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Risk of unfavorable long-term outcome in older adults with traumatic intracranial hemorrhage and anticoagulant or antiplatelet use

Daniel K. Nishijima, MD, MAS¹, Kiarash Shahlaie, MD, PhD², Korak Sarkar, MD³, Nancy Rudisill, RN, MSN², and James F. Holmes, MD, MPH¹

¹Department of Emergency Medicine, UC Davis School of Medicine, Sacramento, CA

²Department of Neurological Surgery, UC Davis School of Medicine, Sacramento, CA

³Department of Neurology, UC Davis School of Medicine, Sacramento, CA

Abstract

Study Objective—To compare neurological outcomes at six months in older patients with pre-injury warfarin or clopidogrel use and mild traumatic intracranial hemorrhage (tICH) to those without prior use of these medications.

Methods—This was a retrospective study conducted at a Level 1 trauma center from April 2009 to July 2010. Patients over 55 years of age with isolated mild head injury (Glasgow Coma Scale Score [GCS] 13 to 15 and Abbreviated Injury Score < 3 in non-head body region) were included. Demographic, clinical, and outcome data were abstracted from an existing TBI database. The primary endpoint of unfavorable extended Glasgow Outcome Score (GOS-E) at 6 months was compared between patients with and without pre-injury warfarin or clopidogrel use.

Results—Seventy-seven eligible patients were identified; 27 (35%) with pre-injury warfarin or clopidogrel use and 50 (65%) without. Baseline characteristics (gender, GCS score, Injury Severity Score, computed tomography score, and in-hospital mortality) were similar between cohorts although the pre-injury warfarin or clopidogrel cohort was older than the control group ($p < .05$). Patients in the pre-injury warfarin or clopidogrel cohort were more likely to have an unfavorable outcome (16/27; 59.3%, 95% confidence interval [CI] 40.7–77.8%) as compared to those without (18/50; 36.0%, 95% CI 22.7–49.3%), $p = .05$.

Conclusion—Older adults with pre-injury warfarin or clopidogrel use and mild traumatic intracranial hemorrhage may be at an increased risk for unfavorable long-term neurological outcomes compared to similar patients without pre-injury use of these medications.

Keywords

brain injuries; platelet aggregation inhibitors; anticoagulation; Glasgow Outcome Scale; aged

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Corresponding Author: Daniel Nishijima, MD, MAS, University of California, Davis Medical Center, 4150 V. St. PSSB, 2100, Sacramento, CA 95817, TEL (916) 734.1376, FAX (916) 734.7950, daniel.nishijima@ucdmc.ucdavis.edu.

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INTRODUCTION

With an aging population, older adults with pre-injury anticoagulant or antiplatelet use represent an increasing proportion of patients with head injury evaluated in the emergency department (ED).¹ These patients often have relatively minor mechanisms of injury and benign clinical presentations yet have significant intracranial injuries.² In the presence of traumatic intracranial hemorrhage (tICH), the effects of the anticoagulant or antiplatelet medications increase the risk for hemorrhage progression and bleeding complications during neurosurgery.^{3–5} Prior studies demonstrate an increased risk for in-hospital mortality in these patients with tICH compared to patients without pre-injury anticoagulant or antiplatelet use.^{6–8} However, the impact of pre-injury anticoagulant or antiplatelet use on long-term functional outcomes has not been evaluated.

The objective of this study was to compare long-term functional outcomes in older adults with mild tICH and pre-injury warfarin or clopidogrel use to a similar cohort of patients without pre-injury use of these medications. We hypothesized that the pre-injury warfarin or clopidogrel cohort will have a significantly higher proportion of unfavorable functional outcome at six months compared to the control cohort.

PATIENTS AND METHODS

Study Design and Setting

This was a retrospective, registry study conducted at a Level 1 trauma center. The study was approved by the Institutional Review Board at the study site.

Selection of Participants

The population included older adults (age 55 years and older) with tICH (defined as intracranial hemorrhage or contusion on cranial computed tomography [CT]), mild TBI (Glasgow Coma Scale [GCS] score 13 to 15), and with an isolated head injury (Abbreviated Injury Score [AIS] < 3 in all non-head body regions). Patients meeting these inclusion criteria were divided into two cohorts: 1) patients with pre-injury warfarin or clopidogrel use, and 2) patients without pre-injury use of these medications.

