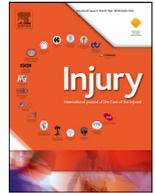




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Retrospective Review

The utility of a second head CT scan after a negative initial CT scan in head trauma patients on new direct oral anticoagulants (DOACs)

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ABSTRACT

Background: New direct oral anticoagulants (DOACs) are commonly used in the management of atrial fibrillation and VTE. Currently, there is no strong evidence to support the current practice of routinely repeating computed tomography (CT) head in anticoagulated patients within 24 hours after their first negative CT scan to assess for new and delayed intracranial hemorrhage (ICH). Our hypothesis is that the vast majority will not have new CT scan findings of ICH and those who do would not require any further intervention.

Methods: This is retrospective cohort study. IRB approval was obtained. Subjects included adults age \geq 18 taking DOACs who presented to our level III trauma center with confirmed or suspected blunt head trauma between August 2013 and October 2019 and received at least one head CT scans.

Results: 498 Patient encounters met inclusion criteria. Only 19 patients (3.8%) had positive traumatic ICH on the initial CT head. Those had a higher ISS. 420 out of 479 initial negative CT encounters received a second CT head. Only 2 (0.5%) had delayed positive second CT scan for ICH. 95%CI [0.06%, 1.7%] Patients who developed a new ICH on the second CT head after an initial negative CT scan had a lower Glasgow Coma Scale (GCS) on presentation and a higher ISS. None of those patients required neurosurgical intervention

Conclusion: Our data suggests that the risk of developing a new or delayed traumatic ICH for patients on DOAC on a second CT head within 24 hours following an initial negative CT is very low and when present did not require neurosurgical intervention and thus does not support routinely obtaining a repeat CT head within 24 hours after a negative initial CT scan. Patients presenting with lower GCS and higher ISS had a higher chance of having a delayed ICH.

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Background

Traumatic injury has become the fifth leading cause of death in the elderly population [1]. According to the National Trauma Data Bank, in 2014, 39% of patients presenting with traumatic injuries were over 55-year-old, and patients in this age range comprised 54% of all trauma related deaths [1]. Of trauma related deaths occurring in patients greater than 65 years of age, 46% are secondary to falls [2]. A large percentage of these patients are on antithrombotic therapy, including anti platelet agents, warfarin, and Direct Oral Anticoagulants (DOACs).

There is an ongoing debate regarding management of head trauma in patients on antithrombotic therapy. Studies have demonstrated that patients on antithrombotic therapy have an in-

creased risk of intracranial hemorrhage (ICH), and a lower mechanism of injury may be necessary to cause hemorrhage [3]. EAST Trauma guidelines recommend anticoagulated patients with supra-therapeutic INR and normal initial CT Head remain in the hospital for observation for at least 24 hours (Level 3 data) but do not give clear guidelines regarding need for repeat CT head or how to manage anticoagulated patients when INR does not reflect anticoagulation status, as with DOACs [4]. Some centers manage these patients with 24-hour observation, while others obtain a repeat CT head in 12-24 hours prior to discharge. Studies have demonstrated that a repeat CT head may not be necessary, and may not provide benefit beyond clinical observation, while utilizing extra resources [5,6]. For instance, a multi-institutional prospective cohort study including 859 patients demonstrated that incidence of delayed intracranial hemorrhage in patients with blunt head trauma on anti-platelet or anticoagulant therapy was low, and comparable to incidence in patient not on any antithrombotic therapies, suggesting that routine repeat imaging is not necessary [7]. There is a paucity

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of data on the need for repeat CT head in patients specifically on direct oral anticoagulants.

DOACs include direct factor Xa inhibitors Apixaban, Rivaroxaban, Edoxaban, and direct thrombin inhibitor Dabigatran. DOACs have multiple benefits over the classic vitamin K antagonist, warfarin, which has a narrow therapeutic window, long half-life, multiple interactions with foods and other pharmaceuticals, and requires weekly monitoring. DOACs have a shorter half-life and do not require monitoring to ensure therapeutic range. On the other hand, newly developed reversal agents for DOACs, including Idarucizumab, and Adnexanet, are costly and not uniformly available. Studies have shown that patients with significant trauma who are on DOACs may have improved mortality and blood transfusion requirements compared to patients on warfarin [8]. As DOACs become increasingly utilized by the population it is imperative to investigate their impact on clinical course and management of head trauma.

Elderly patients presenting with low-velocity head trauma including ground level falls while on anticoagulant therapy make up a significant portion of cases presenting to our trauma center. Current organization specific practice entails placing the patient in observation and obtaining a repeat CT head within 24 hours of initial imaging. This requires an increase in healthcare resource utilization with increasing costs and potentially an increase in hospital related adverse events and may also pose a burden to patients and their families. We hypothesize that the vast majority of low mechanism blunt head trauma patients on DOACs with no abnormal initial CT head findings will not have new delayed intracranial bleeding and do not in fact benefit from extended hospital stay or repeat imaging. In order to assess the utility of repeat imaging in this growing patient population, we undertook a retrospective review of all consecutive head traumas patients on DOAC therapy presenting to our institution.

