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Research Article

The Introduction Timing of Oral Anticoagulants in the Early Phase of Acute Stroke Patients

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Keywords

- Non-vitamin K antagonist oral anticoagulants
- Warfarin
- Cardiogenic embolism
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- Hemorrhagic transformation

Abstract

Objective: This study was aimed to reveal the possibility of newly emerged hemorrhagic complication in acute ischemic stroke patients after the introduction of oral anticoagulants, including warfarin and direct oral anticoagulants (DOACs).

Methods: Acute ischemic stroke patients who admitted to the hospital within 24 hrs following onset were consecutively screened between July 2012 and June 2013. Then, patients with oral anticoagulant as secondary stroke prevention introduced within 2 weeks were enrolled in this study (n=95). The hemorrhagic complication following the institution of anticoagulants was assessed by repeated brain CT or MRI.

Results: Warfarin was prescribed to 34patients and DOACs were prescribed to 61patients (dabigatran 27and rivaroxaban 34). Patients with DOACs showed significantly milder deficits compared with warfarin ($p<0.01$: NIH Stroke Scale 5.5and 10.3, respectively). Regarding the newly emerged hemorrhagic complication following the institution of anticoagulants, its frequency was not significantly different between warfarin and DOACs (16.1% and 23.9%, respectively). The hemorrhagic complication was not observed, if anticoagulation was started later than4, 5and 6 days following onset in the small, moderate and large infarctions, respectively. No recurrent ischemic stroke was observed during the observation period.

Conclusion: Not only warfarin but also DOACs could be safely started from the acute phase of stroke depending on the lesion size in the real clinical world. Further study might need to confirm our findings.

INTRODUCTION

Warfarin has been used for secondary prevention against cardiogenic embolic stroke which is mainly caused by atrial fibrillation. Nowadays, direct oral anticoagulation medicines (DOACs), such as dabigatran, rivaroxaban, apixaban and edoxaban, have become available for clinical use along with warfarin [1,2]. Each DOAC was reported to show the advantage of safety and efficacy against warfarin in the secondary stroke prevention as well as primary stroke prevention in their clinical trials [3-7]. However, there was no data in which the safety and efficacy of DOACs was investigated at the acute phase of stroke. Meanwhile, the European Society of Cardiology mentioned that reinstitution of anticoagulation should be after 1 day in transient ischemic attack, 3 days in small, non-disabling infarct, 6 days in a moderate stroke and 2 to 3 weeks in a large infarcts as clinical advocate [8].Thus far, it is argued to reveal the safety and efficacy of introducing DOACs at the acute phase of stroke. Herein, we retrospectively screened the acute ischemic stroke patients who were treated with oral anticoagulants within 2 weeks following the onset.

METHODS

All procedures in this study was approved by the Ethical Committee of the Research Institute for Brain and Blood Vessels –Akita. Written informed consent was obtained from the patient or family member if applicable. Between July 2012 and June 2013, acute ischemic stroke patients who admitted to the hospital within 24 hr of the stroke onset and were started oral anticoagulation within 2 weeks were consecutively screened. Then, 95cases were enrolled in this study. All patients had examined by brain computed tomography (CT) or brain magnetic resonance imaging (MRI) on admission. The size of ischemic lesion was evaluated from the acquired images on admission. For the CT findings, early ischemic change and low density area was adopted as the ischemic lesion. For the MRI findings, high intensity area on diffusion weighted images was adopted as the ischemic lesion. The “large” was defined as the lesion size larger

