Routine platelet transfusion in patients with traumatic intracranial hemorrhage taking antiplatelet medication: Is it warranted?

Christopher Wolff, MD
Farid Muakkassa, MD
Robert Marley, MD
Ayah El-Khatib, MD
Courtney Docherty, MD
Linda Muakkassa, BS
Hannah Stephen, BS
Ann Salvator, MS

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Correspondence to:
F. Muakkassa
Department of Surgery
Cleveland Clinic Akron General
1 Akron General Ave
Akron OH 44307
USA
muakkaf@ccf.org

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Background: After a traumatic intracranial hemorrhage (tICH), patients often receive a platelet transfusion to reverse the effects of antiplatelet medication and to reduce neurologic complications. As platelet transfusions have their own risks, this study evaluated their effects on tICH progression, need for operations and mortality.

Methods: In this retrospective study, we identified patients admitted to a level 1 trauma centre with a tICH from 2011 to 2015 who were taking acetylsalicylic acid (ASA) or clopidogrel, or both. We categorized patients into 2 groups: platelet transfusion recipients and nonrecipients. We collected data on demographic characteristics, changes in brain computed tomography findings, neurosurgical interventions, in-hospital death and intensive care unit (ICU) length of stay (LOS). We used multivariable logistic regression to compare outcomes between the 2 groups.

Results: We identified 224 patients with tICH, 156 (69.6%) in the platelet transfusion group and 68 (30.4%) in the no transfusion group. There were no between-group differences in progression of bleeds or rates of neurosurgical interventions. In the transfusion recipients, there was a trend toward increased ICU LOS (adjusted odds ratio [OR] 1.59, 95% confidence interval [CI] 0.74–3.40) and in-hospital death (adjusted OR 3.23, 95% CI 0.48–21.74).

Conclusion: There were no differences in outcomes between patients who received platelet transfusions and those who did not; however, the results suggest a worse clinical course, as indicated by greater ICU LOS and mortality, in the transfusion recipients. Routine platelet transfusion may not be warranted in patients taking ASA or clopidogrel who experience a tICH, as it may increase ICU LOS and mortality risk.

Contexte : Après une hémorragie intracrânienne traumatique, les patients reçoivent souvent une transfusion de plaquettes pour inverser les effets des médicaments antiplaquettaires et réduire les complications neurologiques. Les transfusions de plaquettes comportent des risques particuliers; l'étude portait sur leurs effets sur la progression de l'hémorragie intracrânienne traumatique, ainsi que sur la nécessité d'une opération et la mortalité.

Méthodes : Dans cette étude rétrospective, nous avons ciblé des patients atteints d'une hémorragie intracrânienne traumatique admis dans un centre de traumatologie de niveau 1, de 2011 à 2015, qui prenaient de l'acide acétylsalicylique (AAS) ou du clopidogrel, ou les deux. Ces patients ont été classés en 2 catégories : ceux ayant reçu une transfusion de plaquettes et ceux n'ayant pas reçu de transfusion. Nous avons recueilli des données sur les caractéristiques démographiques, les changements des résultats de la tomodensitométrie cérébrale, les interventions neurochirurgicales, les décès à l'hôpital et la durée de séjour en unité de soins intensifs. Nous avons eu recours à une analyse de régression logistique multivariée pour comparer les résultats entre les 2 groupes.

Résultats : Nous avons ciblé 224 patients atteints d'une hémorragie intracrânienne traumatique : 156 (69,6 %) ayant reçu une transfusion de plaquettes et 68 (30,4 %) n'ayant pas reçu de transfusion. Il n'y avait aucune différence entre les groupes concernant la progression des saignements ou les taux d'interventions neurochirurgicales. Chez les patients ayant reçu une transfusion, on a observé une tendance à la hausse de la durée de séjour en unité de soins intensifs (rapport de cotes [RC] ajusté de 1,59; intervalle de confiance [IC] de 95 %, 0,74–3,40) et des décès à l'hôpital (RC ajusté de 3,23; IC de 95 % de 0,48–21,74).

Conclusion : On n'a observé aucune différence au chapitre des résultats entre les patients ayant reçu une transfusion de plaquettes et les autres. Toutefois, les résultats suggèrent une évolution clinique défavorable chez les patients ayant reçu une transfusion, se traduisant par une durée de séjour en unité de soins intensifs plus longue et un taux de mortalité plus élevé. La transfusion plaquettaire systématique pourrait ne pas être avisée chez les patients prenant de l'AAS ou du clopidogrel qui souffrent d'une hémorragie intracrânienne traumatique, car elle pourrait faire augmenter la durée de séjour en unité de soins intensifs et exacerber le risque de mortalité.

