Is it time to implement preoperative platelet function testing before invasive procedures?

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Antiplatelet therapy is the current standard for the prevention of cardiovascular ischaemia and stent thromboses. Owing to the widespread use of drug-eluting stents, increasing numbers of patients are maintained on life-long antiplatelet therapy with aspirin and clopidogrel. A clinical dilemma for pain physicians and anaesthetists arises when non-invasive pain treatments fail, and a neuraxial or regional blockade becomes one of the few options for patients on combined aspirin/clopidogrel therapy.

In their article in the current issue of British Journal of Anaesthesia, Benzon and colleagues report the serial assessments of platelet function using the VerifyNow (Accumetrics, San Diego, CA, USA), and PFA-100 (Siemens Diagnostics, Deerfield, IL, USA) in 13 patients undergoing epidural injection after stopping clopidogrel (Table 1). The small sample size of this study limits implementing a specific interval for clopidogrel cessation before neuraxial blocks. Nevertheless, the authors should be congratulated for providing objective data on the time course of platelet recovery, which is rather difficult to obtain in the outpatient setting. Based on the extent of platelet inhibition on VerifyNow, the authors empirically used three categories: >30% as therapeutic P2Y12 inhibition, 11–29% as partial inhibition, and <10% as no inhibition. By the third day after stopping clopidogrel, only two of 13 patients had >30% inhibition, while seven had partial inhibition. Only three patients showed partial inhibition after the fifth day, and all recovered normal function from the seventh day after stopping clopidogrel. On the PFA-EPI assay, seven subjects on aspirin had abnormal closure time at baseline, which persisted for 7 days in two subjects. Only two of 13 patients had abnormal PFA-ADP closure time. None had any bleeding complication after epidural injections.

The clinical management in this study followed the current consensus guidelines. Seven patients with coronary stents had been taking clopidogrel for at least 1 yr. The rate of cardiovascular events is highest within 90 days of stent placement, but becomes much lower after 1 yr. In order to reduce bleeding risks associated with regional and neuraxial anaesthesia, a 7 day interval is recommended based on the pharmacology of clopidogrel. Aspirin monotherapy is not considered as a bleeding risk, but continuing both clopidogrel and aspirin can potentially increase haematoma formation or haemorrhage after neuraxial or other regional block procedures. According to the present data, it is possible that some patients only require 5 days for the return of platelet function, and 2 extra days could be hazardous in terms of thrombotic risks. Indeed, some patients with CYP2C19 genetic variations are poor metabolizers of clopidogrel, a pro-drug, and they can be more susceptible to cardiovascular events in the long term. Testing ADP-induced platelet aggregation may allow an individualized approach to peri-procedural clopidogrel cessation, improving the balance between bleeding and thrombotic risks.

Several points in this study are worthy of further comment. First, the sensitivity and specificity for platelet inhibition are variable for different platelet function tests. Selecting a

| Table 1 Characteristics of in vivo hemostasis, VerifyNow and PFA-100. WB, whole blood; AA, arachidonic acid; Epi, epinephrine; ADP, adenosine-5′-diphosphate; vWF, von Willebrand factor |
|-----------------|-----------------|-----------------|
| **In vivo haemostasis** | **VerifyNow** | **PFA-100** |
| Blood           | Native WB       | Citrated WB     | Citrated WB |
| Blood flow shear rate | 300–1600 s⁻¹ in artery, up to 10 000 s⁻¹ in stenotic artery | Minimal | ~5000 s⁻¹ |
| Endpoint        | Blood coagulation | Agglutination of fibrinogen-coated beads | Closure of a membrane aperture |
| Agonists        | Collagen, thrombin, ADP, TxA2, etc. | AA (aspirin test), ADP (P2Y12 test) | Collagen/Epi, Collagen/ADP |
| Ligands         | vWF, fibrinogen | Fibrinogen | vWF, fibrinogen |
correct assay is important in evaluating the platelet recovery because VerifyNow, but not PFA-100 (collagen/ADP assay), was capable of demonstrating the effects of clopidogrel. Secondly, the efficacy of antiplatelet agents can be influenced by multiple factors. These include the location, type, or number of stents, severity of vascular disease, co-existing disease (e.g. diabetes, renal impairment), concomitant medication (e.g. statins), race, genetic factors, and compliance with the medication. Lastly, platelet activation is involved in many aspects of physiological haemostasis and pathological vascular thrombosis. In contrast to multi-modal platelet activation in vivo (Table 1), platelet function testing only reflects platelet reactivity to a specific platelet agonist. The combination of an oral anti-Xa inhibitor, clopidogrel and aspirin, has been reported to increase the major bleeding events. In this regard, optimal methods of monitoring, and withdrawal of concomitant antiplatelet and anticoagulant agents are largely unknown.

The question remains how platelet testing before a procedure can be efficiently implemented in the outpatient setting. Point-of-care platelet function assays are likely to help us establish more objective criteria for perioperative antiplatelet management, but further studies of clinical and economic outcomes are necessary to justify their routine use.

Conflict of interest
None declared.

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