PLATELET NEEDS FOR ANTIPLATELET THERAPY IN PATIENTS WITH SPONTANEOUS INTERACEREBRAL HEMORRHAGE

By Mark T. Friedman, DO
NYU Langone Health
NYU Grossman Long Island School of Medicine
Mineola, NY

Platelet concentrates are often transfused to patients receiving antiplatelet therapy who present with intracerebral hemorrhage (ICH). Yet, this practice remains controversial. While some data support the concept that platelet transfusion in patients with isolated ICH improves aspirin-induced platelet dysfunction, the *European Guideline on Management of Major Bleeding and Coagulopathy Following Trauma* (5th edition) supports platelet transfusion for patients with ICH only if surgical intervention is planned.[1] At the same time, the results of recent studies have not found a clear benefit for platelet transfusion in patients with either traumatic or nontraumatic (i.e., spontaneous) ICH.[1] This column will examine the evidence surrounding platelet transfusions for patients experiencing nontraumatic ICH while receiving antiplatelet medications.

Patients with cardiovascular comorbidities are commonly prescribed dual antiplatelet therapy, consisting of aspirin and clopidogrel, medications designed to inhibit platelet function irreversibly. Aspirin, known as acetylsalicylic acid (ASA), has antipyretic, nonsteroidal anti-inflammatory, analgesic and antiplatelet properties. It affects platelet function via acetylation of platelet cyclooxygenase (COX). These enzymes catalyze the conversion of arachidonic acid to prostaglandins and thromboxane, preventing access to substrate arachidonic acid at the enzyme catalytic site.[2] This results in irreversible inhibition of platelet-dependent thromboxane formation. ASA is much more potent against COX-1 (constitutive, platelet enzyme isoform) than against COX-2 (inducible, inflammatory/cytokine isoform), explaining the different dosage requirements of ASA as a platelet inhibitor versus an anti-inflammatory agent. Furthermore, COX enzymes also protect the integrity of the gastrointestinal mucosa, such that inhibition may increase the risk for intestinal ulceration, leading to the advice not to take ASA on an empty stomach.[3] Meanwhile, clopidogrel, a thienopyridine P2Y12 receptor blocker, irreversibly inhibits platelets via adenosine diphosphate (ADP) agonist inhibition.

Several recent studies have examined the role of platelet transfusions in patients with nontraumatic ICH. In a retrospective review conducted in a single tertiary center in the United States, 97 patients with nontraumatic spontaneous ICH who had received antiplatelet therapy during a three-year span (2012-2015) were assessed, 39 (40%) of whom had been transfused platelets and 58 (60%) of whom had not.[4] The majority (87 [90%]) had received ASA alone, 2 (2%) had received clopidogrel alone,

and 8 (8%) had received dual antiplatelet therapy. In the matched cohort subanalysis of 62 patients, 31 had received platelet transfusions, and 31 had not; the breakdown included 55 patients receiving ASA alone, one receiving clopidogrel alone, and six receiving dual antiplatelet therapy. The center used leukocyte-depleted apheresis platelets exclusively in the first portion of the study period (until February 2014), following which leukocyte-depleted pooled whole-blood-derived platelets were used through the end of the study. Non-transfused patients in the general cohort of 97 patients were older (mean age 70 years versus 64 years), with a higher percentage of patients aged 80 years or older (28% vs. 8%) than transfused patients; both groups had higher percentages of men than women (53% and 59%, respectively). Comorbid conditions were significant in that a higher percentage of patients underwent coronary artery bypass graft surgery, had peripheral vascular disease and had cancer in the non-transfused group. In contrast, patients in the transfused group had a higher percentage with end-stage renal disease on dialysis, coronary artery disease and deep venous thrombosis. All (100%) of the patients in the non-transfused group received ASA therapy alone; in the transfused group, 75% received ASA alone, 5% received clopidogrel alone and 20% received dual antiplatelet therapy. There were also significant differences in the severity of ICH between the two groups in that patients in the non-transfused group had less severe ICH based on higher median Glasgow Coma Scale (GCS) scores and smaller radiographic estimates of mean ICH volumes with fewer cases involving intraventricular extension. A subanalysis of 62 patients eliminated these differences by matching for ICH severity. Negative outcomes were associated with platelet transfusion in the general cohort, as mortality (odds ratio (OR) >6 times), neurological deterioration (OR nearly 5 times), and surgical intervention (i.e., craniotomy for hematoma evacuation, OR >7 times) were greater in transfused than in non-transfused patients. However, differences in negative outcomes were no longer significant in the matched cohort analysis. The study concluded that the usefulness of platelet transfusion in this population remains to be determined.