Methods

Institutional Review Board approval was obtained for this retrospective study. A waiver of consent was obtained. A retrospective chart review was performed that included all adult patients who presented to our American College of Surgeons designated Level III trauma center between August 2013 and October 2019 who had either confirmed or suspected blunt head trauma who were on a DOAC (Apixaban, Rivaroxaban, or Dabigatran) and received at least one CT head scan. Exclusion criteria included patients who were

less than 18 years of age or who were transferred outside of our Health System.

Per our hospital protocol, patients on DOAC therapy who present within 12 hours of suspected or confirmed head trauma were admitted for observation and received a timed repeat CT head imaging 12 hours following the initial CT head scan. Thus, patients presenting late (>12hours) after head trauma would not require a repeat CT scan of the head if the initial one was negative.

The primary measure was the frequency of new or delayed acute intracranial hemorrhage found on a second CT of the head. Secondary measures included identification of key patient factors that may predict likelihood of developing new or delayed acute intracranial hemorrhage on repeat CT head imaging. Through chart review, we identified key factors and demographic information including age, sex, traumatic mechanism, Glasgow Coma Scale (GCS), Injury Severity Score (ISS), concurrent use of aspirin or clopidogrel, and type of DOAC.

Numerical data is reported as mean (standard deviation), [median]. Categorical data is reported as frequency (percent). Continuous variables including age, GCS, ISS were analyzed using the Wilcoxon Rank Sum Test. Fisher's Exact Test was used to compare sex and traumatic mechanism in patients with a negative versus positive initial CT of the head, and used for sex, DOAC type and traumatic mechanism in comparing patients second CT scan findings following an initial negative CT scan. Chi-Square test was used to analyze DOAC type in patients with initial negative CT head versus initial positive CT head. An alpha value of $p < .05$ was used to differentiate statistical significance.

Results

The study included a total of 498 patient encounters for confirmed or suspected blunt head trauma in adult patients on DOACs. 400 unique patients comprised all 498 encounters as 15.5% of patients presented more than once during the study period. Mean age of patient encounters was 76 (SD 14) years. 277 were females (55.6%) and 221 (44.4%) were males. Fall was the most common mechanism of injury (96.9%) with most being low height or ground level fall.

The first CT scan of the head was negative in 479 of these encounters (96.2%). Of these patients encounters with a negative initial CT scan of the head, 59 patient encounters (12.3%) did not have a repeat head CT scan and 420 patient encounters (87.7%) under-

Table 1
Comparison Results for Initial Negative CT Head versus Initial Positive CT Head.

		Negative First CT (N=479)	Positive First CT (N=19)	Comparison P-value
Age		75.8 (13.6), [79.0]	80.1 (9.7), [82.0]	0.240 (W)
Sex	Female	262 (54.7%)	15 (78.9%)	0.058 (F)
	Male	217 (45.3%)	4 (21.1%)	
DOAC	Apixaban	311 (64.9%)	10 (52.6%)	0.420 (C)
	Dabigatran	33 (6.9%)	1 (5.3%)	
	Rivaroxaban	135 (28.2%)	8 (42.1%)	
Mechanism	Assault	6 (1.3%)	0 (0.0%)	0.529 (F)
	Fall	461 (96.2%)	18 (94.7%)	
	MVC	7 (1.5%)	1 (5.3%)	
	Struck**	5 (1.0%)	0 (0.0%)	
GCS		14.9 (0.6), [15.0]	14.8 (0.4), [15.0]	0.106 (W)
ISS		3.3 (3.2), [1.0]	9.9 (6.5), [6.0]	<0.001 (W) *
ASA	No	--	11 (57.9%)	--
	Yes	--	8 (42.1%)	
Clopidogrel	No	--	18 (94.7%)	--
	Yes	--	1 (5.3%)	

Table 1: Comparison Results for patient encounters with initial negative CT of the head versus initial positive CT scan of the head. Numerical data is given as Mean (Standard Deviation), [Median]. (W) = Wilcoxon Rank Sum Test. (C) = Chi-Square Test. (F) = Fisher's Exact Test. * Statistically Significant, $P < 0.05$. ** Head struck with hard object.

Table 2
Comparison Results for Second Negative CT Head versus Second Positive CT Head Using only Patients with a Negative First CT Result.