Traumatic brain injury (TBI) is associated with substantial mortality, morbidity and cost. The Centers for Disease Control and Prevention reported that, in 2014, 2.87 million cases of TBI-related presentations were seen in emergency departments across the United States.[1] Among them, there were 288 345 TBI-related hospital admissions and 56 800 TBI-related deaths. The majority of patients were older than 75 years, and a fall was the leading cause of injury.[1]

The risk of traumatic intracranial hemorrhage (tICH) and associated mortality is increased in patients who take antiplatelet medications (APMs) to prevent and treat cardiovascular and related diseases.[2] It is estimated that nearly one-third of adults older than 40 years of age and 55% of those older than 70 years of age in the US take preventive APMs.[3] Of the APMs, acetylsalicylic acid (ASA) is used for its potential benefit in adults at high risk for coronary artery disease and stroke,[4] whereas clopidogrel is a preferred drug in the prophylaxis of subacute stent thrombosis and postischemic stroke treatment.[5] Both drugs are irreversible inhibitors of platelet activation; therefore, the effects of these medications are not related to the half-life of the specific agent but, rather, the half-life of the affected circulating platelets. As such, when antiplatelet therapy is stopped, normal platelet function returns within 4–5 days.[6]

The acquired coagulopathy from APMs may place patients at higher risk for tICH expansion until the return of platelet function. Fabbri and colleagues[7] showed that taking an APM and being older than 75 years increased the odds of tICH in patients with mild TBI. This has prompted the practice of platelet transfusions in an effort to immediately reverse the effects of APMs in tICH.

The benefits of platelet transfusion to correct the APM effects on clotting are controversial and poorly supported.[8] Platelet dysfunction is present in patients with TBI, even without an APM.[9] This trauma-related platelet dysfunction in patients with tICH is not corrected with platelet transfusion.[10] A platelet transfusion may not work if active APM is circulating in a patient's plasma, which would inhibit the transfused platelets.

A 2015 systematic review showed no significant differences in mortality between patients with primary ICH or tICH who were taking APMs and who received or did not receive platelet transfusion; the evidence for use of platelet transfusion was inconclusive owing to methodologic limitations.[11] In addition, platelet transfusion is not benign: Naidech and colleagues[12] reported an incidence of transfusion-related adverse events of 16% in patients with nontraumatic brain injury who were taking an APM. Transfusions in the general population carry risk, including blood type incompatibility reactions, sepsis, arrhythmia, transfusion-associated circulatory overload, acute lung injury, stroke and death. The risk of acute lung injury is associated more closely with plasma-rich components such as platelets.[13]

The aim of the present study was to evaluate whether platelet transfusion improves outcomes after a tICH in patients with recent exposure to APMs. We hypothesized that patients prescribed ASA or clopidogrel, or both, who receive a platelet transfusion have worse outcomes than patients prescribed ASA or clopidogrel, or both, who do not receive a platelet transfusion.

Methods

This study was approved by the Cleveland Clinic Akron General Institutional Review Board with a waiver of informed consent. The study was a retrospective chart review of all adult (> 18 yr) patients who were admitted to a level 1 trauma centre verified by the American College of Surgeons between 2011 and 2015 and were diagnosed with a tICH, and had been taking ASA or clopidogrel, or both. The presence of any tICH qualified these patients for inclusion in this study, regardless of the size or characteristics of the bleed. Inclusion criteria did not account for patient compliance with dosing regimen or most recent dosage before the traumatic event. Patients with any other form of coagulopathy (metabolic derangements causing coagulopathy such as hypothermia or acidosis; inherited coagulation factor deficiencies; or use of any other forms of anticoagulation such as warfarin, low-molecular-weight heparin or direct oral anticoagulants) were excluded from the study.

We classified patients into 2 groups based on whether they had received a platelet transfusion. As there were no written guidelines for reversal of antiplatelet therapy in this patient population during the study period, platelet administration was based on physician discretion and included 1 unit of apheresis platelets. During the study period, our institution standard was to give apheresis platelets only. Random donor platelets were not supplied by the American Red Cross. Further goal-directed care, including initial routine intensive care unit (ICU) admission orders, frequent neurologic examinations, blood pressure control and repeat brain computed tomography (CT), was uniform for all patients. Repeat brain CT was typically done in the morning after initial presentation, although the interval between the 2 scans varied depending on the severity of the tICH, the time of admission and provider discretion. Repeat brain CT results were documented as improvement, no change or worsening of tICH compared to the initial brain CT, based on the official radiologist interpretation or, if no such statement was provided in subsequent reads, researcher interpretation.

