Impact of Platelet Transfusion on Intracerebral Hemorrhage in Patients on Antiplatelet Therapy—An Analysis Based on Intracerebral Hemorrhage Score

Gregory D. Arnone[1], Prateek Kumar[1], Matt C. Wonais[1], Darian R. Esfahani[1], Sally A. Campbell-Lee[2], Fady T. Charbel[1], Sepideh Amin-Hanjani[1], Ali Alaraj[1], Andreea Seicean[1,3], Ankit I. Mehta[1]

■ OBJECTIVE: **Platelet transfusions for patients with intracerebral hemorrhage (ICH) on antiplatelet therapy (APT) remain controversial. Diverging past research and differences in platelet preparation warrant further investigation of this topic. In this study, the association between platelet transfusion and clinical outcomes of ICH is investigated in patients matched by ICH score, a validated predictor of mortality.**

■ METHODS: **A consecutive review of all patients from 2012 to 2015 with nontraumatic ICH was performed. Risk factors including demographics, medical comorbidities, APT use, and ICH score were reviewed. Standardized differences were used to assess baseline characteristics; logistic regression models were performed to determine whether platelet transfusions were associated with adverse outcomes, both before and after matching for ICH score.**

■ RESULTS: **A total of 538 patients with nontraumatic ICH were investigated. Of these, 168 were on APT; 71 were excluded. Thirty-nine patients (40%) received platelet transfusions and 58 (60%) did not. An overall mortality of 9.3% was measured, with 29.9% of patients enduring complications. In the unmatched cohort, patients who received platelet transfusions were more likely to deteriorate (odds ratio [OR], 4.7), undergo surgical intervention during their hospital stay (OR, 7.2), be discharged with a worse modified Rankin Scale score (OR, 3.6), or die (OR, 6.1). After matching by ICH score, platelet transfusion was not a significant predictor for any negative outcome.**

■ CONCLUSIONS: **This is the first analysis of platelet transfusions in patients with ICH based on ICH score. For patients on APT, platelet transfusion is not associated with clinical outcomes in an ICH score—matched sample.**

INTRODUCTION

Spontaneous, nontraumatic intracerebral hemorrhage (ICH) is a devastating condition in neurosurgery exacerbated by antiplatelet use, including aspirin and clopidogrel.[1,2] Management of patients with ICH on antiplatelet therapy (APT) is both important and controversial because the use of antiplatelet agents has increased dramatically in the last decade and is expected to continue to rise.[3] In antithrombotic-associated ICH, it is established that rapid reversal of coagulopathy may help limit hematoma expansion and improve outcomes.[4] However, the effects of APT on ICH outcomes are less evident and the usefulness of platelet transfusion is unclear.[5]

The effect of APT on ICH progression and clinical outcomes remains undecided. Although APT has been associated with hematoma expansion, higher rates of mortality, and worse functional outcomes in some studies,[1,2,6-11] others[12-16] have shown no effect on ICH characteristics and outcomes. Studies investigating

Key words
- Antiplatelet therapy
- Aspirin
- Clopidogrel
- ICH score
- Intracerebral hemorrhage
- Platelets
- Transfusion

Abbreviations and Acronyms
APT: Antiplatelet therapy
CI: Confidence interval
CT: Computed tomography
EVD: External ventricular drain
GCS: Glasgow Coma Scale
ICH: Intracerebral hemorrhage
mRS: modified Rankin Scale
PMP: Platelet-derived microparticle
SD: Standard difference

From the Departments of [1]Neurosurgery, [2]Pathology, and [3]Psychiatry, University of Illinois at Chicago, Chicago, Illinois, USA

To whom correspondence should be addressed: Ankit I. Mehta, M.D. [E-mail: ankitm@uic.edu]

Citation: World Neurosurg. (2018) 111:e895-e904.
https://doi.org/10.1016/j.wneu.2018.01.006

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

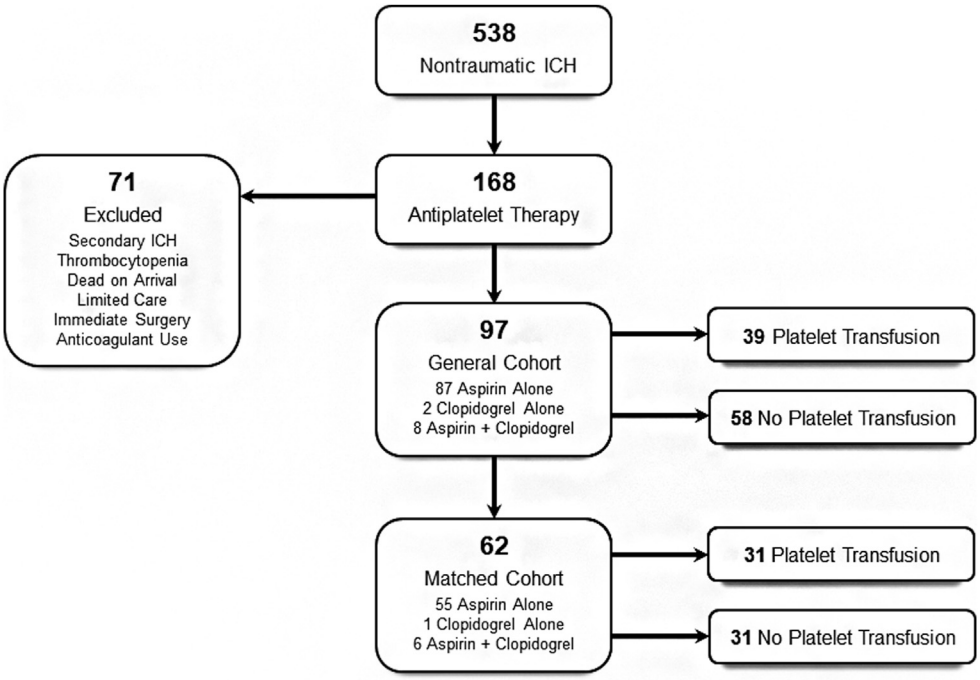

Figure 1. Study patient flowchart. ICH, intracerebral hemorrhage.

the effects of platelet transfusion have also provided variable results. Although some studies[17,18] have suggested that platelet transfusion can lead to smaller ICH volumes, better functional outcomes, and decreased mortality, others[3,19,20] have failed to show an impact on hemorrhage volume or outcome.

