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Clinical commentary

Reversal of antiplatelet therapy in traumatic intracranial hemorrhage: Does timing matter?

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ABSTRACT

Reversal of antiplatelet therapy with platelet transfusion in traumatic intracranial hemorrhage remains controversial. Several studies have examined this topic but few have investigated whether the timing of transfusion affects outcomes. Patients admitted to a level 1 trauma center from 1/1/14 to 3/31/16 with traumatic intracranial hemorrhage taking pre-injury antiplatelet therapy were retrospectively analyzed. Patients on concurrent pre-injury anticoagulant therapy were excluded. Per institutional guideline, patients on pre-injury clopidogrel received 2 doses of platelets while patients on pre-injury aspirin received 1 dose of platelets. Patients with worsening hemorrhage defined by an increase in the Rotterdam score on follow up CT were compared to those without worsening. Mortality, need for neurosurgical intervention, and timing of platelet transfusion were analyzed. A total of 243 patients were included with 23 (9.5%) having worsening hemorrhage. Patients with worsening hematoma had higher injury severity score, head abbreviated injury scale, incidence of subdural hematoma, mortality, and lower Glasgow coma scale. There was no significant difference in the number of minutes to platelet transfusion between groups. After logistic regression analysis the presence of subdural hematoma and lower admission Glasgow coma scale were predictors of worsening hematoma, while there remained no significant difference in minutes to platelet transfusion. The timing of platelet transfusion did not have any impact on rates of worsening hematoma for patients with traumatic intracranial hemorrhage on pre-injury antiplatelet therapy. Potential risk factors for worsening hematoma in this group are the presence of subdural hematoma and lower admission Glasgow coma scale.

1. Introduction

Antiplatelet therapy (APT) for the management of cardiovascular disease, peripheral vascular disease and stroke is increasingly prevalent in an ever aging U.S. population [1,2]. Aspirin works by irreversibly acetylating platelet cyclooxygenase thereby inhibiting the formation of prostaglandin and subsequent platelet aggregation, while clopidogrel blocks the ADP P2Y12 receptor, thereby inhibiting aggregation through a different pathway [3]. The routine use of APT has shown a reduction in non-fatal myocardial infarction (−32%), non-fatal stroke (−25%) and cardiovascular death (−17%) [4]. While use of APT has shown benefit in cardiovascular disease, it is also known to increase the risk of bleeding complications [5].

Previous investigations have demonstrated that the use of antiplatelet agents is associated with higher mortality in patients with traumatic intracranial hemorrhage [6–11]. For this reason, many trauma centers around the country have instituted standardized platelet transfusion protocols for patients on pre injury APT that sustain traumatic intracranial hemorrhage (TICH) [12].

Hemorrhage expansion has been shown to be associated with increased mortality [13–18]. It remains unclear which factors most contribute to the risk of hemorrhage expansion in patients on APT. Previous investigations have been unable to demonstrate a benefit to platelet transfusion in this patient population [2,19–23]. These investigations, however, have all suffered from suboptimal methodologies and none have examined the effect of the timing of transfusion on patient outcomes. As a significant proportion of TICH expansion occurs within the first few hours after injury [13–15,18], it stands to reason that the effect of platelet transfu-

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sion may be time sensitive with earlier transfusion being of greater benefit. Hence, the purpose of this study was to determine whether the timing of platelet transfusion affects the rate of worsening TICH. Secondary outcomes of interest were in hospital mortality and the need for neurosurgical intervention. In addition, we sought to better define what clinical and radiologic characteristics are risk factors for worsening TICH in patients on pre injury APT.

2. Methods

After approval from the Institutional Review Board at our level 1 trauma center, medical records of all trauma patients with blunt TICH who were admitted between 1/1/14 and 3/31/16 were retrospectively reviewed. Patients taking aspirin and/or clopidogrel prior to injury were included. Patients on concurrent anticoagulant medication such as warfarin or any of the newer oral anticoagulants were excluded.

According to institutional protocol, all patients with TICH on preinjury APT receive platelet transfusion. One dose of single donor apheresis platelets is transfused for aspirin reversal, while 2 doses are given for clopidogrel reversal.

Baseline characteristics including age, injury severity score (ISS), gender, head abbreviated injury scale (AIS), admission Glasgow coma scale (GCS), and admission platelet count were collected. Initial admission CT scans and the first post transfusion CT scans of the head were interpreted by a board certified neuro radiologist. Type of intracranial hemorrhage and Rotterdam score were recorded. Rotterdam score was calculated for each CT scan by assigning a score for each of the following: basal cisterns, midline shift, epidural mass lesion, and intraventricular blood or traumatic subarachnoid hemorrhage.