An open-label, randomized trial examining platelet transfusions in patients receiving antiplatelet therapy presenting with nontraumatic spontaneous ICH was conducted at 60 centers in the Netherlands (36 hospitals), the United Kingdom (13 hospitals) and France (11 hospitals).[5] Enrollment was limited to patients aged 18 years or older presenting within six hours of supratentorial ICH symptom onset if they had been receiving antiplatelet therapy for at least seven days and had a GCS score of at least 8. Patients were randomized to receive either standard care or standard care with platelet transfusion within 90 minutes of diagnostic brain imaging. Participating sites enrolled 190 patients between February 2009 and October 2015, with 97 patients randomly assigned to platelet transfusion and 93 to standard care alone. Of the 97 platelet transfusion patients, four did not receive platelets (included in the intention-to-treat analysis), while of the 93 standard care alone patients, two received platelets (included in the intention-to-treat analysis); thus, there were 93 and 91 patients, respectively, included in the as-treated analysis. The groups were closely matched with mean ages of 74.2 and 73.5 years, respectively, and male predominance (57% and 61%). Comorbid conditions and mean ICH volumes and brain locations were not significantly different between the two groups. The majority of patients had taken COX inhibitor (i.e., ASA) medication alone (73% versus 84%, respectively), followed by COX inhibitor with dipyridamole

(19% versus 14%, respectively), ADP inhibitor (i.e., clopidogrel) alone (4% versus 1%, respectively), and COX and ADP inhibitors (i.e., dual antiplatelet therapy, 3% versus 1%, respectively), and one patient in the platelet transfusion group had not taken any antiplatelet medications. Platelet products given included both leukocyte-depleted apheresis and buffy coat-derived concentrates. No patients were lost to follow-up at three months, and all were included in the final analysis. Although this study's researchers had hypothesized that platelet transfusion would reduce ICH expansion, their findings showed that platelet transfusion was associated with higher mortality, which they conjectured could be due to patients who possibly had hemorrhagic conversion of infarction, rather than ICH, prothrombotic and proinflammatory effects of platelet transfusion leading to increased vascular permeability, or that the absolute increase in ICH associated with antiplatelet therapy may not be significant enough to be meaningfully modified by platelet transfusion.

Another study, a meta-analysis published in 2020, evaluated the effectiveness of platelet transfusion in patients with ICH on antiplatelet therapy.[6] This study included randomized, case-controlled, cohort studies, both prospective and retrospective, comparing outcomes in adult patients receiving antiplatelet therapy with traumatic or spontaneous ICH. The primary outcome was the effect of platelet transfusion after ICH on mortality, severe neurologic outcome (i.e., severe disability at follow-up or discharge), and hematoma expansion (i.e., radiologically documented volume); secondary outcomes evaluated included possible complications such as myocardial infarction, cerebral vascular accident and extremity embolism. Out of more than 780 identified articles, 16 were included in the review analysis. The researchers concluded that platelet transfusion after either traumatic or spontaneous ICH in patients receiving antiplatelet therapy has no clear benefit for the evaluated outcomes and may slightly increase thromboembolic complications, though not of statistical significance.

Ultimately, while additional studies will undoubtedly be forthcoming to clarify the role of platelet transfusions in the management of patients receiving antiplatelet therapy who present with nontraumatic ICH, individual healthcare facilities will need to weigh the currently available evidence to validate their current practice or revise their transfusion guidelines.

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