The first randomized trial of platelet transfusions in patients with ICH (PATCH [Platelet Transfusion Versus Standard Care After Acute Stroke due to Spontaneous Cerebral Haemorrhage Associated with Antiplatelet Therapy]) was recently completed in Europe and showed significantly greater odds of death or dependence at 3 months in patients receiving transfusions compared with patients who did not receive transfusions.[21,22] The investigators therefore recommended against platelet transfusions for this patient population. Despite these results, it remains a common practice at many institutions to provide platelet transfusions for patients with ICH on APT.[23] Furthermore, because platelet preparation differs by country,[24] researchers may need to consider local practice differences when reviewing the generalizability of the European trial to other regions. In this study, we describe results of a retrospective analysis conducted at a single tertiary center in the United States and report the association between platelet transfusions and clinical outcomes in patients with ICH matched by ICH score.

METHODS

A consecutive review of all patients with nontraumatic spontaneous ICH presenting to a tertiary academic neurosurgery service over a 3-year period (2012–2015) was performed in a retrospective manner. Exclusion criteria included patients with a history of thrombocytopenia, use of other anticoagulant medications such as warfarin or heparin, patients on arrival who were dead, underwent surgery immediately, or whose families requested hospice or limited care. At our center, computed tomography (CT) angiography is performed on arrival to assess for an underlying hemorrhage source if a secondary intracerebral hemorrhage score[25] of 1 or 2 is calculated, and conventional angiography for a score of 3 or higher, or if a strong suspicion for a vascular lesion exists. Patients with ICH found to have a secondary cause, such as an aneurysm or arteriovenous malformation, were excluded. This study was approved by the university institutional review board before data collection. Because data collection involved no risk to participants and patient identifiers were not used, a waiver for consent was granted.

Platelet components were obtained from a blood supplier licensed by the U.S. Food and Drug Administration. Between January 2012 and February 2014, our institution used only apheresis (also referred to as single-donor) platelets. From February, 2014 onward, our institution used pooled whole blood–derived platelets. All platelets were leukoreduced. At our center, platelet transfusion for aspirin generally occurs if a patient meets 2 criteria: a sensitive laboratory (accumetric) assay and a clinical indication, such as need for craniotomy, external ventricular drain (EVD), hemorrhage expansion on successive CT scans, or a large hemorrhage in a hazardous location, such as the posterior fossa. Any platelet transfusion during hospital stay was considered, and time from admission to transfusion was recorded.

Table 1. Baseline Characteristics of General Cohort by Platelet Transfusion

	No Platelets (n = 58) (60%)	Platelets (n = 39) (40%)	Absolute Standardized Difference*
Demographics			
Mean age (years ± standard deviation)	70 ± 15	64 ± 13	**0.45**
Age ≥ 80 years	16 (28)	3 (8)	**0.54**
Male	31 (53)	23 (59)	0.11
Female	27 (47)	16 (41)	
Comorbidities			
Stroke	15 (26)	11 (28)	0.05
Intracerebral hemorrhage	1 (2)	0	0.19
Hypertension	53 (92)	34 (87)	0.14
Diabetes mellitus	19 (33)	16 (41)	0.17
Hyperlipidemia	18 (31)	12 (31)	0.01
Chronic kidney disease	13 (22)	9 (23)	0.02
End-stage renal disease on dialysis	3 (5)	5 (13)	**0.27**
Congestive heart failure	7 (12)	6 (15)	0.10
Coronary artery disease	9 (16)	10 (26)	**0.25**
Coronary artery bypass graft	5 (9)	1 (3)	**0.27**
Coronary/vascular stent	5 (9)	5 (13)	0.14
Myocardial infarction	2 (3)	2 (5)	0.08
Arrhythmia	3 (5)	1 (3)	0.13
Deep vein thrombosis	1 (2)	3 (8)	**0.28**
Peripheral vascular disease	4 (7)	1 (3)	**0.20**
Cancer	4 (7)	1 (3)	**0.20**
Hypercoagulable state	1 (2)	0	0.18
Medical coagulopathy	1 (2)	0	0.18
Medication			
Aspirin alone	58 (100)	29 (75)	**0.83**
Clopidogrel alone	0	2 (5)	
Aspirin and clopidogrel	0	8 (20)	
Statin	27 (47)	21 (54)	0.15

Values are number (%) except where indicated otherwise.
*Significant standardized differences (≥0.20) are in bold type.