An existing, institutional traumatic brain injury (TBI) database was searched from April 2009 to July 2010 for patients aged 55 years and older and with the presence of tICH on initial cranial CT imaging. Patients included in the TBI database met at least one of the following criteria that prompted neurosurgical consultation: (1) suspected TBI due to clinical history, clinical symptoms, or signs of neurological deficits on physical examination, or (2) abnormal CT scan findings after trauma, including any tICH (defined as subarachnoid hemorrhage, epidural hematoma, subdural hematoma, intraventricular hemorrhage, intraparenchymal hemorrhage/contusion, or diffuse axonal injury). Data points within the TBI database were prospectively collected by trained research personnel using a standardized data collection form. Patients or their surrogates receive a structured interview by trained research personnel at six months to assess global functioning using the extended Glasgow Outcome Scale (GOS-E).

Methods and Measurements

Variables abstracted from the TBI database included age, gender, post-resuscitation GCS score, medication use, indication for medication use, Injury Severity Score (ISS), AIS for head, cranial CT findings, Marshall CT classification score, mortality, and GOS-E score at six months. Medication use included the presence of warfarin or clopidogrel use seven days

prior to head injury. The Marshall CT classification score is a validated descriptive scale for findings on cranial CT scan.⁹

Outcomes

The primary outcome measure was an unfavorable GOS-E score at 6 months. The GOS-E is the most commonly used measure of global functional performance after TBI and has been recommended as the gold standard outcome measure for TBI studies.^{10,11} It has demonstrated excellent inter-rater reliability and content validity.¹² It uses an eight category scale which is typically dichotomized into favorable (score 5–8) and unfavorable (scores 1–4) outcomes to facilitate interpretation (Table 1).¹³

Analysis

Data formatting and recoding of variables were conducted using STATA 11.0 statistical software (STATA Corp, College Station, TX). We described the study population using descriptive statistics. Non-normal interval data were reported with medians and interquartile ranges (IQRs). Proportions were presented with 95% confidence intervals. We compared patient characteristics between cohorts with the Mann-Whitney test for non-normal interval data and chi-square test for categorical data. We analyzed the primary outcome with the chi-square test.

RESULTS

A total of 153 patients aged 55 years and older and with tICH were identified in the TBI database from April 2009 to July 2010; 77 patients met inclusion criteria, 27 patients in the pre-injury warfarin or clopidogrel cohort and 50 patients in the control cohort (Figure). The primary indication for warfarin use was atrial fibrillation (11/15 patients, 73%) and the primary indication for clopidogrel use was coronary artery disease (10/12 patients, 83%). The most common cranial CT findings were subdural hematoma (42 patients, 56%), subarachnoid hemorrhage (31 patients, 41%), and intraparenchymal hematoma/contusion (23 patients, 31%). Patients in both cohorts were similar with respect to gender, GCS score, ISS, AIS for head, Marshall CT classification score, and in-hospital mortality (Table 2). Patients in the pre-injury warfarin or clopidogrel group were older compared to the control cohort ($p=.04$).

Assessing the primary outcome of unfavorable GOS-E at 6 months, there was a higher proportion of patients in the pre-injury warfarin or clopidogrel cohort (16/27 patients; 59%, 95% CI 41–78%) with an unfavorable outcome compared to the control cohort (18/50 patients; 36%, 95% CI 23–49%), $p=.05$. In addition, 7/27 patients (26%, 95% CI 11–46%) in the pre-injury warfarin or clopidogrel cohort were dead at 6 months compared to 6/50 patients (12%; 95% CI 5–24%) in the control cohort (Table 3). Only 4 patients (15%, 95% CI 4–34%) in the pre-injury warfarin or clopidogrel cohort had a GOS-E of 8 (best functional outcome) at 6 months compared to 17 patients in the control cohort (34%, 95% CI 21–49%).

DISCUSSION

The results of our study suggest that older adults with pre-injury warfarin or clopidogrel use and mild traumatic intracranial hemorrhage may be at increased risk for unfavorable long-term neurological outcomes compared to similar patients without pre-injury use of these medications. To our knowledge, this is the first study to evaluate the effect of pre-injury anticoagulant or antiplatelet use on longer-term outcomes in older adults with TBI.

Both cohorts demonstrated a high proportion of patients with unfavorable GOS-E at 6 months (59% for the pre-injury anticoagulant or antiplatelet cohort and 36% for the control cohort). This is consistent with prior literature demonstrating overall poor long-term functional outcomes in older patients with TBI, particularly compared to younger patients with a similar severity of injury.^{14,15} The worse outcome in those with pre-injury anticoagulant or antiplatelet use, however, is a novel contribution to the TBI literature.

