ORIGINAL ARTICLES

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Analysis of factors affecting time in therapeutic range control after warfarin administration

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The protective efficacy of warfarin for cardiogenic cerebral embolism has been established. However, warfarin is generally administered to only approximately 35% of the atrial fibrillation patients who required warfarin therapy. It has been reported that international normalized ratio (INR) control was carried out appropriately in < 50% of such patients. Therefore, from the viewpoint of prevention of the onset and recurrence of embolism, the maintenance of a stable anticoagulant level is necessary. In warfarin therapy, in addition to INR control, time in therapeutic range (TTR) also markedly affects the efficacy of warfarin therapy. Therefore, we classified patients into two groups on the basis of the cutoff TTR $\geq$ 65% at which the inhibitory effect of warfarin on stroke has been observed. We aimed to examine the association between INR and TTR with the correction of the therapeutic efficacy of warfarin by analyzing the factors leading to poor TTR control. The most valuable finding of this study is that marked fluctuations of brain natriuretic peptide levels in patients with complication of heart failure was a risk factor for poor TTR control. Identification of the factors leading to the poor TTR control is useful for making the decision to switch to other anticoagulants, such as dabigatran or apixaban, or to continue warfarin by correcting risk factors in atrial fibrillation patients receiving long-term warfarin therapy.

1. Introduction

In Japan, the number of patients with atrial fibrillation increases with the aging of the population and poor lifestyle choices. Epidemiological studies by the Japanese Circulation Society have shown that the number of patients with atrial fibrillation is approximately 0.8 million. It has also been reported that the number of such patients will surpass 1 million in 2030 (Inoue et al. 2009). Atrial fibrillation is the most important risk factor for thromboembolism regardless of whether it is paroxysmal, persistent, or chronic. In particular, once cerebral embolism develops, it severely compromises the prognosis or quality of pipe of a patient, which is a serious problem. In view of the increase in the number of patients with atrial fibrillation, we hypothesize that the number of such patients who will develop cardiogenic cerebral infarction will increase in the future, which may cause problems for society. The prognosis of cardiogenic cerebral embolism due to atrial fibrillation is very poor, with an approximately 50% chance of surviving 1 year after its diagnosis, as shown by the Hisayama Study (Kubo et al. 2006). The protective efficacy of warfarin for cardiogenic cerebral embolism has been established for nonvalvular atrial fibrillation patients. It has been reported that warfarin can prevent cardiogenic cerebral embolism in approximately 68% of the patients (Atrial Fibrillation Investigators 1994). Therefore, warfarin is recommended in the Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013) (JCS Joint Working Group 2013) for nonvalvular atrial fibrillation patients with a risk of embolism. There are clinical reports stating warfarin dose is insufficient in patients requiring warfarin therapy (Lip and Lim 2007). The reason why some physicians hesitate to administer warfarin is to avoid related complications. There has been a report that major bleeding due to warfarin is associated with the frequency of warfarin doses formulated by physicians (Choudhry et al. 2006). The efficacy of warfarin therapy depends on the target treatment level during the therapy, i.e., time in therapeutic range (TTR). In addition, the international normalized ratio (INR) should be controlled to attain the target treatment level during warfarin therapy. This means that TTR markedly affects the efficacy of warfarin therapy. Morgan et al. (2009) reported that TTR and the incidence of cerebral infarction strongly correlate; i.e., the incidence of cerebral infarction is low when TTR control is good. When TTR is low, we cannot expect warfarin to be therapeutically efficacious, and it increases the risk of complications such as bleeding (Wallentin et al. 2010). It has been reported that when TTR is < 65%, the therapeutic efficacy of warfarin cannot be achieved (Connolly et al. 2008). Thus, the usefulness of TTR control has been reported, but few reports about the factors that lead to a poor TTR control exist. Therefore, in this study, we investigated such factors in patients with atrial fibrillation who were receiving warfarin.

