

Antiplatelet agents and perioperative bleeding

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Intravascular thrombosis begins with an endothelial lesion, either spontaneous or mechanical that exposes the underlying subendothelium, provoking the adhesion of platelets. This adhesion is facilitated by subendothelial glycoproteins such as von Willebrand factor, fibronectin, and collagen. Collagen activates the platelets (resulting in the release of thromboxane A₂ and arachidonic acid) and stimulates the release of ADP, serotonin, fibrinogen, and other substances that increase platelet activation. Activated platelets change form, resulting in exposure of the glycoprotein (GP IIb/IIIa) receptors. These changes constitute the final common pathway leading to the aggregation of platelets. Ultimately, thrombin activated by the coagulation cascade transforms fibrinogen into fibrin, stabilizes the thrombus, but also contributes to the activation of platelets. These steps are schematically shown in Figure 1.

Because this chain of events is so important to the arterial circulation, it is not surprising that the objective of much cardiology research has been focussed on blocking platelet activation and aggregation. There are many drugs, both old and new, that can prevent a thrombus from developing in the coronary and peripheral blood systems. These drugs have different mechanisms of action, variable half-lives, and may or may not be reversed by antagonists. On the other hand, medications such as acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used for other indications, in particular for rheumatological problems. This usage can pose problems when surgery is necessary, either electively or in an emergency.

This inaugural issue of *Anesthesiology Rounds* will review the hemorrhagic risk associated with the currently available antiplatelet agents and present the principles needed to guide the evaluation of these risks, based on current research (which is often sparse) from the medical literature.

WHAT ARE ANTIPLATELET AGENTS?

There are mainly 3 types of agents. The mechanisms of action of the available antiplatelet agents are indicated in Figure 1.

Aspirin and other thromboxane A₂ inhibitors

Aspirin (ASA) has been available for more than 100 years and is present in many medications. The advantages of ASA in the field of cardiovascular medicine are well known. It can reduce vascular events by approximately 25%, especially in patients with acute myocardial infarction (MI) or unstable angina. It is estimated that 32% of patients do not respond to the usual recommended dose and this can have a direct effect on the risk of thrombosis, as well as the risk of perioperative hemorrhage.

The thienopyridines (ticlopidine and clopidogrel)

The thienopyridines irreversibly inhibit both platelet aggregation and its amplification induced by ADP. When the thienopyridines are used in combination with ASA, there is a synergistic effect that further decreases the risk of thrombosis associated with endovascular stents. Clopidogrel has many advantages when compared to ticlopidine: it has a faster onset of action and fewer of the side-effects (neutropenia and medullar aplasia) that are associated with ticlopidine. Ongoing studies suggest that a combination of ASA and a thienopyridine will frequently be used in high-risk patients.

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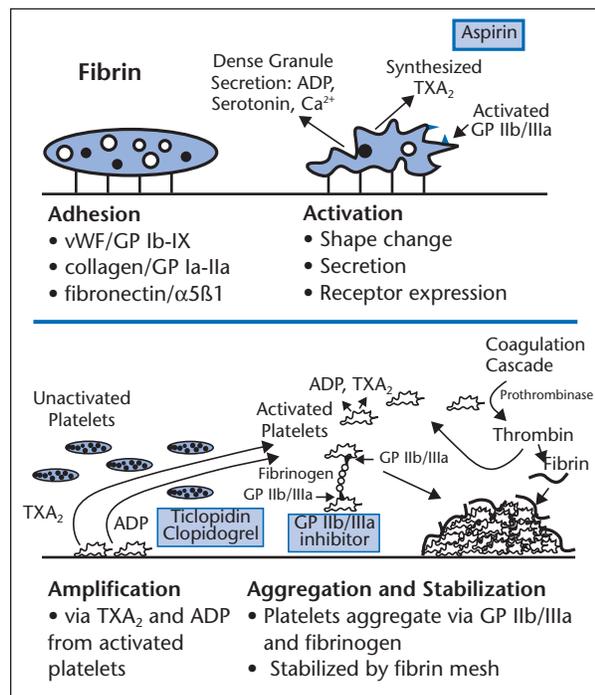
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FIGURE 1 : Steps leading to coronary thrombosis. Agents are written beside mechanisms of action that they inhibit. (Reproduced from Steinhubl¹)



