Consensus recommendations for using the Multiplate® for platelet function monitoring before cardiac surgery

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SUMMARY

Patients requiring urgent cardiac surgery are usually already taking antiplatelet drugs including aspirin and a P2Y₁₂ ADP receptor antagonist (e.g., clopidogrel, prasugrel or ticagrelor). This presents clinicians with the challenge of balancing the risk of thrombotic complications, if antiplatelet drugs are stopped before surgery, with the problems of excessive bleeding when surgery is performed in the absence of adequate platelet function. Preoperative platelet function monitoring is able to identify when patients have recovered platelet function. The Multiplate® (multiple electrode impedance platelet aggregometer) is a point of care device that enables monitoring of platelet function. The authors offer recommendations based on real-world, collective experience in the use of platelet function monitoring. These cover the use of the Multiplate® analyser to predict the need for platelet transfusion in the perioperative period and the individualized waiting period after cessation of P2Y₁₂ ADP receptor antagonists before cardiac surgery.

BACKGROUND

The acute coronary syndromes encompass a range of clinical conditions including unstable angina, non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI). Their common underlying pathological basis arises from thrombus formation involving circulating platelets on an atheromatous plaque within the wall of a coronary artery. Initial treatment for patients admitted with acute coronary syndrome includes administration of antiplatelet drugs that interfere with acute thrombus formation by inhibiting platelet aggregation. Standard therapy is initially with aspirin and the addition of a P2Y₁₂ ADP receptor antagonist (e.g., clopidogrel, prasugrel or ticagrelor) depending on the clinical situation. Further treatment may involve coronary revascularization by percutaneous coronary...
intervention (PCI) or coronary artery bypass grafting (CABG) [1, 2]. Surgical intervention for patients on dual antiplatelet therapy carries an increased risk of excessive perioperative bleeding that is associated with higher rates of postoperative morbidity, mortality, and transfusion of blood products. A decision has to be made as to whether surgical revascularization in an individual patient on antiplatelet therapy is urgent enough to outweigh the risk of increased bleeding, or to withhold antiplatelet agents until platelet function is sufficiently restored.

European and American guidelines on the management of antiplatelet agents in STEMI patients requiring urgent coronary artery bypass surgery advise stopping P2Y$_{12}$ antagonist before surgery [3, 4]. The recommended durations of withholding the different agents before surgery were based on drug characteristics and clinical outcome in observational studies where patients on recent dual antiplatelet therapy have undergone cardiac surgery. Although the indicative times for each drug are generally useful, they do not take account of interindividual differences in response to different agents. Experts in the field acknowledge that the ability to monitor platelet function may help inform timing of cardiac surgery more precisely and could be used to supplement existing clinical guidelines [5].

**CONSENSUS RECOMMENDATIONS**

The guidance presented here is the product of real-world, collective experience in the use of platelet function monitoring by the authors—all clinicians who routinely manage patients undergoing cardiac surgery. The authors can be considered “early adopters” of perioperative platelet function monitoring, specifically using the Multiplate® (multiple electrode impedance platelet aggregometer) analyzer, which is one of several point-of-care platelet function monitors currently available.

**SCOPE**

There is a paucity of data available to clinicians on how to interpret test results of platelet function to anticipate the likelihood of excessive perioperative bleeding and the need for platelet transfusion. The scope of this guidance covers the following:

- Use of the Multiplate® analyzer to predict the need for platelet transfusion in the perioperative period for patients undergoing cardiac surgery who have been taking P2Y$_{12}$ antagonists.
- Use of the Multiplate® analyzer to help determine an individualized waiting period after cessation of P2Y$_{12}$ antagonist before cardiac surgery.

**DRIVERS FOR PREOPERATIVE PLATELET FUNCTION TESTING**

The use of antiplatelet therapy continues to rise due to the increased prevalence of cardiovascular disease. Each month in the UK, more than 2.5 million people receive a prescription for aspirin and approximately half a million for clopidogrel. Patients taking antiplatelet drugs who need to have urgent cardiac surgery present clinicians with the challenge of balancing the risk of thrombotic complications, if antiplatelet drugs are stopped before surgery, with the problems of excessive bleeding when surgery is performed [6]. According to the National Health Service for England, each day spent waiting in hospital for surgery costs around £350 [7].

Antiplatelet drugs differ in their pharmacokinetic and pharmacodynamic characteristics. Current guidelines recommend stopping antiplatelet drugs 3 to 7 days before surgery [8–10], however a proportion of individuals are ‘resistant’ to aspirin or the P2Y$_{12}$ antagonist or both [11–13]. The Society of Thoracic Surgeons Clinical Practice Guidelines (updated in 2012) states: “for patients on dual antiplatelet therapy, it is reasonable to make decisions about surgical delay based on tests of platelet inhibition rather than arbitrary use of a specified period of surgical delay” [14].