than one third of total middle cerebral artery perfusion area or larger than half of total anterior cerebral artery or posterior cerebral artery perfusion area (L group). The "small" was defined as that the lesion was less than 2cm in maximum diameter (S group). The "moderate" was defined as the lesion size between small and large (M group). Representative pictures were shown in Figure 1. Hemorrhagic transformation was evaluated from the repeated brain images of CT or MRI T2* WI obtained at the next day, 1 week and 2 weeks, if available. Following the ECASS criteria, hemorrhagic transformation was defined as HI-1: hemorrhagic infarction with small petechiae, HI-2: hemorrhagic infarction with more confluent petechiae, PH-1: less than 30% of the infarcted area with some mild space-occupying effect and PH-2: higher than 30% of the infarcted area with a significant space-occupying effect or a clot remote from the infarct area. Then, the newly emerged hemorrhagic complication was defined as the lesion in which the hemorrhagic transformation was newly observed or the existed hemorrhagic area was enlarged after the institution of anticoagulant [9-11]. Neurologic severity was assessed by the National Institute of Health Stroke Scale (NIHSS) on admission. The risk factors were defined as: hypertension (>140 mmHg systolic or >90 mmHg diastolic, or currently prescribed anti-hypertensive medication), diabetes mellitus (spontaneous blood sugar level>200 mg/dL or currently prescribed anti diabetic medication), dyslipidemia (>140 mg/dL serum low-density lipoprotein or >150 mg/dL triglyceride, or currently prescribed anti hyperlipidemia medication), drinking (>30 mL of converted alcohol amount per day) and smoking. Renal function was assessed by calculating the creatinine clearance rate (CCr). All data was obtained from patients' clinical records. The timing of starting oral anticoagulation and the choice of medicine was basically based on the guidelines [12-14], including the instruction document provided from the pharmaceutical company, and was entrusted to each attending doctor. If a patient showed some hemorrhagic transformation such as HI-1, prescription of anticoagulant was started without delay. While, in cases of hemorrhagic transformation such as HI-2 and PH-1 observed on CT images, a doctor prescribed an anticoagulant, if repeated CT examination demonstrated the decrease of the hemorrhagic area. If a patient showed PH-2 lesion, prescription of anticoagulant was postponed until 1 week and the reduction of hemorrhagic area was demonstrated by CT images. For patients treated with warfarin, continuous drip infusion of heparin (10000U/day) was used until PT-INR would reach optimal amount. For patients treated with DOACs, no additional anticoagulant was adopted.

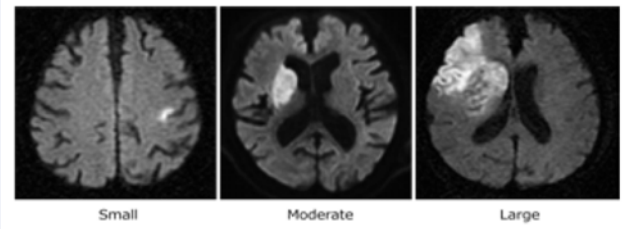

Figure 1 Representative pictures of ischemic lesion in each size group, evaluated by MRI diffusion weighted axial images.

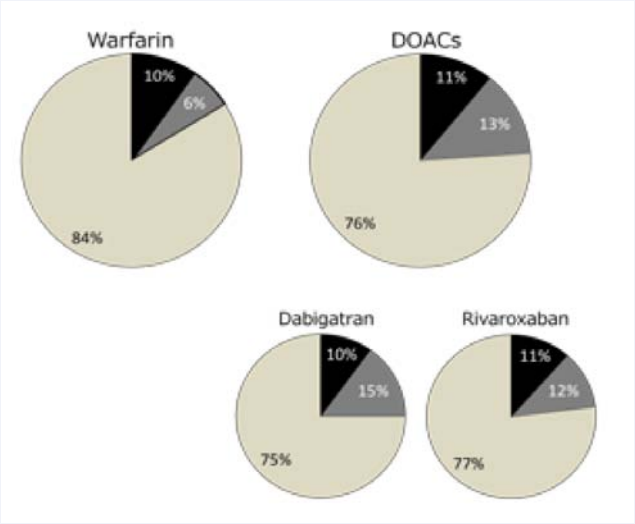

Figure 2 Percentage of hemorrhagic transformation following institution of anticoagulation agents. Newly observed hemorrhagic transformation was colored in black, and the expansion of hemorrhagic lesion was colored in dark gray in each pie chart. The rest (light gray) was in no hemorrhagic complication.

