Original Article

Bull Emerg Trauma 2017;5(2):110-115.

Bulletin of Emergency And Trauma

Effects of Pre-Injury Anti-Platelet Agents on Short-Term Outcome of Patients with Mild Traumatic Brain Injury: A Cohort Study

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Received: October 10, 2016
Revised: December 15, 2016
Accepted: January 24, 2017

ABSTRACT

Objective: To determine the effects of pre-injury consumption of anti-platelet agents on the 30-day outcomes of patients with mild traumatic brain injury (TBI).
Methods: This prospective cohort study was conducted at three general hospitals in Tehran, Iran between July 2013 and July 2014. The study population included all patients with mild TBI aged over 18 years that medicated with aspirin or clopidogrel before occurring trauma. Within hospitalization, all patients were assessed with respect to in-hospital conditions especially complications and adverse events. After discharge, the individuals were followed for 30 days by telephone to assess mortality and disability using the Glasgow outcome scale (GOS).
Results: Of 1140 patients with mild TBI, only 135 had previously received aspirin and/or clopidogrel. The mean age was dramatically higher in those who were taking aspirin or clopidogrel (p<0.001). The patients with previously use of anti-platelets were more transferred by ambulance when compared to another group (p=0.006). The patients on anti-platelets had significantly lower GCS on admission when compared to others (p<0.001). Length of hospitalization was significantly longer in those receiving anti-platelets (p=0.003). In follow-up, 30-day mortality and disability was revealed in 2.8% of patients that received only aspirin and 7.5% in aspirin with clopidogrel and in 1.6 % of those who did not receive drugs without any significant difference between aspirin and control group (p=0.208) and significant difference in aspirin with clopidogrel group (p<0.001).
Conclusion: The premedication by anti-platelets (aspirin and/or clopidogrel) in patients with mild TBI leads to prolonged hospital stay, and increase rate of disability. Age and on admission GCS are the independent risk factors for predicting the outcome in patients with mild TBI receiving anti-platelet agents.

Keywords: Mild Traumatic Brain Injury (TBI); Outcome; Aspirin; Clopidogrel.

Please cite this paper as:
Farsi D, Karimi P, Mofidi M, Mahshidfar B, Rezai M, Hafezimoghadam P, Abbasi S. Effects of Pre-Injury Anti-Platelet Agents on Short-Term Outcome of Patients with Mild Traumatic Brain Injury: A Cohort Study. *Bull Emerg Trauma*. 2017;5(2):110-115.

Introduction

Development of science and technology results in increased percentage of elderly people as well as increased life expectancy. In line with increasing age, the prevalence of some disorders such as cardiovascular disorder [1]. Nowadays, cardiovascular diseases are the most common causes

of mortality and disability especially among old population [2]. Thus, more government's focus is on the prevention of cardiovascular complications in old population particularly by administrating antiplatelet and antithrombotic drugs [3]. Some recent reports showed that about 1-1.5% of American people use warfarin that most of them aged over 65 years [4]. Besides, traumatic events especially head trauma have been identified as one of the most etiologies for mortality and disabilities in the elderly [5]. In the United States, about 500,000 brain injuries occur annually that 80% of them cause from mild traumatic trauma leading severe brain abnormalities in 2% to 3% of patients [6]. There is now a serious disagreement about the use of preventive medications of cardiovascular events such as aspirin and clopidogrel especially in old individuals who experienced head trauma. Some studies could reveal that the use of these drugs may increase mortality and morbidity in patients who experienced head trauma [7, 8]. Although anticoagulation by inhibiting platelets or coagulation cascades can effectively improve outcomes in patients at risk for acute coronary syndromes, cerebrovascular accidents, or embolic events, these benefits come at a price, though, of increased tendency toward bleeding, and impaired ability to mount a coagulation response at sites of hemorrhage [9]. This is particularly dangerous for victims of head trauma, who may harbor small but steadily growing intracranial hematomas in the absence of outward signs [10]. Some recent articles address this problem, and propose a protocol for managing mild traumatic brain injury in anticoagulated patients while minimizing risk of missed intracranial injury [11, 12]). In fact, patients receiving warfarin, aspirin, or clopidogrel are considered at increased risk for traumatic intracranial hemorrhage after blunt head trauma, even following mild trauma. On the other hand, some authors emphasized high mortality rate associated with aspirin or clopidogrel or both in elderly patients who have mild TBI may even resulting in intracranial hemorrhage [13, 14].

