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Retrospective Cohort Study: Open Access

Warfarin is Associated with Increased Intracranial Hemorrhage and Mortality in Patients with Ground Level Falls: A Retrospective Cohort Study

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Abstract

Background: Fall is the number one mechanism of injury for admissions to trauma centers across the US. The use of anticoagulation therapy has also increased significantly, particularly among the older population. We hypothesized that anticoagulation with warfarin increases the risk of intracranial hemorrhage (ICH) and death after a ground level fall.

Methods: A retrospective cohort of all patients admitted to a level 1 trauma center, between 2008 and 2011, after a ground level fall was identified. Warfarin use, ICH and in-hospital mortality were assessed from review of medical records. Exposure was defined as current warfarin use or an International Normalization Ratio (INR) ≥1.3. Age, gender, Glasgow Coma Scale (GCS), Injury Severity Score (ISS) and acute traumatic injuries identified on chest and extremity radiographs were evaluated. Univariate and multivariate logistic regression analyses were performed.

Results/Discussion: Of the 1,535 patients admitted for ground level falls, 135 (8.8%) were taking warfarin and 16.5% had INR ≥1.3. 725 (47.2%) patients met criteria for CT head and 7.6% had an ICH. In-hospital mortality was 2.75%. Warfarin was associated with higher incidence of ICH (Crude OR 2.28; 95% CI, 1.36-3.84) and mortality (Crude OR 2.80; 95% CI, 1.31-6.00). Similarly, INR ≥ 1.3 had significant association with ICH (OR 2.14; 95% CI, 1.40-3.28) and mortality (OR 3.88; 95% CI, 2.04-7.40). After controlling for age and gender in logistic regression model, warfarin use and INR ≥ 1.3 continued to be independent predictors of ICH with adjusted ORs of 2.02 (95% CI, 1.19-3.44) and 2.00 (95% CI, 1.30-3.09) respectively. Adjusted odds ratios of mortality with warfarin use and INR ≥ 1.3, after controlling for age, gender and ISS, were 2.65 (95% CI, 1.19-5.91) and 3.75 (95% CI, 1.89-7.42) respectively.

Conclusions: Warfarin use or elevated INR are associated with ICH and mortality after ground level falls.

Introduction

The use of anticoagulation therapy has increased significantly in the United States. One of the reasons for this is the increase in the proportion of the population who are elderly, and the high prevalence of atrial fibrillation in this patient population. Currently, atrial fibrillation affects approximately 2.2 million Americans [1]. The prevalence of atrial fibrillation increases with age, with more than 38% of patients older than 65 years of age being affected [2].

Similarly, the incidence of falls has increased over the past few years [3]. Fall is now the number one mechanism of injury for admissions to trauma centers in the United States [3-5]. This is of particular importance among the elderly because almost half of all falls occur in patients older than 65 years [6]. Furthermore, one out of three adults ages 65 and over sustain falls each year in the United States [7-9]. This represents an important cause of morbidity and mortality in this patient population. Ground level falls are particularly important for the elderly, because of the significant risk of mortality (3.4%) [10]. The presumption in the medical field is that some of these patients have such a high risk of falling that placing them on warfarin could increase their risk of intracranial hemorrhage [11]. The purpose of this study is to determine whether treatment with warfarin increases the risk of intracranial hemorrhage and mortality after a ground level fall. The objective of this study will be achieved by comparing the incidence of traumatic brain injury and mortality among two groups of patients who sustained ground level falls; those who report active warfarin treatment, and those who are not being treated with warfarin and presented to our American College of Surgeon's Verified Level 1 Trauma Center.

Methods

The University of Toledo Medical Center is an American College of Surgeons verified Level I trauma center and therefore maintains a database of all trauma related admissions to the hospital. A retrospective cohort of all patients admitted after sustaining a ground level fall between 2008 and 2011 was identified. The mechanism of injury was determined using ICD-9 Fall E-codes E885 (Fall on same level from slipping, tripping, or stumbling) and E886 (Fall on same level from collision, pushing, or shoving, by or with other person.). The data pertaining to exposure, outcome and associated factors was obtained from review of medical records and entered into a Microsoft Excel worksheet.

