

Antiplatelet therapy is associated with a high rate of intracranial hemorrhage in patients with head injuries

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Received 26 May 2020

Revised 17 September 2020

Accepted 25 October 2020

ABSTRACT

Background Antiplatelet agents are increasingly used in cardiovascular treatment. Limited research has been performed into risks of acute and delayed traumatic intracranial hemorrhage (ICH) in these patients who sustain head injuries. Our goal was to assess the overall odds and identify factors associated with ICH in patients on antiplatelet therapy.

Methods A retrospective observational study was conducted at two level I trauma centers. Adult patients with head injuries on antiplatelet agents were enrolled from the hospitals' trauma registries. Acute ICH was diagnosed by head CT. Observation and repeat CT to evaluate for delayed ICH was performed at clinicians' discretion. Patients were stratified by antiplatelet type and analyzed by ICH outcome.

Results Of 327 patients on antiplatelets who presented with blunt head trauma, 133 (40.7%) had acute ICH. Three (0.9%) had delayed ICH on repeat CT, were asymptomatic and did not require neurosurgical intervention. One with delayed ICH was on clopidogrel and two were on both clopidogrel and aspirin. Patients with delayed ICH compared with no ICH were older (94 vs 74 years) with higher injury severity scores (15.7 vs 4.4) and trended towards lower platelet counts (141 vs 216). Patients on aspirin had a higher acute ICH rate compared with patients on P2Y12 inhibitors (48% vs 30%, 18% difference, 95% CI 4 to 33; OR 2.18, 95% CI 1.15 to 4.13). No other group comparison had significant differences in ICH rate.

Conclusions Patients on antiplatelet agents with head trauma have a high rate of ICH. Routine head CT is recommended. Patients infrequently developed delayed ICH. Routine repeat CT imaging does not appear to be necessary for all patients.

Level of evidence Level III, prognostic.

INTRODUCTION

Antiplatelet agents are increasingly being used in the treatment or prevention of cardiovascular disease.^{1,2} Patients taking these medications appear to have an increased risk of traumatic bleeding.³⁻¹⁰ When patients suffer head trauma, an intracranial hemorrhage (ICH) can occur acutely or delayed. A number of studies have looked at acute traumatic ICH in patients taking an antiplatelet agent, with ICH occurring in approximately 3.6%–67.3% of patients on antiplatelet therapy and 1.6%–50.5% of patients not on this therapy.⁵ The reported risk

of delayed ICH after head injury has varied in the literature from 0% to 4%.¹⁰⁻¹⁶

Several clinical guidelines highlight the risk of traumatic delayed ICH in patients taking antiplatelet agents.¹⁷⁻¹⁹ According to the 2014 National Institute of Health and Care Excellence guidelines on head injury, for patients on aspirin or clopidogrel, 'the reference standard should include CT head scan and a follow-up period of sufficient duration to capture delayed bleeding, for example, at 7 days and 1 month'.¹⁷ Nonetheless, neither *The American College of Surgeons Resources for Optimal Care of the Injured Patient*, sixth edition released in 2014 nor the *Recommendations of the National Expert Panel on Field Triage* published by the Center for Disease Control and Prevention in 2011 include head trauma or fall in a patient taking an antiplatelet as a criterion for trauma activation.^{18,19} In addition, the current American College of Emergency Physicians' clinical guidelines do not specifically list antiplatelet medications as a risk factor for traumatic ICH.²⁰

With the limited amount of available research regarding the risk of both acute and delayed ICH, and the varying methodology and quality of the literature in patients taking antiplatelet agents, the objective of our study was to assess the odds of acute and delayed ICH among head trauma victims with pre-injury exposure to antiplatelet agents.

METHODS

Study design and setting

This multicenter retrospective investigation was conducted at two level I trauma centers between January 1, 2016 and December 31, 2017. The first site of investigation in central Michigan is a 68-bed emergency department (ED) with annual census of 100 000 patients and 676 inpatient beds. The second site in southeast Florida is a 36-bed ED with annual census of 70 000 patients and 463 inpatient beds.