We extracted data retrospectively from the electronic medical records and validated them for accuracy by referring to the patients' medical charts manually as needed. Extracted data included patient demographic characteristics (age, sex) and the following clinical characteristics: Glasgow Coma Scale score on admission, APM prescribed,

Injury Severity Score, international normalized ratio on admission, mechanism of injury and details of complications (incidence of any form of infection, respiratory failure and transfusion complications).

Outcomes

Primary outcomes of interest included changes in brain CT findings, incidence of neurosurgical operative interventions, in-hospital death and ICU length of stay (LOS), in days. For the purpose of this study, any number of operative interventions was counted as a single event for each patient. Owing to the retrospective nature of the study, information about the timing of the intervention with relation to presentation, initial or subsequent brain CT, and platelet transfusion was not always available.

Statistical analysis

We conducted univariate analyses to compare demographic characteristics, clinical characteristics and outcomes between platelet transfusion recipients and nonrecipients. We used Student *t* tests for normally distributed continuous variables and Mann–Whitney *U* tests for nonnormally distributed continuous variables. We used Shapiro–Wilk tests to test for normality. For categoric variables, we used the χ^2 test of association or the Fisher exact test, as appropriate. We performed multiple logistic regression analysis to assess the effect of platelet transfusions on each outcome while controlling for covariates. All variables were included in the regression model, and backward elimination was used to remove covariates with $p > 0.02$. For ICU LOS, we used the regression model to predict an ICU LOS greater than 3 days, as this LOS reached significance. We used Firth bias correction to minimize the small sample bias resulting from a small number of deaths. We conducted analyses using SAS version 9.4 (SAS Institute). A p value < 0.05 was considered statistically significant.

Results

The inclusion criteria were met in 224 patients, with 156 (69.6%) in the platelet transfusion group and 68 (30.4%) in the no transfusion group. There were no between-group differences in any of the baseline characteristics (Table 1).

The median ICU LOS was significantly longer for the platelet transfusion recipients than for the nonrecipients (2.0 d v. 1.0 d, $p = 0.01$) (Table 2). In addition, the platelet transfusion group had a significantly higher median Injury Severity Score than the no transfusion group (17.0 v. 16.0, $p = 0.002$).

When we controlled for Injury Severity Score, age and respiratory failure, platelet transfusion recipients were more likely than nonrecipients to have an ICU LOS greater than 3 days; however, the difference was not statistically significant ($p = 0.2$) (Table 3). After we controlled for Injury Severity Score and renal failure, the risk of death in the transfusion group was 3 times higher than that in the no transfusion group; however, the difference was not statistically significant ($p = 0.2$).

Discussion

We found no significant improvement in outcomes of patients with tICH taking APM after platelet transfusion; in fact, the data suggest a slight trend toward worse outcomes.

The theoretical advantage of platelet transfusions in tICH must be weighed against the risks associated with the transfusion. Transfusion-related lung injury is the leading cause of transfusion-related morbidity and mortality in the US and is associated with plasma-rich components such as platelets.[13] Platelet transfusion during surgery has been shown to result from "clinical judgment" rather than scientific evidence.[14] In a statement for health care professionals from the Neurocritical Care Society and Society of Critical Care Medicine, Frontera and colleagues[15] reported that, in studies of patients with intraparenchymal hemorrhage, platelet transfusions were associated with a 14%–16%

Table 1. Demographic characteristics and comorbidities of patients with a traumatic intracranial hemorrhage who were admitted to a level 1 trauma centre between 2011 and 2015 and were taking an antiplatelet medication, by platelet transfusion status

Variable	No. (%*) of patients†		Test coefficient	*p* value‡
	Platelet transfusion *n* = 156	No platelet transfusion *n* = 68		
Age, median (IQR), yr	76.0 (63.0–84.0)	73.5 (63.0–84.3)	$U = 5892.5$	
Male sex	82 (52.6)	38 (55.9)	$\chi^2_1 = 0.21$	
Comorbidities				
Coronary artery disease	41 (26.3)	18 (26.5)	$\chi^2_1 = 0.001$	0.98
Hypertension	108 (69.2)	45 (66.2)	$\chi^2_1 = 0.204$	0.6

IQR = interquartile range.
*Proportions do not reflect missing values.
†Except where noted otherwise.
‡Obtained from Mann–Whitney *U* test or χ^2 test where applicable.