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Table 1: Demographics of the patient cohort

	WARFARIN	NO WARFARIN	P-VALUE
AGE	77 ± 18	69 ± 29	<0.001
MORTALITY	6.7% (9)	2.5% (32)	0.006
ICH	15% (20)	7% (93)	0.002
GENDER (Male)	36% (49)	38% (489)	0.723
GCS (15)	77% (36)	74% (432)	0.605
ISS	5 ± 5	5 ± 5	0.526
INR	2.2 ± 1.07	1.1 ± 0.14	<0.001
ABNORMAL CXR	3% (3)	3% (28)	0.948
LONG BONE FRACTURE	59% (31)	62% (314)	0.586

(ICH: Intracranial Hemorrhage, GCS: Glasgow Coma Scale, ISS: Injury Severity Score, INR: International Normalization Ratio, CXR: Chest Radiograph. Continuous variables are presented as median ± interquartile range, categorical variables as percent (number of patients)).

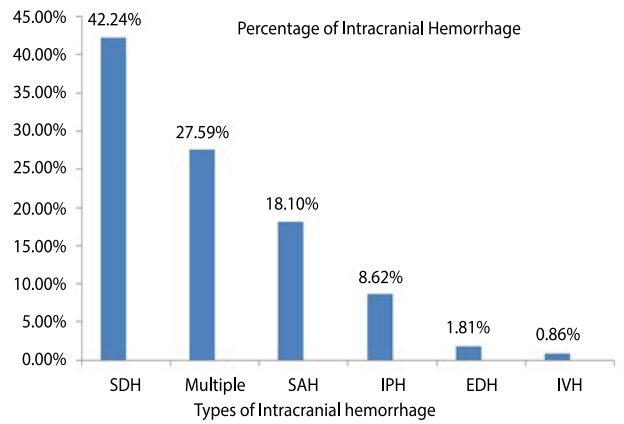

Figure 1: Category of Intracranial Hemorrhages in patients after level falls. (SDH: Subdural Hematoma, SAH: Subarachnoid Hemorrhage, IPH: Intraparenchymal Hemorrhage, EDH: Epidural Hematoma, IVH: Interventricular Hemorrhage)

Table 2: Univariate analysis of factors associated with intracranial hemorrhage

	ICH	NO ICH	P-VALUE
AGE	78 ± 20	70 ± 28	0.002
ISS	16 ± 8	4 ± 5	<0.001
INR	1.12 ± 0.53	1.07 ± 0.18	0.008
GCS (15)	51% (28)	77% (349)	<0.001
GENDER (Male)	50% (58)	36 (514)	0.004
WARFARIN	18% (20)	11% (60)	0.034
INR >1.3	32% (35)	18% (217)	<0.001

(ICH: Intracranial Hemorrhage, GCS: Glasgow Coma Scale, ISS: Injury Severity Score, INR: International Normalization Ratio. Continuous variables are presented as median ± interquartile range, categorical variables as percent (number of patients)).

The exposure assessed was anticoagulation which was primarily defined as history of active warfarin use. An International Normalization Ratio (INR) ≥ 1.3 on admission was also used as a marker for anticoagulation and used as an alternate measure of exposure. Outcomes assessed were intracranial hemorrhage (ICH), as determined by clinical assessment and Computerized Tomography (CT) of the head on admission, and in-hospital mortality determined from the discharge data. All patients with physical evidence of severe head injury underwent a CT scan of the head. Among patients with suspected minor head injury, the decision to perform the CT was based on the New Orleans Criteria and the Canadian Head CT rules [12,13]. Other potential confounders and risk factors measured were age, gender, Glasgow Coma Scale (GCS), Injury Severity Score (ISS) and acute traumatic injuries identified on chest and extremity radiographs. A review of patients' prescription home medications was performed to look for other anti-platelet and anticoagulant agents. Patients taking other anti-platelet or anticoagulant medication were included in the non-exposed group. The study was approved by the University of Toledo Institutional Review Board.