		Negative First CT/ Negative Second CT (N=418)	Negative First CT/ Positive Second CT (N=2)	Comparison P-value
Age		75.4 (13.9), [79.0]	61, 81, [71.0]	0.524 (W)
Sex	Female	229 (54.8%)	1 (50.0%)	1.000 (F)
	Male	189 (45.2%)	1 (50.0%)	
DOAC	Apixaban	278 (66.5%)	1 (50.0%)	0.559 (F)
	Dabigatran	29 (6.9%)	0 (0.0%)	
	Rivaroxaban	111 (26.6%)	1 (50.0%)	
Mechanism	Assault	3 (0.7%)	0 (0.0%)	1.000 (F)
	Fall	405 (96.9%)	2 (100%)	
	MVC	5 (1.2%)	0 (0.0%)	
	Struck**	5 (1.2%)	0 (0.0%)	
GCS		14.9 (0.6), [15.0]	10, 15, [12.5]	0.033 (W) *
ISS		3.0 (3.1), [1.0]	6, 17, [11.5]	0.022 (W) *
ASA	No	---	1 (50.0%)	---
	Yes	---	1 (50.0%)	---
Clopidogrel	No	---	2 (100.0%)	---
	Yes	---	0 (0.0%)	---

Table 2: Comparison results for a negative second CT of the head versus positive second CT of the head using only Patients with a negative first CT result. Numerical data is given as Mean (Standard Deviation), [Median]. Individual patient values presented in Column two for Age, GCS and ISS, N=2. (W) = Wilcoxon Rank Sum Test, (F) = Fisher's Exact Test. * Statistically Significant, P < 0.05. ** Head struck with hard object.

went a second head CT scan. Of those 420 encounters with a repeat head CT scan, 418 encounters had a negative second CT head (99.5%) and 2 had a positive second CT head scans (0.5%). 95% CI [0.06%, 1.7%].

Of the 19 total patient encounters with a positive initial CT scan of the head (3.8%), 15 (78.9%) had a positive repeat CT head scan. 2 patient encounters (10.5%) had repeat CT head scans which were negative for acute intracranial hemorrhage. 2 of the 19 patient encounters (10.5%) did not have a repeat CT head imaging.

Looking at the results of the initial CT scan imaging, we found that the positive initial CT scan encounters have a significantly higher median ISS than the negative first CT scan encounters (6.0 vs 1.0, $p < 0.001$). We also found that the first positive CT scans for intracranial hemorrhage were more likely, but did not reach statistical significance, to involve female patients when compared to patients with an initial negative CT scan (78.9% female vs 54.7%, $p = 0.058$). The type of DOAC, presenting GCS and the type of trauma mechanism did not have a statistically significant impact on the likelihood of a positive first CT scan. Table 1.

Looking at the second CT scan results, we only had two patients (0.5%) who had a new positive finding on their second head CT scan after having a negative initial CT scan which limits the statistical power to make clinical guidelines and conclusions. We found that those patients had statistically significant higher median ISS than those with a negative second CT scan (11.5 vs 1.0, $p = 0.022$) with actual ISS of 6 and 17 for those two patients. We also found that those two patients had lower median GCS compared to those who did not have a new intracranial hemorrhage (12.5 vs 15, $p = 0.033$) but with actual values of 10 and 15 making it hard to draw clinically significant conclusions due to low statistical power. There was no statistically significant relationship between sex, type of DOAC (Apixaban, Rivaroxaban, or Dabigatran), and mechanism of injury with the likelihood of developing a positive repeat CT scan after an initial negative scan. (see Table 2).

Discussion

This study evaluates the rate of initial and delayed intracranial hemorrhage in patients on DOACs after confirmed or suspected blunt head trauma. Presently, there are a limited number of studies that assess the risk of delayed intracranial hemorrhage exclusively

in patients on DOACs. Of these studies, the results regarding the necessity of repeat imaging to assess for delayed intracranial hemorrhage are mixed [9–12]. Furthermore, the sample sizes of patients on DOACs in these studies are limited compared to the sample size used in this study. Given the rising use of these medications in clinical practice for treatment of atrial fibrillation and venous thromboembolism, particularly in geriatric patients who are at higher risk of falls, this data is important in evaluating the risks and benefits of their use and help in the management guidelines after head trauma. Admitting all head trauma patients on DOACs to perform a routine repeat head CT scan does increase healthcare costs and resource utilization with a potential increase in hospital acquired patient related adverse events. Presently, there is data to suggest that foregoing repeat CT head imaging following a normal initial CT head in patients on aspirin, clopidogrel, and vitamin K antagonists with therapeutic INR may be reasonable due to low rates of delayed intracranial hemorrhage [9,13–17]. Furthermore, repeat CT head imaging in patients who developed delayed intracranial hemorrhage did not significantly change management, regardless of the type of antithrombotic therapy [18].

