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Routine Repeat CT Head Does Not Change Management in Trauma Patients on Novel Anticoagulants

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ABSTRACT

Introduction: Guidelines for imaging anticoagulated patients following a traumatic injury are unclear. Interval CT head (CTH) is often routinely performed after initial negative CTH to assess for delayed intracranial hemorrhage (ICH-d). The rate of ICH-d for patients taking novel oral anticoagulants (NOACs) is unknown. We hypothesized that the incidence of ICH-d in patients on NOACs would be similar, if not lower to that of warfarin, and routine repeat CTH after initial negative would not change management, and thus, may not be indicated.

Materials and Methods: Anticoagulated patients presenting with blunt trauma to a level I trauma center between 2016 and 2018 were evaluated. Exclusion criteria included: positive initial CTH and those taking nonoral anticoagulation or antiplatelet agents alone (without warfarin or NOAC). Outcomes included: ICH-d, discharge GCS, administration of reversal agents, neurosurgical intervention, readmission, and death. Multivariable regression was performed to evaluate patient factors associated with the development of ICH-d.

Results: A total of 332 patients met the inclusion criteria. Patients were divided into a warfarin group ($n = 191$) and NOAC group ($n = 141$). The incidence of ICH-d in the warfarin group was 2.6% (5/191) and 2.1% (3/141) in the NOAC group ($P = 0.77$). There were no reversal agents administered, neurosurgical interventions, readmissions, or deaths in the NOAC group.

Conclusions: Little is known about the impact of NOACs in the setting of trauma, especially regarding risks of ICH-d following traumatic injury. In the NOAC group, ICH-d occurred only 2.1% of the time. In addition, there were no reversal agents given, neurosurgical interventions, or deaths. These data, taken together, suggest the limited utility of repeat imaging in this patient population.

Background

Over the past decade, there has been a shift in prescription from warfarin, a vitamin K antagonist, to the novel oral anticoagulants (NOACs): dabigatran, apixaban, and rivaroxaban.[1] NOACs are used mainly for the prevention of stroke from atrial fibrillation and are recommended as a first-line treatment for acute venous thromboembolism (VTE) by the

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American College of Chest Physician 2016 Guidelines.[2] These drugs have been shown to have faster onset, shorter half-lives, and less food and drug interactions.[3] Given the rise in utilization of NOACs over warfarin, trauma patients are presenting on these medications with increased frequency. Furthermore, the FDA (Food and Drug Administration) approved reversal agents, idarucizumab and andexanet alfa exist, both for dabigatran and the Xa inhibitors (apixaban and rivaroxaban), respectively, allowing for a reversal in the event of bleeding or overdose.

The management of anticoagulated trauma patients commonly includes a computed tomography of the head (CTH) at the time of arrival to evaluate for intracranial hemorrhage. If there is no intracranial hemorrhage on the initial CTH, a repeat CTH within a 24-h time period is often routinely performed to evaluate for delayed intracranial hemorrhage (ICH-d).[4-7] This practice is hospital or provider-dependent, as there are no national guidelines recommending repeat imaging after an initial negative CTH in anticoagulated patients. Rates of ICH-d in this population range from 0.51% to 6%.[4,8-12] However, these rates are largely based on studies of patients taking warfarin or warfarin and aspirin together. Much less is known about patients on NOACs. Recent data suggest that patients on NOACs have similar rates of initial ICH and decreased mortality after injury compared to patients on warfarin.[13,14] What remains unknown is the incidence of ICH-d after normal initial CTH in patients taking NOACs and their clinical outcomes.

Understanding the risks of ICH-d and their clinical implications in this large and growing population of anticoagulated patients may help develop guidelines that improve patient care and reduce hospital spending. We hypothesized that the incidence of ICH-d in patients on NOACs would be low, similar to that of warfarin, and that routine repeat CTH after initial negative CTH in patients on NOACs may not be indicated.

Methods

After institutional review board approval including a waiver of consent, a retrospective analysis was performed on all adult trauma patients who presented to our level I trauma center from 2016 to 2018. Chart review and documentation of data were performed in accordance with the ethical standards of the institution and the Alameda Health System. Our institutional trauma registry was specifically queried to identify patients with a prehospital diagnosis of "anticoagulation" and a CTH scan on arrival. In addition, the query included the date of admission, baseline demographics, comorbidities, injury severity score (ISS), arrival Glasgow Coma Scale (GCS), and discharge GCS. After these patients were identified by the query, a detailed chart review was performed to verify that these same patients met inclusion criteria. Patients were included if they were on prehospital oral anticoagulation, suffered from blunt trauma, and obtained an initial CTH. Charts were then reviewed to identify and document key patient variables, including specific anticoagulation medication, indication for anticoagulation, mechanism of injury, INR level at arrival, CTH findings based on radiologist report documented in the electronic medical record, time interval between CTH scans if repeat was performed, reversal agents administered, massive transfusion protocol activation, administration of packed red blood cells within 4 h of arrival, neurosurgical intervention based on operative reports, readmission within 30 d, and death.

