Medication History versus Point-of-Care Platelet Activity Testing in Patients with Intracerebral Hemorrhage

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Objective: We evaluated whether reduced platelet activity detected by point-of-care (POC) testing is a better predictor of hematoma expansion and poor functional outcomes in patients with intracerebral hemorrhage (ICH) than a history of antiplatelet medication exposure. *Methods:* Patients presenting with spontaneous ICH were enrolled in a prospective observational cohort study that collected demographic, clinical, laboratory, and radiographic data. We measured platelet activity using the PFA-100 (Siemens AG, Germany) and VerifyNow-ASA (Accumetrics, CA) systems on admission. We performed univariate and adjusted multivariate analyses to assess the strength of association between those measures and (1) hematoma growth at 24 hours and (2) functional outcomes measured by the modified Rankin Scale (mRS) at 3 months. *Results:* We identified 278 patients for analysis (mean age 65 ± 15, median ICH score 1 [interquartile range 0-2]), among whom 164 underwent initial neuroimaging within 6 hours of symptom onset. Univariate association with hematoma growth was stronger for antiplatelet medication history than POC measures, which was confirmed in multivariable models (β 3.64 [95% confidence interval [CI] 1.02-6.26], $P = .007$), with a larger effect size measured in the under 6-hour subgroup (β 7.20 [95% CI 3.35-11.1], $P < .001$). Moreover, antiplatelet medication history, but not POC measures of platelet activity, was independently associated with poor outcome at 3 months (mRS 4-6) in the under 6-hour subgroup (adjusted OR 3.6 [95% CI 1.2-11], $P = .023$). *Conclusion:* A history of antiplatelet medication use better identifies patients at risk for hematoma growth and poor functional outcomes than POC measures of platelet activity after spontaneous ICH. **Key Words:** Intracerebral hemorrhage—intracranial hemorrhage—hemorrhagic stroke—hemostasis—platelet dysfunction—antiplatelet.

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Received October 9, 2017; revision received November 1, 2017; accepted November 23, 2017.

Grant support: Dr. Maas receives support from National Institutes of Health grants K23NS092975 and L30NS080176. Dr. Naidech receives support from Agency for Healthcare Research and Quality grant K18HS023437. Dr. Liotta receives support from National Center for Advancing Translational Sciences grant KL2TR001424 and National Institutes of Health grant L30NS098427. Research reported in this publication was supported, in part, by the National Institutes of Health's National Center for Advancing Translational Sciences grant UL1TR000150. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Agency for Healthcare Research and Quality.

Conflict of interest: All authors declare that they have no conflict of interest.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.11.033

Introduction

Antiplatelet medication exposure and reduced platelet activity detected using point-of-care (POC) tests have been associated with worse functional outcomes and greater mortality in patients with spontaneous intracerebral hemorrhage (ICH).[1-5] Similar to anticoagulant exposure, platelet dysfunction is believed to mediate harm through hematoma expansion.[6,7] Although platelet dysfunction imparts less risk of harm than anticoagulants, approximately a quarter of all ICH patients report pretreatment with antiplatelet medications.[1] Few therapeutic options exist to improve outcomes after ICH, so platelet dysfunction is a therapeutic target of interest.[8,9]

Individual patient responses to antiplatelet medications are variable, with a considerable proportion exhibiting diminished or absent antiplatelet effects.[10,11] Moreover, POC platelet activity screening in patients with acute ICH has found that 24% of cases with no discernible history of antiplatelet medication exposure show reduced platelet activity, suggesting that medication history may be an inaccurate identifier of exposure.[6] As a result, it is not known which approach, POC testing or eliciting medication history, is superior for identification of patients at risk for platelet dysfunction-related morbidity after ICH, or whether they may be complementary. The objective of this study was to determine whether reduced platelet activity detected by POC testing is more strongly associated with hematoma expansion at 24 hours and poor functional outcomes at 3 months than a history of antiplatelet medication exposure.

Methods

Patients presenting to Northwestern Memorial Hospital with spontaneous ICH between January 2010 and March 2016 were prospectively enrolled in an observational cohort study. All cases were diagnosed by a board-certified vascular neurologist or neurointensivist utilizing computed tomography (CT) and/or magnetic resonance imaging. Patients with ICH attributed to trauma, hemorrhagic conversion of ischemic stroke, structural lesions, or vascular malformations were excluded. All patients were admitted to a neuro/spine-intensive care unit with a standard order set in the electronic order entry system. The Glasgow Coma Scale (GCS) score was prospectively recorded at the time of initial evaluation by a trained neurologist and/or neurosurgeon. Our protocol included at least 1 repeat noncontrast head CT, generally after 24 hours, to assess for hematoma growth, as previously reported in detail.[12]

Demographic information, medical history, medication history, standardized clinical instruments (GCS, pre-ICH modified Rankin Scale [mRS]), pretreatment blood pressure, laboratory data, imaging data, medical management variables, surgical interventions, and medical complications were prospectively recorded. Hematoma volumes were measured on industry standard DICOM images using Analyze software (Mayo Clinic, Rochester, MN) with a semiautomated process, a technique with high reliability that has been used as an end point in other ICH studies.[13] We routinely measured platelet activity by POC testing using both the PFA-100 (Siemens AG, Germany) and the VerifyNow-ASA (Accumetrics, CA) systems on admission. We used the PFA-EPI measurement from the PFA-100 system and aspirin reaction units (ARUs) from the VerifyNow system as previously described.[6,14] ARU ≤550 indicates reduced platelet activity in the range of therapeutic aspirin medication effect.[6] Medication history, including over-the-counter medications, was obtained by a critical care pharmacist through mandated medication reconciliation by interviewing the patient and/or their family, and contacting outpatient pharmacies as previously reported.[14] Because initial laboratory data were not uniformly available for patients transferred to our institution from another facility, this study included only patients who presented initially to our hospital. Likewise, patients were excluded if a repeat noncontrast head CT was unavailable to measure hematoma volume change, as well as patients in whom platelet function testing was not performed.

After evaluating continuous variables for distribution characteristics, we determined that hematoma volume change from initial CT to first repeat CT imaging was normally distributed and appropriate for linear regression modeling. We built a fully adjusted multivariate model by initially including clinical variables that were associated with hematoma growth by univariate testing. We then used a stepwise elimination approach to create a parsimoniously adjusted model with less susceptibility to overfitting, and observed whether POC platelet activity measurements or antiplatelet use history was preferentially retained in the adjusted model. Next, we analyzed outcomes using the 3-month mRS adjusted for age, admission GCS, and initial hematoma volume. After determining that the data did not fulfill the proportional odds assumption for ordinal regression modeling as assessed by the test of parallel lines, we dichotomized the mRS treating 0-3 as good outcome and 4-6 as poor outcome, and used a binary logistic regression model. Given that the mechanism of harm from platelet dysfunction is hypothesized to be mediated through hematoma growth, we separately performed the same analyses on the subgroup of patients who presented early enough to undergo initial head CT within 6 hours of symptom onset, as these patients are at highest risk for observable hematoma growth. As exploratory secondary analyses, we sought to identify possible confounding due to warfarin exposure, platelet transfusions, and desmopressin use first by repeating the models for hematoma growth excluding all patients with a history of warfarin exposure, and then adding terms of platelet transfusion and desmopressin treatment to the initial model and repeat-