Pharmacology

Perioperative Platelet Function Monitoring

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Anti-platelet therapy for cardiac diseases ranging from acute myocardial infarction to simply having cardiac risk factors has become the standard of care. Indeed, timely dosing of aspirin at hospital arrival during a possible myocardial event is a measure of treatment quality and hospital performance [1]. It is increasingly common to encounter patients with anti-platelet medications in the perioperative cardiac surgical setting. Since anti-platelet medications can profoundly affect hemostasis, having a timely, objective measure of platelet function may aid in perioperative hemostatic control and decrease blood transfusion requirements. Additionally, the use of cardiopulmonary bypass (CPB) decreases platelet counts and increases platelet dysfunction through contact system activation and initiation of the systemic inflammatory response, hypothermia, hemodilution, and surgical activation and consumption of hemostatic factors [2].

Platelet aggregation is a process initiated by platelet glycoprotein IIb/IIIa (GPIIb/IIIa) receptors bonding with fibrinogen to form a stable three-dimensional network of platelet-fibrin clot. Thrombin is the primary and most potent activator of the GPIIb/IIIa receptors. Two other major platelet receptors, thromboxane A2 (TxA2) and adenosine-5'-diphosphate (ADP) also mediate the activation of the GPIIb/IIIa receptors. Aspirin and clopidogrel inhibits each of the two receptors, respectively. Aspirin inhibits the conversion of arachidonic acid to TxA2 by cyclooxygenase and clopidogrel is a direct inhibitor of the ADP receptor. Both mechanisms independently disrupt the formation of a stable clot between platelets and fibrin, leading to impaired hemostasis.

The standard point of care (POC) monitoring for cardiothoracic surgery is the activated clotting test (ACT). However, ACT measures the degree of heparin anticoagulation and adequacy of heparinization during CPB but does not address the effects of platelet dysfunction [2]. POC testing of platelet function is available for rapid results analysis and intervention; the major tests are the thromboelastograph (TEG), PlateletMapping, Sonoclot, Platelet Function Analyzer-100, and Plateletworks. Each instrument provides information about different aspects of platelet function and/or dysfunction.

The most widely used and studied platelet analyzer is the TEG (Haemoscope, U.S.A.), which provides a graphic representation of the stages of clot formation and lysis [3]. It is performed on a small quantity of whole blood that is placed in a warmed (37°C) oscillating cup. Five parameters are measured: 1) the R time: clotting factor sufficiency, 2) the k time: clotting kinetics, 3) the angle: fibrinogen function, 4) the maximum amplitude (MA): platelet function, and 5) amplitude at 60 minutes (MA60): clot lysis. The TEG analyzer provides a global POC test of hemostasis that can identify if the bleeding is due to surgery, coagulopathy, platelet dysfunction, or residual heparinization. The strength of the TEG analysis is the measurement of MA deviation from normal. If the MA is elevated, it is indicative of a prothrombotic state and the patient may be at risk for an ischemic event [4]. If the MA is decreased, it is indicative of decreased platelet function [4]. The degree of MA deviation has also been incorporated into treatment protocols suggested for optimal intervention [4]. Several studies have shown the effectiveness of such TEG-guided intervention therapy [4].

A modified TEG assay, PlateletMapping (Haemoscope, U.S.A.), measures the percentage of platelet ADP and arachidonic acid binding inhibition. PlateletMapping is the only assay to use both the patient’s high and low end-points to determine the effect of net aggregation. This allows one to initiate interventional therapies specific to each patient’s needs and requirements. PlateletMapping achieves this by using the baseline TEG, which is unaffected by platelet inhibitors, and aliquots of thrombin-inhibited whole blood. The end result correlates with optical platelet aggregation on net aggregation [5]. A recent study suggests that the PlateletMapping assay is superior in identifying the aspirin and clopidogrel effects on platelet aggregometry [6].

Rotation thromboelastostaphograph analysis, or ROTEG (Pentapharm, Germany), provides similar data analysis of blood clotting via a pin sensor fixed to a rotating shaft that measures blood elasticity [7]. The loss of elasticity upon clotting of the sample leads to changes in the rotation of the shaft that is detected by opto-mechanic sensors from mirrors attached to the shaft [7]. The ROTEG alpha angle has a high predictive value for identification and targeted treatment of surgical bleeding versus coagulopathies [8]. However, there is limited data supporting the use of the ROTEG analysis data for hemostatic intervention.

The Sonoclot analyzer (Sienco Inc., U.S.A.) measures the changes in the viscoelastic properties of blood clots which are recorded in the form of a graph called the Sonoclot signature. This signature reveals: 1) a lag period, corresponding to the ACT (called SonACT); 2) a primary wave, which reflects the fibrin polymerization (clot rate); 3) an inflection, which is produced by incorporation of platelets into the fibrin mesh; 4) a secondary upslope leading to peak, which occurs at completion of fibrin mesh formation; 5) a downslope, produced as platelets induce further clot retraction [9]. The time to peak, measured in minutes, reflects clot retraction and is an indicator of platelet count and function [9]. Several studies have found that Sonoclot analysis may provide helpful indicators on platelet functions following CPB [9,10]. Unlike the TEG, Sonoclot analyzer results have not yet been used to guide transfusion needs [3].

The Platelet Function Analyzer-100, or PFA-100 (DADE Behring Inc, U.S.A.), assesses whole blood platelet function by measuring the closure time required for platelets in citrated whole blood to occlude a precisely defined aperture cut into a synthetic membrane coated with either collagen and epinephrine or collagen and ADP [11]. The shear force of whole blood being drawn through a vacuum causes the platelets to adhere, activate, and aggregate [11]. The analyzer determines the duration until aperture occlusion, which indicates the level of platelet activity [3]. The use of the different cartilages and synthetic membranes allows determination of platelet function alteration due to intrinsic platelet defects or to antiplatelet drug therapy [3]. Conflicting reports have been published regarding the usefulness of PFA-100 data in assessing blood loss in patients after CPB [3,12].

ICHOR/Plateletworks (Helena Laboratories, U.S.A.) is a POC platelet aggregation test based on the measured difference in the number of unaggregated platelets in an agonist-treated test sample compared to a baseline sample [13]. The gold standard for platelet aggregation is light transmission aggregometry (LTA). However, LTA is time consuming [13]. Recent investigations
reveal that Plateletworks platelet inhibition results mirror that of LTA and may serve as a surrogate for LTA as a POC system [13].

In summary, there is no perfect platelet function test. Many conflicting studies have been published regarding the usefulness of these tests in guiding clinical hemostasis management. TEG analysis has shown promise in its ability to decrease chest tube output and transfusion requirements after CPB. The other tests (PlateletMapping, ROTEG, Sonoclot, PFA-100, and Plateletworks) have experienced less use in clinic practice and therefore less consensus as to the usefulness of each test. POC systems in monitoring platelet function continue to be investigated and pursued for the goals of minimizing transfusion requirements and improving patient care outcome.