It is our hospital protocol to repeat CTH in all anticoagulated trauma patients 6 h after the initial CTH. In the interim between CTH scans, the nursing staff make an hourly GCS assessment. Patients taking an antiplatelet agent in combination with anticoagulation were included. We excluded patients who had a positive initial CTH and those taking nonoral anticoagulation or antiplatelet agents alone (without warfarin or NOAC). Patients with equivocal CTH readings on initial CTH were also excluded.

Collected data included patient demographics, ISS, international normalized ratio (INR), specific prehospital anticoagulant medication, number of medical comorbidities, and mechanism of injury. Clinical outcomes included ICH-d, discharge GCS, administration of reversal agents, neurosurgical intervention, readmission, and death. The primary outcome was the incidence of ICH-d. Secondary outcomes included the identification of key patient factors associated with ICH-d.

Baseline characteristics and outcomes data were analyzed using Chi-squared and paired Student's *t*-test, as applicable. Demographic values are reported as mean ± standard error. An alpha value of <0.05 was used to define statistical significance. Univariable logistic regression analysis was used to evaluate the impact of individual patient factors on the development of ICH-d. Variables with $P < 0.2$ on univariable analysis were subsequently included in a multivariable regression analysis. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.

Results

A total of 387 anticoagulated patients presenting after blunt trauma were identified during the study period. Patients with a positive initial CTH ($n = 33$) were excluded. Those without a repeat CTH ($n = 16$) or with an equivocal initial CTH ($n = 6$) were also excluded. In our study, 95% of patients received a routine repeat CTH in accordance with the protocol, leaving 332 remaining patients who met the study criteria. There were 191 patients in the warfarin group and 141 in the NOAC group (Figure). The average age in the warfarin and NOAC groups was similar at 78 ± 1.0 y *versus* 77 ± 1.1 y, $P = 0.7$, respectively. The groups were also similar in terms of sex, arrival GCS, ISS, number of medical comorbidities, and indications for anticoagulation. As expected, the INR was higher in the warfarin group than the NOAC group. Patient characteristics are listed in Table 1.

In the warfarin group, 11 patients were taking warfarin and an antiplatelet agent. Of the 191 patients in the warfarin group, five had ICH-d, and none of these five patients were taking concomitant antiplatelet agents. This resulted in an incidence rate of 2.6% (5/191). The mechanisms included fall ($n = 4$) and MVC ($n = 1$). Reversal agents were given in four out the five patients. Two of the patients with ICH-d had a

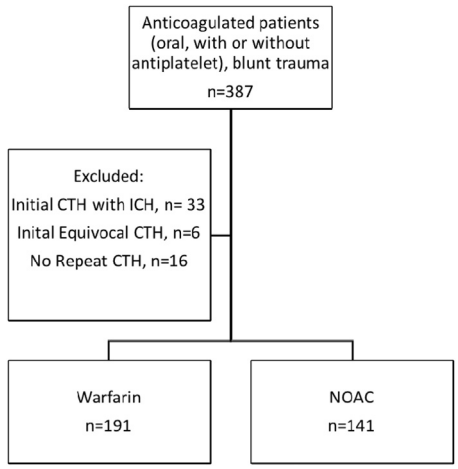

Fig – Inclusion and exclusion criteria for study. GCS: Glasgow Coma Scale. CTH: Computed tomography of head. *within 24 h after initial CTH. ICH = Intracranial hemorrhage; ASA = Aspirin.

supratherapeutic INR (>3) at arrival, and each received reversal with fresh frozen plasma (FFP) and vitamin K after ICH-d was identified. One experienced worsening intracranial hemorrhage requiring neurosurgical intervention and ultimately died in hospital on day 10. Notably, this patient had an element of renal dysfunction with elevated creatinine on arrival and was diagnosed with cholecystitis during the hospitalization. The four other patients with ICH-d on warfarin did not clinically worsen and were discharged at their baseline neurologic status without neurosurgical intervention; however, one patient was re-admitted within 30 d for hip pain.