The clinical challenge of how to manage antiplatelet agents in patients undergoing CABG has been comprehensively discussed by the European Society of Cardiology’s working groups on cardiovascular surgery and on thrombosis [5]. The aim of preoperative testing is to identify when the platelet function has recovered to a level that does not predispose the patient to excessive perioperative bleeding and allow surgery to be scheduled without unnecessary delay. Moreover, as there are concerns about inappropriate use and wastage of platelets and other blood products in the UK [15], preoperative platelet function testing will
enable clinicians to avoid unnecessary prophylactic use of these products. At one center in the UK, platelet transfusion rate was reduced by around 30% by implementing preoperative Multiplate® testing [16].

**WHICH MULTIPLATE® PARAMETERS ARE MOST USEFUL IN THE PREOPERATIVE SETTING?**

The ADP test assesses platelet aggregation that should be inhibited by exposure to P2Y<sub>12</sub> antagonists. The authors consider the ADP test to be the most useful in the preoperative setting for anticipating the likelihood of excessive bleeding and need for perioperative platelet transfusion. The authors’ clinical experience suggests that an area under the curve (AUC) value above 50 AU in an ADP test makes it unlikely that platelet transfusion will be required.

The TRAP test acts as the comparator to the ADP test and should be performed at the same time. A normal TRAP test is expected; an abnormal (low) AUC in this test suggests an alternative cause of platelet dysfunction, thrombocytopenia, or issues with the way in which the test(s) have been performed.

Some institutions may wish to perform the ASPI test to ascertain aspirin responsiveness. Most guidelines recommend that patients taking aspirin should continue to take it until surgery, and the authors have assumed that aspirin is not planned to be withheld prior to surgery. As the aim of this guidance is to predict excessive bleeding as a result of significant inhibition of platelet aggregation by P2Y<sub>12</sub> antagonists, expressed as the likelihood of requiring platelet transfusion, the authors deliberately focused their attention on testing only for the effect of P2Y<sub>12</sub> antagonists.

Platelet dysfunction is only one component of hemostasis. Where there is clinically significant bleeding during and after surgery, clotting factor and fibrinogen deficiencies should be excluded by other assessment methods [17].

**POINT-OF-CARE TESTING**

The Multiplate® analyzer is easy to use and suited to testing at the point-of-care by nonlaboratory personnel. However, the authors accept that institutions might choose to locate the device further away from

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**Perform ADPtest and TRAPtest in Hirudin sample tubes**

<table>
<thead>
<tr>
<th>ADPtest Result [U]</th>
<th>Interpretation</th>
<th>Action</th>
<th>Post-OP</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC &gt;50</td>
<td>Platelets normal</td>
<td>No platelets required</td>
<td>Heparin reversed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consider other causes. Consider retesting.</td>
</tr>
<tr>
<td>AUC 30–50</td>
<td>Some evidence of platelet inhibition</td>
<td>Reserve/ order platelets*</td>
<td>Significant bleeding post protamine **</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Transfuse platelets</td>
</tr>
<tr>
<td>AUC &lt;30</td>
<td>Platelet severely inhibited transfusion likely to be required.</td>
<td>Consider postponing operation***/ Order platelets</td>
<td>Transfuse platelets</td>
</tr>
</tbody>
</table>

*If TRAPtest result is low, retest before interpreting, if still low consider cause of platelet dysfunction.*

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Figure 1. Consensus recommendations for appropriate transfusion of platelets. Recommendations for preoperative Multiplate testing in patients who have taken a P2Y12 antagonist (this includes Clopidogrel, Prasugrel and Ticagrelor) in the 5–7 days prior to cardiac surgery. *The decision to reserve or order platelets will depend on the distance of the blood bank to the institution and the length of time it will take for them to be delivered, if required. **Suggestive of the presence of ADP receptor antagonists. ***What is considered significant bleeding will vary between institutions, but is generally sufficient to delay chest closure. If there is no bleeding, do not transfuse platelets. Suggestions are based on the best current advice, February 2013.

the clinical area according to staffing and logistic considerations. In all cases, interpretation of results must be informed by a thorough understanding of the pathophysiology of perioperative hemostatic dysfunction and in the context of the current clinical situation.

CONCLUSIONS

Prospective studies are needed to define the cut-off values that might indicate adequate platelet function for surgery. In their absence, the authors of this guidance have provided recommendations to give clinicians a pragmatic and objective reference, based on their clinical experience of managing cardiac surgery patients using the Multiplate® analyzer. It is hoped that these recommendations will help clinicians, when faced with patients taking P2Y12 antagonists before cardiac surgery, to anticipate the likelihood of excessive perioperative bleeding and make appropriate, patient-specific decisions regarding the ordering of platelets preoperatively (Figure 1). Indirectly, platelet function monitoring can assist decision-making about the timing of surgery after cessation of antiplatelet drugs, minimizing unnecessary delay, and reducing exposure of the patient to a higher than necessary risk of bleeding complications.

REFERENCES