Selection of participants

The trauma registry at each hospital was queried for inclusion criteria of patients with pre-injury use of antiplatelet therapy (defined as aspirin, clopidogrel, prasugrel and ticagrelor) seen in the ED by the trauma team for any head trauma. Exclusion criteria were age <18 years, no use of antiplatelet therapy in the last 7 days, prior use of an anticoagulant and those suffering head trauma >24 hours

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To cite: Alter SM, Mazer BA, Solano JJ, et al. *Trauma Surg Acute Care Open* 2020;**5**:e000520.

prior to ED presentation. All patients meeting these criteria were included, making up the study sample. Trauma activation at both hospitals was determined by the prehospital paramedics, who followed local protocols that mirror the CDC Guidelines for Field Triage of Injured Patients.¹⁹ Antiplatelet use alone did not warrant trauma activation in the study population. Within the ED, patients also may have been upgraded to the trauma service at treating physicians' discretion.

Measurements

At both hospitals, the typical trauma workup in the ED consisted of complete blood count, comprehensive metabolic panel, coagulation studies (prothrombin time, international normalized ratio (INR) and partial thromboplastin time) and head CT. Some patients on antiplatelet therapy were admitted for neurological observation and repeat head CT based on clinician discretion, although neither hospital had practice management guidelines dictating such.

A standardized data abstraction form was used that included the following: age, sex, ethnicity, mechanism of injury, signs and symptoms, Glasgow Coma Scale (GCS), injury severity score, initial vital signs, platelet count, coagulation studies, findings of initial head CT, findings of repeat head CT, performance of neurosurgical intervention and mortality. Radiographic imaging was interpreted by board-certified radiologists at both institutions. All data were obtained by chart review from the respective hospitals' electronic medical records by one of the coauthors at each institution.

Outcomes

The primary outcome of the study was the presence of acute or delayed ICH. An acute ICH is defined as having an acute intracranial bleed on the initial head CT. A delayed ICH is defined as having an acute finding of intracranial bleeding on the repeat CT after an initial negative CT. Secondary outcomes included need for neurosurgical intervention and mortality during the hospitalization. Neurosurgical intervention was defined as the performance, use or placement of an intracranial pressure monitor, an intraventricular catheter, a subdural drain, a craniotomy/craniectomy or treatment with mannitol or hypertonic saline.

Analysis

Patients were grouped by aspirin alone, P2Y12 alone or aspirin with P2Y12. Background characteristics of patients were compared between antiplatelet categories at a significance level of 0.05 using z-tests for proportions and t-tests for means. Patients in each antiplatelet group were analyzed by primary outcome (no ICH, acute ICH and delayed ICH). Pearson's χ^2 tests were performed and odds ratios were calculated using Stata V.16 (StataCorp, College Station, Texas, USA) to compare the rates of acute and delayed ICH between each of the antiplatelet groups. The types of ICH (epidural, subdural, subarachnoid and intraparenchymal) were identified for each antiplatelet category. The reason for repeat head CT (routine, clinical change or not repeated) was identified for each primary outcome group. Any patients with missing data points were excluded from only that portion of the analysis.

RESULTS

Characteristics of study subjects

Three hundred twenty-seven patients were included in the analysis: 128 patients on aspirin only, 60 on clopidogrel only, 3 on ticagrelor only, 0 on prasugrel only, 128 on both aspirin and

Table 1 Patient characteristics by antiplatelet category

	Aspirin (n=128)	P2Y12 (n=63)	Aspirin+P2Y12 (n=136)
Age, mean (SD), years	75 (13)	76 (13)	76 (13)
Female, no. (%)	57 (45%)	27 (43%)	57 (42%)
Ethnicity, no. (%)			
Caucasian	111 (87%)	54 (86%)	119 (88%)
African-American	10 (8%)	6 (10%)	7 (5%)
Hispanic/Latino	6 (5%)	3 (5%)	7 (5%)
Other	1 (1%)	0 (0%)	3 (2%)
Mechanism of injury, no. (%)			
Fall	100 (78%)	56 (89%)	110 (81%)
Motor vehicle crash	14 (11%)	1 (2%)*	19 (14%)*
Bicycle accident	2 (2%)	2 (3%)	1 (1%)
Motorcycle accident	3 (2%)	0 (0%)	1 (1%)
Pedestrian struck by vehicle	5 (4%)	1 (2%)	2 (1%)
Blunt injury to head (not fall)	3 (2%)	3 (5%)	2 (1%)
Other	1 (1%)	0 (0%)	1 (1%)
Signs of head trauma, no. (%)	113 (88%)*	52 (83%)	99 (73%)*
Symptoms, no. (%)			
Loss of consciousness	55 (43%)*	22 (35%)	31 (23%)*
Headache	63 (49%)	32 (51%)	52 (38%)
Seizure	1 (1%)	1 (2%)	2 (1%)
Nausea	5 (4%)	5 (8%)	10 (7%)
Vomiting	3 (2%)	3 (5%)	5 (4%)
Dizziness	5 (4%)	5 (8%)	11 (8%)
Initial GCS group, no. (%)			
Mild (13–15)	119 (93%)	61 (97%)	129 (95%)
Moderate (9–12)	5 (4%)	2 (3%)	4 (3%)
Severe (3–8)	4 (3%)	0 (0%)	3 (2%)
Injury severity score, mean (SD)	10 (9)	9 (10)	12 (13)
Initial vital signs, mean (SD)			
Systolic blood pressure, mmHg	147 (30)	148 (24)	145 (27)
Diastolic blood pressure, mmHg	76 (18)	76 (18)	74 (18)
Heart rate, beats/min	85 (17)*	81 (15)	79 (18)*
Respiratory rate, breaths/min	19 (4)*	18 (3)	18 (2)*
Oxygen saturation, %	97 (3)	96 (5)	96 (8)
Platelet count, mean (SD), $\times 10^9/L$	218 (63)	209 (64)	208 (72)
INR, mean (SD)	1.04 (0.10)	1.05 (0.12)	1.06 (0.11)

