Peri-operative diagnosis and treatment of platelet disorders

Kozek-Langenecker SA, MD, MBA
University Clinic for Anaesthesia, General Intensive Care Medicine and Pain Management, Medical University, Vienna, Austria, Division for Anaestheia and Intensive Care Medicine, Evangelical Hospital, Vienna
Correspondence to: Prof Sibylle Kozek-Langenecker, e-mail: sibylle.kozek@meduniwien.ac.at

Introduction

The important role of platelets in the physiology and pathophysiology of haemostasis was acknowledged after the introduction of the cell-based model of coagulation.[1] Hyperactive platelets may contribute to stent thrombosis or disseminated microembolism, leading to organ dysfunction.[2,3] Platelet inhibition may provoke peri-operativen bleeding, independent of platelet counts.[4,5] Taken together, on-site diagnosis of actual platelet reactivity may permit rapid and goal-directed therapeutic interventions in patients at risk. There is still no consensus on the appropriate method for measuring platelet function. In this refresher course lecture Platelet Funktion Analyzer PFA-100 and Multiple Electrode Aggregometry MEA will be discussed among other tests for the perioperative use.

Methodology

In the Platelet Funktion Analyzer PFA-100, 800 µl of citrated whole blood is added to a reservoir well in a disposable cartridge.[6] The instrument aspirates the blood sample under high shear rates and constant vacuum through a capillary and the microscopic aperture within a membrane coated with platelet agonists, collagen and either epinephrine or adenosine diphosphate (ADP). This leads to the attachment, activation and aggregation of platelets, forming a plug. The time taken to occlude the aperture is known as closure time (CT): the shorter the CT, the better the platelet function. Maximum test duration is 300 s. Normal values: < 165 s epinephrine test, < 186 s ADP test.

Platelet Function Analyzer PFA-100

This method rapidly identifies aspirin effects and platelet disorders prior to surgery.[7-10] Therefore, the PFA-100 has gained acceptance for identification of Von Willebrand syndrome.

In patients with prolonged CT and without contra-indications against desmopressin, shortening of the CT after desmopressin infusion (0.3 µg/kg infusion over 30 mins) should be assessed ("desmopressin response test").[7] In cardiac surgical patients, the pre-operative PFA-100 CT correlated with postoperative blood loss in some studies,[11] but not in others.[12] Major limitations of the PFA-100 as an intra-operative point-of-care system in massive transfusion include its strong dependence on platelet count (> 100 G/l), hematocrit (> 30%) and Von Willebrand factor.[13] The diagnostic gap for clopidogrel limits drug-monitoring in patients under dual anti-platelet therapy.[14]

Platelet aggregometry

Platelet aggregometry assesses platelet reactivity by measuring changes in luminescence or impedance between two electrodes upon platelet agonist stimulation. In Multiple Electrode Aggregometry MEA (Multiplate, Dynabyte); hirudinised whole blood (300 µl)[15] is added to a reservoir well in a disposable cartridge with a magnet.[16] After addition of agonists at standardised concentrations using an automated pipetting system (collagen, arachidonic acid, ADP, thrombin receptor activator peptide TRAP, ristocetin), the electrical current between the two electrodes changes according to platelet adhesion and aggregation. Conventional test duration is 6 mins. Maximum aggregation, aggregation velocity and area under the aggregation curve are test parameters.

Widespread adoption of anti-platelet agents into everyday clinical practice has revolutionised contemporary care of cardiovascular patients. There is a high rate of non- or low-responders to dual anti-platelet therapy (5 - 30%); these individuals are not sufficiently protected against ischaemic events.[17] MEA is sensitive for aspirin effects[14,18] and clopidogrel.[19-22] Clopidogrel low-responders in MEA had a 10-fold increased risk for stent thrombosis (2,2% vs. 0,2% compared to responders) and a 3-fold increased 30-day mortality (1,2% vs. 0,4%).[23] Aggregation ≥ 42 U in ADPtest was identified as the cut-off for low-response.

MEA could provide differential diagnostic information in acute bleeding especially after extracorporeal circulation of cardiopulmonary bypass[5,19,24] and predict blood loss.[25,26] At platelet counts < 100 G/l only qualitative analysis is possible.

Other test options

Other test options have been summarised previously.[24,27,28] **Optical aggregometry (Born)** has only been performed in specialised laboratories by experienced technicians. The need for time-

consuming preparation of platelet rich plasma limited widespread application, not only in the peri-operative setting. Further limitations were the dependence of temperature, stirring rate, and limited standardisation. Nevertheless, optical aggregometry remains the "gold standard" for the detection of platelet function.

Platelet Mapping Assay (Haemoscope), Cone and Plate Analyser (CPA Impact, Diamed), Rapid Platelet Function Analyser (Ultegra, Accumetrics), and PlateletWorks (ICHOR, Helena Bio Sience) are not available in Europe, and evidence is scarce.

The pre-operative assessment of the bleeding history of the patient and of his/her relatives remains the most important tool for detection of both mild and severe inherited or acquired bleeding disorders which may increase the risk of peri-operative bleeding.[29] Standardised questionnaires have been designed in order to assess the type of bleeding (mucosal versus non-mucosal) and the timing of bleeding (immediate versus delayed, since early childhood versus late in life) among other parameters, such as use of anti-coagulant or anti-platelet drugs.[30] The platelet function tests described above are first level tests in the pre-operative evaluation of patients with positive bleeding history[7, 8] and second level tests in actively bleeding patients if anti-platelet therapy, inherited or acquired platelet defects, or extracorporeal circulation are involved, and if thrombelastometry and/or "routine coagulation panel" tests cannot reveal a defect in haemostasis responsible for bleeding.

Not recommended for platelet function testing

The in vivo bleeding time is an old test in which the time until cessation of bleeding after incision of the skin by a specific device is determined. In vivo bleeding time is poorly standardised, temperature and drug dependent (e.g. catecholamines), influenced by vascular disorders, lacks specificity and sensitivity, and is not predictive of bleeding.[31] The bleeding time increases unspecifically during surgery and transfusion,[32] and does not allow the differentiation between bleeding and non-bleeding patients.[33] Platelet count, routine coagulation tests (aPTT, PT), and thrombelastometry/-graphy[34] do not permit diagnosis of platelet disorder.

Practical considerations

Preactivation of platelets can be avoided by blood withdrawal without venous stasis, use of atraumatic needles, and discarding the first millilitres. Transport of blood samples to the laboratory should be performed without sharp acceleration/deacceleration. Sedimentation of blood components may be avoided by slow slewing. Platelets must not have been frozen and temperatures above 22°C should be avoided during storage.[35] Storage time until analysis should be standardised; for PFA-100, storage for 30 mins are recommended by the manufacturer.

Therapeutic stimulation of platelet function

Treatment options to improve platelet function include platelet concentrate, desmopressin, tranexamic acid, coagulation factor concentrates (Von Willebrand factor/factor VIII; fibrinogen, recombinant factor VIIa).[7,36-40] Official prescribing information and national approval status need to be acknowledged.

Conflicts of interest statement

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