The American Journal of Surgery 217 (2019) 1051–1054

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

The risk of delayed intracranial hemorrhage with direct acting oral anticoagulants after trauma: A two-center study

Galinos Barmparas [a, *], Leslie Kobayashi [b], Navpreet K. Dhillon [a], Kavita A. Patel [a], Eric J. Ley [a], Raul Coimbra [b], Daniel R. Margulies [a]

[a] Department of Surgery, Division of Acute Care Surgery and Surgical Critical Care, Cedars-Sinai Medical Center, Los Angeles, CA, USA
[b] Department of Surgery, Division of Trauma, Surgical Critical Care, Burns and Acute Care Surgery, University of California, San Diego, CA, USA

ARTICLE INFO

Article history:
Received 15 March 2018
Accepted 9 October 2018

Keywords:
Oral anticoagulants
Delayed intracranial hemorrhage
Traumatic brain injury
NOACs
DOACs

ABSTRACT

Background: The aim of this study was to characterize the risk of a delayed intracranial hemorrhage (ICH) in trauma patients on direct-acting oral anticoagulants (DOACs).
Methods: Patients on DOACs admitted to two Level I Trauma Centers between 2014 and 2017 were reviewed. Only patients with a negative admission CT brain were included. The primary outcome was a delayed ICH.
Results: Overall, 249 patients were included. The median age was 81 years with 82% undergoing a repeat CT. Three patients developed a delayed ICH (1.2%). One developed an ICH after receiving tissue plasminogen activator for a cerebrovascular accident after two negative CTs. Excluding this patient, the incidence dropped to 0.8%. None required neurosurgical intervention.
Conclusion: For patients at risk for a TBI who are on DOACs, repeat cross-sectional imaging of the brain when the initial imaging is negative is not necessary. A period of clinical observation may be warranted.

Introduction

Mounting evidence supports the use of direct-acting oral anticoagulants (DOACs) for various clinical entities including venous thromboembolism, pulmonary embolism and atrial fibrillation.[1–3] The safety profile of these agents appears to be acceptable,[4,5] making their use more attractive to patients and caregivers given no routine blood tests are required to ensure appropriate and adequate anticoagulation effect. This has led to a substantial increase in their prescription.[6,7] In fact, the use of these agents has now surpassed the use of vitamin K antagonists in the United Kingdom and Canada.[7,8]

Pre-admission anticoagulants may lead to an increased risk for bleeding and other complications following trauma.[9] For traumatic brain injuries (TBI) in particular, the use of warfarin prior to admission is associated with an increased risk for injury progression leading to increased mortality, especially in the elderly.[10–12] Given the increasing trends in DOAC prescription for the prevention of cerebrovascular events and pulmonary emboli,[7,8] the use of these agents is expected to increase in trauma patients, potentially replacing warfarin as the most common anticoagulant. Developing safe and cost effective guidelines to appropriately screen these patients for TBI can lead to earlier identification of these injuries, improved outcomes, and appropriate resource utilization.

The indications for obtaining a computerized tomography (CT) of the brain in anticoagulated patients remain controversial. The need for repeat imaging to rule out delayed intracranial hemorrhage (ICH) in the absence of injury on admission CT may be even more debatable, with older literature supporting[13] and more recent studies questioning its utility.[14,15] Much of this literature refers to the use of warfarin and antiplatelet agents, however, very little is known about the risk for a delayed ICH in patients on DOACs.

The purpose of this study was to examine the risk for a delayed ICH in patients on DOACs who are at risk for a TBI and who have a negative admission CT of the brain. Our hypothesis was that delayed ICH risk is small and justifies observation with serial neurological exams in lieu of repeat CT imaging of the brain prior to discharge.