*Indicates statistically significant difference between items within the row at $p < 0.05$ by z-test for proportions and t-test for means.

GCS, Glasgow Coma Scale; INR, international normalized ratio.

clopidogrel, 6 on both aspirin and ticagrelor and 2 on both aspirin and prasugrel. Overall, the average patient age was 76 years (range 18–97), 43% were female and patients were predominantly Caucasian (87%). The majority of head injuries occurred as the result of falls (81%), followed by motor vehicle collisions (10%). Grouping the patients by antiplatelet classification, 63 patients were on a P2Y12 inhibitor alone and 136 patients were on both aspirin and a P2Y12 inhibitor. Background characteristics of patients between groups were mostly similar, although notably, the aspirin+P2Y12 inhibitor group had more motor vehicle crashes than the P2Y12 group and patients in the aspirin group had higher rates of signs of head trauma and loss of consciousness than the aspirin+P2Y12 group (table 1).

Table 2 Antiplatelet category by head CT result for intracranial hemorrhage (ICH), no. (%; 95% CI)

	No ICH	Acute ICH	Delayed ICH	Total
Aspirin	66 (52%; 95% CI 43 to 60)	62 (48%; 95% CI 40 to 57)	0 (0%; 95% CI 0.0 to 2.8)	128
P2Y12	43 (68%; 95% CI 55 to 79)	19 (30%; 95% CI 19 to 43)	1 (1.6%; 95% CI 0.0 to 8.5)	63
Aspirin+P2Y12	82 (60%; 95% CI 52 to 69)	52 (38%; 95% CI 30 to 47)	2 (1.5%; 95% CI 0.2 to 5.2)	136
Total	191 (58%; 95% CI 53 to 64)	133 (41%; 95% CI 35 to 46)	3 (0.9%; 95% CI 0.2 to 2.7)	327

Main results

Overall, 133 patients (40.7%) had an acute ICH and three patients (0.9%) had a delayed ICH (table 2). Of the patients with delayed ICH, one was on clopidogrel alone and the other two were on both clopidogrel and aspirin. When comparing by antiplatelet groups, patients on aspirin alone had a higher rate of acute ICH compared with the P2Y12 agents alone (48% vs 30%; 18% difference, 95% CI 4% to 33%; $p=0.016$; OR 2.18, 95% CI 1.15 to 4.13). There was no significant difference in rate of delayed ICH when comparing these groups (table 3).

When comparing patients on single antiplatelet therapy (aspirin or a P2Y12 inhibitor alone) with dual antiplatelet therapy (aspirin and a P2Y12 inhibitor), there were no significant differences in the rates of acute or delayed ICH (table 3).

Of patients with acute ICH across all antiplatelet groups, most had either subdural or subarachnoid hemorrhages (table 4). Of the 191 patients with no initial ICH, 98 had a routine repeat head CT. No patients with an initial head CT negative for ICH had repeat imaging due to clinical change. All three patients with delayed ICH had subdural hemorrhages that were identified by routine repeat CT imaging (table 5). One patient with acute ICH did not have indication for repeat CT imaging documented. Neurosurgical intervention was required for nine patients with acute ICH. No patients with delayed ICH required intervention. No study patients died.