2. Investigations and results

2.1. Patients' background features

Table 1 shows the result of comparison of the background features between the good-TTR-control group (male, 24; female,

Table 1: Comparison of the background features between the good TTR control group and the poor TTR control group

Variables	All patients (n = 55)	good TTR control group (n = 31)	poor TTR control group (n = 24)	*p* value
Male (%)	41 (75)	24 (77)	17 (71)	0.5782
Age (years)	67.8 ± 1.4	66.1 ± 11.7	70.0 ± 7.8	0.2548
Weight (kg)	64.4 ± 10.3	66.2 ± 11.0	62.3 ± 9.6	0.2637
BMI (kg/m^2)	23.9 ± 2.8	23.9 ± 2.8	23.9 ± 2.8	0.9594
Heart failure (%)	34 (62)	14 (45)	20 (83)	0.0039
Hypertension (%)	31 (57)	17 (55)	14 (58)	0.7955
Diabetes (%)	15 (27)	6 (19)	9 (37)	0.1340
Stroke (%)	5 (9)	2 (6)	3 (13)	0.4390
TIA (%)	1 (2)	1 (3)	0 (0)	0.3745
Dyslipidemia (%)	15 (27)	7 (23)	8 (33)	0.3745
Smoking (%)	26 (47)	15 (48)	11 (46)	0.5176
Average WF dose (mg)	3.5 ± 1.5	3.4 ± 1.6	3.6 ± 1.4	0.2555
Average INRs/WF dose (mg)	0.7 ± 0.2	0.7 ± 0.3	0.6 ± 0.2	0.0899
Combination of antiplatelet drugs (%)	13 (24)	8 (26)	5 (21)	0.6668
History of bleeding (%)	4 (7)	3 (10)	1 (4)	0.6237
Frequency of measurements of PT-INR	8.5 ± 1.5	8.3 ± 1.5	8.7 ± 1.8	0.3314
CHADS2 score (point)	1.6 ± 1.3	1.6 ± 1.1	2.4 ± 1.3	0.0278
HAS-BLED score (point)	1.2 ± 0.9	1.1 ± 0.8	1.3 ± 1.0	0.4718

Abbreviations: Warfarin, WF; BMI, Body Mass Index; TIA, transient ischemic attacks.
Values are mean ± S.D. *p* value (Student's t-test, Mann–Whitney U-test, χ^2 test, Fisher's exact test)

7) and the poor-TTR-control group (male, 17; female, 7). There were no significant differences in sex, age, weight, body mass index (BMI), complications (hypertension, diabetes, stroke, transient ischemic attack (TIA), or dyslipidemia), the percentage of patients with smoking history, average warfarin dose, average INR/warfarin dose, the percentage of patients receiving a combination of antiplatelet drugs, the percentage of patients with a history of bleeding, the frequency of measurements of prothrombin time-international normalized ratio (PT-INR), and HAS-BLED score between these two groups. The percentage of patients with a history of heart failure were 45% and 83%, $CHADS_2$ scores were 1.6 ± 1.1 points and 2.4 ± 1.3 points, respectively. These data showed significantly lower values in the good-TTR-control group.

2.2. Comparison of laboratory data

Table 2 shows the result of comparison of laboratory data before warfarin administration between the two groups. There were no significant differences in aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), serum creatinine (Scr), estimated glomerular filtration rate (eGFR), total cholesterol (T-Cho), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), C-reactive protein (CRP), total protein (TP), albumin (Alb), red blood cell (RBC) count, hemoglobin (Hb), hematocrit (Hct), brain natriuretic peptide (BNP), systolic blood pressure (SBP), and diastolic blood pressure (DBP). The coefficient of variation-INR (CV-INR) values were 0.2 ± 0.1 and 0.3 ± 0.1 in the good- and poor-TTR-control groups, respectively. This data showed significantly lower values in the good-TTR-control group. %INR was significantly higher (71.7 ± 17.8%) in the good-TTR-control group than in the poor-TTR-control group (42.0 ± 15.0%).

2.3. Multiple logistic regression analysis

We analyzed various factors associated with the poor TTR control in all the 55 patients by multiple logistic regression analysis. As a result, significant differences were observed in the percentage of patients with heart failure as a complication (Table 3).