Time to platelet transfusion was defined as the number of minutes elapsed from hospital presentation to the start of platelet transfusion. For patient's transferred from outlying facilities, time of presentation to the outlying hospital was utilized rather than time of presentation to our level 1 trauma center.

The sample was divided in to patients with worsening hemorrhage on follow up CT scanning and those without significantly worsening hemorrhage. We defined worsening hemorrhage as any interval increase in the Rotterdam score on the immediate follow up CT scan. Baseline characteristics and outcomes between the groups were then compared. Variables analyzed included mortality, need for neurosurgical intervention, minutes to platelet transfusion, type of intracranial hemorrhage, and complications.

Percentages were compared between independent groups using chi-square tests. Where informative, odds ratios were reported, along with the corresponding 95% confidence interval. Means for continuous variables were compared between independent groups using t-tests (or, in the case of non-normal variables, Wilcoxon two-sample tests). Dichotomous outcomes were modeled using logistic regression.

3. Results

A total of 311 patients with TICH on preinjury APT met initial inclusion criteria. Pre-injury APT was determined from review of the history and physical and electronic medication reconciliation data. History was obtained from patient and/or family interview as well as inquiry from pharmacies and primary care providers as necessary. Patients on concurrent anticoagulant medication were excluding leaving 276 patients on APT. In addition, those patients who did not receive a repeat CT scan or who had incomplete data were excluded, ultimately leaving 243 patients for final analysis.

Table 1
Baseline characteristics.

Characteristic	*N* (%) or Mean (SD)
Age	72.8 (13.41)
Female	112 (46.1%)
Male	131 (53.9%)
Glasgow coma scale	14.0 (2.99)
Injury severity score	16.3 (8.20)
Head abbreviated injury scale	3.4 (1.09)
Initial Rotterdam score	0.7 (0.68)
Minutes to platelet transfusion	321.9 (225.06) n = 234
Worsening hemorrhage	23 (9.5%)
Neurosurgical intervention	35 (14.4%)
Mortality	22 (9.1%)
Transferred from outlying hospital	164 (67.2%)
Admission platelet count	220.3 (69.7)
Complications	28 (11.5%)

Baseline characteristics for the entire cohort are illustrated in Table 1. Mean age of the overall cohort was 72.8 (13.41). The overall rate of worsening hemorrhage was 9.5% while the mortality rate was 9.1% for the sample. Neurosurgical intervention was performed in 14.3% of patients. A total of 87.3% of the sample was on preinjury aspirin and 29.9% were on preinjury clopidogrel, while 17.2% were on both. Average time to platelet transfusion was 321.9 (225.06) minutes and average time to repeat CT scan was 798.6 ± 54.2 min. Complications occurred in 28 patients (11.5%). The most common complication was urinary tract infection (32%), followed by pneumonia (25%), unplanned intubation (21%), venous thromboembolism (11%), and stroke (7%). The were no recorded incidents of transfusion related reaction in the study population. The most common type of hemorrhage was subdural hemorrhage (SDH), followed by subarachnoid hemorrhage (SAH), and intraparenchymal hemorrhage (IPH) as listed in Table 2.

A total of 22 out of 244 (9.5%) patients had worsening intracranial hemorrhage. Age, gender, and initial Rotterdam score were similar between the expansion and no expansion groups. Those patients in the worsening TICH group had significantly higher ISS, head AIS, and lower admission GCS. In addition, patients in the worsening group had a significantly higher proportion of SDH (87% vs. 61%, p = 0.014), higher rate of neurosurgical intervention (35% vs 12%, p = 0.003), and higher mortality rate (22% vs 8%, p = 0.026). There was no difference in the mean number of minutes to transfusion (354 vs 319, p = 0.45) between the groups or the mean interval to repeat CT scan (Table 3).

After using logistic regression analysis to control for confounding variables, lower admission GCS and the presence of SDH were associated with an increased risk for worsening TICH. There remained no significant difference in the mean minutes to platelet transfusion between groups.

4. Discussion

Previous studies have shown that pre injury APT including clopidogrel and aspirin can lead to worse outcomes such as hematoma expansion and mortality in patients sustaining TICH. [6,7,8,9,10,11] Whether or not platelet transfusion is an effective

Table 2
Types of Traumatic Intracranial Hemorrhage.

Type	N (%)
Subdural Hemorrhage	154 (63.4%)
Subarachnoid Hemorrhage	121 (49.8%)
Intraparenchymal Hemorrhage	67 (27.6%)
Intraventicular Hemorrhage	31 (12.8%)
Epidural Hemorrhage	3 (1.2%)

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