

## Selected Topics: Neurological Emergencies

### DELAYED INTRACRANIAL HEMORRHAGE IN ANTICOAGULATED GERIATRIC PATIENTS AFTER GROUND LEVEL FALLS

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**Abstract—Background:** The reported risk of delayed intracranial hemorrhage (ICH) in a trauma patient on warfarin is estimated to be between 0.6% and 6%. The risk of delayed ICH in trauma patients taking novel oral anticoagulants (NOACs) is not well-defined. **Objective:** We hypothesized that there was a significant number of delayed presentations of ICH in patients on NOACs. **Methods:** A retrospective review of our trauma registry was performed on geriatric patients (age older than 64 years) who were initially evaluated at our level I trauma center, had fall from standing height or less, and were anticoagulated (warfarin or NOACs), from April 2017 to March 2018. **Results:** Seventy-seven patients met inclusion criteria. The mean age was  $80 \pm 7.7$  years and 46% of patients were male. The admission head computed tomography scan was positive in 20.8% of patients. Positive scans were more common in patients on warfarin vs. NOACs (30% vs. 14%;  $p = 0.074$ ) and had a significantly higher Injury Severity Score (median [interquartile range]: 9 [3–15] vs. 5 [1–9];  $p = 0.030$ ) and Abbreviated Injury Scale–Head score (median [interquartile range]: 1 [0–3] vs. 1 [0–2];  $p = 0.035$ ). The agreement between loss of consciousness (LOC) and ICH was 72% ( $\kappa = -0.064$ ;  $p = 0.263$ ). Fifty-one percent of patients had a repeat head CT. New ICH was diagnosed in

9.6% of patients. All of these patients were on NOACs. **Conclusions:** A fall from standing or less in anticoagulated geriatric patients is a significant mechanism of injury resulting in ICH. The absence of LOC does not eliminate the possibility of ICH. There is a significant risk of delayed ICH for patients on NOACs and repeat evaluations should be performed. A prospective multicenter evaluation of this finding is warranted. © 2019 Elsevier Inc. All rights reserved.

**Keywords—**NOAC; apixaban; dabigatran; rivaroxaban; warfarin; traumatic brain injury; intracranial hemorrhage; geriatric

#### INTRODUCTION

The leading cause of death in trauma patients is traumatic brain injury (TBI) (1). According to the Centers for Disease Control and Prevention, there are about 2.5 million TBI-related emergency department visits annually (1). Falls account for nearly half of all TBI-related emergency department visits and 81% of TBI-related visits in adults aged 65 years and older (2).

Patients on anticoagulation and antiplatelet medications are at increased risk for intracranial hemorrhage (ICH) after blunt head trauma and have worse outcomes (1,3,4). During the last decade, prescribers have rapidly shifted from warfarin to novel oral anticoagulants

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(NOACs) for stroke prevention in patients with atrial fibrillation (A-fib). Zhu et al. found patients initiating anticoagulation for nonvalvular A-fib increased from 8.1% at the end of 2010 to nearly 80% in the beginning of 2017 (5). NOACs have been preferred over warfarin due to their superior safety profile and the ability to dose patients without trending coagulation studies (4–6).

Delayed ICH is defined as “blunt head injury with initial normal cranial computed topographic (CT) scan followed by an interval development of traumatic ICH on repeat imaging” (1,7). The risk for delayed ICH in a trauma patient on warfarin is estimated to be between 0.6% and 6%, and nearly all traumatic ICHs in these patients are captured on initial cranial (CT) scan. Therefore, routine repeat CT is not considered necessary in a patient taking warfarin that has experienced blunt head trauma (1,3,7–9).

Scant literature is currently available regarding the prevalence and risk for traumatic ICH and delayed ICH in patients taking NOACs. Chenoweth et al. reported that dabigatran has a similar risk of ICH after minor head trauma compared to warfarin (4.3%), but this study was limited by its small number of patients ( $n = 33$ ) and was a single-center retrospective analysis (6). However, Beynon et al. reported that rivaroxaban had a higher mortality rate and worsened ICH in patients with minor TBI compared to no antithrombotics or antiplatelet agents (10).