2.4. Association between PT-INR fluctuation range (ΔPT-INR) and BNP fluctuation range (ΔBNP)

We investigated the association between ΔPT-INR and ΔBNP in 44 patients whose ΔBNP was measured before and after the warfarin therapy out of all the 55 surveyed patients suspected of having heart failure. As a result, the ΔBNP < 49.7 pg/mL group and the ΔBNP ≥ 49.7 pg/mL group showed ΔPT-INRs of 1.1 ± 0.4 and 1.6 ± 0.8, respectively. These data showed a significantly higher ΔPT-INR in the ΔBNP ≥ 49.7 pg/mL group (Fig.).

3. Discussion

The most valuable finding of this study is that BNP levels fluctuated markedly in patients with heart failure, indicating that this is a risk factor for poor TTR control. The usefulness of TTR control has been reported, but there have been few studies analyzing the factors for poor TTR control. This is a radically new finding on factors for poor TTR control. It is necessary to pay particular attention to the factor revealed in this study as surrogate marker in the future. In addition, it is necessary to keep on monitoring PT-INR to improve TTR control by pharmacists, who should intervene actively and suggest to the physician the need for warfarin dose adjustment. It is considered that it is necessary to educate patients to improve their treatment adherence.

The protective efficacy of warfarin for cardiogenic cerebral embolism has been established (Atrial Fibrillation Investigators 1994). However, warfarin was generally administered to only approximately 35% of the atrial fibrillation patients who required warfarin therapy. It has been reported that INR control was carried out appropriately in < 50% of such patients (Samsa et al. 2000). Moreover, it has been reported that in many patients who developed embolism during warfarin therapy, their anticoagulant level was unstable (Inoue et al. 2006). Therefore, from the viewpoint of the prevention of the onset and recurrence of

Table 2: Comparison of laboratory data between the good TTR control group and the poor TTR control group

Variables	All patients (n = 55)	Good TTR control group (n = 31)	Poor TTR control group (n = 24)	*p* value
AST (IU/L)	30.0 ± 18.6	26.0 ± 6.3	35.2 ± 26.7	0.3455
ALT (IU/L)	26.0 ± 15.5	22.2 ± 6.4	31.0 ± 21.7	0.2273
BUN (mg/dL)	17.3 ± 6.1	17.5 ± 6.1	17.1 ± 6.2	0.7656
Scr (mg/dL)	0.9 ± 0.4	0.9 ± 0.2	0.9 ± 0.5	0.3333
eGFR (mL/min)	59.1 ± 18.3	60.8 ± 16.7	57.0 ± 20.2	0.4636
T-Cho (mg/dL)	171.2 ± 27.7	175.5 ± 28.1	166.3 ± 27.2	0.2795
TG (mg/dL)	103.7 ± 47.7	105.7 ± 41.3	100.0 ± 55.8	0.4816
HDL-C (mg/dL)	53.6 ± 18.4	50.7 ± 12.3	56.6 ± 23.2	0.3257
LDL-C (mg/dL)	96.6 ± 21.3	99.8 ± 20.4	92.5 ± 22.2	0.2286
CRP (mg/dL)	0.4 ± 1.2	0.6 ± 1.6	0.2 ± 0.1	0.9804
TP (g/dL)	7.0 ± 0.6	7.1 ± 0.5	6.9 ± 0.6	0.3497
Alb (g/dL)	4.0 ± 0.4	4.1 ± 0.5	4.0 ± 0.4	0.2905
RBC ($\times 10^6/\mu$L)	4.4 ± 0.6	4.4 ± 0.6	4.3 ± 0.7	0.7315
Hb (g/dL)	13.8 ± 1.9	14.0 ± 1.7	13.5 ± 2.1	0.3410
Hct (%)	41.4 ± 6.0	41.7 ± 5.5	40.9 ± 5.8	0.5244
BNP (pg/mL)	222.4 ± 276.4	169.1 ± 155.0	288.4 ± 370.8	0.2994
SBPs (mmHg)	126.8 ± 22.1	121.9 ± 18.8	132.8 ± 24.6	0.1144
DBPs (mmHg)	75.5 ± 13.7	73.9 ± 13.1	77.5 ± 14.5	0.3374
CV-INR	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.1	0.0017
%INR (%)	58.8 ± 22.1	71.7 ± 17.8	42.0 ± 15.0	< 0001