The present study addressed the 30-day outcome of anticoagulated patients with aspirin or clopidogrel who experienced mild traumatic brain injury. The results of this study can propose a protocol for managing mild traumatic brain injury in anticoagulated patients while minimizing risk of missed intracranial injury.

Materials and Methods

Study Population

This prospective cohort study was conducted at Hazrat-e-Rasoul-e-Akram, Haft-e-Tir, and Firouzgar academic Hospitals in Tehran, Iran between July 2013 and July 2014. The study population included adult patients (>18 years of age) with mild TBI defined as TBI with Glasgow Coma Scale (GCS) score of 14 or 15, that medicated with aspirin or clopidogrel before occurring trauma. Inclusion criteria were as follows: patients with TBI with GCS 15 who need to be scanned, all with TBI who have had GCS 14, taking ASA 80 mg per day and/or clopidogrel 75mg per day in last week before trauma and more than 18 years old. Exclusion criteria were patients with TBI who have had GCS <14, patients with thrombocytopenia and/or bleeding diathesis such as hemophilia, taking anticoagulants such as warfarin, heparin or low molecular weight heparins. The study protocol was approved by the institutional review board (IRB) and the medical ethics committee of Iran University of Medical Sciences and all the patients or their gurdians provided their informed written consents.

Study Protocol

All patients referred initially to emergency departments because of direct head trauma, falling from height, falling at par, and accidents leading the GCS of 14 to 15. On admission, the patients or their caregivers were interviewed with regard to baseline characteristics including demographics, medical history, oral medications, mechanism of trauma, and also route and dose of aspirin or clopidogrel used. In this regard, the patients were categorized in one of the two groups including aspirin and/or clopidogrel users as the case group and non-users of these two drugs as the control group. After completing baseline parameters, the patients were treated according to the Advanced Trauma Life Support course (ATLS) guideline. Within hospitalization, all patients were assessed with respect to in-hospital conditions especially complications and adverse events and all of them had brain CT before discharge. After discharge, the individuals were followed for 30 days by phone to assess mortality and morbidity. None of the patients underwent CT scan after discharge. The study endpoint was to determine 30-day outcome. The researchers used the Glasgow Outcome Scale (GOS) to score the patients' disabilities defined as the presence of at least one of these events: death occurred within 30 days of discharge from hospital because of trauma-related complications, vegetative status with minimal response to stimulus, the presence of consciousness with severe disability, moderate disability but with ability to do daily activities and complete or good recovery. intracranial hemorrhage, or focal neurologic defects confirmed by examination or para-clinic methods.

Statistical Analysis

Sample size was calculated using the following formula and considering Z_1-$\alpha/_2$=1.96, 1- β=0.2, power=0.8)

$$n = \frac{(Z_1 - \alpha/2 + Z_1 - \beta)^2 pq}{(P1 - P2)^2}$$

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5 were observed. Quantitative variables were also compared with t or Mann- Whitney U test. For the statistical analysis, the statistical software SPSS version 22.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results

Table 1 summarizes the baseline characteristics of the patients. Of 1140 patients with mild TBI, only 69 had previously received aspirin (6%) and 66 had received aspirin with clopidogrel (5.7%) (Figure 1). No difference was revealed between the two groups in terms of gender distribution (Men: 60.9% *vs.* 70.3%, p=0.329), however mean age was significantly higher in those who had history of receiving aspirin or clopidogrel (80.78±8.76 *vs.* 46.33±18.77 years, p<0.001). The patients with previously use of aspirin and/or clopidogrel were more transferred by ambulance (65.2% *vs.* 37.1%, p=0.006). As shown in Table 2, the mechanisms of mild TBI were significantly different between the

Table 1. Baseline characteristics of the patients 1140 patients with mild head trauma presenting to our emergency departments during the study period.