* Corresponding author. Cedars-Sinai Medical Center, Department of Surgery, 8635 W. 3rd Street – Suite 650W, Los Angeles, CA, 90048, USA.
E-mail address: Galinos.Barmparas@cshs.org (G. Barmparas).

https://doi.org/10.1016/j.amjsurg.2018.10.016
0002-9610/

Material and methods

Trauma patients admitted to two tertiary, Level I Trauma Centers between November 2014 and September 2017 were reviewed for the following inclusion criteria:

1. Use of DOACs including apixaban, dabigatran and rivaroxaban prior to admission.
2. CT of the brain obtained upon admission that was interpreted as negative for an acute intracranial injury.

Patients who were on DOACs and had TBI identified on admission and patients who did not undergo CT brain were excluded.

Demographics, injury characteristics and the presence of co-morbid conditions were reviewed. All admission and subsequent CT scans of the brain were reviewed in detail, as were all subsequent interventions pertaining to the brain. The primary outcome was development of a delayed ICH, defined as an ICH identified on subsequent imaging obtained either due to a routine protocol or due to an observed change in neurological exam.

The institutional protocols at the two participating centers differ. At the University of California, San Diego (UCSD), all trauma patients on anticoagulants are routinely admitted for observation and serial neurological exams. A repeat head CT is also routinely obtained within 4–6 h, independent of the results of the initial CT. Reversal of anticoagulation for DOACs depends on the presence of a TBI and/or an associated major hemorrhage. At the Cedars-Sinai Medical Center (CSMC) all patients on DOACs are routinely admitted for observation and serial neurological exams, however, a routine repeat CT brain is not mandatory, unless a change in the neurological exam is observed. The practice of reversal of DOACs is similar to that at UCSD and these agents are reversed only in the presence of associated life-threatening hemorrhage and/or TBI.

Standard descriptive statistics were utilized to characterize the study cohort. Continuous variables were reported as medians with interquartile ranges (IQR) and binary variables were reported as percentages. All statistical analyses were performed using the IBM SPSS Statistics package, version 24. Independent Institutional Review Board approval was obtained by each participating center.

Results

Over the almost 3-year study period, a total of 249 trauma patients on DOACs were admitted to the two participating trauma centers with a negative initial CT of the brain. The median age was 81 years (IQR: 68, 88 years) and 54.6% were male (Table 1). The most common injury mechanism was from a fall (n = 200 or 80.3%), followed by motor vehicle collision (n = 20 or 8.0%). The majority of patients were admitted with a Glasgow Coma Scale (GCS) score of 15 (n = 176 or 70.7%), with only 4 patients (1.6%) being admitted with a GCS score of 8 or less. The median injury severity score (ISS) was 5 (IQR: 1, 10). Patients often had multiple co-morbidities, with 69.1% having a cardiac history, 56.2% a history of hypertension requiring medications, and 20.5% a history of diabetes mellitus (Table 1).

Rivaroxaban was the most commonly used DOAC (n = 117 or 47.0%), followed by apixaban (n = 103 or 41.4%) and dabigatran (n = 29 or 11.6%) (Table 2). A total of 12 patients (4.8%) were also receiving an antiplatelet agent, including acetylsalicylic acid (ASA) (n = 9) or clopidogrel (n = 3).

A small proportion of these patients received blood products within 24 h from admission, which included packed red blood cells (n = 3), fresh frozen plasma (n = 4) and platelets (n = 4). Fifteen patients (6.0%) required mechanical ventilation. The overall mortality was 1.2% (n = 3) (Table 3).

Table 1
Demographics and injury characteristics.

