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Utility of Platelet Transfusion in Adult Patients with Traumatic Intracranial Hemorrhage and Pre-Injury Anti-Platelet Use: A Systematic Review

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BACKGROUND

As the US population ages, the use of anti-platelet medications for the prophylaxis and treatment of stroke and heart disease is steadily increasing.^{1,2} Prior studies suggest that patients with pre-injury anti-platelet use are at increased risk for mortality following blunt head trauma and traumatic intracranial hemorrhage (tICH).^{2–4} Rapid control of hemorrhage in tICH is important, since the majority of expansion occurs in the first 24 hours after injury and hemorrhage expansion is an independent risk factor for mortality.^{5–8} It is proposed that this increased risk for mortality among patients with pre-injury anti-platelet use may be related to impaired platelet function.⁹

Transfusion of platelets has been suggested as a means to counteract the anti-platelet effects of clopidogrel and aspirin.¹⁰ Many institutions have implemented protocols for platelet transfusion for the reversal of anti-platelet medications in the presence of tICH.¹¹ However, it is unclear whether this practice is based on evidence demonstrating improved patient-oriented outcomes. In adult patients with pre-injury oral anti-platelet use and tICH, does urgent transfusion of platelets within 24 hours of injury, improve patient-oriented outcomes such as mortality or neurological outcomes, compared to no platelet transfusion?

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METHODS

Anti-platelet agents of interest included: aspirin, clopidogrel, ticlodipine, prasugrel, and ticagrelor. We did not include non-oral agents such as abcixamab or eptifibatide, nor did we include other non-steroidal anti-inflammatory agents such as ibuprofen or naproxen, due to the short duration of their anti-platelet effects.¹² We did not limit our inclusion criteria to any specific dose of platelet transfusion and included studies that transfused platelets to tICH patients in the intervention group regardless of the dose of platelets.

We restricted platelet transfusions to the first 24 hours post injury since the majority of hematoma progression occurs within this period.^{5,6} However, we did not exclude the study if it did not report the timing of platelet transfusion.

Participants

Participants were adult (18 years or older) ED patients with pre-injury oral anti-platelet use and tICH. The presence of tICH is defined as intracranial hemorrhage or contusion evident on computed tomography (CT) scan or Magnetic Resonance Imaging (MRI) of head.

Intervention

Intervention consisted of transfusion of platelets at any dose, within 24 hours of injury. This was compared to a strategy of no platelet transfusion (control group).

Outcomes

The primary outcome measure was mortality from all causes, assessed at the end of the follow-up period scheduled by each study. Additional primary outcome measures included neurological outcome measures by any method such as Glasgow Outcome Score Extended (GOS-E).¹³ Secondary outcome measures included transfusion related morbidity including infection, transfusion related lung injury (TRALI), and transfusion reaction.

Target study design

We targeted peer-reviewed, randomized clinical trials or observational studies that compared platelet transfusion to no transfusion and reported the primary outcome measure.

SEARCH AND SELECTION METHODS

We searched the MEDLINE database from 1966 to August 2011 and the EMBASE database from 1980 to August 2011. Additional databases searched included the Cochrane Library, Web of Science, Google Scholar, and ClinicalTrials.gov. We reviewed the bibliographies of pertinent articles for citations of eligible studies. Our MEDLINE search strategy is presented in the Appendix.

Two authors (DN and JB) used an algorithm with selection criteria to identify eligible studies (Figure). They extracted data from eligible studies using a standardized worksheet. If disagreement arose, three authors (DN, JB, SZ) conferred to reach consensus. When relevant data from a study were missing or unclear, we attempted to contact the primary author.

The search strategy identified a total of 541 studies from the databases (Figure). A total of 19 full text articles were reviewed. Fourteen articles were excluded.^{2,9,14–25} A total of five studies met our inclusion criteria.^{3,4,26–28} Characteristics of the included studies are presented in Table 1.

QUALITY ASSESSMENT

We used the “Grades of Recommendation, Assessment, Development, and Evaluation” (GRADE) criteria to assess the limitations of the studies and the risk of bias in the reported results.²⁹

The primary limitation in included studies was related to the failure to adequately control for confounding factors and to measure all known prognostic factors. All but one study reported key prognostic variables between cohorts. One study adjusted outcomes for differences in prognostic variables.²⁶ Due to the overall limitation of comparability of cohorts, included studies were given a very low to low quality of evidence grade.²⁹

RESULTS

DESCRIPTION OF STUDIES

All five studies had a retrospective chart review design based on cases identified in trauma registry. Two studies were performed with the primary research question matching our research question (outcome of patients with pre-injury anti-platelet use and tICH with and without platelet transfusion).^{26,28} The other three studies had different primary research questions, such as identifying the predictors of mortality in tICH/antiplatelet patients²⁷ or the impact of antiplatelet use on outcome of tICH/antiplatelet patients^{3,4} but performed their study on subjects similar to our population of interest. We were able to extract the necessary data from the latter studies either directly from the manuscripts or by contacting the authors.