Data Collection

Data of patient baseline characteristics and outcomes were collected. Baseline characteristic categories included demographics, comorbidities, medications, and ICH characteristics. Demographics collected included sex and age. Comorbidities of interest included history of stroke, ICH, hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, end-stage renal disease on dialysis, congestive heart failure, coronary artery disease, coronary bypass graft, coronary or vascular stent, myocardial infarction, arrhythmia, deep vein thrombosis, peripheral vascular disease, cancer, hypercoagulable state, and medical coagulopathy. Medications of interest included aspirin, clopidogrel, and statins. Baseline ICH was characterized by volume, location (deep, lobar, cerebellar, or brainstem), laterality (left, right, midline, or bilateral), intraventricular extension, presence of subdural hemorrhage, and expansion on repeat imaging. Patients were also classified by Glasgow Coma Scale (GCS) score on admission, mean platelet count, aspirin and clopidogrel sensitivity by accumetrics, average time to transfusion and first admission scan, whether an EVD was placed, and ICH score.[26]

Outcomes of interest included presence of ICH expansion, unplanned surgeries (craniotomy, ventriculoperitoneal shunt, tracheostomy, or gastrostomy tube), modified Rankin Scale (mRS) score on discharge, neurologic deterioration, mortality, length of

Table 2. Admission Findings of General Cohort by Platelet Transfusion

	No Platelets (n = 58) (60%)	Platelets (n = 39) (40%)	Absolute Standardized Difference*
Clinical			
Median Glasgow Coma Scale score (IQR)	14 (5–15)	11 (3–15)	NA
13–15	46 (79)	17 (44)	**0.88**
5–12	12 (21)	16 (41)	
3–4	0	6 (15)	
Mean platelet count ± standard deviation	224 ± 64	237 ± 87	0.17
Mean aspirin sensitivity ± standard deviation	493 ± 91	499 ± 72	0.07
Mean clopidogrel sensitivity ± standard deviation	273 ± 71	199 ± 77	**1.00**
Median hours to transfusion (IQR)	NA	3.4 (1.7–7.7)	NA
Mean hours admission to scan ± standard deviation	4.3 ± 5.4	4.2 ± 5.7	0.02
External ventricular drain	6 (10)	15 (39)	**0.69**
Radiographic			
Mean ICH volume (mL) ± standard deviation	20.3 ± 27.9	40.8 ± 36.8	**0.63**
ICH volume ≥30 mL	13 (22)	20 (51)	**0.63**
Deep	29 (50)	16 (41)	**0.30**
Lobar	22 (38)	16 (41)	
Cerebellar	3 (5)	5 (13)	
Brainstem	4 (7)	2 (5)	
Left	30 (52)	17 (44)	**0.27**
Right	25 (43)	19 (49)	
Midline	3 (5)	2 (5)	
Bilateral	0	1 (3)	
Intraventricular extension	22 (34)	24 (62)	**0.48**
Infratentorial location	7 (12)	7 (18)	0.16
Subdural hemorrhage present	1 (2)	1 (3)	0.05
Expansion from outside hospital scan	0	5 (13)	**0.54**

Values are number (%) except where indicated otherwise.
IQR, interquartile range; NA, not available; ICH, intracerebral hemorrhage.
*Significant standardized differences (>0.20) are in bold type.

stay, readmission within 30 days, and complications including thromboembolism, myocardial infarction, ischemic stroke, transfusion reaction, infection, and seizure. Prolonged length of stay was defined as greater than 16 days, as proposed in a recent large database study that examined change point analyses for ICH patient hospital stays.[27]

Before data collection, 3 investigators were trained and underwent practice trials, after which coded elements were verified by the researchers to ensure accuracy. After training, charts of studied patients were analyzed twice by 2 different investigators to ensure interrater reliability.

Statistical Analysis

Baseline characteristics were compared using standardized differences run on SAS software (version 9.2 [SAS Institute Inc., Cary, North Carolina, USA]). This statistical measure is an ideal tool to analyze intragroup differences with small patient populations because standard differences (SDs) are not affected by sample size, unlike significance tests that use P values, such as a Fisher test or Pearson χ^2 test.[28] This factor is important in studies with limited patient numbers, because the consistently smaller sample size of the cohort may result in statistically insignificant P values that may be interpreted as improved covariate balance. An absolute standardized difference of >0.20, a standard value of significance in statistics,[29] was established as the statistically significant cutoff.

Outcome measures were analyzed using logistic regression to determine whether platelet transfusions were associated with adverse outcomes in the general cohort; data were reported using odds ratios with confidence intervals (CIs). After data collection

Table 3. Intracerebral Hemorrhage Scores of General and Matched Cohorts by Platelet Transfusion

	General Cohort (n = 97)			Matched Cohort (n = 62)		
Intracerebral Hemorrhage Score	No Platelets (n = 58) (60%), n (%)	Platelets (n = 39) (40%), n (%)	Absolute Standardized Difference*	No Platelets (n = 31) (50%), n (%)	Platelets (n = 31) (50%), n (%)	Absolute Standardized Difference*
0	21 (36)	6 (15)		6 (19)	6 (19)	
1	15 (26)	9 (23)		9 (29)	9 (29)	
2	12 (21)	6 (15)		6 (19)	6 (19)	
3	9 (16)	12 (31)	**0.76**	9 (29)	9 (29)	0
4	1 (2)	4 (16)		1 (3)	1 (3)	
5	0	2 (5)		0	0	
Mean	1.21	2.13		1.68	1.68	

*Significant standardized differences (>0.20) are in bold type.

but before analysis, patients who did versus did not receive platelet transfusion were matched based on exact ICH scores, a validated measurement established as a reliable predictor for mortality.[26,30] For example, a patient with an ICH score of 1 who received a transfusion was matched with a patient with an ICH score of 1 who did not receive a transfusion. Once patients were paired and matched, a logistic regression was performed to assess differences between the 2 groups.

RESULTS

A total of 538 patients were identified with nontraumatic, spontaneous ICH. A total of 168 patients (31%) were taking APT on admission. Seventy-one patients were excluded, and are described in Figure 1. Thirty-six patients were found to have a secondary ICH from another source. Eighteen patients had a history of thrombocytopenia, were dead on arrival, or the family requested hospice or limited care. Three patients went to surgery immediately and were transfused platelets. Fourteen patients were excluded for history of anticoagulant medications. The final study general cohort consisted of 97 patients. Propensity matching by ICH score was then performed, with 62 patients in the matched cohort: 31 who received platelet transfusion and 31 who did not.

