Intracerebral Hemorrhagic Expansion Occurs in Patients Using Non–Vitamin K Antagonist Oral Anticoagulants Comparable with Patients Using Warfarin

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Background: Non–vitamin K antagonist oral anticoagulant (NOAC) use has significantly reduced intracerebral hemorrhagic (ICH) risk compared with standard anticoagulant treatment. Hematoma expansion (HE) is a known predictor of mortality in warfarin-associated ICH. Little is known about HE in patients using NOACs. *Methods:* We conducted a retrospective chart review of patients with ICH admitted to Cedars-Sinai Medical Center from October 2010 to June 2016. We identified patients with concomitant administration of an oral anticoagulant and collected data including evidence of HE on imaging and modified Rankin Scale (mRS) at discharge. We defined HE as relative (≥33% increase) or absolute expansion (≥12 mL). We compared outcomes of patients with and without HE. *Results:* Out of 814 patients with ICH who were admitted, we identified 9 patients with recent NOAC use and 18 intentionally matched controls on warfarin. We found no significant differences in National Institutes of Health Stroke Scale or ICH score on presentation (median [interquartile range] 15 [5,21] versus 7 [1.25,19.5] [$P = .41$] and 2 [1,4] versus 1 [1,3] [$P = .33$]) between patients on NOACs and those on warfarin. Four out of the 9 patients on NOAC and 5 of the 18 patients on warfarin demonstrated HE, with no significant difference ($P = .42$). There were no significant differences in mRS on discharge between groups ($P = .52$). *Conclusions:* In our coagulopathic NOAC patient population, HE occurs within 6 hours in 44% of patients. This case series did not have sufficient statistical power to detect significant differences between the groups. To our knowledge, this is one of the largest case series reporting on HE with concomitant NOAC use. **Key Words:** Critical care—hematoma expansion—intracerebral hemorrhage—novel oral anticoagulants—stroke.

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Ethics approval was obtained from the Cedars-Sinai Medical Center institutional review board (IRB). The need for patient consent was waived by the IRB as it is a retrospective analysis.

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest: Dr Asma Moheet served on the Scientific Advisory Board for Portola Pharmaceuticals. The remaining authors declare that they have no conflict of interest.

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Introduction

Intracerebral hemorrhage (ICH) following use of anticoagulants has been well described in the past 75 years.[1-3] Currently, the annual incidence of warfarin-associated major bleed is 0%-16%.[4-9] In the last 6 years, 4 non–vitamin K antagonist oral anticoagulants (NOACs) have been approved by the Food and Drug Administration (FDA) for the treatment of non-valvular atrial fibrillation (AF) and venous thromboembolism: dabigatran in October 2010, rivaroxaban in November 2011, apixaban in December 2012, and edoxaban in January 2015. NOACs are being used increasingly over warfarin because of their relative ease of use and significant reduction of ICH risk by about 50% as compared with standard treatment,[10,11] specifically, by 60%-69% with dabigatran,[12] 33% with rivaroxaban,[13] and 58% with apixaban.[14] ICH still occurs in 0.2%-0.5% of patients on NOACs.[10-14] The 3-month mortality is similar to that of warfarin-associated ICH[10] and occurs at a rate of 52%-67%.[15]

ICH hematoma expansion (HE) is a substantial predictor of mortality in warfarin-associated ICH.[7,15-21] Patients on warfarin are at almost double the risk of HE compared with non-anticoagulated patients (56% versus 26%).[17,22] Little is known about how NOAC use contributes to HE. Delayed HE risk in dabigatran use is minimal in animal models.[23,24] To date, there are only a handful of reported cases of HE in humans following dabigatran,[25-29] rivaroxaban,[30,31] and apixaban use. We sought to understand in better detail if and how HE contributes to mortality in patients with ICH while taking a NOAC.

Methods

This study was approved by the institutional ethical standards committee on human experimentation. Approval for exemption for written informed consent was received. This analysis met criteria for exclusion from informed consent as it was a retrospective chart review, and the patients had already consented to the collection and storage of the data and the principal investigator of the study had already been granted access to the data as the caring physician of the subjects. The data were de-identified before being viewed by any other research members.

We conducted a retrospective chart review of patients with ICH admitted to Cedars-Sinai Medical Center (CSMC) from October 2010 to June 2016 by searching the CSMC stroke patient registry that records key data on every patient with stroke and transient ischemic attack admitted via the emergency department. Non-emergent patients were identified by querying for all patients who came in with a possible acute stroke and ultimately diagnosed with ICH, as well as querying all patients admitted to the CSMC Neurocritical Care Unit between October 10, 2010 and June 30, 2016, who had ICH listed as diagnosis with a concomitant anticoagulant in their documented medication list. Patients aged 18 years or older with clinically definitive diagnosis of ICH with brain magnetic resonance (MR) or computerized tomography (CT) scans were included.

Patients with CT or MR angiograms that demonstrated underlying vascular lesions including arteriovenous malformation, cerebral aneurysms, or cavernous malformation were excluded. Patients with subdural, epidural, or subarachnoid hemorrhage but with no intraparenchymal hemorrhage were excluded. Patients with evidence of intracranial tumor on imaging were also excluded. Patients were excluded if they did not have both initial and follow up scans available for review, for reasons including withdrawal of life support before the second scan or if the original scan was obtained at an outside hospital.

We identified patients with concomitant administration of either a NOAC or warfarin and collected data, including the following: reason for agent prescription, time to brain imaging, evidence of HE on imaging, discharge status, and modified Rankin Scale (mRS) at discharge. Patient charts were evaluated for age, gender, ethnicity, NOAC type, NOAC dose, indication for NOAC, smoking status, statin use, hypertension, diabetes, AF, history of prior stroke or transient ischemic attack, ischemic heart disease, abnormal renal or liver function on admission, renal function on presentation, concomitant antithrombotics including aspirin, clopidogrel, enoxaparin or heparin, prior anticoagulation use, bleeding history or predisposition, last known well, symptom discovery time, time to presentation or triage, National Institutes of Health Stroke Scale (NIHSS) score on arrival, Glasgow Coma Scale score on arrival, scan time, subsequent scans time, CT or MRI done, vessel imaging, time to imaging, ICH score, ICH volume, presence of intraventricular hemorrhage, lobar location, underlying vascular lesion, glucose, International Normalized Ratio (INR), partial thromboplastin time (PTT), prothrombin time (PT), intervention, surgery, reversal agent given, mechanical ventilation while in intensive care unit, blood pressure (BP) on presentation, mean arterial pressure, follow-up BP at time of second scan, length of stay in hospital, length of stay in intensive care unit, mRS on discharge, and discharge disposition.

MRI and CT images were assessed for ICH using volume measurement both by the ABC/2 method[32] and volumetric analysis. Three-dimensional volumetric analyses of the cerebral blood volume were acquired via 3-dimensional rendering software from Vital Images workstation (ViTAL Images' Vitrea version 6.8 software; Minnetonka, MN); source data used for post-processing were from 2.5-mm cut non-contrast CT images. Manual contour segmentation was used to determine the blood pool volume within the cranium post identification of hemorrhage. This workflow was established to deliver accurate assessment of the blood pool versus relying on automation. After segmentation of hemorrhagic volume within