Variable	Value
Age (year)	47.02±19. 23
Gender n (%)	
Male	799 (70.1)
Female	341 (29.9)
Mechanism of trauma n (%)	
Motorcycle accident	131 (11.5)
Car accident	30 (2.63)
Pedestrian	797 (69.9)
Fall	114 (10)
Direct trauma	68 (5.97)

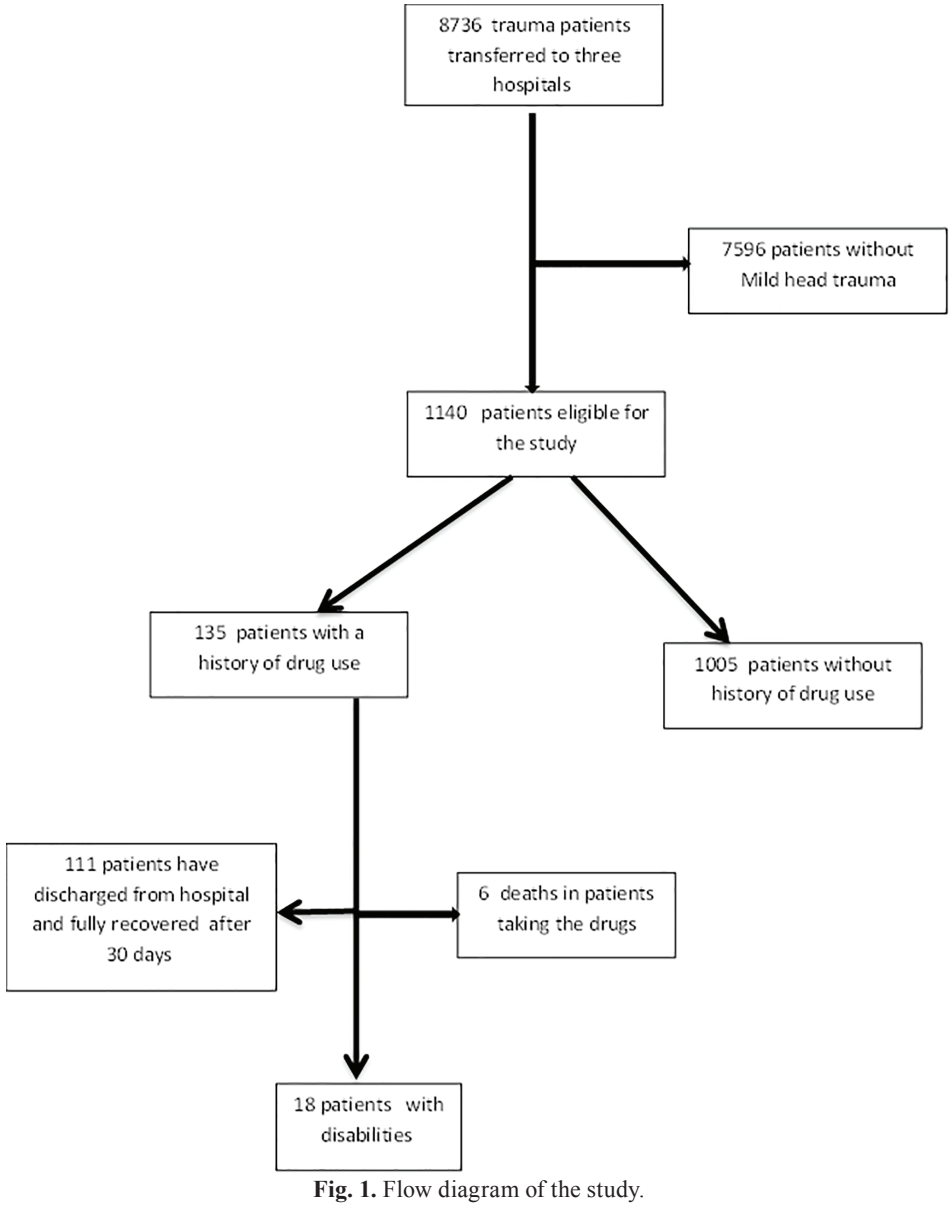

Fig. 1. Flow diagram of the study.

