bypass grafting, in whom the blood loss was effectively increased by 30% to 50% on average, albeit with full intra-operative heparinisation for a cardiopulmonary bypass.^{39,40} There are fewer studies of combined aspirin and clopidogrel use in non-cardiac surgery. One study of patients undergoing orthopaedic, vascular and visceral surgery after implantation of a coronary artery stent showed a transfusion rate of 38.5% in controls and 42.6% in patients taking dual antiplatelet therapy,⁴¹ but the number of orthopaedic patients was only 16 of 204.

Effects of withdrawal of antiplatelet therapy

The risks of withdrawing antiplatelet therapy peri-operatively must be evaluated in the knowledge that both the systemic inflammatory syndrome and the acute-phase reaction to surgery increase platelet adhesiveness and reduce fibrinolysis.^{6,42}

The risks include:

- 1) Increased platelet adhesiveness due to a rebound effect.⁴³
- 2) Doubled infarction and death rates in the acute coronary syndrome.⁴⁴ In a study of 1358 consecutive patients presenting with acute coronary syndrome, those who had recently stopped oral antiplatelet therapy had double the

rate of myocardial infarction or death at 30 days compared to those not previously on oral antiplatelet agents (21.9% *versus* 12.4%). Those who had recently stopped antiplatelet drugs were admitted at a mean of 11.9 days (SD 0.8) after withdrawal.

3) Premature cessation of antiplatelet therapy is the strongest predictor of subsequent stent thrombosis.^{28,29}

4) During the re-endothelialisation phase of coronary stents, the average post-operative rate of myocardial infarction due to stent thrombosis is 35% and the average mortality following this is 20% to 40%.^{28,45}

5) Emergency PCI for revascularisation of a thrombosed coronary vessel or stent during the early post-operative phase is more difficult and associated with a greater risk than transfusion of red cells, being 0.4% if all complications are included,⁴⁶ and surgical haemostasis is achieved intra-operatively.

6) Thrombolysis and medication with abciximab (a platelet GPIIb/IIIa receptor antagonist) for 24 to 48 hours following PCI in order to prevent immediate stent thrombosis, is not an option in the immediate post-operative phase owing to the risk of catastrophic haemorrhage.

There is no significant evidence to suggest that the withdrawal of antiplatelet agents prescribed for primary prevention of cardiovascular disease in the peri-operative period is harmful, and this action may have the added benefit of reducing blood loss and its attendant risks. When it is felt necessary to withdraw antiplatelet therapy peri-operatively, it should be re-introduced within 24 hours after surgery when adequate haemostasis has been achieved.

Prophylaxis for venous thromboembolism

The most recent NICE Guidelines on prophylaxis of venous thromboembolism recommend extended use of either low molecular weight heparin (LMWH), a synthetic polysaccharide (fondaparinux) or a newer oral anticoagulant such as rivaroxaban (Factor Xa inhibitor) or dabigatran (direct thrombin inhibitor).⁴⁷ The addition of these latter two drugs to aspirin and/or clopidogrel has not been investigated in surgical patients. Any tendency to increased haemorrhage, with the attendant risks of wound complications and intra-articular bleeding, must be given serious consideration.

Rivaroxaban (Xarelto) has been shown to increase clinically significant bleeding by a hazard ratio of 3:4 when added to aspirin or clopidogrel in the treatment of acute coronary syndromes.⁴⁸ Dabigatran (Pradaxa) at higher doses significantly increases the risk of haemorrhage when combined with aspirin.⁴⁹ To date, no clinical trials have been published which address the risk of haemorrhage if dabigatran is combined with clopidogrel.

Neuraxial blockade

A consensus conference of the Second American Society for Regional Anesthesia and Pain Medicine (ASRA) on Neuraxial Anesthesia and Anticoagulation in 2003

concurred with the earlier advice that aspirin and other non-steroidal anti-inflammatory drugs appear to represent no added significant risk for the development of spinal haematoma in patients having epidural or spinal anaesthesia. Although no series involving the performance of neuraxial block in the presence of thienopyridine derivatives such as clopidogrel have been performed, the suggested time between discontinuation of this drug and the performance of neuraxial block remains seven days.⁵⁰

The temptation to interrupt antiplatelet therapy in the belief that neuraxial blockade is safer than general anaesthesia in patients with coronary artery disease has also been questioned. In a meta-analysis of 11 randomised trials involving a total of 1173 patients, neuraxial blockade at levels below T6, alone or in combination with general anaesthesia, did not significantly reduce the cardiac risk⁵¹ or the rates of mortality and infarction.⁵²

Antifibrinolytics

A possible option in the management and prevention of excessive blood loss in the presence of continued antiplatelet treatment is the use of antifibrinolytic agents such as aprotinin, tranexamic acid, and ε-aminocaproic acid (EACA). A recent meta-analysis concluded that the use of aprotinin and tranexamic acid in orthopaedic surgery significantly reduces the need for allogenic erythrocyte transfusion, although EACA has not been adequately evaluated.⁵³ However, the trials included were underpowered to evaluate the safety of these agents with regard to venous thromboembolism as well as arterial thrombosis.