Table 3: Univariate analysis of factors associated with Mortality

	DEATH	NO DEATH	P-VALUE
AGE	81 ± 13	70 ± 28	<0.001
ISS	10 ± 8.5	5 ± 5	<0.001
INR	1.24 ± 0.72	1.07 ± 0.18	<0.001
GCS (15)	33% (7)	77% (374)	<0.001
ICH	42% (17)	7% (99)	<0.001
GENDER (Male)	62% (26)	37% (936)	<0.001
WARFARIN	22% (9)	9% (126)	0.006
INR >1.3	46% (18)	18% (234)	<0.001
ABNORMAL CXR	0% (0)	3% (32)	N/A
LONG BONE FRACTURE	71% (12)	62% (354)	0.456

(ICH: Intracranial Hemorrhage, GCS: Glasgow Coma Scale, ISS: Injury Severity Score, INR: International Normalization Ratio, CXR: Chest Radiograph. Continuous variables are presented as median ± interquartile range, categorical variables as percent (number of patients)).

Statistical analysis was performed using the SAS 9.2 (SAS Institute Inc, Cary, NC) software. Shapiro-Wilk Test was used to check for normality of distribution of continuous variables. Student's t-test and Wilcoxon Rank-Sum test were used for comparing normally distributed and non-normally distributed variables between the exposure groups respectively. Normally distributed data is presented as mean with standard deviation, non-normally distributed data as median with inter-quartile range. Categorical variables were compared using the chi-square test. Significance was set at p-value of less than 0.05. Univariate analysis of factors associated with the two outcomes was also performed using statistical methods outlined above. Crude odds ratios (OR) are presented with the 95% confidence interval (CI). These were obtained from 2x2 tables between the exposure variables (warfarin exposure, INR ≥ 1.3) and outcome variables (mortality, ICH). Potential causative and confounding variables that were found to have significant association with the outcomes were then entered into a logistic regression model. We also controlled for variables which were found to have significantly different distribution between the exposure groups. Non-normally distributed independent variables were recorded into categorical variables for purpose of regression analysis. Missing data was not replaced. Adjusted ORs with accompanying 95% CI are presented.

Results

Between January 2008 and December 2011, a total of 5,223 patients were admitted to the University of Toledo Medical Center for acute traumatic injuries. Of these, 1,535 consecutive patients sustaining ground level falls formed our study cohort. One hundred and thirty-five (8.8%) patients reported active warfarin use. In addition, 321 (21%) patients were on some form of antiplatelet therapy (aspirin, clopidogrel or both). On admission, 254 (17%) patients were found to have an INR ≥ 1.3. The demographics of the patients is presented in table 1. Patients taking warfarin were older and had higher INR values. No significant difference was found in gender, GCS, ISS, acute injury on chest radiograph or acute long bone injury.

Computerized Tomography of the head was performed in 725 (47.2%) patients. Intracranial hemorrhage was found in 116 (8%) patients. The most common type of ICH was subdural hematoma (42.2%), followed by multiple hemorrhages (27.6%), subarachnoid hemorrhage (18.1%), intraparenchymal hemorrhage (8.6%), epidural hematoma (1.8%) and interventricular hemorrhage (0.9%) (Figure 1). Univariate analysis of factors associated with ICH is presented in table 2. Patients who sustained ICH were more likely to be older, male and have a higher ISS. They were also less likely to have a normal GCS on presentation. Patients found to have ICH sustained 15% mortality compared to 2% among those without ICH.

The overall mortality in our cohort was 2.75% with 42 in-hospital deaths. Table 3 represents the univariate analysis of factors associated with mortality. Patients who died were more likely to be older, male and have a higher ISS. They were also less likely to have a normal GCS on presentation. None of the patients who died had an acute injury on chest radiograph. There was no significant difference in incidence of long bone injuries between the two groups.