Table 2. Comparison of mechanisms of traumatic brain injury in two treatment groups

Mechanism	ASA/Clopidogrel (n=135) n (%)	Control (n=1005) n (%)	P value
Direct trauma to head	17 (12.6)	734 (73.03)	<0.001
Pedestrian-motor vehicle crashes	52 (38.51)	114 (11.34)	<0.001
Motorcycle-vehicle crashes	8 (5.92)	53 (5.27)	0.14
Vehicle-vehicle crashes	7 (5.1)	0 (0.0)	<0.001
Falling from height	45 (33.34)	46 (4.57)	<0.001
Dispute	5 (3.7)	58 (5.78)	0.31
Others	1 (0.74)	0 (0.0)	0.04

two groups. The pedestrian-motor vehicle crashes and falling from height were more found in those who received aspirin and/or clopidogrel, while the prominent mechanism in control group was direct trauma to head (p<0.001). The patients taking aspirin or clopidogrel had significantly lower GCS on admission compared to those who did not received medications (p<0.001). Simultaneous use of warfarin was more found in those who received aspirin and/or clopidogrel than in those who did not receive medications (21.7% *vs.* 2.2%, p<0.001). Regarding clinical manifestations on time of admission (Table 3), no difference was found between the two groups in prevalence of vomiting (p=0.351), unconsciousness (p=0.366), scalp injury (p=0.897), facial injury (p=0.123), otorrhagia (p=0.998), rhinorrhagia (p=0.160), rhinorrhea (p=0.999), and ocular ecchymosis (p=0.999). In the group received aspirin and/or clopidogrel, 82.6% were discharged, and 17.4% leaved the hospital against medical advice, while in another group, 98.6% were discharged, and 1.4% leaved the hospital against medical advice (p<0.001). Length of stay in emergency department was more than one day in 8.1% of those with history of receiving aspirin and/or clopidogrel, while only in 4.0% of patients in another group length of stay was more than one day (p=0.003).

In follow-up, 30-day disability was revealed in 2.8% of patients received only aspirin and 7.5% in aspirin with clopidogrel group and in 1.6 % of those who did not receive any medication. We did not find any significant difference between aspirin and control groups (p=0.208); but significant difference between aspirin with clopidogrel and control groups was determined (p<0.001). Also significant difference was seen between the groups received only aspirin and aspirin plus clopidogrel (p<0.001**)** The patients' outcome is summarized in Table 4. We determined that higher age and lower GCS was associated with poor outcome in patients consuming antiplatelet agents (p<0.001 and p=0.002 respectively). The patients receiving anti-platelets had worse outcome in comparison with others (p<0.001). In multivariate analysis, we found that higher age and taking anti-platelets were independently associated with worse outcome (Table 5).

Discussion

Because of controversial findings on the effects of pre-injury anticoagulation and Antiplatelet treatments on outcome of patients with head trauma

Table 3. Symptoms and signs of patients on admission in two groups

Signs and symptoms	Anti-platelet group (n=135) n (%)	Control group (n=1005) n (%)	P value
Vomiting	35 (25.92)	185 (18.4)	0.11
Unconsciousness	17 (12.6)	79 (7.86)	0.025
Scalp injury	71 (52.6)	354 (35.22)	0.08
Facial injury	12 (8.8)	239 (23.78)	<0.001
Otorrhagia	0 (0.0)	13 (1.3)	0.61
Rhinorrhea	0 (0.0)	108 (10.74)	<0.001
Ocular ecchymosis	0 (0.0)	27 (2.68)	0.32