	Study Cohort (n = 249)
Age (years), Median (IQR)	81 (68, 88)
Male, % (n)	54.6 (136)
Race, % (n)	
Black	4.4 (11)
Hispanic	18.1 (45)
White	70.7 (176)
Other	5.2 (13)
Unknown	1.6 (4)
Mechanism of Injury, % (n)	
Fall	80.3 (200)
MVC	8.0 (20)
Found down	4.0 (10)
Assault	2.8 (7)
Other	4.8 (12)
Admission GCS, Median (IQR)	15 (14, 15)
Admission GCS, % (n)	
= 3	0
≤8	1.6 (4)
= 14	24.9 (62)
= 15	70.7 (176)
Admission SBP (mmHg), Median (IQR)	140 (125, 156)
Admission SBP < 90 mmHg, % (n)	0.4 (1)
ISS, Median (IQR)	5 (1, 10)
Co-morbidities, % (n)	
Alcohol abuse	6.4 (16)
Cardiac history	69.1 (172)
Diabetes mellitus	20.5 (51)
Hypertension	56.2 (140)
Obesity	14.9 (37)
Malignancy	7.6 (19)
Renal failure	14.5 (36)
Smoking	6.0 (15)

IQR, Interquartile Range; MVC, Motor Vehicle Collision; GCS, Glasgow Coma Scale; SBP, Systolic Blood Pressure; ISS, Injury Severity Score.

Overall, 81.5% (n = 203) had at least one repeat head CT during their hospital stay, with the remaining being observed clinically. Patients who received a repeat CT were observed for at least one hospital day and those who did not were observed for a minimum of 2 hospital days. None of the patients presented again to the hospital with a delayed ICH.

Only three patients (1.2%) developed a delayed ICH found on subsequent CT brain and all three were on different DOACs (Table 1). None of these patients required a surgical intervention in the form of craniotomy and/or craniectomy. Two patients were admitted with a GCS of 14. The third patient, who was admitted with a GCS of 15, had two negative CTs of the brain but was subsequently found to have cerebrovascular infarction. The patient received tissue plasminogen activator (tPA) resulting in a subarachnoid hemorrhage (Table 4 and Fig. 1). After excluding this patient, the incidence of a delayed ICH decreased to 0.8% (2/249) or 8 per 1000 admissions.

Table 2
Prehospital anticoagulants.

	Study Cohort (n = 249)
DOAC, % (n)	
Apixaban	41.4 (103)
Dabigatran	11.6 (29)
Rivaroxaban	47.0 (117)
Other anticoagulants, % (n)	
ASA	3.6 (9)
Warfarin	0 (0)
Clopidogrel	1.2 (3)
Other anticoagulants	0 (0)

DOAC, Direct-acting Oral Anticoagulant; ASA, Acetylsalicylic Acid.

Table 3
Interventions and outcomes.

	Study Cohort (n = 249)
Endotracheal intubation, % (n)	6.0 (15)
Required transfusion within 24 h, % (n)	
PRBC	1.2 (3)
FFP	1.6 (4)
Platelets	1 (0.4)
Required surgical intervention, % (n)	7.2 (18)
Hospital days, Median (IQR)	3 (2, 6)
ICU days, median (IQR)	3 (2, 4)
Ventilator days	5 (2, 9)
Mortality, % (n)	1.2 (3)

PRBC, Packed Red Blood Cells; FFP, Fresh Frozen Plasma; ICU, Intensive Care Unit.

Discussion

In this largest to date review of trauma patients on prehospital DOACs with an initially negative CT brain, the incidence of a delayed ICH was less than 1%. The two patients who developed a delayed ICH presented with altered mental status (GCS of 14) were diagnosed on a routine repeat CT within 6 h after admission and neither required subsequent neurosurgical intervention. A third patient received tPA for a cerebrovascular accident and developed a delayed subarachnoid hemorrhage after two negative repeat CTs so this complication was unlikely related to the prior use of DOAC. There was no association between a specific DOAC and the development of a delayed ICH.

The observed low incidence of delayed ICH and the universal absence of a need for a subsequent neurosurgical intervention in these patients suggest that a policy of routine repeat imaging for all patients on DOACs with a negative initial CT of the brain is unnecessary. However, a routine period of clinical observation for serial neurological exams can be considered.

