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Original Article

Trends in physiological coagulation factors in Japanese patients receiving novel oral anticoagulants

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ABSTRACT

Background: Little is known about physiological anticoagulation effects via antithrombin III (AT III) and protein C/S (PC/PS) in patients using new oral anticoagulants (NOACs).
Methods: We evaluated 120 consecutive patients with non-valvular atrial fibrillation (AF) receiving NOACs. Patients were randomly divided into three groups: a dabigatran group (DG, $N=40$), a rivaroxaban group (RG, $N=40$) or an apixaban group (AG, $N=40$). A warfarin group (WG, $N=40$) was matched with NOAC groups for age, sex and type of AF during the same time period. Blood samples were obtained in pretreatment, trough and peak phases to measure the activity of physiological coagulation inhibitors, including AT III and PC/PS or thrombus formation markers such as D-dimer and thrombin–antithrombin complex (TAT).
Results: D-dimer, TAT and AT III values for the NOAC groups were equivalent in the peak and trough phases. PC/PS activity in both phases was equally maintained in the pretreatment phase in the NOAC groups, while the activity in the WG was significantly suppressed in steady state. Moreover, no differences in trends for PC/PS activity were observed among NOAC groups.
Conclusions: PC/PS activity was constant in both peak and trough phases in the patients on NOACs compared with activity of those on warfarin. In addition, there was no difference in the findings among NOACs.

1. Introduction

Anticoagulation therapy for patients with atrial fibrillation (AF) is essential for prophylaxis against ischemic stroke and systemic embolism [1,2]. There has been a rapid shift in anticoagulants used for this purpose, from conventional anticoagulants, vitamin K antagonists (VKA) to novel oral anticoagulants (NOACs) [3]. NOACs include the direct thrombin inhibitor, dabigatran, and factor Xa (FXa) inhibitors, rivaroxaban and apixaban. Recently published randomized clinical trials have supported the efficacy and safety of NOACs compared with the VKA, warfarin [4–6].

Warfarin acts as an anticoagulant by inhibiting the production of the vitamin K-dependent coagulation factors II, VII, IX, and X. In contrast, NOACs selectively and reversibly target thrombin or FXa. Additionally, NOACs have a rapid onset and short half-lives. This causes fluctuations in their effects between peak and trough phases compared with warfarin, which develops a constant anticoagulation effect throughout the entire day [7]. The aforementioned clinical trials have demonstrated a similar incidence of stroke and systemic embolism despite the unique pharmacological features of NOACs [4–6]. Meanwhile, Protein C/Protein S (PC/PS) and AT III have additional antithrombotic effects as physiological anticoagulation factors. However, little is known about whether NOAC use has influence on trends in these physiological anticoagulant factors. Therefore, the purpose of the study is to reveal the trends in physiological inhibitors such as AT III, PC or PS, and

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markers of thrombus formation in patients receiving NOACs compared with those using warfarin.

2. Methods

2.1. Study population

We prospectively investigated 120 consecutive patients with non-valvular AF who were prescribed NOACs at the Chubu Rosai Hospital between April 2015 and May 2016. The 120 patients were randomly divided into three groups: dabigatran group (DG, $N=40$), rivaroxaban group (RG, $N=40$), or apixaban group (AG, $N=40$). This study was approved by our Institutional Committee on Human Research. In addition, all patients provided written informed consent for study participation. Exclusion criteria were as follows: patients with congenital coagulation defects or creatinine clearance (Ccr) < 30 mL/min. Ccr was determined using the Cockcroft Gault formula. The dabigatran dose was decided according to the renal function or age of patients. A low dose of dabigatran (110 mg twice daily) was administered to patients who had the following conditions: moderate renal dysfunction (Ccr 30–50 mL/min), advanced age (≥ 70 years), a history of upper gastrointestinal ulcer, or co-administration of glycoprotein inhibitors (amiodarone or verapamil). A low dose of rivaroxaban (10 mg once daily) was administrated to patients with mild renal dysfunction (Ccr 30–50 mL/min). The apixaban dose was decided according to age, body weight, or renal function. A low apixaban dose (2.5 mg twice daily) was administered to patients with any two of the following characteristics: advanced age (≥ 80 years), renal dysfunction (serum creatinine concentration ≥ 0.5 mg/dL) and lower body weight (≤ 60 kg). The patients in the RG were administrated rivaroxaban as a morning dose. The warfarin group (WG) consisted of the same number of patients as each NOAC group, matched for age, sex, and type of AF during the same time period. The warfarin dose was adjusted to maintain a target international normalized ratio (INR) of 1.6–2.6 for older (≥ 70 years) and 2.0–3.0 for younger individuals (< 70 years).