Cohort Data

Of the 97 patients in the general cohort, 87 (90%) were on aspirin alone, 2 were on clopidogrel alone, and 8 were on aspirin and clopidogrel dual therapy before admission. Thirty-nine (40%) received platelet transfusions (platelet group) and 58 (60%) did not (nonplatelet group). The median time from admission to platelet transfusion was 3.4 hours (interquartile range, 1.7–7.7).

Analysis of baseline variables showed significant differences between the 2 unmatched groups (Tables 1 and 2). The nonplatelet group was older (70 ± 15 vs. 64 ± 13; SD, 0.45), more likely to have history of coronary artery bypass graft (SD = 0.27), peripheral vascular disease (SD = 0.2), and cancer (SD = 0.2). The platelet group was more likely to be taking clopidogrel (alone or in combination with aspirin) (SD = 0.83), have coronary artery disease (SD = 0.25), end-stage renal disease on dialysis (SD = 0.27), and deep vein thrombosis (SD = 0.28). The platelet group had a worse GCS score on arrival (SD = 0.88), had hemorrhages that were larger (40.8 mL vs. 20.3 mL; SD = 0.63), were more likely to show intraventricular extension (SD = 0.48), require an EVD (SD = 0.69), and expand on repeat CT scan (SD = 0.54). In addition, the 2 groups had significant differences in ICH location (SD = 0.3) and side of ICH (SD = 0.27). Aspirin sensitivity on activity assay (accumetrics) was not significantly different between patients who received platelets versus those who did not (SD = 0.07). However, clopidogrel was more sensitive in the platelet group (SD = 1), confirming the finding that all patients who were on clopidogrel received platelets.

ICH score was selected as a composite ordinal variable to generate the matched cohort. ICH score considers admission GCS score, age, ICH volume, intraventricular hemorrhage, and hemorrhage location (supratentorial vs. infratentorial) and has been validated in numerous studies in predicting risk of 30-day mortality. Before matching, the platelet group was found to have a higher mean ICH score (2.13 vs. 1.21; SD = 0.76), suggesting the population was more ill on presentation (Table 3).

Platelet Transfusion Outcomes

Analysis of negative outcomes including medical complications, neurologic deterioration, and mortality showed significant differences in the general cohort (Tables 4 and 5). The overall mortality was 9.3%, with 29.9% of patients experiencing 1 or more complications, including thromboembolism, myocardial infarction, ischemic stroke, transfusion reaction, infection, or seizure. Patients who received platelets were 3.6 times (95% CI, 1.7–8.0) more likely to have a worse mRS score. Mortality was 6.1 times (95% CI, 1.2–31) more likely in the platelet group. In addition, the platelet group was 4.7 times (95% CI, 1.5–15) more likely to deteriorate, and 7.2 times (95% CI, 1.4–36) more likely to require surgery. Three patients underwent craniotomy for hematoma evacuation, 2 of whom had sensitive laboratory assays and received platelet transfusions. The first patient was

Table 4. 30-Day Complications in General and Matched Cohorts by Platelet Transfusion

Outcomes	General Cohort (n = 97)		Matched Cohort (n = 62)	
	No Platelets (n = 58), n (%)	Platelets (n = 39), n (%)	No Platelets (n = 31), n (%)	Platelets (n = 31), n (%)
Discharge Modified Rankin Scale score				
0	3 (5)	0	0	0
1	3 (5)	3 (8)	2 (6)	3 (10)
2	5 (9)	1 (3)	1 (3)	1 (3)
3	16 (28)	7 (18)	8 (26)	7 (23)
4	25 (43)	11 (28)	14 (45)	10 (32)
5	6 (10)	10 (26)	6 (19)	8 (26)
6	0	7 (18)	0	2 (6)
4–6	31 (53)	28 (72)	20 (65)	20 (65)
Hospital course				
Deterioration	5 (9)	12 (31)	3 (10)	7 (23)
Surgery required	2 (3)	8 (21)	2 (6)	6 (19)
Expansion of intracerebral hemorrhage	1 (2)	2 (5)	0	1 (3)
Medical complication	13 (22)	16 (41)	8 (26)	13 (42)
Thromboembolism	5 (9)	6 (15)	2 (6)	6 (19)
Myocardial infarction	1 (2)	1 (3)	0	1 (3)
Ischemic stroke	0	0	0	0
Transfusion reaction	0	0	0	0
Infection	11 (19)	10 (26)	8 (26)	8 (26)
Seizure	0	2 (5)	0	1 (3)
Discharge outcomes				
Mortality	2 (3)	7 (18)	2 (6)	2 (6)
Prolonged length of stay	10 (17)	9 (23)	7 (23)	7 (23)
Readmission <30days	3 (5)	4 (10)	2 (7)	4 (14)

transfused 2.3 hours after admission for reversal of aspirin-induced thrombocytopathy and underwent surgery 14 hours later for neurologic deterioration despite stable hemorrhage size. The second patient was given platelets and went to surgery because of significant hematoma mass effect, although interval CT scans showed stable hemorrhage size. The patient whose assay was not sensitive did not receive platelet transfusion and went to the operating room for concern of a possible underlying hemorrhagic mass, although pathology returned blood products only. No differences were observed in clinical outcomes between the use of apheresis (single-donor) platelets and pooled whole blood–derived platelets.

When the groups were matched by ICH scores (Table 3), the differences that were observed in the general cohort were no longer significant (Table 5). After matching, platelet transfusion was not a significant predictor for any negative outcome measure, including hematoma expansion, deterioration, mortality, medical complications, or mRS score (Figure 2A and B).

