Clinical Neurology and Neurosurgery 174 (2018) 63–67

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

The dose of direct oral anticoagulants and outcomes of intracerebral hemorrhage: Preliminary findings

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ARTICLE INFO

Keywords:
Overdose
Under-dose
Optimal dose
Hematoma volume
Outcome

ABSTRACT

Objectives: The effect of a direct-acting oral anticoagulant (DOAC) dose on intracerebral hemorrhage (ICH) severity and outcome remains unclear. The aim of this study is to clarify the frequency of off-label dosing of DOAC treatments in ICH patients and compare clinical characteristics.

Patients and methods: We studied 43 patients with ICH who were treated with DOAC for nonvalvular atrial fibrillation before the onset of ICH. DOAC treatments were categorized into three groups based on the following doses: optimal dose, under-dose, and overdose.

Results: Overall, 31 patients were optimally dosed, 10 were under-dosed, and 2 were overdosed. $CHADS_2$ and CHA_2DS_2-VASc scores were the highest in the overdose group (median, 4, 6, respectively) and the lowest in the optimal dose group (median, 2, 4, respectively) ($p = 0.006$, $p = 0.005$, respectively). ICH severity measured using the National Institutes of Health Stroke Scale scores was the highest in the overdose group (median, 26.5) and the lowest in the under-dose group (median, 6.5) ($p = 0.244$). Larger initial hematoma volume was observed in the overdose group. The ratio of good outcome (modified Rankin Scale score ≤ 2) was higher in the under-dose group (40%) than the other groups, but this difference was not significant.

Conclusion: Our study shows only a few patients received overdosing of a DOAC before the onset of ICH, and they were associated with poorer functional outcomes. Conversely, under-dosing was associated with better functional outcomes than the other groups.

1. Introduction

Direct-acting oral anticoagulants (DOAC) are increasingly used as substitutes for warfarin because of their more favorable safety and efficacy profiles [1,2]. In randomized, clinical trials, patients taking a DOAC showed almost half the frequency of intracerebral hemorrhage (ICH) compared with warfarin [2]. Moreover, recent studies have shown that even if ICH occurs, DOAC-related ICH results in smaller ICH volumes and better clinical outcomes than warfarin-related ICH [3–6]. This may be because of the different mechanisms in the coagulation pathway targeted by warfarin and DOAC; the effects of DOAC can be readily overcome by tissue factor-mediated activation of blood coagulation compared with warfarin [7].

The effect of DOAC dosing on ICH severity and outcome has not been elucidated, although under-dosing or overdosing of DOAC prescriptions are common in general practice [8–10]. Patients overdosed with a DOAC may develop larger ICH volumes or experience poorer outcomes than those under-dosed with a DOAC.

The aim of this study is to clarify the frequency of off-label dosing of DOAC treatments in ICH patients and compare clinical characteristics, stroke severity, ICH volume and clinical outcomes, with each dose of a DOAC (optimal dose, under-dose and overdose).

2. Material and methods

This study included 43 consecutive Japanese patients with nonvalvular atrial fibrillation who were treated with a DOAC before the onset of ICH and then admitted to our hospital for ICH between March 2014 and February 2018. For the purpose of the study, DOAC treatments were categorized into three groups as follows: (1) the optimal dose group, (2) the under-dose group, and (3) the overdose group. The DOAC dose was evaluated based on the manufacturer's labeling

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https://doi.org/10.1016/j.clineuro.2018.09.011
Received 27 July 2018; Received in revised form 2 September 2018; Accepted 4 September 2018
Available online 05 September 2018

Table 1
Dosing information for patients with non-valvular atrial fibrillation according to the Japanese summary of product characteristics.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Release date	March 2011	April 2012	February 2013	September 2014
Standard dose	300 mg/day	15 mg/day	10 mg/day	60 mg/day
Reduced dose	220 mg/day	10 mg/day	5 mg/day	30 mg/day
Dose adjustment	No definite dose reduction criteria 220 mg/day recommended if: ● Age ≥70 years ● CrCl 30–50 mL/min ● History of major bleeding ● Use of p-glycoprotein inhibitors	10 mg/day if: ● CrCl 15–50 mL/min	5 mg/day if two of: ● Body weight ≤60 kg ● Serum Cr levels ≥1.5 mg/dL ● Age ≥80 years	30 mg/day if: ● Body weight ≤60 kg ● CrCl 15–50 mL/min ● Use of p-glycoprotein inhibitors

CrCl: Creatinine clearance, Cr: Creatinine.