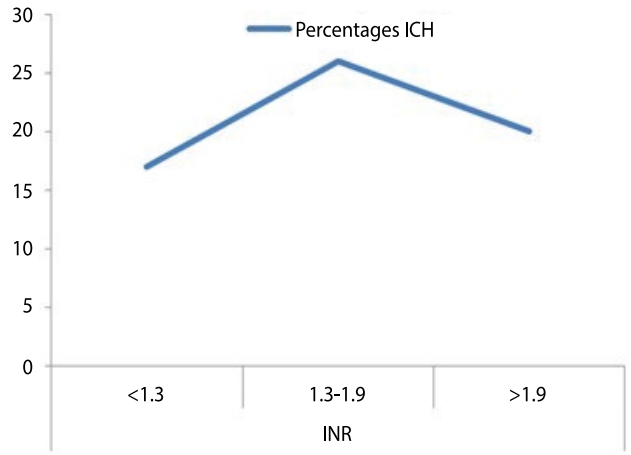

Figure 2: The percentage of intracranial hemorrhage (ICH) by level of therapeutic INR

On univariate analysis, patients using warfarin were found to have 15.0% incidence of ICH and 6.7% mortality compared to 7.3% incidence of ICH and 2.5% mortality among patients not taking warfarin ($p<0.01$) (Table 1). Warfarin use was associated with a higher incidence of ICH (Crude OR 2.28, 95% CI 1.36-3.84) and mortality (Crude OR 2.80, 95% CI 1.31-6.00). Similarly, those patients with an INR ≥ 1.3 sustained 14% incidence of ICH and 7% mortality compared to 7% incidence of ICH and 2% mortality among patients with a lower INR ($p<0.01$). INR ≥1.3 had a statistically significant association with ICH (Crude OR 2.14, 95% CI 1.40-3.28) and mortality (Crude OR 3.88, 95% CI 2.04-7.40).

Logistic regression model for ICH was created with age (more than 65 years) and male gender as potential independent variables, in addition to the exposure variables. Although ISS and GCS were found to be significant in univariate analysis, we did not include them in our final model because, by definition, both these scores are intrinsically dependent on head injury. Age more than 65 years, male gender, warfarin use and an INR ≥ 1.3 were found to be statistically significant independent predictors of ICH. Adjusted odds ratios of ICH with warfarin use and INR ≥1.3 were 2.02 (95% CI 1.19-3.44) and 2.00 (95% CI 1.30-3.09) respectively.

Logistic regression model for mortality included age (more than 65 years), male gender and ISS (greater than 5) as potential independent variables. Although GCS were found to be significant in univariate analysis, it was not included in the model. This is because the ISS is a more comprehensive trauma scoring system which already includes a score for head injury. Thus, including two scores for head injury would have led to significant collinearity, invalidating the regression analysis. Age more than 65 years, male gender, ISS greater than 5, warfarin use and an INR ≥ 1.3 were found to be statistically significant independent predictors of mortality. Adjusted odds ratios of mortality with warfain use and INR ≥ 1.3 were 2.65 (95% CI 1.19-5.91) and 3.75 (95% CI 1.89-7.42) respectively.

Discussion

The leading cause of injury related death among patients 65 years and older, is now due to falls [3]. The proportion of people aged 65 and older has been steadily increasing, and this trend is expected to continue. According to projections, by the year 2030, as the baby boomers come to age, approximately 1 out of every 5 US residents is expected to be 65 and older [14]. Furthermore, by the year 2050, the population "pyramid" that currently resembles a Christmas tree will begin to look progressively more like a rectangle due to an even larger increase in the elderly population [14]. Consequently, as the proportion of the elderly population increases, the incidence of falls would also increase. Similarly, the prevalence of atrial fibrillation is expected to increase by nearly 3-fold to approximately 12.1-15.9 million in the US by the year 2050 [15]. Since the majority of people on anticoagulation therapy are elderly, who also carry a high risk of falling, there could potentially be an increase in the incidence of ICH and mortality in this age group.

