Platelet function testing and prediction of bleeding in patients exposed to clopidogrel undergoing coronary artery surgery

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Platelet Function Testing and Prediction of Bleeding in Patients Exposed to Clopidogrel Undergoing Coronary Artery Surgery

Reed GW et al. *Clin Cardiol.* 2015;38:92–98.

We read with great interest the recently published study by Reed et al.[1] The authors conducted a proof-of-principle, prospective, observational pilot study of 39 clopidogrel-treated patients scheduled for on-pump coronary artery surgery (CAS).[1] Briefly, the authors found that the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA) can predict bleeding within the first 24 hours after CAS.[1] This pilot study certainly adds to the current knowledge; however, some methodological considerations should be addressed.

It is important to note that 37 (95%) patients were exposed to aspirin doses of 81 to 325 mg for ≥7 days prior to enrollement.[1] Of those, 31 (80%) patients were exposed to aspirin doses ≥324 mg in close proximity (within 24 hours) to surgery.[1] Considering preoperative antiplatelet therapy management, in particular aspirin dosage and discontinuation management, we may assume that the lack of aspirin-specific platelet function testing was a major drawback of the study.[1] The VerifyNow system provides 2 different assays, (1) VerifyNow P2Y12 and (2) VerifyNow aspirin. VerifyNow aspirin incorporates the agonist arachidonic acid to activate platelets and has been shown to reliably detect aspirin effect.[2] Recently, we have conducted a prospective observational study with the aim to assess bleeding risk using a point-of-care impedance aggregometer in patients undergoing CAS.[3] Patients transfused with packed red blood cells had significantly lower aspirin-sensitive platelet function test values,[3] and those values significantly correlated to the amount of 24-hour chest tube output.[3] In our study, patients were preoperatively exposed to a daily aspirin dose of 100 mg.[3] Thus, we assume that prediction of bleeding using aspirin-sensitive platelet function testing could be even more accurate in a group of patients exposed to more aggressive preoperative aspirin dosage regimens. This assumption may be further corroborated by the fact that, when coadministered, aspirin and clopidogrel achieve greater inhibitory effects on platelet aggregation than either agent alone.[4] The role of aspirin should not be underestimated. By disregarding the variability in the individual responsiveness to aspirin, as well as the possibility that some patients can actually have a profound platelet inhibitory effect on higher aspirin doses, the authors have negated the possible independent contribution of aspirin response as a confounding variable in their pilot study.[1]

To the best of our knowledge, 2 other studies previously addressed the prediction of bleeding complications using the same VerifyNow device in CAS patients.[5,6] Of those studies, one was retrospective analysis,[5] whereas another study was conducted in a prospective observational fashion.[6] Still, small cohorts in studies may not be overcome with pooling of the evidence due to heterogeneity in both study designs and definitions of excessive bleeding. Findings are further elusive due to the separate prediction of bleeding amount and transfusion requirements, which is reasonably expected to be inversely related. Apparently, we need the composite outcome consisting of both bleeding amount and transfusion requirements.[5] Standardization of outcomes is very important for further pooling of the evidence, and to date, Dyke et al[7] provide the most comprehensive and reliable grading of bleeding outcomes that should be consistently used and validated through further research.

Finally, our working group would underline some important considerations for studies evaluating the role of point-of-care platelet function test devices in CAS patients.

First, preoperative platelet function testing may be useful in terms of preoperative bleeding risk stratification that would direct preoperative antiplatelet drug management as well as timing of surgery. Drug-specific platelet function tests should inextricably evaluate platelet inhibitory response to both aspirin and clopidogrel. Furthermore, point-of-care assessment of platelet function should be continued to time points during and after cardiopulmonary bypass, as measurements at these time points may more accurately detect hemostatic alterations, and thus more reliably predict bleeding complications by accounting for accumulative effects of both preoperative antiplatelet therapy and cardiopulmonary bypass on platelet function.

Second, emerging evidence on early postoperative platelet hyperactivity suggests the need for postoperative platelet function assessment aiming to detect patients with high residual on-treatment platelet reactivity. The comprehensive approach to patients based on point-of-care platelet function tests should finally yield a comprehensive algorithm for personalized management of perioperative antiplatelet therapy. In such an approach, the risk of excessive bleeding associated with antiplatelet therapy must always be weighed against the risk for adverse ischemic events. The definition of a perioperative "therapeutic window" for the most commonly administered antiplatelet drugs, as well as the development of a personalized algorithm based on point-of-care platelet function assessment, warrants further investigations that would test the hypotheses about reduction of both bleeding and adverse ischemic events in the pre- and postoperative phase associated with implementation of point-of-care–guided antiplatelet therapy management.

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We congratulate the authors on their elegant and timely research. This article certainly sheds light onto the field and adds to the current knowledge. However, further efforts to elucidate the role of point-of-care platelet function analyzers in developing a personalized approach and optimizing patient outcomes in perioperative setting are needed. Platelet function is a continuous variable ranging from weak function to high platelet reactivity, reflecting in turn a proclivity toward bleeding and ischemic events, respectively. A personalized approach based on a predefined therapeutic window is desirable, and requires further studies standardized in a study design and end points assessed that would facilitate further pooling of the evidence. In that regard, multicentric studies, with the collaboration of centers having the expertise in specific platelet function test, could be the best way to conduct a large cohort study. The basic research concept in this field should be "from observation to intervention." Observational studies should first delineate the therapeutic window (step 1) for aspirin and clopidogrel using a drug-specific point-of-care platelet function analyzer. The therapeutic window should be validated (step 2) through interventional studies assessing both bleeding and adverse ischemic events.

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