RESULTS

A total of 635 patients with pre-injury anti-platelet use and tICH were enrolled in the included studies. All studies reported in-hospital mortality. A comparison of mortality rates in patients with and without platelet transfusion is presented in Table 2. Due to heterogeneity between studies, we did not perform a meta-analysis.

The largest study by Downey et al, showed no difference between treatment and control groups (relative risk [RR] 10.04, 95% confidence intervals [CI] 0.65–1.69).²⁶ A high number of patients had concomitant warfarin use (89% of study group and 80% of the control group). The authors of this study report fresh frozen plasma (FFP) transfusion in a small number of patients (27/328) but do not provide the group assignments. Patients in the platelet transfusion group were older and more likely to be on warfarin or clopidogrel. However, adjusting for these variables did not impact the relationship between mortality and platelet transfusion in the subjects.

No benefit in mortality was observed in patients receiving platelet transfusion in the study by Washington et al.²⁸ The spectrum of patients were more narrow in this study since the investigators only enrolled patients with mild traumatic brain injury (GCS 13 and tICH)

and excluded patients who required surgical interventions such as those with epidural hematoma). This study excluded patients who were on warfarin but does not report the number of patients who received FFP.

Ivascu et al demonstrated a trend towards increased mortality in the treatment group (RR 2.12, 95% CI 0.96–4.65).²⁷ They did not report concomitant warfarin use but did report a mean INR of 1.1 for both study and control groups. The number of patients who were transfused FFP was not reported.

Ohm et al showed an unadjusted increase in mortality in the platelet transfusion group (RR 2.42, 95% CI 1.18–4.96).³ The subjects in this study were classified based on presence or absence of anti-platelet therapy and not based on platelet transfusion, thus we were unable to compare prognostic variables between the groups.

Only Wong et al showed improved unadjusted in-hospital mortality in patients receiving platelet transfusion (RR 0.21, 95% CI 0.05–0.95).⁴ The primary analysis of this study was based on the presence or absence of pre-injury anti-platelet use rather than platelet transfusion. There was a large difference between the number of patients in the two groups (92 in the transfusion cohort and 19 in the usual care cohort), suggesting that the cohorts were likely different despite comparability in age, GCS, and Injury Severity Score (ISS).

No study reported neurocognitive outcomes or transfusion related morbidity.

DISCUSSION

Aspirin and clopidogrel are by far the most commonly prescribed anti-platelet drugs.¹ Both clopidogrel and aspirin render platelets dysfunctional and inhibit aggregation.^{26,27,30} Drug related platelet dysfunction in head injured patients has been associated with larger degrees of intracranial hemorrhage and worse outcomes compared to patients without pre-injury anti-platelet use.^{2–4} This effect appears greater with adenosine diphosphate (ADP) receptor inhibitors (i.e., clopidogrel) compared to aspirin, which imposes its effect on platelet function through the cyclooxygenase pathway.³⁰

It has been postulated that platelet transfusion can restore platelet function and thus limit hemorrhage progression.¹⁰ Studies have shown that in patients with non-traumatic bleeds, infusion of platelets increases the platelet activity in vivo.^{19,30,31} One unit of single donor apheresis platelets (most common type used in the US) or six units of multiple donor whole blood-derived platelets administered to a normal sized adult raises the platelet count by approximately 30,000/microliter at one hour after the infusion with increased platelet activity seen almost immediately.³¹

However, in vitro studies testing platelet aggregation after clopidogrel reveal that about 40–60% of platelets remain dysfunctional at steady-state after platelet transfusion and an infusion of 12.5 units of pooled platelets might be needed to achieve full normalization of platelet function.³² It is not clear whether full platelet functional recovery is necessary to achieve a clinically significant improvement. Moreover, patients may have varied responses

to anti-platelet medications.¹⁹ Measurements of platelet function (e.g., PFA-100) may further evaluate this heterogeneity.

Our study has a number of limitations. Only two of the included studies had designed their studies to address the research question posed by this EBM review. This issue limits the comparability of groups (anti-platelet transfusion versus routine care). All included studies were based on registry data and thus suffer from limitations inherent to retrospective analysis of a secondary data set.³³ Studies failed to control for confounding variables (e.g., concomitant warfarin use) between treatment and routine care cohorts. Even with attempts to adjust for differences in baseline prognostic variables, it is probable that significant bias existed in the decision to transfuse platelets or not. Our primary outcome measures were all-cause mortality and neurological outcomes. An alternative outcome measure might include mortality from brain injury. None of the included studies used this alternative outcome measure. Finally, the included studies provided limited information regarding the timing of transfusion after injury which may impact outcomes.

