Reduced Platelet Activity Is Associated With Early Clot Growth and Worse 3-Month Outcome After Intracerebral Hemorrhage

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Background and Purpose—Antiplatelet medication use and reduced platelet activity may be associated with mortality after intracerebral hemorrhage (ICH). We tested the hypothesis that reduced platelet activity is associated with early ICH clot growth and worse outcomes.

Methods—We prospectively identified patients with spontaneous ICH, measured platelet activity (VerifyNow-ASA, Accumetrics) on admission, and recorded antiplatelet medication use. ICH volume was calculated using computerized volumetric analysis. Data were analyzed with nonparametric statistics and repeated measures ANOVA as appropriate. Patients were prospectively followed for functional outcomes. Data are presented as mean±SD or median [Q1 to Q3].

Results—Reduced platelet activity (≤550 aspirin reaction units [ARU]) was associated with increased ICH volume growth (P<0.05) for patients with the diagnostic CT within 12 hours. In the subset of patients not known to take aspirin, 24% had reduced platelet activity. Sixteen (24%) patients received a platelet transfusion 21.2±11.4 hours after symptom onset with an increase in platelet activity (448 [414–479] to 586 [530–639] ARU, P=0.001), but without impact on outcomes. Reduced platelet activity was associated with worse modified Rankin Scores at 3 months (P=0.02).

Conclusions—Reduced platelet activity was associated with early ICH volume growth and worse functional outcome. Because platelet activity can be increased with platelet transfusion, increasing platelet activity is a potential method to reduce ICH volume growth and improve functional outcomes. (Stroke. 2009;40:2398-2401.)

Key Words: ICH • intracranial hemorrhage • neurocritical care • platelets

The morbidity and mortality of intracerebral hemorrhage (ICH) are closely linked to ICH volume1 and clot growth.2 Clot growth typically occurs within 12 hours of symptom onset. Proposed treatments for ICH center on minimizing ICH volume growth, such as aggressive blood pressure control3 and factor VII.4,5

Antiplatelet medication has been associated with clot growth and increased ICH volume.6–9 Aspirin use is confounded, however, by increased age and disability in patients who take it.10 A history of aspirin use may not be as important as an objective measurement of platelet activity.

Aspirin decreases platelet activity by irreversibly acetylating a residue on the surface of platelets. The effect of aspirin can be measured by reference assays such as light transmission aggregometry or thromboelastography, but these are impractical in patients with ICH because of sample timing (patients with ICH usually present after hours),11 the need for specialized laboratory personnel, the time needed to perform the assay, and high cost. The VerifyNow-ASA (Accumetrics, San Diego, Calif) reliably correlates with these reference assays in patients known to take aspirin.12,13

Reduced platelet count and platelet activity may be associated with ICH volume,14 higher ICH score,1 and increased mortality.15 We tested the hypothesis that platelet activity is associated with increased clot growth and worse outcome.

Materials and Methods

Study Population

We prospectively enrolled consecutive patients with ICH. All patients were diagnosed by a board-certified neurologist or neurosurgeon with confirmation by computed tomography (CT). Patients with ICH attributable to trauma, ruptured aneurysms, arteriovenous malformation rupture, vasculitis, and other structural lesions were excluded. Clinical data, laboratory data, and follow-up were prospectively recorded. The study was approved by the Institutional Review Board (IRB). Written informed consent to collect data and clinical outcomes was obtained from the patient or a legally authorized representative in all cases, except when the patient died in hospital or no representative could be located for an incapacitated patient. In that case the IRB approved collection of data in a registry without consent.

Data Recording

We collected baseline demographic and past medical history data and prospectively recorded the date and time of symptom onset.
Table 1. Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>mean±SD, or Median [IQR]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.9±12.7</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>40 (59)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>25 (37)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>East Asian/Oceania</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>29 (43)</td>
<td></td>
</tr>
<tr>
<td>Aspirin dose before ICH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>45 (66)</td>
<td></td>
</tr>
<tr>
<td>81 mg/day</td>
<td>12 (18)</td>
<td></td>
</tr>
<tr>
<td>325 mg/day</td>
<td>10 (15)</td>
<td></td>
</tr>
<tr>
<td>650 mg/day</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel before ICH</td>
<td>6 (9)</td>
<td></td>
</tr>
<tr>
<td>Warfarin use before ICH</td>
<td>5 (7)</td>
<td></td>
</tr>
<tr>
<td>INR on admission</td>
<td>1.1 [1–1.2]</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>109 [78–137]</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure on admit</td>
<td>186±41</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure on admit</td>
<td>103±27</td>
<td></td>
</tr>
<tr>
<td>Platelet activity, ARU</td>
<td>554 [465–644]</td>
<td></td>
</tr>
</tbody>
</table>

When the event was not witnessed we assumed the last time the patient was observed as normal to be the time of symptom onset.