Patients with delayed ICH all sustained falls, had signs of head trauma and were older than 90 years. When compared with no ICH, patients with delayed ICH were older with mean age of 94 vs 74 years ($p=0.009$), had a higher injury severity score (15.7 vs 4.4, $p<0.001$) and trended towards a lower platelet count (141 vs 216, $p=0.053$). No other variables predicted development of delayed ICH, including presenting symptoms, GCS, initial vital signs or INR.

DISCUSSION

In our study of 327 patients taking antiplatelet medications who sustained blunt head trauma, 40.7% were found to have an acute ICH. Nine required neurosurgical intervention and

none died during the hospitalization. Only three patients (0.9%) with an initial negative head CT scan were found to have a delayed ICH on repeat head CT. These delayed ICH were all found on routine repeat head CT imaging, and not due to any clinical change. None of these patients required neurosurgical intervention and none died during the hospitalization.

As mounting evidence from the 1960s to the 1980s show low-dose aspirin to be an effective means of reducing cardiovascular risk, its use in adults has become widespread. An epidemiological analysis showed that nearly 30% of all adults aged 40 years or older in the USA self-report taking low-dose aspirin for primary or secondary cardiovascular disease (CVD) prevention, and the prevalence of aspirin use only increases with age.²¹ The US Preventive Services Task Force currently recommends low-dose aspirin use for primary CVD prevention and colorectal cancer.²² Despite the known association between antiplatelet agents and increased bleeding risk in general, few studies have looked directly at the odds of acute or delayed traumatic ICH in patients taking these medications. Among these studies, rates of ICH in patients on antiplatelet medications presenting with blunt head trauma ranged from 3.6% to 67.3%.⁵

Although our study included all adult patients, our patient population had an average age of 76 years. Our high rate of ICH may be related to this factor. Prior research has shown that the geriatric population suffers from a higher rate of acute ICH. As the brain ages, there is volume loss, making bridging vein more vulnerable to bleeding along with decreased elasticity.²³ The aging US population has led to increased utilization of antiplatelet medications, likely contributing to the increased incidence of bleeds.²⁴

The reported incidence of delayed ICH in the antiplatelet patient population is 0%–4%.^{10–16} These studies differed in their methodology and quality, several were retrospective, others were from trauma registries and some included patients on vitamin K antagonists. Our study found that the rate of delayed ICH is 0.9%, on the lower end of the previously reported range. This suggests that admitting all patients taking antiplatelet medications with blunt head trauma and a negative initial head CT may

Table 3 Comparison of antiplatelet categories by head CT result for intracranial hemorrhage (ICH)

	No ICH	Acute ICH	Delayed ICH
Aspirin vs P2Y12	52% vs 68% –17%* (95% CI –31 to –2) $P=0.028$ OR 0.50 (95% CI 0.26 to 0.93)	48% vs 30% 18% (95% CI 4 to 33) $P=0.016$ OR 2.18 (95% CI 1.15 to 4.13)	0% vs 1.6% –1.6% (95% CI –4.7 to 1.5) $P=0.153$
Aspirin vs aspirin+P2Y12	52% vs 60% –9%* (95% CI –21 to 3) $P=0.153$ OR 0.70 (95% CI 0.43 to 1.14)	48% vs 38% 10% (95% CI –2 to 22) $P=0.094$ OR 1.52 (95% CI 0.93 to 2.48)	0% vs 1.5% –1.5% (95% CI –3.5 to 0.6) $P=0.168$
P2Y12 vs aspirin+P2Y12	68% vs 60% 8% (95% CI –6 to 22) $P=0.280$ OR 1.42 (95% CI 0.75 to 2.66)	30% vs 38% –8% (95% CI –22 to 6) $P=0.269$ OR 0.70 (95% CI 0.37 to 1.32)	1.6% vs 1.5% 0.1% (95% CI –3.5 to 3.8) $P=0.950$ OR 1.08 (95% CI 0.10 to 12.14)

*Correct due to rounding.