Of the 5,223 patients admitted during the study period to our level 1 trauma center, 1,535 patients sustained ground level falls. The average age of our patients was 67 years, which is an important finding because we found age to be a risk factor for sustaining an ICH. In fact, patients aged 65 or greater, were 1.93 times more likely to sustain an ICH and 4.7 times more likely to die after a fall from standing height. This is similar to previously cited data [16]. This is not only common, but poses a significant economic burden. On the order of 689,000 patients were admitted to the hospital for fall related injuries in 2011 [7]. In 2010, falls in the elderly population had an estimated $30 billion dollar cost [17,18]. A significant number of patients in our study population (7.6%) had sustained an intracranial hemorrhage after ground level falls, which was also consistent with other studies [12,19].

The most prevalent intracranial hemorrhage in our study was a subdural hematoma. As humans age, the brain begins to atrophy and therefore the bridging veins are stretched. This makes it more likely for the bridging veins to tear during a fall as the momentum of the brain provides a shearing force within the skull. One thing that is obvious in our study is that falls from a standing height is a cause of significant morbidity and disability, especially in patients on warfarin. This was consistent with prior studies [4,19,20].

This study demonstrates that warfarin use and abnormal INR are independent predictors of increased risk of ICH and death after ground level falls. Patients taking warfarin are twice as likely to sustain ICH and 2.7 times more likely to die compared to the non-exposed patients. Nishijima and colleagues had similar findings in their study looking at blunt head trauma in patients on warfarin or clopidogrel. In their study they found that clopidogrel had a higher immediate traumatic ICH than warfarin use; 12.0% vs 5.1% respectively [19]. Their study was slightly different because they also included direct trauma, motor vehicle crashes, and only 83.3% of injuries were ground level falls. However, they had a similar rate of ICH in their patient cohort. A prospective study by Menditto and colleagues, also agreed that INR was an independent factor for ICH. They looked at minor head injury in patients on oral anticoagulation and concluded that patients with an INR>3 were at an increased risk of ICH [21].

Results of this study raise an important question about the decision to prescribe warfarin to elderly patients, especially if they have sustained a fall or are at risk for falling. Inamasu et al. in concluded that the risk of traumatic ICH should be explained in great detail to elderly patients when considering placing them on warfarin [4]. We propose that justification for anticoagulation in the elderly for atrial fibrillation take into consideration both the patient's risk of stroke per year, as well as their risk of fall. The annual risk of stroke in patients with atrial fibrillation is estimated using the $CHADS_2$ score [22] which takes into account patient's age and specific co-morbidities. A score of 0 is considered low risk and does not require anticoagulation. Daily aspirin is however recommended. A patient with a score of 1 is considered intermediate risk and can be prescribed either daily aspirin or warfarin. A $CHADS_2$ score of ≥ 2 is considered high risk with recommendation for warfarin treatment, to keep INR between 2 and 3. The majority of patients with atrial fibrillation have a $CHADS_2$ score of 1. If an elderly patient has a low risk of fall with a $CHADS_2$ score of 1, depending on the patient's preference, anticoagulation should be considered. For, patients with high risk of fall however, a $CHADS_2$ score of 1 may not be sufficient to justify anticoagulation with warfarin. This takes into consideration the fact that mortality among patients on warfarin in our study, after ground level falls, was 6.7% as oppose to a 2.8% yearly risk of stroke in patients with a $CHADS_2$ score 1. For patients with a $CHADS_2$ score ≥ 2 (high risk), anticoagulation is certainly justified. A patient with a $CHADS_2$ score of 2 has a yearly stroke risk of 4% compared to a mortality of 6.7% from a ground level fall, if on warfarin. Therefore, anticoagulating patients with $CHADS_2$ scores of 2 are prudent, only

if the patient's risk of fall is low. This is simply because the risk of death from a ground level fall while on warfarin outweighs the yearly risk of stroke in a patient with a $CHADS_2$ score of 2. Current studies on patients with atrial fibrillation suggest a lower risk of stroke in patients not taking warfarin than previously estimated. Singer et al estimated the overall rate of stroke in patients with atrial fibrillation and not taking warfarin to be 2%, compared to earlier studies with an overall rate of stroke of 4.5% [23]. It is also important to know that warfarin only reduces the risk of stroke in patients with atrial fibrillation by approximately 60% [24].