As the U.S. population grows and the number of geriatric patients prescribed NOACs rises, it is imperative to characterize the risk for immediate and delayed ICH to guide physicians in managing these patients. Following institutional analysis of our trauma outcomes, we identified several cases of delayed ICH among NOAC patients and, as a result, instituted repeat head CT scans in this population. The aim of this study is to determine the incidence of delayed ICH and the need for repeat imaging for geriatric trauma patients on NOACs.

## MATERIALS AND METHODS

Institutional Review Board approval of this study was obtained. A retrospective review was performed using the trauma registry at our academic level I trauma center. Inclusion criteria were geriatric patients (aged older than 64 years) who were initially evaluated at our institution, had a fall from standing height or less, and were on anticoagulation (warfarin or NOACs) from April 2017 to March 2018. Chart review was used to characterize head CT scan results of the initial and repeat head CT scans. Patient characteristics were abstracted from the registry and electronic medical record. The type of anticoagulation medication, as well as information on loss of consciousness (LOC), were also abstracted.

Data were analyzed using several methods. Normally distributed continuous variables are presented as mean  $\pm$  standard deviation. Non-normally distributed continuous variables are presented as median and interquartile range. Continuous variables were compared between groups using the two-tailed  $t$ -test. Categorical variables were compared between groups using  $\chi^2$  analysis. A  $p$  value  $< 0.05$  was used as a measure of statistical significance. SPSS, version 24.0 (IBM Corp., Armonk, NY) was used for all analysis.

## RESULTS

Between April 2017 to March 2018, 77 patients met inclusion criteria. Overall, patient characteristics were similar between those taking warfarin vs. NOACs (Table 1). The average age of both groups was approximately 80 years and there were equal numbers of males and females in each group. Presentation Glasgow Coma Scale and discharge Glasgow Outcome Scale scores were also similar between the two groups. Patients taking warfarin had a significantly higher Injury Severity Score (median [interquartile range]: 9 [3–15] vs. 5 [1–9];  $p = 0.030$ ) and AIS-Head (median [interquartile range]: 1 [0–3] vs. 1 [0–2];  $p = 0.035$ ). Otherwise, there were no other statistically significant differences between the two groups (Table 2).

The admission head CT scan was positive in 20.8% of patients (Figure 1). Positive scans were more common in patients on warfarin vs. NOACs (30% vs. 14%;  $p = 0.074$ ). The agreement between LOC and TBI was 72% ( $\kappa = -0.064$ ;  $p = 0.263$ ).

Fifty-one percent of patients with a negative initial head CT had a repeat head CT. None of the patients with negative initial head CT scans had any form of

**Table 1. Patient Characteristics**

Characteristic	Coumadin ( $n = 33$ )	NOAC ( $n = 44$ )	$p$ Value
Age (years), mean $\pm$ SD	81.5 $\pm$ 7.7	79 $\pm$ 7.6	0.160
Male, $n$ (%)	17 (51.5)	18 (40.9)	0.355
Aspirin, $n$ (%)	9 (27.3)	19 (43.2)	0.151
Plavix, $n$ (%)	0 (0)	2 (4.5)	0.215
Admit GCS, mean $\pm$ SD	14.4 $\pm$ 2.3	14.7 $\pm$ 0.9	0.342
Discharge GCS, mean $\pm$ SD	14.8 $\pm$ 0.6	14.9 $\pm$ 0.3	0.491
Discharge GOS, mean $\pm$ SD	4.2 $\pm$ 0.9	4.3 $\pm$ 1.1	0.680
ICU LOS (d), median (IQR)	0 (0–3)	0 (0–2)	0.591
Hospital LOS (d), median (IQR)	4 (1–9)	2 (1–6)	0.057

GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; NOAC = novel oral anticoagulant; SD = standard deviation.