The NOAC group consisted of patients taking rivaroxaban ($n = 66$), apixaban ($n = 40$), and dabigatran ($n = 26$). There were several patients taking a concomitant antiplatelet ($n = 11$). In the NOAC group, there were three patients who developed ICH-d, each one after a fall and with one patient taking rivaroxaban and the other two taking apixaban (none of the three patients were taking concomitant antiplatelet agents). This resulted in an ICH-d incidence rate of 2.1% (3/141). The incidence rates between the warfarin group and the NOAC group were not different, ($P = 0.77$). The three NOAC patients with ICH-d were discharged without the administration of a reversal agent, neurosurgical intervention, or readmission. One of the three patients left the hospital on day two against medical advice. The patient was at normal baseline neurologic status at the time of follow-up visit and suffered no sequela from the injury (Table 2).

There were seven patients who received reversal agents, although they did not have ICH-d on routine repeat CTH. All seven were on prehospital warfarin and presented with a supratherapeutic INR. Additionally, there were two patients on prehospital warfarin who did not have a routine repeat CTH performed; however, they received reversal agents. One had an INR of 2.2 but was reversed for a hematoma from an aortic dissection. The other had a supratherapeutic INR and went to the OR for a fasciotomy. None of the patients on

Table 1 – Patient demographics, injury characteristics, and anticoagulation indication in NOAC and warfarin groups.

Patient factors	Warfarin, $n = 191$	NOAC, $n = 141$	P-value
Age, ave years (SE)	78 (1.0)	77 (1.1)	0.7
Sex, % male (*n*)	48 (92)	52 (74)	0.44
INR, ave (SE)	2.6 (0.1)	1.4 (0.03)	<0.05*
Initial GCS, ave (SE)	14.7 (0.1)	14.7 (0.05)	0.32
ISS, ave (SE)	4.2 (0.4)	3.5 (0.4)	0.21
# Comorbidities, ave (SE)	3.6 (0.1)	3.9 (0.2)	0.22
Mechanism of injury, % (*n*)			
Fall	88 (168)	91 (128)	0.41
MVC	6 (11)	2 (3)	0.10
Struck by auto	3 (6)	4 (5)	0.84
Assault	3 (5)	4 (5)	0.62
Other	0.01 (1)	0	N/A
Indications, % (*n*)			
Afib	63 (121)	61 (86)	0.66
DVT/PE	16 (30)	24 (34)	0.05
Heart valve	6 (12)	0	N/A
Malignancy	0.01 (1)	0	N/A
Other	14 (27)	14 (20)	0.99

NOAC = novel oral anticoagulant; Ave = average; SE = standard error; INR = international normalized ratio; GCS = Glasgow Coma Scale; ISS = injury severity score; MVC = motor vehicle collision; Afib = Atrial fibrillation; DVT = deep venous thrombosis; PE = pulmonary embolism.
*$P < 0.05$.

Table 2 – Patient characteristics and injury details of patients who developed a delayed intracranial hemorrhage.

Age	Sex	Medication	MOI	INR	ISS	Repeat CTH	N.I.	GCS A/d	Death (Y/N)
81	F	Apixaban	Fall	1.2	12	IVH*	N	14/14	N
84	M	Rivaroxaban	Fall	1.2	6	SAH	N	15/15	N (AMA)
68	F	Apixaban	Fall	1.3	22	IVH	N	15/15	N
95	F	Warfarin	Fall	3.9	14	Hemorrhagic contusion	N	15/15	N
76	M	Warfarin	Fall	3.2	17	IVH	Y	14/3	Y
71	M	Warfarin	Fall	2.4	22	IVH	N	15/15	N
79	M	Warfarin	MVC	1.9	29	SDH	N	14/15	N
86	M	Warfarin	Fall	1	5	IVH	N	14/15	N

Note. None of the patients with ICH-d (NOAC or warfarin group) were taking concomitant antiplatelet agents.
MOI = mechanism of injury; INR = international normalized ratio; ISS = injury severity score; CTH = computed tomography of head; N.I. = neurosurgical intervention; A/D GCS = arrival and discharge Glasgow Coma Scale; MVC = motor vehicle crash; IVH = intraventricular hemorrhage; SAH = subarachnoid hemorrhage; SDH = subdural hematoma; Y/N = yes/no; SNF = skilled nursing facility; AMA = against medical advice.
*Findings on MRI, then repeat CT head scan within 24 h.

prehospital NOACs received reversal agents (regardless of ICH-d).