3. Blood sampling

Blood samples for NOAC groups were obtained from each patient before beginning the administration, immediately before morning dose (trough phase) and approximately 3 hours after they had received the anticoagulants (peak phase) when the peak plasma concentration of NOACs had been reached.

In addition, the samples in the peak and trough phases were collected > 7 days after the start of anticoagulant therapy as a steady state measurement in the DG, RG, or AG, while the samples in the WG were obtained at random times. Measurement parameters in each phase included prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer, thrombin–antithrombin complex (TAT), AT III, and PC/PS, which were compared across phases and anticoagulant groups. In tests of blood coagulation, values for PT and APTT were obtained using Thromborel S® and Thrombocheck aPTT-SLA® as the reagent, respectively. D-dimer or TAT was determined using a quantitative latex agglutination assay or enzyme immunoassay, respectively. AT III, PC or PS activity was measured using the Factor Xa-based method, chromogenic method, or free protein S antigen latex immunoassay method, respectively.

3.1. Statistical analysis

All continuous variables were expressed as mean ± SD or as median and interquartile ranges. All categorical variables were reported as number (percentage) of patients. A paired Student's *t* test, Mann–Whitney *U* test, one-way analysis of variance (ANOVA), or Kruskal–Wallis test was used to compare the continuous variables, and categorical variables were compared using a chi-square or Fisher exact test. Differences were considered statistically significant at $P < 0.05$. All the results were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

4. Results

4.1. Patients' characteristics

Blood samples were collected from a total of 120 patients using NOACs. Groups of 40 patients were allocated to the DG, RG, or AG. The 40 patients receiving warfarin were extracted matched for age, sex and type of AF with the patients in each NOAC group during the same time period. The baseline characteristics of each group are summarized in Table 1. Overall, no significant difference in any factor was observed among the groups except for the data on the rate of low-dose treatments.

4.2. Trends in the coagulation markers in each anticoagulant group

Trends for coagulation markers in each anticoagulant group are shown in Table 2. In the peak phase, the PT value for the RG and WG was longer than that of the DG and AG (13 ± 2 s, 17 ± 2 s, 13 ± 1 s and 27 ± 4 s in the DG, RG, AG and WG, respectively; Table 2) while the APTT for the DG and RG was longer than that of the other groups (46 ± 3 s, 47 ± 5 s, 35 ± 2 s, and 41 ± 3 s in the DG, RG, AG, and WG, respectively; Table 2). Moreover, APTT values

Table 1
Patient characteristics.

	DG $N=40$	RG $N=40$	AG $N=40$	WG $N=40$	*P* value
Age (years)	69 ± 8	70 ± 7	70 ± 6	69 ± 10	0.85
Sex (female)	10 (25)	10 (25)	13 (33)	12 (30)	0.84
Body weight (kg)	60 ± 18	58 ± 11	58 ± 11	56 ± 7	0.79
Paroxysmal AF	20 (50)	18 (45)	19 (48)	18 (36)	0.98
Coronary artery disease	9 (23)	9 (24)	8 (20)	7 (18)	0.94
Hypertension	21 (53)	16 (40)	23 (58)	18 (45)	0.41
Diabetes mellitus	15 (38)	8 (20)	10 (25)	10 (25)	0.21
History of heart failure	6 (15)	7 (18)	3 (8)	4 (10)	0.52
Prior stroke/TIA	5 (13)	3 (8)	3 (8)	4 (10)	0.85
CHADS2 score	1.7 ± 1.5	1.6 ± 1.1	1.8 ± 1.2	1.6 ± 1.3	0.94
0	5 (13)	6 (15)	4 (10)	8 (20)	0.62
1	12 (30)	13 (33)	11 (28)	12 (30)	0.97
≥ 2	23 (58)	21 (53)	25 (63)	20 (50)	0.32
CHA2DS2-VASc score	3.2 ± 2.0	2.8 ± 1.3	3.2 ± 1.5	2.2 ± 1.6	0.26
LA size (mm)	41 ± 4	43 ± 6	44 ± 5	44 ± 7	0.53
LVEF (%)	68 ± 7	59 ± 10	67 ± 10	65 ± 6	0.17
BNP (pg/mL)	95 (15, 286)	194 (87, 513)	140 (90, 232)	149 (46, 300)	0.41
Ccr (mL/min)	59 ± 13	59 ± 11	54 ± 14	54 ± 14	0.61
Low dose	28 (70)	20 (50)	10 (25)	–	< 0.001

Values are the mean ± standard deviations (SD) or *n* (%). **Abbreviations**: WG, warfarin group; DG, dabigatran group; RG, rivaroxaban group; AG, apixaban group; AF, atrial fibrillation; TIA, transient ischemic attack; LA, left atrium; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; Ccr, creatinine clearance; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time.

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