STATISTICAL ANALYSIS

Data are presented as mean ± standard deviation (SD) for continuous variables and percentage (%) for categorical variables. Clinical characteristics were compared between warfarin and DOACs or dabigatran and rivaroxaban by the non-parametric one-way ANOVA test for continuous variables and by the Pearson χ^2 test for categorical variables. All statistical analysis was performed by JMP9 software (SAS Institute Inc., Cary, NC).

RESULTS

Clinical characteristics of all patients were shown in Table 1. Warfarin was prescribed to 34patients and DOACs were prescribed to 61patients (dabigatran 27and rivaroxaban 34). There was no patient who was prescribed apixaban nor edoxaban in this period. Age, sex and distribution of risk factors were not significantly different between patients of warfarin and DOACs. The neurological severity on admission was significantly higher in warfarin compared with DOACs (p=0.007: 10.3 ± 8.6and 5.5 ± 6.0, respectively). While, within DOACs (Table 2), patients of dabigatran were significantly younger and milder neurological deficit compared with rivaroxaban (p=0.028: 74.7 ± 9.6 yo. vs 79.9 ± 8.5 yo. and p=0.012: 3.5 ± 3.7 vs 7.4 ± 7.0, respectively). There was no recurrence of ischemic stroke within 2 weeks among all patients.

The hemorrhagic transformation prior to anti coagulation was observed in 33.7% of all cases. After introducing anticoagulation (Figure 2), the newly emerged hemorrhagic complication was observed in 16.1% of the patients who started warfarin and examined by repeated CT or MRI examination (n=31) and in 23.9% of the patients who started . Among DOACs and examined by repeated CT or MRI examination (n=46). The differences of the frequency was not significant (p=0.587).Among the patients with DOACs, the frequency of hemorrhagic complication was

Table 1: Clinical characteristics of all patients.

	Total	Warfarin	DOACs
N	95	34	61
Age (mean ± SD)	77.6 ± 9.2	77.7 ± 9.2	77.4 ± 9.4
Sex (m/f)	52/43	18/16	34/27
Previous stroke (n, %)	30 (31.6)	12 (35.3)	18 (29.5)
Hypertension (n, %)	61 (64.2)	21 (61.8)	40 (65.6)
Dyslipidemia (n, %)	24 (25.3)	8 (23.5)	16 (26.2)
Diabetes (n, %)	19 (20.0)	7 (20.6)	12 (19.7)
Atrial fibrillation (n, %)	47 (49.5)	21 (61.8)	26 (42.6)
Smoking (n, %)	36 (37.9)	10 (29.4)	26 (42.6)
Cre (mean ± SD)	0.82 ± 0.33	0.90 ± 0.46	0.76 ± 0.22
CCr (mean ± SD)	53.0 ± 10.1	57.7 ± 27.0	58.9 ± 17.9
(range)	(11-128)	(11-128)	(24-114)
NIHSS on admission (mean ± SD)	7.3 ± 7.4	10.3 ± 8.6	5.5 ± 6.0 †

Abbreviations: DOACs: Direct Oral Anticoagulants, Cre: Creatinine, Ccr: Creatinine Clearance, NIHSS: National Institute of Health Stroke Scale. †: p=0.0070

Table 2: Clinical characteristics of patients prescribed DOACs.

	Dabigatran	Rivaroxaban
N	27	34
Age (mean ± SD)	74.7 ± 9.6	79.9 ± 8.5 ‡
Sex (m/f)	16/11	18/16
Previous stroke (n, %)	10 (37.0)	8 (23.5)
Hypertension (n, %)	17 (63.0)	23 (69.7)
Dyslipidemia (n, %)	8 (29.6)	8 (24.2)
Diabetes (n, %)	6 (22.2)	6 (17.6)
Atrial fibrillation (n, %)	13 (48.1)	13 (38.2)
Smoking (n, %)	14 (51.9)	12 (36.4)
Cre (mean ± SD)	0.79 ± 0.22	0.77 ± 0.22
CCr (mean ± SD)	62.0 ± 18.3	56.0 ± 17.3
(range)	(26-114)	(24-98)
NIHSS on admission (mean ± SD)	3.5 ± 3.7 *	7.4 ± 7.0

Abbreviations: Doacs: Direct Oral Anticoagulants; Cre: Creatinine; Ccr: Creatinine Clearance; NIHSS: National Institute of Health Stroke Scale. ‡: P=0.028, *: P=0.012

similar indabigatran (25.0%) and rivaroxaban (23.1%).