Medication Reconciliation
A dedicated ICU pharmacist reviewed the medication history with the patient (if able to provide this information) or next of kin as part of a mandatory medication reconciliation process. We prospectively recorded the dose of aspirin and the use of clopidogrel or warfarin.

Critical Care
Critically ill patients in the Neuro-ICU are cared for by a dedicated multi-disciplinary team including attending medical staff, house officers, an ICU pharmacist, and critical care nurses. Systolic blood pressure was lowered by 25% or to ≤140 mm Hg⁴ with intravenous medications if needed (admit blood pressures are shown in Table 1).

Assessment of Platelet Activity
We routinely measured platelet activity on admission. The VerifyNow-ASA uses an optical detection system that measures platelet-induced aggregation as an increase in light transmittance. Citrated whole blood is exposed to lyophilized human fibrinogen–coated beads. Cationic propyl gallate is used to induce platelet activation without fibrin formation. The results are reported as aspirin reaction units (ARU), with ≤550 ARU indicative of reduced platelet activity attributable to aspirin. We prospectively recorded the date and time of any platelet transfusion.

ICH Volume Measurement
Data from all available CT scans were transferred to a dedicated workstation with specialized software (Siemens multimodality work platform, Siemens AG) for volume calculation. Intraventricular hemorrhage (IVH) was excluded from measurement. The date and time of CT acquisition was recorded. We validated the measurement technique in 23 first available CT scans between 2 separate evaluators and found the results had excellent correlation (Spearman rho=0.99, P<0.001).

Follow-Up
A certified examiner recorded the NIH Stroke Scale at 14 days or discharge, whichever came first. The modified Rankin Scale (mRS) was recorded at 14 days or discharge, 28 days, and 3 months with a standardized questionnaire.

Table 2. CT Scan Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%) or Median [IQR]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours from symptom onset to first CT</td>
<td>4.8 [1.4–11.7]</td>
</tr>
<tr>
<td>Hours from symptom onset to last CT</td>
<td>40.9 [28.2–60]</td>
</tr>
<tr>
<td>First measured ICH volume, mL</td>
<td>11.6 [3.5–23.9]</td>
</tr>
<tr>
<td>Follow-up measured ICH volume, mL</td>
<td>12.8 [4.2–29.2]</td>
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Statistical Analysis
Change in ICH volume was computed by subtracting the ICH volume on a follow-up CT from the first available CT (the times to first and follow-up CT scans are shown in Table 2). Normally distributed data are presented as mean±SD, and nonnormally distributed data as median [Q1 to Q3]. Grouped data were compared with Mann-Whitney U (2 groups) or Kruskal-Wallis H for (>2 groups). We used repeated measures ANOVA to analyze ICH volume from baseline to follow-up. Statistics were performed with SPSS v.16.

Results
There were 68 patients in the sample. An additional 6 patients had no ICH volume data because of death after an outside CT scan without source data available (2), craniotomy done on the basis of an outside CT without source data available (2), or technical inability to measure ICH volume (2). Demographics are shown in Table 1.

There was a bimodal distribution of platelet activity on either side of the prespecified cut-off for platelet inhibition (550 ARU). Platelet activity was associated with aspirin dose before ICH (P=0.02). Of the patients not known to take antiplatelet medication, 16 patients (24%) had platelet activity consistent with aspirin use (≤550 ARU). Platelet activity was not related to ethnicity, gender, age, admission blood pressure, or time to the diagnostic CT (P>0.1 for all). No patient was thrombocytopenic.

We restricted repeated measures analysis to the 37 patients with the first ICH volume measurement within 12 hours of symptom onset and a follow-up ICH volume measurement. ICH volume grew from the baseline to the follow-up CT (P=0.03), and reduced platelet activity was associated with increased ICH volume growth (time by platelet activity interaction P=0.045). Patients with reduced platelet activity (≤550 ARU) had more ICH volume growth (1 [–0.05 to 7.3] versus −0.1 [−0.6 to 0.5] mL, P=0.046, Figure 1.) The first ICH volume measurement was not different in patients with reduced platelet activity (P>0.1).

We repeated the analysis but restricted to the 25 patients with the first ICH volume measurement within 6 hours of symptom onset and a follow up measurement. ICH volume grew over time (P=0.05), and reduced platelet activity was associated with larger ICH volumes (P=0.003). Patients with reduced platelet activity (≤550 ARU) had more ICH volume growth (1.4 [0.05 to 8.45] versus −0.2 [−0.5 to 0.4] mL, P=0.047).

Platelets were transfused in 16 (24%) patients. There was no association between platelet transfusion and age, warfarin use, gender, ethnicity, aspirin dose before ICH, or admission blood pressure (P>0.1 for all). Platelet transfusion was related to less platelet activity on admission, 479 [422–548] versus 627 [494–647] (P=0.002). The platelet transfusion was given 11.6±11.4 hours after admission and 21.2±11.4 hours after symptom onset. Platelet transfusion led to an...
increase in platelet activity on repeat measurement in the 8 patients with a repeated measurement (448 [414–479] to 586 [530–639], P = 0.001). Platelet transfusion was not related to NIH Stroke Scale at 14 days, mRS at 14 days, 28 days, or 3 months (P > 0.1).