DISCUSSION

Within the last decade, studies have begun investigating the outcomes of clinical management strategies for ICH.[31] The effect of APT on ICH outcomes is unclear. Although some researchers suggest that APT is associated with hematoma expansion, increased mortality, and poor functional outcomes,[6-11] others have found no differences.[12-16] Reviewers have called attention to major differences in sample size, demographics, study design, and statistical analysis among existing studies.[4,15] Two recent meta-analyses have investigated these differences. One[32] found that APT was independently associated with increased mortality but not poor functional outcome, whereas another[33] showed a

Table 5. Platelet Transfusion and Complications in General and Matched Cohorts

Outcomes	General Cohort, Logistic Regression Odds Ratio (Confidence Interval)	Matched Cohort, Logistic Regression Odds Ratio (Confidence Interval)
Discharge Modified Rankin Scale score	**3.6 (1.7–8.0)***	1.3 (0.5–3.3)
4–6	2.2 (0.9–5.3)	1.0 (0.4–2.8)
Deterioration	**4.7 (1.5–15)**	2.7 (0.6–12)
Surgery required	**7.2 (1.4–36)**	3.5 (0.6–19)
Expansion intracerebral hemorrhage	3.1 (0.3–35)	NA
Medical complication	2.4 (1.0–5.9)	2.1 (0.7–6.1)
Thromboembolism	1.9 (0.5–6.8)	3.5 (0.6–19)
Myocardial infarction	1.5 (0.1–25)	NA
Infection	1.5 (0.6–3.9)	1.0 (0.3–3.1)
Seizure	NA	NA
Mortality	**6.1 (1.2–31)**	1.0 (0.1–6)
Prolonged length of stay	1.4 (0.5–4.0)	1.0 (0.3–3.3)
Readmission <30 days	2.5 (0.5–12)	2.2 (0.4–13)

NA, not available.
*Significant odds ratios are in bold type.

higher risk of hematoma expansion and poor functional outcome but no significant difference in baseline hematoma volume or mortality. These reviews, although helpful, show that more data is needed to elucidate the effect of APT on ICH outcomes.

Transfusion for Platelet Thrombocytopathy

As a consequence, the usefulness of platelet transfusion in treating medication-induced thrombocytopathy in ICH is also unclear.[5] Platelet activity assays can be used as adjuncts to identify sensitivity to APT and may guide decision making whether or not to transfuse. At our center, transfusion typically occurs if a patient has both a sensitive assay and meets a clinical indication, such as need for a procedure. No correlation was found between aspirin sensitivity and whether or not a patient was transfused, suggesting that most patients, even if sensitive to aspirin, did not meet clinical criteria for transfusion and had either stable hemorrhages or did not require a procedure. Clopidogrel, conversely, showed a strong correlation, an expected finding because all patients on clopidogrel received a platelet transfusion. The benefit of these sensitivity tests for routine use remains unproven, however.[34]

Some clinicians suggest that reversing APT through platelet transfusion may improve hemostasis and prevent hematoma expansion. Clinical factors are often relevant in this decision making. In our cohort, we found that older patients, generally, were subject to lower rates of transfusion and less aggressive interventions. Similarly, patients requiring an EVD, hemorrhages expanding on successive CT scans, or those in hazardous locations were more likely to be transfused. Certain observational studies have shown benefit to reversal, showing that platelet transfusion improves platelet activity assay results and is associated with smaller final hemorrhage volume, better functional outcome, and decreased mortality.[17,18] One study[35] even described the benefit of direct application of platelets during surgery for ICH in a patient on APT. Other observational studies[3,19,20] have failed to show an impact of platelet transfusion on mortality, functional outcome, or ICH expansion. Previous research on platelet transfusions in patients with ICH has been mostly retrospective and heterogeneous, with variable sample sizes, inclusion/exclusion criteria, statistical analyses, and outcome measures.[36,37] Some studies, for example, do not have control groups (patients not given platelet transfusions), and in some that do, significant confounding persists between cohorts. Given these limitations, a recent systematic review has suggested that methodological limitations preclude any conclusions regarding the usefulness of platelet transfusion.[36]

The PATCH Trial

In contrast to the studies described earlier, the first randomized trial of platelet transfusion in patients with ICH (PATCH) reported worse outcomes with platelet transfusion. Patients given transfusions had significantly greater odds of death or dependence at 3 months compared with patients who did not receive transfusion.[21,22] The generalizability of these results outside Europe warrant further consideration, however. First, differing methods of platelet preparation exist, and it is unclear how platelet preparation affects the morbidity and mortality of transfusion in ICH. PATCH was performed in Europe, where platelet components are manufactured by removal from whole blood using the buffy coat method, versus the platelet-rich plasma method in the United States. Although the buffy coat method may leave a smaller number of donor leukocytes before leukoreduction, inflammatory mediators still accumulate in the platelet component with this

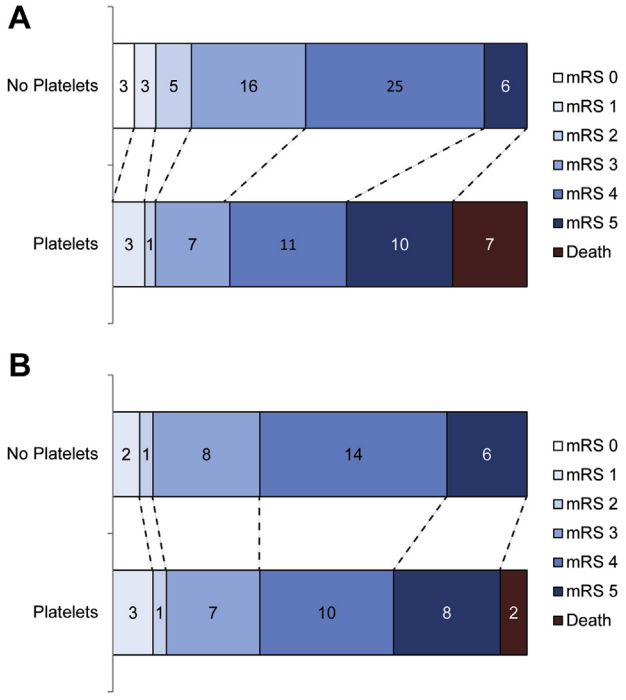

Figure 2. (**A**) Modified Rankin Scale (mRS) score at discharge, general cohort. (**B**) Modified Rankin Scale score at discharge, matched cohort.