**Table 2. Injury Characteristics**

Characteristic	Total, Median (IQR) (n = 78)	Coumadin, Median (IQR)	NOAC, Median (IQR)	p Value
Injury Severity Score	5 (1–10)	9 (3–15)	5 (1–9)	0.030
Abbreviated Injury Scale				
Head	1 (0–2)	1 (0–3)	1 (0–2)	0.035
Face	0 (0–1)	0 (0–1)	0 (0–1)	0.449
Neck	0 (0–0)	0 (0–0)	0 (0–0)	0.248
Thorax	0 (0–0)	0 (0–0)	0 (0–0)	0.251
Abdomen	0 (0–0)	0 (0–0)	0 (0–0)	0.736
Spine	0 (0–0)	0 (0–2)	0 (0–0)	0.126
Upper extremity	0 (0–1)	0 (0–1)	0 (0–1)	0.981
Lower extremity	0 (0–1)	0 (0–1)	0 (0–1)	0.783
External	0 (0–0)	0 (0–0)	0 (0–0)	1.000
Other	0 (0–0)	0 (0–0)	0 (0–0)	1.000

IQR = interquartile range; NOAC = novel oral anticoagulant.

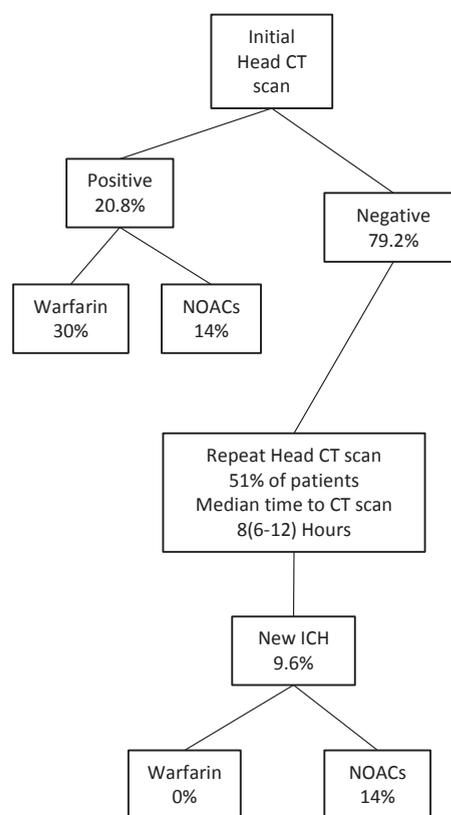
reversal agent administered. The median time to repeat head CT scan was 8 h (interquartile range 6–12 h). New ICH was diagnosed in 9.6% of patients. None of these patients had a change in neurological examination. All of these patients were on NOACs. All types of ICH (subdural, subarachnoid, intraparenchymal, intraventricular) were seen on initial and repeat head CT in both patients taking warfarin and NOACs. On follow-up head CT in patients taking NOACs, additional bleeding was noted in several compartments of the brain: subdural n = 1, subarachnoid n = 0, intraventricular n = 2, and intraparenchymal n = 2. One of these delayed ICH patients was clinically significant, resulting in death.

## DISCUSSION

Prescribers have favored NOACs over warfarin since their approval by the U.S. Food and Drug Administration (4). The proportion of patients taking NOACs has increased during the last decade and the geriatric population makes up a large portion of patients that require anticoagulation (4). Among the geriatric population, falls have surpassed motor vehicle collisions as the predominant mechanism of trauma activation and are the leading cause of TBI (2). As the mean age of trauma patients increases and number of geriatric patients prescribed NOACs grows, a systematic approach for evaluating these patients must be in place. Current standards of care for repeat head CT after trauma are based on numerous studies evaluating the risk of delayed ICH in patients taking warfarin. NOACs represent an entirely different class of drugs with different pharmacokinetics and pharmacodynamics. Thus, conclusions drawn from studies of geriatric trauma patients on warfarin cannot be extrapolated and applied to geriatric trauma patients prescribed NOACs. This difference was clearly demonstrated in our retrospective study, in which we found a clinically significant number of delayed bleeds in the NOAC group when we instituted a repeat head CT at

6 h in our NOAC-anticoagulated geriatric trauma patients.