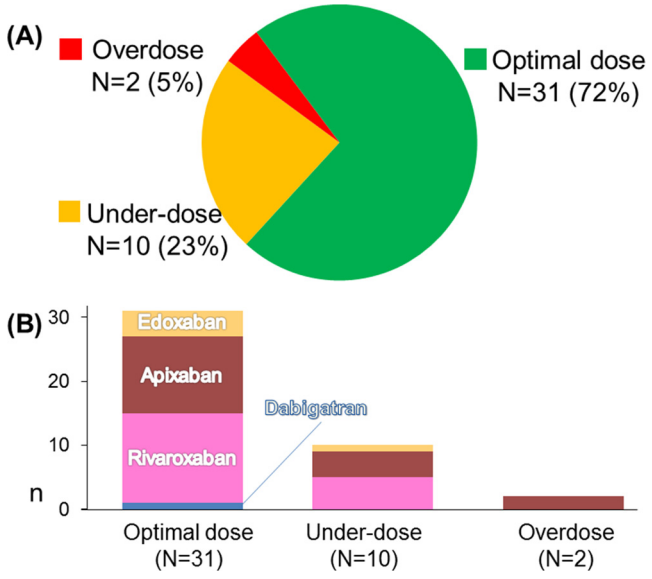

Fig. 1. (A) Direct-acting oral anticoagulants (DOAC) dosing before the onset of intracerebral hemorrhage (ICH). (B) Number of DOAC prescriptions before the onset of ICH. As shown, the number of patients administered DOAC overdoses is very small.

recommendations for Japan (Table 1). Patients who were prescribed a lower drug dose, but did not meet the criteria for dose reduction, were grouped in (2). Patients who were prescribed a standard drug dose, but met the criteria for dose reduction, were grouped in (3).

Electronic medical charts and summaries were retrospectively reviewed to obtain the following variables: demographic information (age and sex), body weight, body mass index, pre-admission modified Rankin Scale (mRS) score [11], DOAC prescriber (from a university hospital, regional hospital, specialist clinic [cardiology, neurology, or neurosurgery], or general clinic), and past medical history. Cardiovascular risk factors were defined as follows: (i) hypertension, a history of using antihypertensive agents, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg before or ≥2 weeks after onset of stroke; (ii) diabetes mellitus, use of hypoglycemic agents, random glucose levels ≥200 mg/dL, or glycosylated hemoglobin ≥6.5% on admission; (iii) dyslipidemia, use of antihyperlipidemic agents, or serum low-density lipoprotein cholesterol levels ≥140 mg/dL; (iv) current smoking; (v) alcohol intake, consumption of more than 10 g alcohol/day ; (vi) prior stroke; (vii) coronary artery disease, angina, or prior myocardial infarction; and (viii) heart failure, a history of congestive heart failure, or an ejection fraction < 40%. The pre-stroke $CHADS_2$ score, CHA_2DS_2-VASc score, or HAS-BLED score was calculated for each patient based on the published literature [12–14].Serum creatinine and creatinine clearance (Cockcroft–Gault equation [15]), prothrombin time-international normalized ratio (PT-INR), and activated partial thromboplastin time (APTT) upon admission were also evaluated.

Stroke severity was assessed by the Glasgow Coma Scale (GCS) score and the National Institutes of Health Stroke Scale (NIHSS) score. ICH location, initial hematoma volume and expansion during follow-up were assessed based on computed tomography. The ICH volume was calculated using the ABC/2 method from the initial axial computed tomography images [16].The diameters of A and B were measured by the screen ruler, and C (slice thickness) was 5 mm. Hematoma expansion was defined as an increase of more than 33% or 6 ml from the initial ICH volume within 72 h [17]. Surgical or conservative therapy, clinical outcome using the mRS score at discharge, duration of hospital stay, and discharge destinations (home, rehabilitation hospital, or nursing home) were also evaluated. The mRS score of 0–2 was defined as a good outcome. All aspects of this study were approved by the institutional ethics committee (approval #18-015).

Data are expressed as the median (interquartile range) or n (%). One-way analysis of variance followed by Bonferroni post-hoc tests for continuous variables, or the Pearson χ^2 test for categorical variables were used to compare differences between the three groups. Statistical analysis was performed using PASW Statistics software (version 20; SPSS Inc., Chicago, IL). All p values are 2-sided, with $p < 0.05$ considered statistically significant.

3. Results

Among 1039 patients with ICH, 43 (4.1%) were taking a DOAC. There were 16 women and 27 men, with a mean age of 73 ± 9 years. Thirty-one patients (72%) were treated with an optimal dose, 10 patients (23%) were under-dosed, and 2 patients (5%) were treated with an overdose before the onset of ICH (Fig. 1A). Dabigatran was prescribed in only one case in our study (Fig. 1B).

The patient profiles of each group are shown in Table 2. The mean age and sex distributions were similar in all groups. Body weight in the overdose group was smaller than the other groups, though this difference was not statistically significant. The pre-admission mRS score was good in all of the groups. BMI and creatinine clearance were the largest in the optimal dose group and the smallest in the overdosed group, though this difference was not statistically significant. The overdoses of DOAC were all prescribed from the general clinic.

The risk factors for each group were not significantly different except for a higher prevalence of diabetes in the overdose group and a higher prevalence of prior ICH in the under-dose group. $CHADS_2$ and CHA_2DS_2-VASc scores were the highest in the overdose group and the