technique.[24,38] Furthermore, the buffy coat method has been shown to contain higher quantities of platelet-derived microparticles (PMPs) versus leukoreduced platelets from apheresis or platelet-rich plasma preparation.[39] PMPs are small plasma membranes that are shed from active platelets and may be associated with higher rates of inflammation and thrombosis formation.[40] Even with apheresis-derived platelet products, metabolites accumulating during storage may have an impact on platelet recovery and survival, which could affect clinical outcomes.[41] Little is known about the impact of PMPs and blood product preparation on transfusion-related events in the clinical setting; however, it is important to consider these factors when examining how platelet transfusions affect the population with ICH.

The investigators of the PATCH trial are to be commended for conducting a persuasive prospective randomized study. However, some limitations to PATCH exist: studied in 190 participants, a small sample size risks chance imbalances in prognostic variables and makes it challenging to analyze the relationship between platelet transfusions and subtypes of adverse events.[21,22] The sample size was smaller than most acute stroke trials, perhaps because of the strict eligibility criteria. Excluded cases included patients with infratentorial and large intraventricular hematomas, which may represent a significant proportion of patients with ICH. These criteria limited the trial to patients with relatively smaller hemorrhages, reflected in the study median ICH score of 1. However, this paper and previous studies report higher baseline ICH scores (Table 3), suggesting that patients in the PATCH study may be less ill than the general population with ICH.

ICH Score Matching

To account for higher ICH scores in the platelet transfusion group, representing sicker patients, patients across the 2 study groups were matched by ICH scores, a validated measurement established as a reliable predictor of mortality.[26,30] ICH score is a clinical grading scale consisting of 5 factors associated with poor outcomes in nontraumatic ICH: GCS score, patient age, ICH volume, intraventricular hemorrhage, and infratentorial origin of hemorrhage. ICH score has been proved to accurately risk-stratify patients and has been externally validated.[42] Each additional point of the ICH score is associated with a progressive increase in 30-day mortality risk: ICH score 0, 10%; 1, 13%; 2, 39%; 3, 78%; and 4, 96%. No patient with an ICH score of 5 or greater survived in validation studies.[30,42] From this validation, the ICH score has become an accurate and valuable prognostic tool for comparing intracerebral hemorrhages. This is the first study of platelet transfusions in patients with ICH that matched patient groups by ICH score, comparing the association between platelet transfusion and clinical outcomes across patients with similar ICH characteristics and likelihood of death.

Both the general and matched cohorts were included in this study to show the significance of patient disease severity as a potential confounder. After matching by ICH score, outcome differences observed in the general cohort were no longer statistically significant. No significant differences in ICH outcomes were detected, including hematoma expansion, mRS score, deterioration, mortality, and medical complications between patients given platelet transfusions and patients not given transfusions (Table 5, Figure 2). This finding shows that platelet transfusion is not associated with a clear benefit or harm compared with not giving a transfusion. These results corroborate the findings of previous studies[3,19,20] that indicate no effect of platelet transfusion on ICH mortality, functional outcome, or ICH growth. However, unlike previous studies, matching by ICH score may provide a more accurate analysis of the effect of platelet transfusion by normalizing the most potent risk factors for poor outcomes.

Generalizability and Limitations

In contrast to the PATCH trial, the results of this study suggest that platelet transfusions are not associated with worse outcomes for ICH. Several reasons may account for this difference. First, matching was confined to ICH score, which, although controlling for most confounders identified in the general cohort, may not account for unmeasured confounders that may influence the decision to transfuse. This study was further retrospectively conducted, performed at a single institution, and included patients with larger hematomas, patients requiring cerebrospinal fluid diversion, and patients needing delayed craniotomy for hematoma evacuation. Although this study carries several limitations, we believe its patient sample may be more inclusive and reflects the heterogeneity of patients in the general ICH patient population.

Although this study did not show any association between platelet transfusion and clinical benefit, several instances exist in

which transfusion may be advisable. First, even in the matched group, a higher proportion of patients requiring EVD received platelets (35% in the transfusion group vs. 16% in the no-transfusion group; standardized difference, 0.45; data not shown). This finding suggests that patients with hydrocephalus, a subgroup established to have worse outcomes,[1,2] were over-represented in the transfusion group. Despite this, mortality and other outcome measures were not worse in patients who received EVDs versus those who did not. The PATCH trial did not collect information about EVD placement, however, so it is unclear if platelet transfusion is harmful in this subgroup. We therefore suggest that the results of the PATCH trial should not deter platelet transfusion before placement of EVD. In addition, although surgery for intracerebral hemorrhage has not been shown to improve patient outcomes,[43,44] other interventions for ICH are under investigation, including catheter-based thrombolysis and clot drainage[45,46] (NCT01827046), as well as minimally invasive techniques for clot evacuation.[47] Further research into the necessity of transfusion for reversal of APT-induced thrombocytopathy in the setting of these procedures is necessary and may become more pertinent if a definitive benefit of these interventions is established.