Table 4. The relation between antiplatelet agents and outcome

Signs and symptoms	Anti-platelet group (n=135) n (%)	Control group (n=1005) n (%)	P value
30-day GOS			
Good Recovery (%)	120 (88.9%)	988 (98.3%)	<0.031
Moderate disability (%)	7 (5.2%)	14 (1.4%)	<0.001
Severe disability (%)	3 (2.2%)	2 (0.2%)	0.022
PVS (%)	0	0	1.000
Death (%)	5 (3.7%)	1 (0.1%)	<0.001

GOS: Glasgow outcome scale; PVS: Persistent vegetative state

Table 5. In logistic analysis, the age and taking antiplatelets were independent factors that predict worse outcome in mild TBI

Factor	OR	95% confidence Interval	P value
Age	7.1	4.06-10.1	<0.001
Antiplatelet medication	3.4	1.7-5	0.002

especially those with mild TBI, the current study aimed to compare 30-day outcome of these patients with those patients with no history of receiving these therapies. Among 1140 patients who were initially assessed, only 135 patients (11.8%) received pre-injury aspirin or clopidogrel and among those, only 66 patients received both medications. Despite prescription of these two drugs in our patients affected by mild TBI, administrating these drugs led to prolonged hospitalization and slightly higher 30-day disease-related disability. In fact, needing use of these drugs due to underlying morbidities such as cardiovascular disorders may result in increased risk for higher early complications and thus poorer outcome in patients who suffered mild TBI. Almost all studies on the effects of aspirin or clopidogrel on elderly traumatic brain injured patients showed inappropriate effects of these drugs on disease outcome. In a study by Wong *et al*., [15] patients on clopidogrel were more likely to die and be discharged to an inpatient long-term facility; however length of hospital stay and intensive care unit stay were not different from control. In Bonville *et al*. study [16], among 3436 trauma patients, 13.3% were taking anticoagulants that was not associated with increased mortality. Overall, in some studies, posttraumatic morbidity as hemorrhage was associated with a significantly increased mortality rate in patients on antiplatelet therapy when compared to controls [17-19]. In contrast, no increased risk of mortality was observed in all traumatic brain injury patients on antiplatelet therapy. Interestingly, it was suggested a high rate of patients with a mild to moderate head trauma in most studies. A study by Spektor and colleagues [20] revealed no higher incidence of posttraumatic hemorrhagic events in those who treated with low-dose aspirin. Since analysis was restricted to mild and moderate TBI, it is unclear whether these findings also apply to severe TBI. Jones and colleagues [21] showed that patients with pre-injury clopidogrel treatment had higher rates of neurosurgical interventions as well as more episodes of re-bleeding and a higher need of transfusion of blood products. Bachelani and colleagues [22] found that neither history of aspirin intake nor platelet inhibition was associated with an increased risk of progression of mortality or poor outcome. In contrast to these findings, Fabbri and colleagues [23] showed that pre-injury use of aspirin or even NSAIDs was associated with an increased risk of posttraumatic intracranial lesions in patients with mild TBI. The results of those studies are conflicting and do not allow a comprehensive characterization of antiplatelet agent effects on patients with mild TBI. In total, it seems that different factors may affect the conflicting results including small study sample sizes, nature of studies as retrospective with notable recall biases, or different considered follow-up time.

In this study, there are several limitations. First of all is the small sample size. The next one is comorbidity conditions such as cardiovascular and cerebrovascular diseases were not matched in our study, therefore, they could affect the morbidity, mortality and the study results.

In conclusion, the premedication by anti-platelets (aspirin and/or clopidogrel) in patients with mild TBI leads to prolonged hospital stay, and increase rate of disability. Age and on admission GCS are the independent risk factors for predicting the outcome in patients with mild TBI receiving anti-platelet agents.

Conflict of Interest: None declared.

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