GP IIb/IIIa receptor antagonists

Inhibition of the GP IIb/IIIa receptors prevents platelet aggregation regardless of the cause. In North America, three GP IIb/IIIa inhibitors are available on the market. Abciximab (ReoPro[®]) is the oldest and it produces an almost irreversible inhibition of the GP IIa/IIIb receptors. Two more recent products, eptifibatid (Integrelin[®]) and tirofiban (Aggrastat[®]), produce a comparable inhibition of the GP IIb/IIIa receptors. All are rapid-acting with short half-lives. Whichever antagonist is used, it must inhibit at least 80% of the receptors to provide clinically significant inhibition of platelet aggregation. At this time, only intravenous formulations are available, since the oral formulas gave disappointing results in initial clinical trials. However, in the near future, it is likely that patients will be treated with double or triple antiplatelet therapy.^{1,2} The anesthesiologist must therefore be well aware of the associated hemorrhagic risks of therapy and deal with the complications that may occur.

ASPIRIN AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

These drugs comprise the most common antiplatelet drugs that are used and, as a result, there is abundant research information available on them. However, the quality of the research varies and precludes any definitive statements on their effectiveness.

Non-cardiac surgery

There are conflicting results in the literature regarding the impact of aspirin on the postoperative risk of bleeding

after non-cardiac surgery. Reasons for these contradictory results include:

- The variability between studies regarding the length of time that aspirin is withheld before surgery, which may range from a few hours to a few days. With a longer delay, platelet function has more time to return to a normal level that can withstand aggressive surgery
- The type of surgery also has an influence on hemorrhagic risk: tonsillectomy, hip arthroplasty, and transurethral prostatectomy³ tend to bleed more than surgeries where hemostasis is done meticulously.
- Finally, it is clear that susceptibility to ASA varies from one individual to another. Even if the risk of bleeding is acceptable or slightly elevated in the majority of surgical patients,⁴ bleeding risk is severe in a minority of patients.⁵

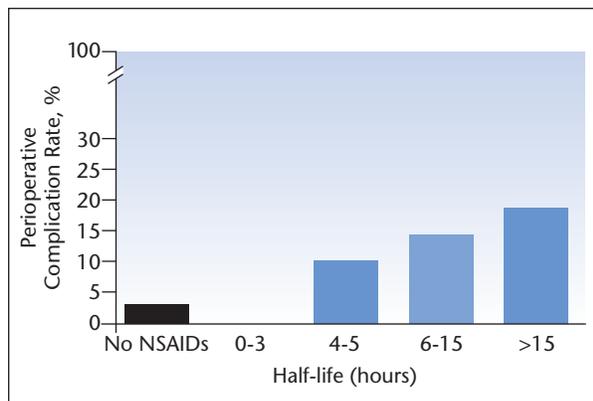
Routine use of ASA (160 mg qd started before the procedure) to prevent thromboembolic events after hip surgery (PEP trial) did not increase perioperative mortality secondary to hemorrhagic complications. However, the authors found an increase in the number of gastrointestinal bleeding events, and more importantly, a drop in postoperative hemoglobin (average of 2 g/L), as well as an increased need for blood transfusions (average of 53 mL). However, this modest level of hemorrhagic complications tended to occur in patients who were also receiving subcutaneous heparin.⁶ Despite the favourable interpretations of these results, conclusions about the perioperative use of aspirin are still debated.⁷

A study conducted by Connelly et al showed that hemorrhagic complications were more frequent after hip arthroplasty in patients taking NSAIDs.⁸ It is interesting to note that the complications were even more frequent in patients using NSAIDs with a half-life of >6 hours (Figure 2).

In a series of 1000 orthopedic surgeries performed on 924 patients, there were no reports of perimedullar hematoma with either spinal or epidural anesthesia. The fact that there was no relation between a history of ASA use and the presence of blood after insertion of the needle or catheter led Horlocker et al to conclude that these agents do not increase the risk of perimedullar hematoma after regional anaesthesia.⁹ Also, in the PEP trial mentioned earlier,⁶ there were no cases of perimedullar hematoma reported in 4603 surgeries for hip fractures performed under regional anesthesia. Since this complication is rare, the statistical power of such studies is debatable. Nevertheless, interpretations must be extremely cautious concerning studies where ASA is mentioned as a contributing factor to the appearance of a perimedullar hematoma after regional anesthesia.¹⁰

