Characteristics of Symptomatic Intracerebral Hemorrhage in Patient Receiving Direct Oral Anticoagulants: Comparison with Warfarin

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Background: Direct oral coagulants (DOAC) have been shown to decrease the frequency of intracerebral hemorrhage (ICH) compared with warfarin. However, the precise characteristics, such as the size and locations of the hemorrhage, and outcome and onset time of ICH in patient taking DOAC are not fully elucidated. *Methods:* We retrospectively analyzed the characteristics of symptomatic patients with ICH taking either DOAC or warfarin between January 2012 and December 2015. *Results:* Out of 400 consecutive patients with ICH, 15 patients were DOAC-ICH and 24 patients were warfarin-ICH. DOAC-ICH was observed in 6 patients with 10 mg of rivaroxaban, 5 patients with 15 mg of rivaroxaban, and 1 patient with 10 mg of apixaban, 5 mg of apixaban, 30 mg of edoxaban, and 60 mg of edoxaban. Prothrombin time was well controlled in most of the warfarin-ICH patients (83.3%). The locations of ICH were similar in both groups; however, median ICH volume was significantly smaller in DOAC-ICH patients than in warfarin-ICH patients ($P < .01$) and ICH around basal ganglia seemed to show great difference between the groups. DOAC-ICH patients showed better neurological outcome at the time of discharge than warfarin patients ($P < .01$), and the ratio of good prognosis was significantly higher in the DOAC-ICH patients than in the warfarin-ICH patients ($P < .01$). The onset of warfarin-ICH was frequently observed in the morning and evening, whereas DOAC-ICH did not show any specific onset time. *Conclusions:* Patients with DOAC-ICH showed smaller ICH volume and better clinical outcomes than patients with warfarin-ICH, and DOAC-ICH did not show any specific onset peak. **Key Words:** DOAC—intracerebral hemorrhage—warfarin—stroke.

Intracerebral hemorrhage (ICH) is one of the most serious complications of oral anticoagulation, with high in-hospital mortality.[1] In large phase 3 trials, patients taking direct oral antagonist coagulants (DOAC) showed almost a half frequency of ICH compared with warfarin, despite the similar efficiency.[2] However, beside the hemorrhagic frequency data, few data on the precise clinical and neurological characteristics of DOAC-ICH are available, such as severity of the hemorrhage and neurological outcome. There is widespread concern that, without any currently available specific antidotes for most of the DOAC, DOAC-ICH might have larger ICH volumes and worse clinical outcomes than warfarin-ICH.[3,4] Furthermore,

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DOAC are shown to have shorter plasma half-life compared with warfarin, and the magnitude of the serological change is thought to be the cause of hemorrhage, but the onset timing of hemorrhage is also unknown. In this study, we aim to elucidate the characteristics of DOAC-ICH in comparison with warfarin-ICH patients who were admitted to our single local comprehensive stroke center.

Methods

Ethical Statement

This study was conducted in accordance with the guideline principles of the Declaration of Helsinki and was approved by the local ethics committee of Otaru General Hospital. All patients or their families gave either oral or written informed consent to participate in this study.

Patients

We retrospectively analyzed symptomatic patients with ICH who were taking either warfarin or DOAC at the time of admission between January 2012 and December 2015. The following clinical factors and outcome at the time of hospital discharge were examined retrospectively: age; sex; previous history of ischemic stroke or ICH, underlying illness; type of DOAC; dose of DOAC or warfarin; concurrent anticoagulation; blood test results; predictive scores for the risk of bleeding (HAS-BLED, ATRIA, ORBIT); number of positive T2* on magnetic resonance (MR) imaging; ICH-related information (location, hematoma volume, surgical treatment), and clinical prognosis at the time of discharge (modified Rankin scale [mRS]). Hematoma volume was calculated with the following formula using measurements of a plain computed tomography image of the brain: maximum length of an ellipsoid representing intracerebral hemorrhage × width perpendicular to maximum length × thickness of hematoma × .5.