Table 2. Patients' clinical characteristics

Characteristic	No. (%*) of patients†		Test coefficient	*p* value‡
	Platelet transfusion	No platelet transfusion		
Glasgow Coma Scale score, median (IQR)	15.0 (13.0–15.0)	15.0 (12.8–15.0)	$U = 897.5$	0.99
ICU length of stay, median (IQR), d	2.0 (1.0–6.0)	1.0 (0.0–5.3)	$U = 6329.5$	0.01
International normalized ratio, median (IQR)	1.05 (0.98–1.10)	1.02 (0.97–1.08)	$U = 3643.5$	0.8
Injury Severity Score, median (IQR)	17.0 (16.0–25.0)	16.0 (12.3–18.0)	$U = 6588.5$	0.002
Antiplatelet medication			$\chi^2_2 = 4.906$	0.09
ASA and clopidogrel	28 (17.9)	5 (7.4)		
Clopidogrel	15 (9.6)	5 (7.4)		
ASA	113 (72.4)	58 (85.3)		
Infection	13 (9.2)	5 (7.8)	$\chi^2_1 = 0.109$	0.7
Infection other than urinary tract infection	5 (3.6)	5 (3.6)	Exact	0.7
Mechanism of injury			$\chi^2_1 = 0.268$	0.6
Fall	130 (83.3)	55 (80.9)		
Other	19 (12.2)	10 (14.7)		
Missing/unknown	7 (4.5)	3 (4.4)		
In-hospital death	12 (7.7)	1 (1.5)	Exact	0.1
Operative intervention	22 (14.1)	6 (8.8)	$\chi^2_1 = 1.207$	0.3
Repeat tICH changes on brain CT			$\chi^2_2 = 2.304$	0.3
Increased	28 (17.9)	9 (13.2)		
No change	95 (60.9)	42 (61.8)		
Decrease	10 (6.4)	8 (11.8)		
Missing/unknown	23 (14.7)	9 (13.2)		
Respiratory failure	6 (3.8)	4 (5.9)	Exact	0.5
Renal failure	5 (3.2)	6 (8.8)	Exact	0.09
Skull fracture	12 (7.7)	3 (4.4)	Exact	06
Transfusion complication	1 (0.7)	—		

ASA = acetylsalicylic acid; CT = computed tomography; ICU = intensive care unit; IQR = interquartile range; tICH = traumatic intracranial hemorrhage.
*Proportions do not reflect missing values.
†Except where noted otherwise.
‡Obtained from Mann–Whitney *U* test, χ^2 test or Fisher exact test where applicable.

Table 3. Multiple logistic regression estimates of the effects of platelet transfusion on intensive care unit length of stay and mortality

Variable	Regression coefficient	Adjusted OR (95% CI)
ICU length of stay > 3 d		
Platelet transfusion	0.4620	1.59 (0.74–3.40)
Injury Severity Score	0.1063	1.11 (1.05–1.18)
Age	–0.0276	0.97 (0.95–0.99)
Respiratory failure	1.4709	4.35 (1.03–18.35)
Mortality		
Platelet transfusion	1.1717	3.23 (0.48–21.74)
Injury Severity Score	0.1899	1.23 (1.10–1.33)
Renal failure	2.2099	9.11 (1.37–60.59)

CI = confidence interval; ICU = intensive care unit; OR = odds ratio.

increase in adverse events such as hypotension, fever, cardiac and respiratory events, and decline in neurologic status. In the present study, 1 patient experienced a platelet-transfusion–related complication. In addition, there was a higher incidence of infections (urinary tract infections and pneumonia) and respiratory failure in the platelet transfusion group than in the no transfusion group; however, these differences were not statistically significant. Nevertheless, our findings are consistent with those of a previous study showing increased rates of complications in patients who received platelet transfusions.[16]

One proposed benefit of platelet transfusion in patients taking APM is that it may stabilize or slow down the progression of tICH. However, we did not find any statistically significant differences between the platelet transfusion recipients and nonrecipients in repeat brain CT findings. This is consistent with the findings of Pandya and colleagues,[17] who reported that timing of platelet transfusions did not affect the risk of tICH worsening in patients taking antiplatelet therapy. In addition, Orgundale and colleagues[18] showed an inability of platelet transfusions to limit the expansion of tICH. In that study, patients with nonsurgical acute subdural hematomas taking APM experienced expansion in their subdural hematoma whether they received platelet transfusions or not.

Another potential benefit of platelet administration is a decrease in neurosurgical operative interventions in tICH. In our study, there was no significant difference in the rate of craniotomy between the platelet transfusion group and

the no transfusion group. This finding is consistent with a previous study that showed no increase in the rate of emergent craniotomy in patients with tICH who received platelets compared to patients who did not.[19] Moreover, in a study in older patients (age > 65 yr) who underwent preoperative or perioperative platelet transfusion for emergent surgery for tICH, Lee and colleagues[19] found no difference in increased perioperative bleeding, hospital LOS or in-hospital death by ASA exposure.