Stopping ASA in a patient with coronary disease may increase the risk of a thrombotic event. The life of a platelet is 10 days; platelets start to recover their functional capacity within 2-3 days after stopping aspirin and are back to normal at 8-10 days. As noted earlier, 80% of the platelets must be inhibited to cause a significant anti-aggregation effect. In healthy subjects, primary hemostasis is back to normal in 48 hours after stopping aspirin,¹¹ indicating that thrombotic risk appears soon after

FIGURE 2 : Perioperative hemorrhagic complications vary according to the half-life of the NSAID used. The NSAIDs with a half-life of 0 to 3h are fenoprofen, ibuprofen, sodium meclofenamate and tolmetin; with 4 to 5h, indomethacin and ketoprofen; with 6 to 15h, diflunisal, naproxen and sulindac; and more than 15h, aspirin and piroxicam. (Reproduced from Connelly et al⁸)



stopping ASA treatment.¹² In vascular surgery patients, Samama et al demonstrated that hemostasis is activated in the immediate postoperative period, indicating an increase in thrombotic risk.¹³ In another study, continuing aspirin in patients undergoing infrainguinal vascular surgery appeared to decrease perioperative mortality and prolong life, which questions the systematic withdrawal of aspirin preoperatively.¹⁴

Nonetheless, it is difficult to make universal recommendations regarding the use of antiplatelet agents in the perioperative period. An expert panel of the Société Française d'Anesthésie et de Réanimation concluded that: "In patients presenting with either coronary or cerebrovascular pathology, long-term treatment with aspirin is recommended and should not be stopped in the perioperative period unless the risk of hemorrhagic complications related to a specific procedure appears to be greater than the increase in the cardiovascular (thrombotic) risk (especially of an acute coronary syndrome) from withholding the antiplatelet agent."¹⁵

Cardiac surgery

As is the case for all surgeries, the importance of hemorrhagic risk associated with NSAIDs, and ASA in particular, remains controversial in cardiac surgery. Conflicting results are abundant in the literature.^{16,17,18} In an extensive review of 50 articles covering more than 10,000 patients under-going operations in 70 hospitals, Bélisle and Hardy concluded that bleeding was only increased by 300 mL in most of the studies. This modest increase in bleeding does not explain the great variation in transfusion rates from one hospital to another.⁴ In practical terms, since it appears impossible to predict the hemorrhagic risk in a given patient, it seems reasonable to wait until the patient is taken off extracorporeal circulation, heparin is neutralized, and surgical hemostasis is completed before transfusing exogenous platelets, as needed.

Aprotinine has been clearly shown to be effective in such circumstances.^{19,20}

THE THIENOPYRIDINES (TICLOPIDINE AND CLOPIDOGREL)

Most of the studies published on these agents have examined their effectiveness in interventional cardiology and indirectly determined their impact on the associated hemorrhagic risk. Very few studies have specifically examined the perioperative risks of hemorrhage related to the use of thienopyridines.

Non-cardiac surgery

Hemorrhagic risks and thromboembolic complications were studied in patients undergoing transabdominal prostatectomy²¹ or aorto-bifemoral bypass.²² In both groups, ticlopidine was started 2 to 5 days preoperatively. In both cases, the increase in bleeding and the need for transfusion was approximately 25%, not statistically significant given the large spread of the results. On the other hand, ticlopidine prolonged platelet survival (known to be diminished in the presence of a vascular graft) and diminished the number of platelets adhering to the graft.²² In both studies, ticlopidine was started a short time before surgery, suggesting that hemorrhagic risk was underestimated and that its antiplatelet activity did not have sufficient time to reach its full impact. Given that ticlopidine has a long half-life, Desager recommends that ticlopidine be stopped 2 weeks prior to any surgery, including dental.

Clopidogrel, like aspirin, has a cumulative effect on platelet aggregation that requires 7 to 9 days to recover. Based on this theory, it appears reasonable to stop thienopyridines at least 1 week (commonly 10 days) before an elective procedure to allow platelet function to return to normal. The risk of a rebound thrombotic accident is comparable to that of stopping aspirin, and this risk suggests restarting the drug early in the postoperative course.

The incidence of thrombotic complications and/or hemorrhages in patients operated on soon after deployment of a coronary endovascular stent is prohibitive.²³ These patients must receive antiplatelet therapy consisting of combination of aspirin and ticlopidine for at least 2 to 4 weeks after angioplasty. Stopping antiplatelet medication considerably increases the risk of a coronary thrombosis, but continuing it is associated with an increased risk of both hemorrhage and the need for blood transfusions.²³ As a result, elective surgery should be avoided for a period of 1 to 3 months following placement of a stent.¹⁵ On the other hand, if coronary angioplasty is necessary before emergency surgery, the deployment of a stent should be avoided. Finally, the safety of regional anesthesia in a patient on thienopyridines has not been established or specifically studied as yet.