The trauma patient population is increasingly aging. The 2016 National Trauma Data Bank report indicates that the proportion of patients over the age of 65 years now exceeds 30% of all admission and these patients have the highest fatality rate.[16] The use of anticoagulants in this patient population to prevent cerebrovascular events is exceedingly common.[17–19] In an American Association for the Surgery for Trauma (AAST) sponsored multi-institutional study, Kobayashi et al. found that 10% of trauma patients on anticoagulants receive DOACs, 50% receive an antiplatelet agent, and over a third receive warfarin.[20] The increased use of anticoagulants among trauma patients has led to rapid reversal protocols to prevent TBI progression and improve outcomes.[21,22] These TBI protocols have become best practice guidelines recommended by the American College of Surgeons.[23]

Less is known about the development of delayed ICH in patients on anticoagulant agents with a negative CT brain on admission. Nishijima et al. conducted a prospective observational study including over 1000 patients on either warfarin or clopidogrel and

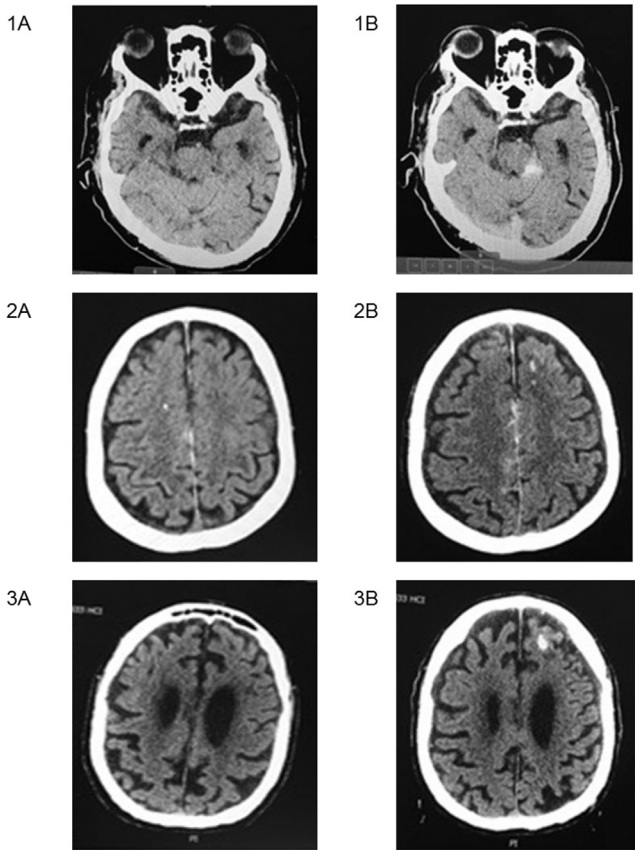

Fig. 1. Representative images from the computerized tomography (CT) on admission (1A, 1B and 1C) and the subsequent (CT) showing a delayed intracranial hemorrhage (2A, 2B, 2C) for patients 1, 2 and 3 respectively (refer to Table 4).

determined that the incidence of a delayed ICH was extremely low (<1%) and was only observed in patients on warfarin.[14] Others have also found similar incidence in patients on warfarin.[23–27] In a recent study from Chenoweth et al., the incidence of delayed ICH in patients on anticoagulants, including DOACs, was similarly very low (<1%).[28] This study however, included only 37 patients on DOACs of which none developed a delayed ICH. The number of patients on DOACs reviewed in the current study was substantially higher with over 80% of patients undergoing a repeat CT of the brain, further validating the observation that the incidence of a delayed ICH with DOACs is exceedingly small.

Based on our findings, a routine repeat CT of the brain in patients on DOACs when the initial CT is unlikely to alter patient care. Further justifying this observation is the fact that neither of the two patients who developed delayed ICH in our series required a neurosurgical intervention. A specified period of clinical

Table 4
Patients who developed a delayed intracranial hemorrhage.