CONCLUSIONS

Spontaneous nontraumatic intracerebral hemorrhage is a devastating condition. For patients on APT before admission to our medical center, there was no difference in outcomes measured between patients given transfusions and those not given transfusions after patients were matched by ICH score. These results are inconsistent with the recent European PATCH trial, although the 2 studies carry several differences. The cohort of this study was retrospective and conducted at a single tertiary medical center in the United States. The selection of patients was more inclusive, however, with patients having higher ICH scores, reflecting the heterogeneity of the general ICH population. Differences in platelet preparation between the United States and Europe also warrant consideration. Despite limitations of the study, these results suggest that the usefulness of transfusion for APT in ICH remains unclear; future randomized controlled trials in the United States may help answer this question.

REFERENCES

1. Alaraj A, Esfahani DR, Hussein AE, Darie I, Amin-Hanjani S, Slavin KV, et al. Neurosurgical emergency transfers: an analysis of deterioration and mortality. *Neurosurgery*. 2017;81:240-250.
2. Esfahani DR, Radnis CA, Hussein AE, Amin-Hanjani S, Charbel FT, Alaraj A. Thresholds for volume and expansion in intraparenchymal hemorrhage: predictors of neurologic deterioration and mortality. *World Neurosurg*. 2017;106:131-138.
3. Martin M, Conlon LW. Does platelet transfusion improve outcomes in patients with spontaneous or traumatic intracerebral hemorrhage? *Ann Emerg Med*. 2013;61:58-61.
4. Frontera JA, Lewin JJ 3rd, Rabinstein AA, Aisiku IP, Alexandrov AW, Cook AM, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016;24:6-46.
5. Campbell PG, Sen A, Yadla S, Jabbour P, Jallo J. Emergency reversal of antiplatelet agents in patients presenting with an intracranial hemorrhage: a clinical review. *World Neurosurg*. 2010;74:279-285.
6. Okada T, Nakase T, Sasaki M, Ishikawa T. Do the antithrombotic therapy at the time of intracerebral hemorrhage influence clinical outcome? analysis between the difference of antiplatelet and anticoagulant agents and clinical course. *J Stroke Cerebrovasc Dis*. 2014;23:1781-1788.
7. Kuramatsu JB, Mauer C, Kiphuth IC, Lucking H, Kloska SP, Kohrmann M, et al. Reported antiplatelet use influences long-term outcome independently in deep intracerebral hemorrhage. *Neurosurgery*. 2012;70:342-350 [discussion: 350].
8. Naidech AM, Batjer HH, Bernstein RA. Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. *Neurology*. 2011;76:1607.
9. Yildiz OK, Arsava EM, Akpinar E, Topcuoglu MA. Previous antiplatelet use is associated with hematoma expansion in patients with spontaneous intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2012;21:760-766.
10. Lacut K, Le Gal G, Seizeur R, Prat G, Mottier D, Oger E. Antiplatelet drug use preceding the onset of intracerebral hemorrhage is associated with increased mortality. *Fundam Clin Pharmacol*. 2007;21:327-333.
11. Naidech AM, Rosenberg NF, Bernstein RA, Batjer HH. Aspirin use or reduced platelet activity predicts craniotomy after intracerebral hemorrhage. *Neurocrit Care*. 2011;15:442-446.
12. Lauer A, Schlunk F, Van Cott EM, Steinmetz H, Lo EH, Foerch C. Antiplatelet pretreatment does not increase hematoma volume in experimental intracerebral hemorrhage. *J Cereb Blood Flow Metab*. 2011;31:1736-1742.
13. Moussouttas M, Malhotra R, Fernandez L, Maltenfort M, Holowecki M, Delgado J, et al. Role of antiplatelet agents in hematoma expansion during the acute period of intracerebral hemorrhage. *Neurocrit Care*. 2010;12:24-29.
14. Nishikawa T, Ueba T, Kajiwara M, Miyamatsu N, Yamashita K. Cerebral microbleeds in patients with intracerebral hemorrhage are associated with previous cerebrovascular diseases and white matter hyperintensity, but not with regular use of antiplatelet agents. *Neurol Med Chir (Tokyo)*. 2009;49:333-338 [discussion: 338-339].
15. Lovelock CE, Rothwell PM. Does antiplatelet therapy at the time of intracerebral hemorrhage bode poor outcome? *Neurology*. 2010;75:1314-1315.
16. Foerch C, Sitzer M, Steinmetz H, Neumann-Haefelin T. Pretreatment with antiplatelet agents is not independently associated with unfavorable outcome in intracerebral hemorrhage. *Stroke*. 2006;37:2165-2167.
17. Suzuki Y, Kitahara T, Soma K, Konno S, Sato K, Suzuki S, et al. Impact of platelet transfusion on survival of patients with intracerebral hemorrhage after administration of anti-platelet agents at a tertiary emergency center. *PLoS One*. 2014;9:e97328.
18. Naidech AM, Liebling SM, Rosenberg NF, Lindholm PF, Bernstein RA, Batjer HH, et al. Early platelet transfusion improves platelet activity and may improve outcomes after intracerebral hemorrhage. *Neurocrit Care*. 2012;16:82-87.
19. Ducruet AF, Hickman ZL, Zacharia BE, Grobelny BT, DeRosa PA, Landes E, et al. Impact of platelet transfusion on hematoma expansion in patients receiving antiplatelet agents before intracerebral hemorrhage. *Neurol Res*. 2010;32:706-710.
20. Creutzfeldt CJ, Weinstein JR, Longstreth WT Jr, Becker KJ, McPharlin TO, Tirschwell DL. Prior antiplatelet therapy, platelet infusion therapy, and outcome after intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2009;18:221-228.
21. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, de Gans K, Koopman MM, Brand A, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *Lancet*. 2016;387:2605-2613.
22. Prodan CI. Platelets after intracerebral haemorrhage: more is not better. *Lancet*. 2016;387:2577-2578.
23. Beshay JE, Morgan H, Madden C, Yu W, Sarode R. Emergency reversal of anticoagulation and antiplatelet therapies in neurosurgical patients. *J Neurosurg*. 2010;112:307-318.