Statistical Analysis

All data were expressed either as median (interquartile range [IQR]) or as average ± standard deviation. Continuous data were compared by unpaired *t* test or chi-square test between 2 groups, and cluster analysis was done by Kolmogorov–Smirnov test. *P* values < .05 were considered statistically significant.

Results

Of 400 consecutive patients with ICH, we have encountered 15 patients (3.8%) with DOAC-ICH and 24 patients (6.0%) with warfarin-ICH. The median age of the patients was slightly higher in the warfarin-ICH group (81 years old) than in the DOAC-ICH group (74 years old) ($P = .05$), but there was no gender difference. The patient with warfarin-ICH had taken 2.9 ± 1.0 mg of warfarin at the time of admission, and DOAC-ICH was observed in 6 patients with 10 mg of rivaroxaban, 5 patients with 15 mg of rivaroxaban, 1 patient with 10 mg of apixaban, 1 patient with 5 mg of apixaban, 1 patient with 30 mg of edoxaban, and 1 patient with 60 mg of edoxaban. Prothrombin time international normalized ratio (PT-INR) of the warfarin-ICH was 2.6 (2.1-2.9) and was well controlled; 20 of 24 warfarin-ICH patients (83.3%) showed PT-INR under 3.0, whereas PT-INR in the DOAC-ICH were as low as 1.2 (1.1-1.8) and was significantly lower than warfarin-ICH ($P < .01$). Coexisting illness was examined between the patients, and the rates of anemia (56.5% versus 13.3%, $P < .01$) and chronic renal failure (17.4% versus .0%, $P < .04$) were higher in the warfarin-ICH group; however, other coexisting illnesses such as congestive heart failure (warfarin versus DOAC; 29.2% versus 26.6), diabetes (29.2% versus 20.0%), hypertension (87.5% versus 90.0%), low total cholesterol (15.4% versus 26.3%), previous history of ischemic stroke (25.0% versus 26.7%), previous history of ICH (8.3% versus 6.7%), and number of positive T2* on MR imaging (1 [IQR 1-7] versus 2 [IQR 2-11]) did not show statistical difference between the groups (Table 1). Concomitant use of antiplatelet drugs was also similar between the groups ($P = .15$), in which 9 patients were observed in the warfarin-ICH group (7 patients with 100 mg of aspirin, 1 patient with 100 mg of ticlopidine, and 1 patient with 100 mg of aspirin and 200 mg of cilostazol), and 2 patients were observed in the DOAC-ICH group (1 patient with 100 mg of aspirin and 1 patient with 75 mg of clopidogrel). Because the warfarin-ICH patients were older and had higher rate of anemia and renal failure, all predictive scores for the risk of bleeding, such as HAS-BLED, ATRIA, and ORBIT, were shown to be statistically higher in the warfarin-ICH group.

The locations of ICH were similar in both groups, such as cerebral cortex, basal ganglia, and cerebellar nucleus, which resemble hypertensive cerebral hemorrhage (Fig 1). However, the median ICH volume was significantly smaller in DOAC-ICH (5.9 mL, IQR 3.5-12.3 mL) than in warfarin-ICH (27.0 mL, IQR7.3-39.3 mL) ($P < .01$). It seemed that the size of ICH around the basal ganglia seemed to be much smaller in the DOAC-ICH than in the warfarin-ICH. Warfarin-ICH showed higher tendency of emergency surgery for evacuation of ICH (50% versus 26%; $P = .15$) and hospital administration days (31 days versus 20 days; $P = .20$) (Table 2). DOAC-ICH patients showed better neurological outcome at the time of discharge (mRS 2, IQR 1-4) compared with warfarin-ICH patients (5, IQR 4-5) ($P < .01$), and the ratio of good prognosis (mRS 0-2 at discharge) was also significantly higher in the DOAC-ICH patients (53%) than in the warfarin-ICH patients (12.5%) ($P < .01$). When comparing the onset of ICH between warfarin and DOAC groups, there were several patients whose onset time were unclear because the patient may live by