	Age (years)	Sex	DOAC	Mechanism	Admission GCS	Number of initial negative CT brain	Synopsis/Outcome	Hospital days	Disposition
1	82	Male	Rivaroxaban	Fall	14	1	Patient observed, no intervention required	12	Long-term facility
2	68	Male	Dabigatran	Found down	15	2	Patient had two negative head CTs, was found to have altered mental status due to a cerebrovascular incident. Patient received tPA and then developed SAH.	19	Long-term facility
3	83	Male	Apixaban	Fall	14	1	Patient observed, no intervention required	9	Home

DOAC, Direct-acting Oral Anticoagulant; GCS, Glasgow Coma Scale; CT, Computed Tomography; tPA, Tissue Plasminogen Activator; SAH, Subarachnoid Hemorrhage.

observation with serial neurological exams is likely a safe practice, especially for patients with a GCS lower than 15.

Despite being the largest review of patients on DOACs examining the risk of delayed ICH following trauma, there are a few limitations that need to be accounted for. The retrospective nature of this work introduces potential selection and other bias. It is possible that patients with unknown home medications were excluded from this analysis. Although the majority of our patients underwent a repeat CT of the brain, almost 20% did not, potentially missing a delayed ICH not captured on imaging. As the minimum period of observation for patients who did not undergo a repeat CT of the brain was 2 hospital days, the possibility of missing a clinically significant delayed ICH was small. The specific indication for obtaining a CT of the brain in these patients and their risk assessment for an associated TBI could not be evaluated and/or categorized. Lastly, the absence of a common protocol by the two participating institutions introduces variation in practices. However, based on available literature the practice of a routine repeat CT in this setting and the practice of clinical observation only with serial neurological exams are both justified.

Conclusions

In conclusion, for patients who are at risk for a traumatic brain injury and who are on prehospital direct-acting oral anticoagulants, mandatory repeat CT brain when the initial imaging is negative is unnecessary. A period of clinical observation with serial neurological examinations however, may be warranted given the small risk for a delayed intracranial hemorrhage.

Author contributions

Study conception and design: Galinos Barmparas, MD; Leslie Kobayashi, MD.

Acquisition of data: Leslie Kobayashi, MD; Navpreet K. Dhillon, MD; Galinos Barmparas, MD.; Kavita A. Patel

Analysis and interpretation of data: Navpreet K. Dhillon, MD; Galinos Barmparas, MD; Leslie Kobayashi, MD.

Literature Review: Galinos Barmparas, MD; Leslie Kobayashi, MD; Navpreet K. Dhillon, MD.

Drafting of manuscript: Galinos Barmparas, MD; Leslie Kobayashi, MD; Navpreet K. Dhillon, MD.

Critical revision: Eric J. Ley, MD; Daniel R. Margulies, MD; Raul Coimbra, MD, PhD.

Conflicts of interest

The authors have no conflicts of interest to report and have received no financial support in relation to this manuscript.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2018.10.016.