Platelet transfusion

Neither aspirin nor clopidogrel can be reversed by other drugs. Hence, transfusion with platelets is the only way to quickly re-establish normal coagulation in the face of excessive bleeding. Haemostasis requires that at least 50% of the circulating platelet pool have a normal function. However, the activity of new platelets may be inhibited by a drug present in the circulation. The half-life of aspirin and clopidogrel is approximately four hours and their plasma level beyond 12 hours is close to zero. Thus, by six to eight hours after the last intake, the transfused platelets will not be significantly inhibited by the drugs, whereas the patient's own platelets are still irreversibly blocked by them.

Prophylactic transfusion of platelets before an invasive procedure, when platelet inhibitor therapy has not been discontinued in a timely manner, is not recommended based on a review of the literature and subsequent recommendations issued by a multidisciplinary group (experts from the fields of transfusion, haematology, anaesthesiology, intensive care medicine) on behalf of the French Safety Agency for Health Products.⁵⁴

Aspirin should not be stopped pre-operatively when prescribed as secondary prevention after stroke, angina, myocardial infarction or any type of coronary revascular-

isation, except in very rare circumstances, such as in intracranial surgery, operations on the spinal medullary canal and on the posterior chamber of the eye. In nearly all routine orthopaedic practice it is safe to continue aspirin peri-operatively. If prescribed for primary prevention of cerebro- or cardiovascular events it may safely be stopped pre-operatively, ideally seven to ten days before surgery.

Clopidogrel should not be discontinued during the re-endothelialisation phase of a coronary stent, nor if prescribed for unstable angina or following myocardial infarction. Consideration may also need to be given to continuing clopidogrel use beyond one year in high-risk patients with a DES. These include those with long (> 35 mm) and proximal stents, multiple stents, overlapping stents, stents in chronic total occlusions, small vessels or bifurcated lesions.⁵⁵ High-risk patients also include those with a history of thrombosis of a stent, a low ejection fraction, diabetes mellitus and prothrombotic conditions.

Patients who are prescribed clopidogrel for indications other than those outlined above may safely have the drug stopped seven to ten days before elective orthopaedic surgery, and it should be recommenced 24 to 48 hours after operation. Bridging therapy with aspirin will provide nearly all the benefits of clopidogrel without significantly increasing the risk.

According to the European Society of Cardiology, non-urgent surgery should not be carried out within 14 days of balloon angioplasty, six to 12 weeks of placement of a bare metal or within 12 months of placement of a drug-eluting stent. Aspirin should be continued outside these timeframes, and clopidogrel can be stopped in most instances (Fig. 1). There are currently no widely available, reliable measures of platelet function which would help to quantify the risk of peri-operative haemorrhage while a patient is on antiplatelet therapy. In patients at high risk of cardiovascular events, pre-operative withdrawal of antiplatelet therapy is not justified in order to perform regional or neuraxial anaesthetic blocks.

Antifibrinolytic agents, albeit effective in reducing the need for peri-operative blood transfusion in patients continued on antiplatelet agents, have not been studied sufficiently to be deemed safe or cost-effective for use in routine practice. In the face of excessive bleeding in patients on antiplatelet therapy transfusion of platelets may be warranted, but prophylactic transfusion is not recommended.

Bridging therapy with heparin has not been shown to be effective in reducing morbidity and mortality when clopidogrel is withdrawn. Replacing it with a short-acting GIIb/IIIa inhibitor has been suggested empirically to bridge the interim period between clopidogrel discontinuation and re-initiation, but this policy has not been adequately studied. If antiplatelet agents are withheld pre-operatively they should be restarted within 24 hours of surgery. The most important consideration when faced with these complex patients is close liaison with a cardiologist and anaesthetist before operation, in order to ensure

optimal medical therapy at a time of increased cardiovascular risk, and to ensure that surgery takes place in a timely and safe manner.

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