Overall, platelet activity on admission was related to mRS at 3 months in the 50 (74%) patients who could be located (P = 0.02). This was chiefly driven by mortality (Figure 2). Patients who were dead at 3 months had less platelet activity on admission, 488 [453–612] versus 633 [493–653] (P = 0.009).

**Discussion**

These data associate platelet activity with more ICH volume growth and worse 3-month outcome. We did not find any association between platelet activity and time to the diagnostic CT scan, number of CT scans, demographics, or other prognostic variables that might confound our results.

Warfarin use and an elevated INR are associated with ICH volume, later clot growth, and poor outcome after ICH. INR was not significant in our models because few patients were taking warfarin (and fewer had an elevated INR), reducing our ability to detect an effect.

These data support the rationale for improving platelet activity in patients with acute ICH, and a trial of platelet transfusion in acute ICH is planned. The feasibility of such a trial will depend on how quickly platelet activity can be improved and whether all patients with reduced platelet activity can be identified by a medication history. We did not find any associations between platelet transfusion and ICH volume or clinical outcomes, but platelets were transfused almost 24 hours from symptom onset, probably too late to have an effect. DDAVP improves platelet activity in a variety of acquired and inherited conditions and might be useful in acute ICH. Recombinant factor VII triggers thrombin generation in platelets after inhibition with antiplatelet medication, and patients with reduced platelet activity might be a subgroup that could benefit from treatment from factor VII, but this is speculative. We have no data on the effects of either treatment on platelet activity in patients with ICH.

A substantial number of patients had reduced platelet activity consistent with aspirin use but were not known to take aspirin. The reason for this is not clear. We suspect these patients took an antiplatelet medication at the onset of headache, although ICH onset is arguably the worst possible time to do so. Measurement of platelet activity may be more important than known antiplatelet medication use just as the measured INR is more important than the known use of a given dose of warfarin. Reduced platelet activity without known aspirin use may explain results that find no association between aspirin use and ICH growth or outcome. Aspirin is metabolized quickly and serum salicylate concentrations are designed to detect an intentional overdose (not therapeutic use), so a serum salicylate level may not detect it. We are unaware of published data on nonsteroidal antiinflammatory drugs and platelet activity measured with this platform. No patients in our sample were known to take such agents, but urine toxicology screens do not detect them, so they may have been missed.

Our work has some other limitations. This single-center study should be replicated elsewhere. We used a specific platform to measure platelet activity, and other methods may or may not be associated with ICH outcomes. Other platelet activity assays are considered more authoritative but are less practical in ICH patients because of the need to process the sample quickly, off-hour admissions, the need for specialized labor, and cost.

It is unknown whether ICH itself changes the measurement of platelet activity. We are unaware of data where platelet activity was measured before and after ICH, and such an experiment is not feasible in humans. Platelet activity is not changed by ischemic stroke, so we think this is unlikely.

We did not specify the timing or frequency of CT scanning after the diagnostic scan, although most patients had at least 1 follow-up CT. Specified CT schedules would markedly increase the complexity and cost of research, and we did not see any bias in CT scanning related to platelet activity. The median
time to the final CT scan was well after ICH volume stabilizes. Some patients only had 1 CT scan because of emergent clot drainage, death, or a change in goals of care, and so we were unable to measure ICH volume growth in these patients.

We did not measure IVH in this study, and IVH was excluded from measurement for technical reasons. IVH is important but presents specific challenges in terms of density of blood mixed with CSF, hydrocephalus, distant hemorrhage in the third and fourth ventricles, and response to ventricular drainage. Research concerning fibrinolysis after IVH is ongoing. We did not routinely measure platelet activity after admission unless platelets were transfused; one would expect the effect of antiplatelet medication to wear off after several days. Future research might measure platelet activity at specified times whether an attempt to increase platelet activity was made or not. Blood pressure was aggressively treated in our cohort, but we did not have data on follow-up blood pressure measurements, so this may be a potential confounder.

Strengths of these data include prospective case ascertainment and follow-up, measurement of platelet activity on admission before potential confounding by therapy, prospective measurement of platelet activity and side effects of platelet transfusion, and computerized volumetric calculations of ICH volume on a platform with high interrater reliability.

**Summary**

We found that reduced platelet activity was associated with increased early clot growth and worse functional outcomes at 3 months. A reliable history of aspirin use was associated with reduced platelet activity, but a substantial number of patients not known to take aspirin had platelet activity consistent with aspirin use. Platelet transfusion led to improved platelet activity but was probably too late to impact results. Improving platelet activity may be a feasible method to reduce clot growth and improve outcomes if it can be done quickly in selected patients.

**Acknowledgments**

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**Disclosures**

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**References**

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