The potential benefits of platelet transfusion must be balanced by the potential harm. The risks of platelet transfusion include infection, ABO-mismatch, alloimmunization, and refractoriness to transfusion. Clinicians may be more apt to transfuse patients that are at a higher risk for bleeding or with have more significant injuries. Conversely, clinicians may consider transfusion futile in patients with very poor prognosis.

CONCLUSION

Five retrospective registry studies with suboptimal methodologies provide inadequate evidence to support the routine use of platelet transfusion in adult ED patients with pre-injury anti-platelet use and tICH.

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Figure.
Flowchart representing the selection process for the included trials.

Table 1

Characteristics of the studies included in the review.

Study	Setting	Design	Patients	Intervention	Comparison	Outcome
Downey et al, 2010	Two US, Level 1 trauma centers	Retrospective registry review; Jan 2003–Dec 2006	328 patients, age < 50 years old with tICH and pre-injury aspirin and/or clopidogrel Excluded: none (concomitant warfarin not excluded)	Transfusion of 6 units of concentrated platelets (unknown time after injury)	Standard care	In-hospital mortality
Washington et al, 2011	Single, US, Level 1 trauma center	Retrospective registry review; Jan 2007–Dec 2008	108 patients with mild traumatic brain injury (GCS 13 and ICH on CT scan) on anti-platelet agents. Excluded: patients who required immediate operative intervention and patients with coagulopathy	Transfusion of platelets (unknown dosing and timing)	Standard care	In-hospital mortality, neurological ^{**} or medical decline ^{**} , requirement of neurosurgical intervention ^{***} , and discharge Glasgow Outcome Scale.
Ivascu et al, 2008	Single, US, Level 1 trauma center	Retrospective registry review; Aug 1999–Nov 2004	109 patients with tICH and pre-injury aspirin and/or clopidogrel Excluded: none (concomitant warfarin not reported)	Transfusion of platelets (unknown dosing and timing)	Standard care	In-hospital mortality
Ohm et al, 2005	Single, US, Level 1 trauma center	Retrospective registry review; Jan 1999–Dec 2002	90 patients, age < 50 years old with tICH and pre-injury aspirin and/or clopidogrel Excluded: none (concomitant warfarin not reported)	Transfusion of platelets (unknown dosing) in first 24 hours after injury	Standard care	In-hospital mortality
Wong et al, 2008	Single, US, Level 2 trauma center	Retrospective registry review; Jan 2001–Dec 2005	111 patients with tICH and pre-injury aspirin and/or clopidogrel Excluded: none (concomitant warfarin not reported)	Transfusion of platelets (unknown dosing and timing)	Standard care	In-hospital mortality

Abbreviations: tICH, traumatic intracranial hemorrhage; GCS, Glasgow Coma Scale; CT scan, computed tomography scan

^{*} Neurological decline defined as an increase in monitoring requirement or intervention because of a decline in mental status or development of a focal neurologic deficit attributable to injury visualized on imaging.

^{**} Medical decline defined as an increase in monitoring or intervention because of cardiac, pulmonary, or renal decline.

^{***} Neurosurgical interventions included craniotomy, craniectomy, placement of intracranial pressure monitor, and placement of an external ventricular drain.

Table 2

Summary of the results of the included studies, comparing mortality rates in patients on antiplatelet therapy and receiving platelet transfusion versus standard care.

Study	Transfusion of platelets No. (%) [95% CI] of Patients	Standard care No. (%) [95% CI] of Patients	Relative risk (95% CI)	NNT ^a (95% CI)
Downey et al, 2010	29/166 (17.5) [12.5–24.0]	27/162 (16.7) [11.7–23.2]	1.04 (0.65–1.69)	-
Washington et al, 2011	2/44 (5%) [1.3–15.0]	0/64 (0%) [0–5.6]	-	-
Ivascu et al, 2008	11/40 (27.5) [16.1–42.8]	9/69 (13.0) [7.0–23.0]	2.12 (0.96–4.65)	-
Ohm et al, 2005	10/24 (41.7) [24.5–61.2]	11/64 (17.2) [9.9–28.2]	2.42 (1.18–4.96)	4 (2 to 25) ^{\$}
Wong et al, 2008^b	3/92 (3.4) [1.2–9.5]	3/19 (15.5%) [3.4–39.6]	0.21 (0.05–0.95)	7 (3 to 145)

Abbreviations: CI, confidence interval; NNT, number need to treat.

^aNumber needed to treat (NNT) was only calculated when the difference between the groups was statistically significant, meaning that the confidence interval for the relative risk did not cross 1.

^bAdditional data provided by author.

^{\$}Number Needed to Harm