This study detected an overall incidence of 3.81% of ICH on initial head CT for confirmed or suspected blunt head trauma patients on DOACs. This comparable to rates cited in other studies. Rates as low as 2% has been reported in patients on anticoagulant therapy by Campiglio, et al. [19]. Rates of ICH as high as 10.8% was reported in patients on anticoagulation by Nishijima et al, though interestingly, this study also did not identify anticoagulant therapy as a risk factor for ICH when compared to a rate of 9.1% in patients not on anticoagulant or antiplatelet therapy [20]. Our study detected an incidence of 0.47% (N = 2) for new delayed ICH after an initial negative CT scan. This is lower than previously reported rates in patients on DOACs with head trauma with smaller sample sizes [10,19,21]. Baramparas reported a rate of 0.8% in patients on DOACs, while Cohan et al. reported a rate of 2.1% in patients [21]. Campiglio et. al reported a rate of 1.4%, though it should be noted that this study population was inclusive of patients on warfarin and low molecular weight heparin [19]. There is some data to suggest that the risk of ICH in head trauma patients on DOACs is equal or lower than in patients on vitamin K antagonists [10,22,23].

Of note, the two patients in our study with new delayed ICH on the second CT scan did not require any neurosurgical interven-

tion and both were discharged. These findings support our hypothesis and suggest that routine use of repeat CT head imaging after a negative initial CT in neurologically stable patients on DOACs with low mechanism blunt head trauma did not confer any significant clinical benefits and will result in unnecessary costs and over-utilization of healthcare resources.

In a recent study by Chenoweth et al., 2 out of 3 patients with blunt head trauma developed a delayed intracranial hemorrhage 3–5 days following the initial insult [7]. Thus, it is also possible that repeat head imaging within 24 hours may not be the most reliable method to detect patients with delayed intracranial hemorrhages, however, they are most likely minor [24].

Notably, patients who developed delayed intracranial hemorrhage in this study presented with a statistically significant lower GCS (10 and 15) and higher ISS (6 and 17) than in patients with two negative CT head scans but with limited statistical power due to a very small group size, N=2. This finding poses the question of what risk factors may confer a higher risk of developing intracranial hemorrhage within the population of patients taking DOACs that will guide us in selecting higher risk patient for observation and/or repeat imaging. Cocca, et al. found a substantially higher incidence of delayed intracranial hemorrhage of 20.8% in geriatric patients over the age of 64 taking DOACs, of which 72% of patients experienced loss of consciousness [25]. These results highlight that age and loss of consciousness as possible factors that may identify patients who would benefit from repeat imaging. Another recent study done in Korea identified elderly age, associated craniofacial fracture, neck injury, diabetes mellitus, and hypertension as risk factors for delayed intracranial hemorrhage [26]. Additional research in patients with delayed intracranial hemorrhage is needed to determine what such risk factors are and their utility in medical decision making. Such factors such as age, loss of consciousness, time from last medication dose, amnesia to event, and medical comorbidities may be beneficial to establish clearer guidelines.

It's important to note that 15.5% of our patients presented with more than one fall during the study time period revealing a significant repeat fall risk in these patients. For that reason, our hospital refers all fall patients over 65 year of age to a "Stand Steady" physical therapy program. This intervention is designed to identify patients who are at high risk for falls and provide assistance and interventions that could reduce the risk of future falls.

We believe that only select patients on DOACs might still benefit from an admission and observation following blunt head trauma. High risk presentation criteria include higher ISS, lower GCS or the presence of other injuries requiring an admission. Such patients within this subgroup may require repeat imaging depending on their clinical and neurological status. Some have also suggested that admission with close monitoring of neurological status is as effective as repeat CT head imaging [6].

Conclusion

Our data suggests that the risk of developing a new delayed intracranial hemorrhage for low mechanism severity blunt head trauma patients on Direct Oral Anticoagulation (DOAC) on a second CT head within 24 hours following an initial negative CT head is extremely low, and when present, did not require neurosurgical intervention. These findings do not support routinely obtaining a repeat CT head within 24 hours after a negative initial head CT scan. Close patient follow-up after discharge might be warranted. Patients presenting with lower GCS and higher ISS had a higher chance of having an intracranial hemorrhage. However, observation and selectively repeating head imaging may be beneficial in select high risk patients. Lower GCS and higher ISS upon presentation may be an indicator of such risks.

Previous research presentation

None.

Compliance with ethical standards

All procedures—if any—performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent

Informed consent does not apply to this retrospective study.

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Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Maha Mourad: Conceptualization, Methodology, Data curation, Formal analysis, Validation, Writing – review & editing. **Ayla Senay:** Conceptualization, Methodology, Data curation, Formal analysis, Validation, Writing – review & editing. **Bilal Kharbutli:** Conceptualization, Methodology, Data curation, Formal analysis, Validation, Writing – review & editing.

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