The reason behind the higher proportion of unfavorable outcomes in the pre-injury anticoagulant or antiplatelet cohort is unclear. It is unknown whether pre-injury use of anticoagulants led to more significant injuries and thus poorer outcomes, or whether pre-injury use of these medications was a marker for older patients with more pre-morbid conditions and thus at a higher risk for poor outcomes after TBI. Since patients in the pre-injury anticoagulant or antiplatelet cohort were older than those in the control cohort, age may be a potential confounder. It is likely that the effect of age on long-term neurological outcomes is multi-factorial. From a pathophysiological standpoint, mechanisms of cerebral compensation, plasticity, and cerebral re-organization of the brain are thought to be less effective with older patients.¹⁴ In addition, older adults have pre-morbid physical and cognitive conditions that increase their risk for poor functional outcomes and increase the difficulty in making the required adjustments after TBI.¹⁶

Our results should be interpreted in the context of several limitations. This study was retrospective and subject to the limitations of the chart review. While both cohorts were similar in gender, severity of injury, and cranial CT prognostic scores, there are a number of unmeasured variables such as comorbidity, mechanism of injury, and concomitant medications that may account for the observed differences in outcome between cohorts. Similarly, we did not examine reasons behind unfavorable outcomes and thus it is difficult to ascertain these outcomes were attributed to TBI. In addition, we only evaluated patients with pre-injury warfarin or clopidogrel use. Inclusion of other anticoagulant and antiplatelet medications such as dabigatran or aspirin may also alter the results of the study. The small sample size and number of outcomes resulted in large confidence intervals and prevented the use of regression analysis to adjust for variables.¹⁷

In conclusion, older adults with pre-injury warfarin or clopidogrel use and mild traumatic intracranial hemorrhage may be at an increased risk for unfavorable long-term neurological outcomes compared to similar patients without pre-injury use of these medications. Future work with larger study populations will help to determine if this risk is attributed to pre-injury warfarin or clopidogrel use or other factors.

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Figure 1.

Figure Flow of Patients in the Study

Abbreviations: tICH, traumatic intracranial hemorrhage; GOS-E, Glasgow Outcome Score Extended; AC/AP, pre-injury anticoagulant or antiplatelet

Table 1

Extended Glasgow Outcome Scale (GOS-E)

GOS-E score	Description	Dichotomization
1	Dead	Unfavorable
2	Vegetative state	Unfavorable
3	Lower severe disability	Unfavorable
4	Upper severe disability	Unfavorable
5	Lower moderate disability	Favorable
6	Upper moderate disability	Favorable
7	Lower good recovery	Favorable
8	Upper good recovery	Favorable

Table 2

Characteristics of Included Patients

Patient Characteristic	AC/AP cohort, n=27	Control cohort, n=50
	(IQR or 95% CI)	
Age, median ^a	80 (74–88)	71 (63–86)
Male, n, %	20, 52% (32–71%)	40, 40% (26–55%)
Initial post-resuscitation GCS score	15 (15–15)	15 (15–15)
ISS, median	16 (16–16)	16 (9–16)
AIS head, median (median)	4 (4–4)	4 (3–4)
Marshall CT classification, median ^b	2 (2–3)	2 (2–2)
In-hospital mortality, n, %	1, 4% (0–19%)	1, 2% (0–11%)

Abbreviations: GCS, Glasgow Coma Scale; ISS, injury severity score; AIS, abbreviated injury score; CT, computed tomography; AC/AP, anticoagulant or antiplatelet

^a –p value less than .05

^b –descriptive cranial computed tomography score ranging from 1 (no visible injury on CT scan) to 4 (presence of midline shift greater than 5 mm)

Table 3

Extended Glasgow Outcome Scale (GOS-E) at 6 months

GOS-E at 6 months	AC/AP cohort (n= 27), n (%)	Control cohort (n=50), n (%)
1	7 (26)	6 (12)
2	0 (0)	0 (0)
3	5 (19)	10 (20)
4	4 (15)	2 (4)
5	0 (0)	4 (8)
6	1 (4)	2 (4)
7	6 (22)	9 (18)
8	4 (15)	17 (34)

Abbreviations: AC/AP, anticoagulant or antiplatelet