There were 16 total patients without a repeat CTH. Twelve of these patients were on warfarin and four on a NOAC. The exact reason for the omission of a routine repeat CTH was not available for all the patients. However, three left against medical advice prior to the recommended routine repeat CTH. At least two declined routine imaging since they would not want any neuro-intervention if needed. There was no documented neuro-intervention, readmission within 30 d, or death for these 16 patients. Two did receive reversal, as mentioned previously.

Univariable logistic regression analysis was performed on all patients with a nonequivocal repeat CTH reading ($n = 329$) to evaluate the impact of various patient factors including: age, sex, medical comorbidities, ISS, GCS on arrival, anticoagulation medication, indication for anticoagulation, mechanism of injury, and INR on the development of ICH-d. None of the three patients with an equivocal repeat CTH scan suffered any adverse events. ISS and arrival GCS, $P < 0.01$ and $P = 0.17$, respectively, were included in the multivariable model (Table 3). On multivariable logistic regression analysis adjusting for these patient factors, only ISS was found to increase odds of developing ICH-d, OR 1.2 (95% CI 1.18-1.27) $P < 0.01$.

Because transfusion of blood and blood products can impact the anticoagulation in traumatized patients, we also evaluated blood product transfusion within 4 h of arrival in both groups. At our institution, activation of the massive transfusion protocol (MTP) is triggered by persistent hemodynamic instability, active bleeding requiring operation, or blood transfusion in the trauma bay. However, in this study, only one patient required MTP activation due to a severe extremity degloving injury. This patient was taking dabigatran and did not have a delayed hemorrhage on repeat CTH. Triggers for transfusion of packed red blood cells outside of the massive transfusion protocol included a drop in hemoglobin in a patient on apixaban and aspirin, as well as a gastrointestinal bleed, abdominal wall hematoma, and gluteal hematoma in three patients on warfarin. None of these four patients had ICH-d on repeat CTH.

Discussion

The goals of this study were to evaluate the incidence of ICH-d in the growing population of patients presenting on NOACs, assess key patient factors that contribute to ICH-d, and finally, understand the clinical outcomes associated with ICH-d. Most current literature on the topic of delayed hemorrhage focuses on patients anticoagulated with warfarin, although there is a clear trend in recent years toward the prescription of NOACs for common medical conditions.[15] However, there is only one published study to date that evaluates this issue specifically,[16] and to our knowledge, none that also includes the evaluation of ICH-d in patients taking warfarin. Our hypothesis was that the incidence of ICH-d in patients on NOACs would be low, similar to that of warfarin, and that routine repeat CTH after initial negative CTH in patients on NOACs would not change management, and therefore, may not be indicated. We found

Table 3 – Risk of ICH-d according to univariable analysis of patient factors.

Patient factors	Odds ratio (CI)	P-value
Age	1.0 (0.99 to 1.0)	0.59
Female sex	0.6 (−0.14 to 1.3)	0.6
# Comorbidities	1.2 (1.0 to 1.3)	0.26
ISS	1.2 (1.17 to 1.26)	<0.01*
Arrival GCS	0.7 (0.4 to 0.97)	0.17
NOAC	0.8 (0.1 to 1.5)	0.76
INR	0.94 (0.6 to 1.3)	0.84

ICH-d = delayed intracranial hemorrhage; ISS = injury severity score; GCS = Glasgow Coma Scale; NOAC = novel oral anticoagulant; INR = international normalized ratio; CI = confidence interval.
*$P < 0.05$.

that ICH-d occurred in only 3 out of 141 patients on NOACs, and none required administration of a reversal agent, neurointervention, or died as a result of ICH-d.

The clinical utility of a repeat CTH scan after an initial negative for patients on anticoagulation has been called into question by prior authors citing the low incidence of ICH-d that ranges from 0.51% to 6%.[4,8-12] This point of view is largely based on studies of patients taking warfarin. When intracranial hemorrhage is present on initial CTH after traumatic injury, patients on NOACs have lower mortality than those on warfarin and are less likely to require neurointervention or be discharged to a skilled nursing facility.[14,17] This is in line with our results as there were no reversal agents administered, neurosurgical interventions, or deaths in patients on NOACs. All patients in the NOAC group were discharged without a decline in their GCS.