Cardiac surgery

Few studies have been published on the relationship between the thienopyridines and the perioperative risk of

hemorrhage for surgeries performed under extracorporeal circulation. Theoretically, considering the prolonged half-life of these drugs, one might expect an increase in the risk of hemorrhagic events. This increased risk has been described in at least 2 studies.^{24,25} On the other hand, the use of thienopyridines in the perioperative period appears to decrease thrombosis associated with valvular prostheses.²⁶ The anti-aggregating effect of ticlopidine in the perioperative period could also contribute to fewer thrombotic events related to the oxygenator, without increasing the risk of hemorrhage or transfusion.²⁷ These results are from studies done in the early 80s, and although interesting, have not been confirmed since.

Finally, the efficacy of aprotinine in limiting the bleeding associated with thienopyridines remains unknown.

GP IIB/IIIa RECEPTOR ANTAGONISTS

Non-cardiac surgery

There is no literature regarding the specific hemorrhagic risk related to aggregation inhibition by the GP IIB/IIIa receptor antagonists in the perioperative period. The observations and recommendations that have been drawn from cardiac surgery may then be extended to non-cardiac surgery. A review of the literature on the hemorrhagic risks associated with anti-GP IIB/IIIa allows a presentation of general principles, regarding, for example, the delay between stopping the antiplatelet drug and the start of surgery (see next section).

As a general rule, there must be a balance between the hemorrhagic risk and the significant risk of coronary thrombosis, especially if a transfusion of platelets becomes necessary. Finally, it is important to remember that most patients receiving GP IIB/IIIa receptor inhibitors are also receiving aspirin and are anticoagulated with heparin.

Cardiac surgery

The oldest GP IIB/IIIa receptor antagonist, and certainly the one most clinicians are familiar with, is abciximab. Although, as mentioned earlier, this drug produces an almost irreversible antiplatelet effect,¹ it has been shown that 12 hours after stopping an IV perfusion, the relative occupancy of GP IIB/IIIa receptors drops to around 68%.²⁸ Given the fact that 80% of the receptors need to be inhibited to have a significant clinical impact, this produces a normalization of the bleeding time, (the usual test used to evaluate the efficacy of the treatment).

Three major multicentre studies have evaluated the efficacy of abciximab in decreasing thrombotic complications after coronary angioplasty:

- EPIC (Evaluation of c7E3 to Prevent Ischemic Complications),

- EPILOG (Evaluation of PTCA to Improve Long-term Outcome by c3E7 GP IIB/IIIa receptor blockade), and

- EPISTENT (Evaluation of Platelet IIB/IIIa Inhibitor for Stenting).

During the course of these studies, some patients needed to have an emergency myocardial revascularization. In the EPIC study, the need for transfusions in patients treated with abciximab who were operated on was the same as in those treated with placebo. However, it should be noted that in the majority of cases, the drug was stopped more than 24 hours before surgery.²⁹ The combined results for patients operated on in both the EPILOG and EPISTENT studies are essentially the same, except for an increased need for platelet transfusions.³⁰ Once again, most of the patients were taken to the operating room >12 hours after abciximab was stopped.

A study by Gammie et al demonstrated a marked increase in the hemorrhagic risk and in the transfusion needs of patients operated on <12 hours following the interruption of abciximab.³¹ For emergency surgeries, prophylactic transfusions of platelets reduce both postoperative bleeding and the need for transfusions of red blood cells (RBCs) and fresh plasma, bringing them to a level similar to the one reported in other populations presenting the same risk factors.³² Since any unbound medication in the serum disappears rapidly after stopping the perfusion, the abciximab that remains bonds equally to native and exogenous platelets. This directly diminishes the occupancy rate of the receptors, so that platelet function rapidly normalizes.²⁹

Recently, Steinhubl et al demonstrated that there was great inter-individual variability in the functional recovery of platelets after stopping a GP IIB/IIIa receptor inhibitor perfusion; this recovery was often faster than expected.³³ Systematic transfusion of platelets is therefore not recommended, but should be assessed by considering hemostasis after neutralization of heparin with protamine.²⁹ It is important to remember that abciximab is eliminated by hemofiltration during extracorporeal circulation. A summary of the recommendations regarding abciximab in patients undergoing cardiac surgery is presented in Table 1. It is imperative to note that platelet transfusions before surgery are not recommended, and may even be detrimental. When normalizing platelet function there is a risk of accelerating the thrombotic process which is the the reason why the patient is receiving a GP IIB/IIIa antagonist.

