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Platelet dysfunction and platelet transfusion in traumatic brain injury

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ABSTRACT

Background: Both aspirin therapy and trauma impair platelet function. Platelet dysfunction is associated with worse outcomes in patients with traumatic intracranial hemorrhage (ICH). Platelet transfusion is often used to limit progression of ICH in patients on aspirin, but has not been shown to improve platelet function or outcomes. We hypothesized that platelet transfusion would improve aspirin-induced, but not trauma-induced, platelet dysfunction.

Materials and methods: In this prospective trial, blood samples were collected from patients evaluated in our level 1 trauma center with traumatic ICH, at the time of arrival and at the next clinical laboratory draw after admission. Patients on aspirin therapy were transfused one apheresis unit of platelets. Platelet function was assessed using a Multiplate multiple electrode aggregometer. Platelet activation was induced by collagen (COL) and arachidonic acid (AA). Agonist responses are reported as area under the aggregation curve in units (U). Reference ranges for agonist response were provided by the manufacturer, based on studies of healthy controls.

Results: Seventeen patients with isolated ICH were enrolled, twelve taking aspirin and five not taking aspirin. All patients on aspirin received platelet transfusion. Median admission platelet function in patients taking aspirin was abnormal in response to both agonists. After transfusion, median platelet function in response to AA improved from 19.0 U to 26.0 U ($P = 0.012$), whereas there was no improvement in the COL response. In patients not on aspirin, platelet response to COL was abnormal at both time points.

Conclusions: Patients with isolated ICH have trauma-induced platelet dysfunction. In addition, patients on aspirin have drug-induced abnormalities in platelet response to AA. Platelet transfusion improves aspirin-induced, but not trauma-induced, platelet dysfunction.

1. Introduction

Platelets are critical for initial hemostasis after trauma. Even with a normal platelet count and routine coagulation studies, there can be clinically significant platelet dysfunction after trauma [1,2]. Abnormalities in platelet function have also been observed in patients with traumatic brain injury (TBI) [3], and have been replicated in animal models of TBI as well [4,5]. Antiplatelet therapy is associated with an increased risk of complications and death after TBI [6,7]. Increasing numbers of

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adults are now taking antiplatelet agents, due to a combination of the treatment of cardiovascular, peripheral vascular, and cerebrovascular disease, as well as national guidelines recommending aspirin use for prevention of cardiovascular events.

There currently is no definitive data demonstrating that platelet transfusion in TBI patients on antiplatelet therapy is beneficial. Platelet transfusion has not been shown to improve clinical outcomes in TBI patients on aspirin therapy [8–10]. Studies of the effects of platelet transfusion on platelet function have been conflicting and inconclusive [11–13]. Despite this lack of evidence, transfusion of platelets in TBI patients on antiplatelet therapy is still considered standard of care at many trauma centers. The effect of platelet transfusion on trauma-induced platelet dysfunction has not yet been defined, as studies have focused primarily on platelet activation pathways related to antiplatelet agents, and have not included analysis of other platelet activators.

We hypothesized that platelet transfusion would improve aspirin-induced, but not trauma-induced, platelet dysfunction. To investigate this, we measured platelet function before and after transfusion in patients taking aspirin who presented with traumatic intracranial hemorrhage (ICH).

2. Methods

2.1. Patient selection

The protocol for this prospective study was approved by the institutional review board. Patients evaluated from October 2012–October 2013 in our level 1 trauma center with traumatic ICH (subdural and/or epidural hematoma, intraparenchymal hemorrhage, subarachnoid hemorrhage) were included in the study. Patients were excluded from the study if they were on any anticoagulation therapy other than aspirin or clopidogrel, if they had a known history of thrombocytopenia, platelet disorder, or other preexisting coagulopathy. Patients with an Abbreviated Injury Scale of greater than three outside of the head, neck, or face regions were excluded from the study. Informed consent for platelet transfusion was obtained. A waiver of consent for enrollment in the study was obtained from the institutional review board under the guidelines for use of discarded blood for research purposes, as the blood used for analysis was excess blood that was collected for clinical use but not used for laboratory testing.

2.2. Data collection

Demographic data including age, sex, Glasgow Coma Scale score, and type of ICH were collected on arrival of the patient to the trauma center. Initial and subsequent platelet counts and hematocrit were also recorded. Injury Severity Score and Abbreviated Injury Scale were obtained from the trauma registry.

2.3. Blood collection and assessment of platelet function

Citrated blood was collected from patients at two time points: the time of arrival and at the next clinical laboratory draw (4.5 to 17 h after admission). In all patients receiving platelet transfusion, the second time point occurred after transfusion. Platelet function was assessed using a Multiplate multiple electrode aggregometer (Verum Diagnostica GmbH, Munich, Germany) within 3 h of sample collection. Platelet activation was induced by collagen (COL) and arachidonic acid (AA). Each test used 300 μL of citrated whole blood. For COL testing, blood samples were added to a test cell containing 300 μL of calcium chloride solution (0.9% sodium chloride and 3 mM calcium chloride), which had been preheated at 37°C. This sample was incubated for 3 min, after which time 20 μL of COL reagent was then added to a final concentration of 3.2 μg per milliliter. In AA testing, blood samples were added to a test cell containing 300 μL of preheated 0.9% sodium chloride, which had been preheated at 37°C. After 3 min of incubation time, 20 μL of AA reagent was added to a final concentration of 0.5 mM AA. In each case, activated platelets then adhere to silver-coated sensor wires in test cells, causing the resistance in these wires to rise. Impedance is subsequently plotted in arbitrary aggregation units (U), with the area under the curve being the best expression of platelet activity. Reference ranges for platelet activation were provided by the manufacturer based on studies of healthy controls.

2.4. Platelet transfusion

All patients with traumatic ICH on pre-injury aspirin therapy were transfused one unit of apheresis platelets within 4 h of arrival according to the standard of care at our facility. The results of the Multiplate assay were not shared with the clinicians and could not be used to alter clinical practice.

2.5. Statistics

Baseline characteristics of the patients were presented as percentages for categorical variables and median with 25th–75th percentile interquartile range (25th–75th) for continuous variables. Univariate comparison between the patients taking aspirin that were transfused and those who were not taking aspirin, and did not receive platelet transfusion, was evaluated with nonparametric methods using Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical data. Changes between paired samples (before and after) were assessed with Wilcoxon signed-rank sum tests for transfusion patients and non-transfusion patients, respectively. All statistical tests were two-sided, with a type 1 error of 0.05. A P value of <0.05 was considered to be statistically significant. All statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

In this pilot study, a total of 17 patients were prospectively enrolled. Twelve patients were taking aspirin, and three of these were also taking clopidogrel. Of these twelve patients, 10 were taking 81 mg doses of aspirin, whereas two were taking 325 mg doses of aspirin. Five patients were enrolled who were