References

1. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799–808.
2. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. *Cochrane Database Syst Rev*. 2015;12:CD010957.
3. Sterne JA, Bodalia PN, Bryden PA, et al. Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis. *Health Technol Assess*. 2017;21(9):1–386.
4. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med*. 2018;378(7):615–624. https://doi.org/10.1056/NEJMoa1711948.
5. Monaco L, Biagi C, Conti V, et al. Safety profile of the direct oral anticoagulants: an analysis of the WHO database of adverse drug reactions. *Br J Clin Pharmacol*. 2017;83(7):1532–1543.
6. Weitz JI, Semchuk W, Turpie AGG, et al. Trends in prescribing oral anticoagulants in Canada, 2008-2014. *Clin Therapeut*. 2015;37(11):2506–2514. e4.
7. Loo SY, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. *Br J Clin Pharmacol*. 2017;83(9):2096–2106.
8. Yu AYX, Malo S, Svenson LW, Wilton SB, Hill MD. Temporal trends in the use and comparative effectiveness of direct oral anticoagulant agents versus warfarin for nonvalvular atrial fibrillation: a Canadian population-based study. *J Am Heart Assoc*. 2017;6(11), e007129.
9. Ferrera PC, Bartfield JM. Outcomes of anticoagulated trauma patients. *Am J Emerg Med*. 1999;17(2):154–156.
10. Williams TM, Sadjadi J, Harken AH, Victorino GP. The necessity to assess anticoagulation status in elderly injured patients. *J Trauma Inj Infect Crit Care*. 2008;65(4):772–777.
11. Karni A, Holtzman R, Bass T, et al. Traumatic head injury in the anticoagulated elderly patient: a lethal combination. *Am Surg*. 2001;67(11):1098–1100.
12. Mina AA, Knipfer JF, Park DY, Bair HA, Howells GA, Bendick PJ. Intracranial complications of preinjury anticoagulation in trauma patients with head injury. *J Trauma*. 2002;53(4):668–672.
13. Guidelines for minor head injured patients' management in adult age. The Study Group on Head Injury of the Italian Society for Neurosurgery. *J Neurosurg Sci*. 1996;40(1):11–15.
14. Nishijima DK, Offerman SR, Ballard DW, et al. Immediate and delayed traumatic intracranial hemorrhage in patients with head trauma and preinjury warfarin or clopidogrel use. *Ann Emerg Med*. 2012;59(6):460–468. e7.
15. Miller J, Lieberman L, Nahab B, et al. Delayed intracranial hemorrhage in the anticoagulated patient. *J Trauma Acute Care Surg*. 2015;79(2):310–313.
16. American College of Surgeons. *NTDB Reports and Publications. National Trauma Data Bank Report*; 2016. Published https://www.facs.org/quality-programs/trauma/ntdb/docpub. Accessed February 20, 2018.
17. Friberg L, Bergfeldt L. Atrial fibrillation prevalence revisited. *J Intern Med*. 2013;274(5):461–468.
18. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *J Am Med Assoc*. 2001;285(18):2370–2375.
19. Hobbs FDR, Fitzmaurice DA, Mant J, et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technol Assess*. 2005;9(40):1–74. iii-iv, ix-x.
20. Kobayashi L, Barmparas G, Bosarge P, et al. Novel oral anticoagulants and trauma. *J Trauma Acute Care Surg*. 2017;82(5):827–835.
21. Gulati D, Dua D, Torbey MT. Hemostasis in intracranial hemorrhage. *Front Neurol*. 2017;8:80.
22. Frontera JA, Lewin III JJ, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. *Neurocritical Care*. 2016;24(1):6–46.
23. Peck KA, Sise CB, Shackford SR, et al. Delayed intracranial hemorrhage after blunt trauma: are patients on preinjury anticoagulants and prescription antiplatelet agents at risk? *J Trauma Inj Infect Crit Care*. 2011;71(6):1600–1604.
24. Docimo S, Demin A, Vinces F. Patients with blunt head trauma on anticoagulation and antiplatelet medications: can they be safely discharged after a normal initial cranial computed tomography scan? *Am Surg*. 2014;80(6):610–613.
25. Miller J, Lieberman L, Nahab B, et al. Delayed intracranial hemorrhage in the anticoagulated patient. *J Trauma Acute Care Surg*. 2015;79(2):310–313.
26. Difiori M, Lamb L, Kis L, et al. Readmissions in anticoagulated intracranial hemorrhage patients. *Crit Care Med*. 2016;44(12):452.
27. Alrajhi KN, Perry JJ, Forster AJ. Intracranial bleeds after minor and minimal head injury in patients on warfarin. *J Emerg Med*. 2015;48(2):137–142.
28. Chenoweth JA, Gaona SD, Faul M, Holmes JF, Nishijima DK, Sacramento County Prehospital Research Consortium. Incidence of delayed intracranial hemorrhage in older patients after blunt head trauma. *JAMA Surg*. February 2018. https://doi.org/10.1001/jamasurg.2017.6159.