Abbreviations: CRP, total protein; TP, albumin; Alb, red blood cell; RBC, hemoglobin; Hb, hematocrit; Hct, brain natriuretic peptide; BNP, systolic blood pressure; SBP, diastolic blood pressure; DBP, coefficient of variation-INR; CV-INR; AST, aspartate aminotransferase; ALT, alanine aminotransferase; blood urea nitrogen; BUN, serum creatinine; Scr, estimated glomerular filtration rate; eGFR, total cholesterol;T-cho, triglyceride; TG, high-density lipoprotein cholesterol; HDL-C, low-density lipoprotein cholesterol; LDL-C, c-reactive protein; CRP.
Values are mean ± S.D. *p* value (Student's t-test, Mann–Whitney U-test, χ^2 test)

embolism, the maintenance of a stable anticoagulant level is necessary. In addition to INR control, INR should be maintained to attain the target treatment level during warfarin therapy, which means that TTR markedly affects the efficacy of warfarin therapy (Morgan et al. 2009). Therefore, we classified patients into two groups on the basis of the cutoff TTR ≥ 65%, at which the inhibitory effect of warfarin on stroke has been observed (Connolly et al. 2008). We aimed to examine the association between INR and TTR with the correction of the therapeutic efficacy of warfarin by analyzing the factors leading to poor TTR control.

The percentage of patients with heart failure as a complication in the poor-TTR-control group was 83%, as determined from the results of univariate analysis, which was significantly higher than that in the good-TTR-control group. It has been reported that heart failure increases the relative risk of embolism in patients with atrial fibrillation (Atrial Fibrillation Investigators 1994). Therefore, anticoagulant therapy is essential in the treatment of atrial fibrillation with concomitant heart failure in conjunction with the treatment of heart failure. However, when we consider the pharmacokinetics of drugs for heart failure, the absorption of drugs administered to patients with heart failure may be poor owing to certain factors such as decreased blood flow or edema in the gastrointestinal tract. For example, in the presence of ascites and pleural effusion, the volume of circulating blood increases, thereby decreasing the total and free drug levels in the blood. In addition, we consider that the clearance from the renal and liver is decreased when renal blood flow and hepatic blood flow are decreased. Therefore, we hypothesized that the warfarin levels in blood may vary owing to hemodynamic fluctuation. Therefore, we investigated the association between ΔPT-INR and ΔBNP in 44 patients whose ΔBNP was measured before and after the warfarin therapy. BNP level is an auxiliary marker for the diagnosis of heart failure (Akazawa et al. 2008) and there are reports that it is related to hemodynamics (Yasue et al. 1994; Maeda et al. 1998). In this study, we suggest that PT-INR varies markedly when BNP levels vary markedly as well, suggesting that the warfarin level is susceptible to the fluctuation of circulating plasma volume. We consider that the cause of PT-INR variation in heart failure patients is the fluctuation of circulating plasma volume due to clinical condition and treatment. We hypothesize that free warfarin levels in

Table 3: Results of stepwise multiple logistic regression analysis for associated with poor TTR control