With its retrospective cohort design, this study has certain limitations. This is a single center study and the results may have limited external validity and thus may not apply to different patient populations. Our findings, however, are similar to those reported by others authors as well as regional trauma databanks [4,21,25]. We may have underestimated the incidence of ICH in our study population due to selective use of head CT scan. Selective use of head CT is common practice in trauma centers across the US, and obtaining a head CT on all patients with a fall would not be justified outside of an experimental study design. Moreover, algorithms such as the New Orleans Criteria, NICE guidelines, and the Canadian Head CT rule have established the guidelines for use of head CT in patients with clinical evidence of mild traumatic brain injury. These guidelines were applied to the patients in our study. Still, underestimation of ICH incidence may have decreased the power of our study. We decided to include patients who were taking aspirin and/or clopidorgel in the non-exposed cohort. These patients comprised 21% of our study population, and excluding these patients from the analysis would have significantly limited the power of our study. It is possible that these patients taking antiplatelet agents also sustained higher ICH and mortality compared to those not on any antiplatelet or anticoagulant medications, however, this analysis was beyond the scope of this study. A small albeit significant difference was seen in a prospective study comparing warfarin and clopidogrel use, and immediate and delayed traumatic brain injury; 5.1% vs 12.0% [19]. We acknowledge that by including these patients in the non-exposed cohort, our observed risk of ICH and mortality with warfarin use is likely weaker than the actual risk. Rendell and colleagues seen a slightly higher incidence of ICH (15%) in their patients on warfarin [25]. Further prospective studies are needed to parse out the ICH risk from use of different antiplatelet agents among patients sustaining ground level fall. Since the data on medications was obtained retrospectively, we did not have the opportunity to assess use of non-prescription herbal medications and other supplements which are known to increase bleeding risk. We also did not have data about patients' comorbidities, and thus we could not control for their impact on multivariate analysis. The outcomes assessed in this study were acute ICH and in-hospital mortality. These acute events are likely to be the direct result of the acute traumatic insult with less significant role of comorbid conditions. Since the vast majority of patients with ICH had a component of subdural hematoma, we made the assumption that the fall led to the ICH and not vice-versa. In our population, 8.8% patients reported warfarin use but 16.5% had an INR ≥ 1.3 on admission. We therefore performed separate analyses for these two measures of exposure. The question remains though, whether elevated INR in the absence of warfarin exposure indicates traumatic coagulopathy, which may have led to worse outcomes. In our population, vast majority of patients had a low ISS and thus unlikely to have developed traumatic coagulopathy. When looking at warfarin as exposure cohort, patients who were not on warfarin but had an elevated INR were classified as not-exposed. Thus, any role that traumatic coagulopathy may have played in causing ICH and death would have weakened the true association. Patients not on warfarin had a median INR of 1.06 while those on warfarin had median INR of 2.21, thus we have fairly robust data with regards to exposure, suggesting high internal validity of the study.

Conclusion

A fall from standing height is a cause of significant morbidity and mortality in the elderly population. It also accounts for great economic burden to our economy each year. Warfarin is associated with increased occurrence of intracranial hemorrhage, as well as the mortality rate after ground level falls. Having an abnormal INR (≥1.3) is associated with a significantly higher mortality, regardless of the presence of intracranial hemorrhage. Warfarin should only be initiated in patients if their risk of fall is low and consideration should be given to their risk of mortality from ground level falls. Healthcare providers should be cognizant of these outcomes when evaluating an elderly patient on warfarin, after a seemingly benign ground level fall. Previously used protocols like the 24 observation rule used by Menditto and colleagues, may be beneficial to trauma patients on anticoagulation [21].

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