A mechanism supporting the potentially improved safety profile of NOACs involves tissue factor, a transmembrane receptor for factor VIIa commonly found in high concentrations in the brain.[18] When tissue factor binds with factor VIIa, it forms a complex believed to act as an intracranial hemostatic agent.[18,19] Patients taking warfarin, a vitamin K antagonist, have decreased functional factor VII since this coagulation factor is dependent on vitamin K as a cofactor for biological function.[20] With decreased levels of factor VII, the intracranial hemostatic complex between factor VII and tissue factor would be unable to form in patients on warfarin. However, factor VII function is not directly affected by NOACs since NOACs target clotting further downstream in the coagulation cascade,[21] allowing the potentially protective hemostatic complex of factor VII and tissue factor to form intracranially.[22]

An alternative theory in support of improved safety with NOACs involves P-glycoprotein, a transporter protein found in intestinal, renal, hepatic, and brain cells.[23] P-glycoprotein is present on capillary endothelial cells and prevents the passage of drugs across the membrane into the brain.[23] The main P-glycoprotein isoform is Mdr1a.[24] Mdr1a-knockout mice are more sensitive (up to 100-fold) than normal mice to the neurotoxicity caused by P-glycoprotein regulated drugs, such as ivermectin.[24] Dabigatran etexilate (a precursor of dabigatran), apixaban, and rivaroxaban are known substrates of P-glycoprotein, and thus, are restricted from crossing the blood-brain barrier, whereas vitamin K antagonists (warfarin) cross unrestricted.[25] Studies using known P-glycoprotein inhibitors[26] and inducers[27] have demonstrated increased and decreased dabigatran bioavailability, respectively. These characteristics of NOACs and recent findings of less severe clinical outcomes after trauma have led to support for the safety profile of NOACs over warfarin in terms of intracranial hemorrhage.[28,29]

This study is limited in several areas. First, it is retrospective and dependent on accurate documentation in the electronic medical record. It is also a single-center study, so the findings may not be generalizable to ICH-d seen in different patient populations and regions. There was only a small number of patients who developed ICH-d, limiting our ability to distinguish specific risk factors for ICH-d. Additionally, we were unable to assess the extent of anticoagulation for patients taking NOACs, as INR does not adequately reflect this metric. Therefore, it is possible that some of the patients on NOACs may have been inadequately anticoagulated without our knowledge, and much less likely to then develop an ICH-d, falsely lowering the observed rate of ICH-d in this group. However, since NOACs are not routinely monitored, these differences in other populations would likely be comparable, and similarly, low rates of ICH-d in patients taking NOACs have been reported.[16] Finally, neurologic assessments were largely based on documented GCS at arrival and discharge, which may not accurately reflect subtle neurologic changes that may be clinically important.

In spite of the limitations, our findings suggest that for patients on NOACs, there is little utility in performing repeat imaging following an initial negative CTH. Only 2.1% ($n = 3$) of NOAC patients were found to have an ICH-d. Regardless of whether a repeat CTH was performed, none of these patients received reversal agents, required neurosurgical intervention, or died as a result of their head bleed, meaning that repeat CTH did not change management for any NOAC patient. However, our study population was relatively small, resulting in a very low number of ICH-d cases. To better evaluate who is at risk for development to ICH-d, a larger sample size is needed, likely as part of a multiinstitutional study. With more cases of ICH-d in NOAC patients, a risk stratification system could be developed with higher risk patients benefiting from a repeat CTH and lower risk patient safely forgoing a repeat CTH. The rate of ICH-d in the lower risk group would be expected to be greater than 0.4%, as this is the rate of ICH-d in trauma patients who are not on anticoagulation.[7] Although the exact incidence cutoff rate is still not determined, the rate of neurointervention and/or death should be very near zero in the lower risk cohort based on retrospective data in order to safely and ethically recommend omission of routine repeat CTH. The next step would be to prospectively observe NOAC patients with neurologic exams in place of a routine repeat CTH. Last, a cost-effectiveness analysis between observation *versus* routine repeat imaging in this population would add important information to this growing issue.

Conclusion

The number of anticoagulated trauma patients is rising, and there has been a shift from the commonly prescribed warfarin to the newer NOACs. In the patients with ICH-d on NOACs, there was no administration of reversal agents, neurosurgical intervention, readmission related to head injury, or deaths, perhaps attributable to a better safety profile of NOACs. Our findings suggest there is limited utility in repeat imaging for patients on NOACs after traumatic injury. Limiting unnecessary imaging in this substantial and growing population of older anticoagulated patients may save time, reduce costs, and improve the allocation of resources. Further work should be done in a multiinstitutional setting to allow for risk stratification of patients on NOACs who develop ICH-d and to determine the cost effectiveness of routine repeat imaging in this population.

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Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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