Variable	Odds ratio	95% CI	*p* value
Heart failure	6.071	1.803–24.743	0.0030

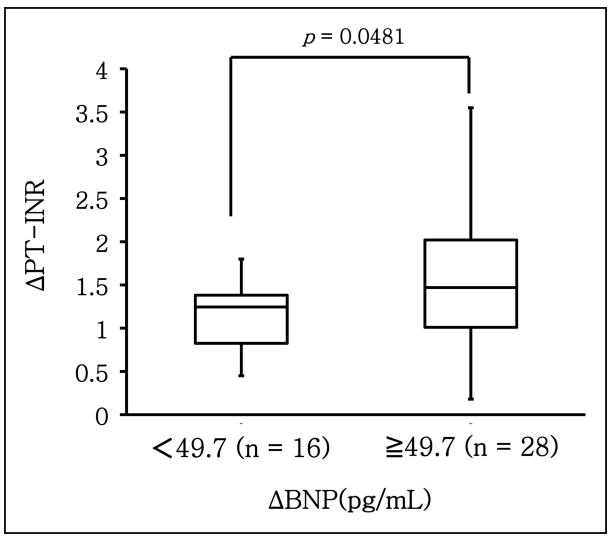

Fig.: Association between ΔPT-INR and ΔBNP. We calculated ΔPT-INR by subtracting the minimum from the maximum during the observation period. We divided the patients into two groups on the basis of the median ΔBNP (49.7 pg/mL).

plasma affect the circulating plasma volume because the distribution volume of warfarin is approximately 0.1 L/kg (Toon et al. 1986), which is very small. Heart failure as factors against unstable control of warfarin therapy has been reported in several studies (Tomita et al. 2013; Toon et al. 1986).

In this study, we were able to obtain the results supporting the previous report.

However, there have been no studies reporting the level of heart failure in previous studies. We were able to reveal the level of heart failure by using ΔBNP. We consider that this is a radically new finding on factors for poor TTR control.

Therefore, we consider that we should exactly measure PT-INR focusing on the fluctuations in circulating plasma volume when we use warfarin for atrial fibrillation patients with heart failure. There is a report that examined whether assessment of warfarin dosing every 12 weeks is as safe as assessment every 4 weeks. The results showed that no significant differences were observed regarding the percentage of time in the therapeutic range and the number of extreme INRs, changes in maintenance dose, major bleeding events, objectively verified thromboembolism, and death (Schulman et al. 2011). However, as shown the results of this study, we consider that PT-INR should be measured at least once a month in the patients with heart failure in whom BNP levels vary markedly.

The limitations of this study are as follows. It is a single-center cross-sectional work. It is necessary to examine a prospective, multicenter study based on the results of this work. In addition, it has been reported that other factors cause fluctuation of patient plasma prothrombin time (PT), such as being carriers of warfarin susceptibility genes (for example, CYP2C9 and vitamin K epoxide reductase complex subunit 1 (VKORC1)), intake of vitamin-K-containing food, medication adherence, and drug interactions (Kodani et al. 2011). However, we were unable to investigate these factors because this study was a retrospective study. It has been reported that in particular, mutation of both the CYP2C9 and VKORC1 genes can explain approximately 60 % of individual differences in warfarin maintenance dose (Takahashi 2010). Therefore, we hypothesize that these factors may have affected the results of this study. In addition, PT-INR is calculated by multiplying the International Sensitivity Index (ISI) and PT ratio (patient's plasma PT/normal plasma PT). However, it is also known that ISI varies depending on the reagents used or the lot number or the combination of instruments used for measuring the same reagent (Kodani et al. 2011). Therefore, we hypothesize that these may also be factors affecting the results of this study.

We found that the factor leading to poor TTR control was heart failure, which causes large hemodynamic fluctuation of BNP level. Recently, subanalysis of apixaban in the Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study of nonvalvular atrial fibrillation patients with heart failure has been carried out. As a result, apixaban was found to more significantly decrease the incidence of systemic embolism or stroke than warfarin (McMurray et al. 2013). Identification of the factors leading to poor TTR control is useful in making the decision to switch to other anticoagulants, such as apixaban, or to continue warfarin by correcting negative factors in atrial fibrillation patients receiving long-term warfarin therapy.

4. Experimental

4.1. Study design

We set the target PT-INR to be in the range of 1.6-2.6 in this study, in accordance with the Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS2013) (JCS Joint Working Group 2013). We categorized patients into the good-TTR-control group when their TTR was > 65% and the poor-TTR-control group when their TTR was < 65%.