24. Vassallo RR, Murphy S. A critical comparison of platelet preparation methods. *Curr Opin Hematol*. 2006;13:323-330.

25. Almandoz JED, Schaefer PW, Goldstein JN, Rosand J, Lev MH, González RG, et al. Practical scoring system for the identification of patients with intracerebral hemorrhage at highest risk of harboring an underlying vascular etiology: the Secondary Intracerebral Hemorrhage Score. *AJNR Am J Neuroradiol*. 2010;31:1653-1660.

26. Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32:891-897.

27. Stein M, Misselwitz B, Hamann GF, Kolodziej MA, Reinges MH, Uhl E. Defining prolonged length of acute care stay for surgically and conservatively treated patients with spontaneous intracerebral hemorrhage: a population-based analysis. *Biomed Res Int*. 2016;2016:9095263.

28. Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. *J Thorac Cardiovasc Surg*. 2007;134:1128-1135.

29. Austin PC, Mamdani MM, Stukel TA, Anderson GM, Tu JV. The use of the propensity score for estimating treatment effects: administrative versus clinical data. *Stat Med*. 2005;24:1563-1578.

30. Meyer DM, Begtrup K, Grotta JC. Recombinant activated factor VIIIHTI. Is the ICH score a valid predictor of mortality in intracerebral hemorrhage? *J Am Assoc Nurse Pract*. 2015;27:351-355.

31. Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46:2032-2060.

32. Thompson BB, Bejot Y, Caso V, Castillo J, Christensen H, Flaherty ML, et al. Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. *Neurology*. 2010;75:1333-1342.

33. Camps-Renom P, Alejaldre-Monforte A, Delgado-Mederos R, Martinez-Domeno A, Prats-Sanchez L, Pascual-Goni E, et al. Does prior antiplatelet therapy influence hematoma volume and hematoma growth following intracerebral hemorrhage? Results from a prospective study and a meta-analysis. *Eur J Neurol*. 2017;24:302-308.

34. Tantry US, Bonello L, Aradi D, Price MJ, Jeong YH, Angiolillo DJ, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol*. 2013;62:2261-2273.

35. Killory BD, Kilbourn KJ, Ollenschleger M. A Novel use of direct platelet application during surgery for clopidogrel-associated intracerebral hemorrhage. *World Neurosurg*. 2015;84:2078.e2071-2078.e2074.

36. Leong LB, David TK. Is platelet transfusion effective in patients taking antiplatelet agents who suffer an intracranial hemorrhage? *J Emerg Med*. 2015;49:561-572.

37. Ziai WC, Mirski MA. The slippery slope of platelet transfusion for intracerebral hemorrhage. *Neurocrit Care*. 2012;17:154-155 [author reply 156-157].

38. Kluter H, Bubel S, Kirchner H, Wilhelm D. Febrile and allergic transfusion reactions after the transfusion of white cell-poor platelet preparations. *Transfusion*. 1999;39:1179-1184.

39. Noulsri E, Udomwinijsilp P, Lerdwana S, Chongkolwatana V, Permpikul P. Differences in levels of platelet-derived microparticles in platelet components prepared using the platelet rich plasma, buffy coat, and apheresis procedures. *Transfus Apher Sci*. 2017;56:135-140.

40. Herring JM, McMichael MA, Smith SA. Microparticles in health and disease. *J Vet Intern Med*. 2013;27:1020-1033.

41. Zimring JC, Slichter S, Odem-Davis K, Felcyn JR, Kapp LM, Bell LN, et al. Metabolites in stored platelets associated with platelet recoveries and survivals. *Transfusion*. 2016;56:1974-1983.

42. Clarke JL, Johnston SC, Farrant M, Bernstein R, Tong D, Hemphill JC 3rd. External validation of the ICH score. *Neurocrit Care*. 2004;1:53-60.

43. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet*. 2005;365:387-397.

44. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *Lancet*. 2013;382:397-408.

45. Hanley DF, Thompson RE, Muschelli J, Rosenblum M, McBee N, Lane K, et al. Safety and efficacy of minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation (MISTIE): a randomised, controlled, open-label, phase 2 trial. *Lancet Neurol*. 2016;15:1228-1237.

46. Mould WA, Carhuapoma JR, Muschelli J, Lane K, Morgan TC, McBee NA, et al. Minimally invasive surgery plus recombinant tissue-type plasminogen activator for intracerebral hemorrhage evacuation decreases perihematomal edema. *Stroke*. 2013;44:627-634.

47. Zan X, Li H, Liu W, Fang Y, Ma J, Lan Z, et al. Endoscopic surgery versus conservative treatment for the moderate-volume hematoma in spontaneous basal ganglia hemorrhage (ECMOH): study protocol for a randomized controlled trial. *BMC Neurol*. 2012;12:34.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Portions of this work were presented as an abstract at the American Association of Neurological Surgeons (AANS) 2017 Annual Scientific Meeting, April 22-26, 2017, Los Angeles, California, USA.

Received 1 September 2017; accepted 3 January 2018

Citation: World Neurosurg. (2018) 111:e895-e904.
https://doi.org/10.1016/j.wneu.2018.01.006

*Journal homepage: **www.WORLDNEUROSURGERY.org***

*Available online: **www.sciencedirect.com***