Table 4 Acute intracranial hemorrhage type by antiplatelet category, no. (%)

	Aspirin (n=62)	P2Y12 (n=19)	Aspirin+P2Y12 (n=52)
EDH	0 (0%)	1 (5%)	0 (0%)
SDH	19 (31%)	8 (42%)	31 (60%)
SAH	19 (31%)	4 (21%)	14 (27%)
IPH	6 (10%)	2 (11%)	3 (6%)
SDH+SAH	12 (19%)	3 (16%)	2 (4%)
SDH+IPH	1 (2%)	0 (0%)	0 (0%)
SAH+IPH	3 (5%)	1 (5%)	1 (2%)
SDH+SAH+IPH	2 (3%)	0 (0%)	1 (2%)

EDH, epidural hemorrhage; IPH, intraparenchymal hemorrhage; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage.

not be warranted. However, it may be prudent to admit nonagenarians, with higher injury severity scores, and lower platelet counts.

While the association between anticoagulation and increased risk of traumatic ICH is well established in the literature, there are fewer studies quantifying the incidence of traumatic ICH in patients taking antiplatelet medications. Several studies have reported no increased risk for bleeding, mortality or neurosurgical interventions with antiplatelet medications.^{25–28} However, a meta-analysis with over 20 000 patients showed a pooled OR of 1.87 (95% CI 1.27 to 2.74) with increased odds of ICH for patients on all antiplatelet therapy, although not for patients on aspirin alone.⁵ This conflicting evidence highlights the need for more prospective trials on the effects of antiplatelet medications on ICH and the risk to patients. This information would be valuable as clinicians weigh the risks and benefits of antiplatelet medications, especially in patients who are older with risk factors for falls.

Our results should be interpreted in the context of several limitations. First, as patients were enrolled retrospectively into this study from trauma registries, there likely were patients with head injuries who presented to the ED and were not seen by the trauma services. Second, antiplatelet use by patients was based on documentation in the medical records. Analysis with platelet function testing was not routinely performed, so it is unclear if patients were compliant with their antiplatelet medications. Third, the protocol for repeat head CT imaging was not universally applied. Many patients did not receive a repeat head CT, limiting the ability to quantify the rate of minor subclinical delayed ICH. Fourth, no follow-up was performed after the hospitalization. Some patients may have had an acute ICH and were discharged to hospice, and others may have had a delayed ICH that occurred after hospital discharge. Although most delayed cases of ICH occur within the first 24 hours, some do occur up to 10 days after the initial head injury which would lead to under reporting of these cases. Finally, this study

Table 5 Head CT result for intracranial hemorrhage (ICH) by reason for repeat head CT, no. (%)

	Routine	Clinical change	Not repeated	Total
No ICH	98 (51%)	0 (0%)	93 (49%)	191
Acute ICH	122 (92%)	5 (4%)	5 (4%)	132*
Delayed ICH	3 (100%)	0 (0%)		3
Total	223 (68%)	5 (2%)	98 (30%)	326

*Missing indication for repeat head CT on one patient with acute ICH.

was not designed to have a control group with patients not on antiplatelets. Therefore, we could only perform comparisons between antiplatelet groups, rather than examine the effects of the individual agents on rates of ICH. Additionally, patients on antiplatelet agents may be more likely to receive a head CT compared with those who are not, which may lead to an increase in the ICH rate of limited clinical significance.

The findings of our study suggest that antiplatelet use increases the odds for the development of acute ICH after head trauma, with low risk for delayed ICH. Therefore, we recommend that all patients on antiplatelets with head injury have immediate head CT imaging. These results are generalizable to patients on the trauma service with head injury, who are potentially sicker than the overall emergency department population. However, even in these patients, we do not recommend routine admission for observation or repeat head CT imaging on asymptomatic patients with negative initial head CT imaging. These patients can safely be discharged home with outpatient follow-up and strict return precautions.

Our research adds to the previously conflicting evidence, demonstrating the need for additional investigation in this area. If future prospective studies confirm the increased rate of ICH in patients on antiplatelet medications with head injury, trauma activation guidelines may need to be amended to include these patients. In addition, identifying risk factors for ICH in patients taking antiplatelet agents may better inform physicians regarding the risk-benefit analysis in deciding on antiplatelet therapy.

Contributors Study conception and design: SMA, JJS, RDS, MJH, LMC, PGH. Data acquisition: BAM, NQT. Data analysis and interpretation: SMA, MJH, SWG. Initial draft: SMA, BAM, RDS, LMC, NQT. Critical revisions: SMA, BAM, JJS, RDS, LMC, SWG, PGH.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This research study was approved by the MetroWest Institutional Review Board, MWMC IRB #00002845, and the Michigan State University human subjects research committee, study #1296, in addition to Sparrow Health System via collaborative agreement with Michigan State University.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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