Original articles that evaluated the safety profile and risk of major bleeding of NOACs compared to warfarin were primarily evaluating the rate of spontaneous ICH. These studies demonstrated lower bleeding risk than warfarin and a superior safety profile with regard to spontaneous hemorrhage (11). Hart et al. reported a lower rate of traumatic ICH in dabigatran vs. warfarin between 2005 and 2007 (12). However, the sample size was smaller and



**Figure 1. Head CT (computed tomography) scan flow sheet. ICH = intracranial hemorrhage; NOAC = novel oral anticoagulant.**

did not evaluate progression or delayed ICH. These studies are limited by small numbers of patients and may or may not pertain to falls from standing height or lower.

NOACs have not been evaluated in a rigorous prospective trial for traumatic injury. The risk of delayed ICH in geriatric patients taking NOACs is unknown. A systematic review and meta-analysis concluded the risk of delayed ICH in warfarin was 0.6% (9). In comparison, we found that 14% of patients taking NOACs, with an initially negative head CT, were positive on repeat imaging. Our study showed a 20.8% overall risk of ICH in geriatric patients following a fall from standing height or lower.

Current National Institute for Health and Care Excellence head injury guidelines (updated 2014) do not recommend head imaging of anticoagulated adult patients with blunt head trauma if there is no reported LOC or amnesia of event (13). However, we found no agreement between reported LOC and ICH. These findings mirror data from Nishijima et al., who reported that among patients taking warfarin and who did not have an LOC, 11% had ICH (1). During evaluation, different practitioners place differential weight on a history of LOC, as it is frequently obtained through a patient self-report. One possibility is that if a patient loses consciousness, the patient might not reliably remember whether or not they had LOC. This suggests that practitioners cannot reliably use LOC as a clinical decision maker for risk of ICH.

### Limitations

Although the results are intriguing, there are several limitations to this study. The sample size is small, so it may be underpowered to detect certain differences in various populations. Additionally, only 51% of patients had a repeat head CT, so the results may not precisely define the incidence of delayed ICH in this population. The retrospective nature of the study carries with it the standard limitations of this study type. We were also not able to determine the time of last dose of anticoagulation before their fall. Given the different mechanism of action and pharmacokinetics, the time from last dose could have an important effect on the results of this evaluation. The timing of the last dose of anticoagulation in relation to the time of the fall is likely a major factor affecting the likelihood of delayed ICH. Future evaluations of timing of anticoagulant dose, as well as advanced coagulation assessment, would be helpful in determining a guideline for evaluating these patients. Finally, we were unable to determine the time from injury to the time of presentation to our trauma center. Despite these limitations, the identification of an increased risk of delayed ICH in patients receiving NOACs had significant clinical implications.

## CONCLUSIONS

The risk of traumatic ICH in geriatric patients taking NOACs compared to warfarin was previously unknown. In our study, the risk of traumatic ICH in patients on NOACs was 20.8%, with a 14% delayed rate of bleed. LOC is not a reliable historical marker to rule out TBI. Based on our findings, our institution has introduced a protocol for repeating a head CT in geriatric trauma patients taking NOACs in order to evaluate for delayed presentation of ICH. Due to the potential clinical ramifications on trauma care in the geriatric population, more data are needed on the delayed effects of NOACs, which would be best accomplished with a prospective multicenter evaluation.

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## ARTICLE SUMMARY

### **1. Why is this topic important?**

The incidence of falls among geriatric patients is increasing rapidly as the population ages. The number of these patients taking novel oral anticoagulants (NOACs) is also increasing, and the management of this trauma patient is not well described.

### **2. What does this study attempt to show?**

This study shows a significant risk for the development of a delayed intracranial hemorrhage in geriatric patients taking NOACs after falls from standing height or less.

### **3. What are the key findings?**

Fourteen percent of geriatric patients taking NOACs may develop a delayed intracranial hemorrhage after falls from standing height or less. A history of loss of consciousness does not help triage these patients into groups that do or do not need head computed tomography (CT) scans to rule out intracranial hemorrhage.

### **4. How is patient care impacted?**

At our institution, we have changed our trauma activation criteria to include geriatric patients taking NOACs. We also perform an additional head CT scan at 6 h to evaluate for intracranial hemorrhage if their initial head CT scan was negative. This is necessary because some of these delayed hemorrhages are severe and require intensive care unit admission and potentially surgery.