For the other GP IIB/IIIa receptor inhibitors, surgical experience is limited. However, since the half-life is shorter and the inhibitory effect is competitive in nature, hemorrhagic risks are probably less important. Recently, we encountered a patient being treated with tirofiban who needed an emergency myocar-

TABLE 1: Emergency coronary surgery: General recommendations for patients taking abciximab^{29,34}

1. When possible, respect a 12-hour delay between stopping the perfusion and performing the surgery,
 - evaluate the risk of postponing the surgery vs the risk of coronary adverse events
 - evaluate the risk of postponing the surgery vs risks related to other morbidity factors
2. Standard heparin anticoagulation,
 - remember that abciximab prolongs ACT from 35 to 85 sec
3. Use hemoconcentration during ECC to help eliminate abciximab
4. Transfuse platelets as needed, after assessing bleeding once heparin has been neutralized
5. Assure optimal mediastinal drainage to decrease the risk of tamponade
6. Re-operate quickly when in doubt

ACT = activated coagulation time
ECC = extracorporeal circulation

dial revascularization; the tirofiban perfusion was stopped just before the surgery. This patient did not experience any excessive perioperative bleeding. In fact, some have suggested that the use of GP IIb/IIIa receptor antagonists might produce a “platelet anesthesia,” contributing protective benefits during extracorporeal circulation. Although this theory is logical and appealing, it is still only a working hypothesis. Further research to evaluate its potential benefits will be possible only when we have at our disposal very short-acting agents.

CONCLUSION

Antiplatelet agents are being used more and more often in modern medical practice, either for their anti-inflammatory effects or for controlling platelet function itself. It is likely that in the near future, coronary patients will be prescribed 2 or 3 antiplatelet agents on a long-term basis. For elective surgery, it will be possible to replace long acting molecules by medications with a short half-life. This will allow the controlled interruption of antiplatelet therapy in the immediate perioperative period and to restart it as soon as the hemorrhagic risk appears reasonable.

In the context of emergency surgery, prolonging the delay between the withdrawal of the antiplatelet agent(s) and the performance of surgery will often permit a decrease in the risk of bleeding. Adjunctive therapy such as aprotinine may also be useful, as is the judicious use of platelet transfusions to allow the normalization of platelet function. However, as with all other transfusion situations, the prophylactic use of platelet transfusions is not recommended, rather, transfusions should be given only as needed to correct clinically significant hemostatic abnormalities.

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Abstracts of Interest

Antiplatelet agents in the perioperative period: Expert recommendations of the French Society of Anesthesiology and Intensive Care (SFAR) 2001 – Summary Statement.

SAMAMA CM, BASTIEN O, FORESTIER F, ET AL., AND THE EXPERT GROUP.

Purpose: Antiplatelet agents are administered to an increasing number of patients. Preoperative treatment with these agents represents a major problem for the anesthesiologist. The results of a French expert meeting on their perioperative management are reported.

Methods: Responses to questions formulated by the Organizing Committee were drafted by a group of experts and reviewed by a multidisciplinary Reading Committee. Recommendations were classified (grade) according to the evidence level of the studies supporting them.

Principal findings: First, antiplatelet agents have a variable effect on hemostasis as far as bleeding risk is concerned. Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) increase intra- and postoperative bleeding moderately, but not transfusion requirements. Very few data are available on clopidogrel and ticlopidine. Anti-glycoprotein (GP) IIb/IIIa agents may increase bleeding when surgery is required in proximity with their administration. Second, the common practice of withdrawing antiplatelet agents is now challenged because an increased incidence of myocardial infarction has been reported in patients in whom treatment was interrupted. Third, aspirin should not be withdrawn for most vascular procedures and in several additional settings. When a definite increase in intraoperative bleeding is feared, or when surgical hemostasis is difficult, aspirin, clopidogrel or ticlopidine can be replaced by short-acting NSAIDs, given for a ten-day period and interrupted the day before surgery. Platelet transfusion should only be given when overt bleeding is observed. Postoperatively, antiplatelet treatment should be resumed immediately after surgery (first six hours).

Conclusion: Anesthesiologists should be aware of the indications, potential complications and means of substitution of these agents.

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