The patients' background features examined as factors were sex, age, weight, BMI, complications (e.g., heart failure, hypertension, diabetes, stroke, TIA, or dyslipidemia), the percentage of patients with smoking history, average warfarin dose, average INR/warfarin dose, the percentage of patients receiving a combination of antiplatelet drugs, the percentage of patients with a history of bleeding, frequency of measurements of PT-INR, CHADS2 score, and HAS-BLED score. The laboratory data, including the levels of AST, ALT, BUN, Scr, eGFR, T-Cho, TG, HDL-C, LDL-C, CRP, TP, Alb, RBC count, Hb, Hct, BNP, SBP, DBP, CV-INR, and %INR, were also collected.

TTR shows the rate that INR can maintain the target treatment level during warfarin therapy. PT-INR was measured every 1-2 months; it is assumed that PT-INR shows a linear regression between measurement points (Rosendaal et al. 1993). We calculated TTR using TTR analysis software Ver. 0.9. that Co., Ltd. Eisai has developed. Next we investigated the association between ΔPT-INR and ΔBNP in 44 patients whose ΔBNP was measured before and after the warfarin therapy out of the 55 surveyed patients suspected of having heart failure. We divided the patients into two groups on the basis of the median ΔBNP (49.7 pg/mL), namely, the ΔBNP < 49.7 pg/mL group and the ΔBNP ≥ 49.7 pg/mL group. The time until the steady state of warfarin is reached is estimated to be 2-3 weeks from the level of prothrombin, which has a very long half-life, i.e., 3-4 days. Therefore, we calculated ΔPT-INR using PT-INRs obtained after the second round of PT-INR measurement. In addition, we defined the observation period for TTR as 1 year. We calculated ΔPT-INR by subtracting the minimum PT-INR from the maximum PT-INR during the observation period. We calculated ΔBNP by subtracting BNP after warfarin administration from BNP before warfarin administration during the observation period. In addition, we considered that the one of the items in the HAS-BLED score, "Labile INRs" is a confounding factor in the present study. Therefore, we excluded this item and calculated HAS-BLED score.

4.2. Subjects

Subjects of this study were 55 patients who met all of the following conditions: (1) patients who visited the Cardiovascular Medicine Department of Yokosuka Kyousai Hospital from March 2011 to May 2013; (2) the number of days that warfarin was administered was equivalent to at least > 1 year; (3) PT-INR was measured at least once every 2 months for > 6 months; (4) inpatients or outpatients with nonvalvular atrial fibrillation.

4.3. Statistical analysis

We divided the patients into the good- and poor-TTR-control groups and compared their background features and laboratory data. The results are presented as mean ± standard deviation. We performed the normality test to compare the data volume between these two groups. We used Student's t-test after we confirmed that the data showed a normal distribution. We used the Mann-Whitney U-test when the data did not show a normal distribution. We used the $\chi 2$ test or Fisher's exact test to compare the categorical data. Next, we adjusted for the confounders, and performed stepwise procedure in multiple logistic regression analysis in the presence or absence of poor TTR control as the dependent variable to investigate the relationship of background features and laboratory data. We chose the significant factor heart failure as an independent variable on the basis of the results of univariate analysis. In addition, we incorporated sex and average warfarin dose as factors into the regression equation compulsorily because sex and the average warfarin dose have been reported to be associated with INR control (Okumura et al. 2011; Tomita et al. 2013). We confirmed by multiple logistic regression analysis using Spearman's rank-correlation coefficient that there was no multicollinearity between factors. The significance level was 5% ($p < 0.05$). Statistical analyses were performed using JMP® (Version 10, SAS Institute Inc., Cary, NC, USA).

4.4. Ethical regulation

This study was conducted with the approval of the Yokosuka Kyousai Hospital Ethics Committee (Approval number: 13-06). In addition, this study was conducted with the approval of the School of Pharmacy, Nihon University Ethics Committee (Approval number: 14-002). This was a retrospective study using medical records, which complied with the Declaration of Helsinki and the "Ethical Guidelines for Clinical Research."

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