In the present study, the crude ICU LOS was significantly longer in the platelet transfusion group than in the no transfusion group. However, this may have been attributable to the significantly higher Injury Severity Score seen in platelet transfusion recipients, indicating a more serious injury requiring prolonged critical care because of age and respiratory failure. When we adjusted for Injury Severity Score, age and respiratory failure, there was a trend toward greater ICU LOS and mortality in the platelet transfusion group, but the difference was not statistically significant. These findings are similar to those of a study in which patients taking ASA or clopidogrel, or both, who received platelets after a tICH had a longer hospital stay after transfusion than patients who did not receive a transfusion.[20] This result occurred despite improvement in platelet function (measured by a thromboelastographic platelet-mapping test) among the platelet recipients.

Studies looking at death in patients taking APM who received a platelet transfusion after a tICH are not conclusive. The PATCH phase 3 trial was a multicentre randomized trial designed to evaluate the use of platelets in patients who had experienced a spontaneous ICH (rather than a tICH) with concomitant use of APM.[21] The odds of death or functional dependence at 3 months were higher in the platelet transfusion group than in the standard care group. The direct contribution of platelet transfusion to these outcomes could not be determined. Our finding of a trend toward increased odds of death with platelet transfusion in patients with tICH is in keeping with the PATCH trial results. In a retrospective study, Fortuna and colleagues[22] showed a higher mortality risk among patients with a tICH who received a platelet transfusion than among nonrecipients; however, those authors did not account for the within-group heterogeneity. Ivascu and colleagues[23] reported a trend toward increased mortality in patients with tICH who received a platelet transfusion; however, the difference was not statistically significant, possibly owing to a small number of patients or an overall higher Injury Severity Score in the transfusion group. Downey and colleagues[24] evaluated 328 patients with TBI and found no difference in mortality between the transfusion and nontransfusion groups; however, they included patients taking warfarin, which may have confounded their data.

Given the low quality of available evidence, the Neurocritical Care Society and the Society of Critical Care Medicine conditionally recommended that patients with a tICH not undergoing neurosurgical intervention should not receive a platelet transfusion.[15] Furthermore, in a platelet reactivity study in patients taking APM who experienced a tICH, Palaez and colleagues[25] found that 29% of patients had no platelet inhibition. The authors concluded that not all patients taking APM who experience a head injury need a platelet transfusion.

After our study was completed, our institution implemented new guidelines on reversal of the effects of APM in patients with trauma, including the use of alternatives to platelet transfusion such as desmopressin. The aim of the guidelines is to limit the arbitrary use of platelet transfusion. We are conducting a follow-up study to assess the impact of the new guidelines and whether they change the frequency of platelet administration in tICH. Prospective randomized trials are needed to determine whether platelet transfusion in patients taking APM who experience a tICH should be reconsidered. Future studies would be strengthened by assessing the utility of platelet transfusions with platelet function assays. Testing before and after platelet administration would provide added objective information on coagulation status and show the impact of platelet transfusion. Future studies should also account for the timing of the platelet transfusion, specifically with relation to the timing of imaging, for better evaluation of the transfusion on the progression of the intracerebral bleed.

Limitations

This study has limitations inherent to its retrospective design, including missing or incomplete data, abstraction error and reliance on documented information. One critical missing value was the platelet count on admission. This was not recorded, and, hence, this study could not ascertain whether physicians administered platelets for severe thrombocytopenia in this patient population. Also, a transfusion reaction was documented only once in 156 transfusions. The expected number of transfusion reactions varies widely but may range from 0.09% to as high as 21%.[26] The value cited in this study is within this wide range but may also represent some degree of underreporting. Furthermore, our findings may have been affected by selection bias, given the heterogeneity in our 2 patient groups with regard to Injury Severity Score and ICU LOS. Having additional details specific to each patient may have provided clarification related to potential cofounders. In addition, some of the attending physicians were more prone than others to order platelet transfusion during the study period. Also, a larger sample may have helped to power the study for detecting significant differences. Last, our data set did not permit study of longer-term functional outcomes. Studies overcoming these limitations may add insight into the effect of platelet transfusions in this patient population.

Conclusion

Our data suggest a trend toward increased ICU LOS and mortality risk with platelet transfusion. However, causation could not be established owing to the retrospective nature of the study. The results suggest that platelet transfusion in patients taking APMs who experience a tICH may not be warranted, as it does not appear to have a clear benefit.

Affiliation: From the Department of General Surgery, Cleveland Clinic Akron General, Akron, Ohio.

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