Then, the newly emerged hemorrhagic complication was assessed depending on the day of introducing anticoagulation in the different stroke size group (Table 3). Regarding the timing of hemorrhagic complication emerged, the average day was 4.0th in warfarin and 2.0nd in DOACs of L group, 2.0nd in warfarin and 2.2nd in DOACs of M group and 2.0nd in warfarin and 1.5th in DOACs of S group. There was no statistical difference. In the L group, hemorrhagic complication was observed in patients who were started warfarin within 5 days following stroke onset, and in patients who were started DOACs within 3 days following the onset. A patient who started warfarin at the 3rd day expressed the expansion of hemorrhagic area within the ischemic lesion along with a space-occupying effect, resulting in the transient worsening of consciousness. In the M group, hemorrhagic complication was observed in patients who were started warfarin within 2 days following stroke onset, and in patients who were started DOACs within 4 days following the onset. A patient who started dabigatran at the 3rd day expressed the hemorrhagic transformation within the ischemic lesion along with a space-occupying effect, resulting in the worsening of hemiparesis. In the S group, hemorrhagic complication was observed in patients started warfarin within 3 days following stroke onset, and in patients started DOACs within 2 days following the onset. A patient who started dabigatran at the 1st day of stroke expressed the hemorrhagic transformation within the ischemic lesion along with a space-occupying effect, resulting in the worsening of hemiparesis.

DISCUSSION

This study retrospectively described the clinical course of acute stroke patients who were treated with oral anticoagulants within two weeks of onset. Any recurrence of ischemic stroke was not observed in all patients during the study period. While, newly emerged hemorrhagic complications after the institution of oral anticoagulation were observed within 5 days of large infarction, 4 days of moderate infarction and 3 days of small infarction.

According to the protocol of clinical trials of DOACs, dabigatran and rivaroxaban had been prescribed to patients in whom more than 2 weeks had passed from stroke onset [3,6]. Therefore, it can be said that the safety and efficacy at the early phase of acute ischemic stroke has not been fully evaluated. Mean while, it was reported that the stroke risk was, rather, increased within the first week following initiation of warfarin [15]. Therefore, warfarin has to be gradually increased its dose to achieve the optimal amount [16], leading to the extension of in-hospital duration. DOACs, on the other hand, may be able to obtain the optimal anticoagulation effect immediately after the institution [17], leading to the shortening of in-hospital length. It is argued to reveal the safety of introducing DOACs in the acute phase for maximizing these merits.

In general, the hemorrhagic transformation may tend to be observed because of the spontaneous recanalization in the acute phase of cardio embolic stroke [18,19]. In this study, the spontaneous hemorrhagic transformation was observed in approximately 30% of all patients prior to the anticoagulation. This rate is similar to the previous reports [20]. Then, our findings revealed that there was no difference of the incidence rate of the newly emerged hemorrhagic complication after the initiation of anticoagulation between warfarin and DOACs. The frequency of hemorrhagic complication after anticoagulation started was relatively high in this study. Actually, our data was based on not all cases but the cases who were performed repeated CT examination after introducing anticoagulant. Therefore, it is assumed that the percentage of hemorrhagic transformation became relatively higher. Meanwhile, this study precisely described the newly emerged hemorrhagic complication depending on the initiation day of anticoagulation

Table 3: The day of initial coagulation and the existence of hemorrhagic complication.

day	1	2	3	4	5	6	7~
Large							
Warfarin	0 (0/1)		25 (1/4)		100 (1/1)	0 (0/1)	
DOAC	100 (1/1)	100 (2/2)	50 (1/2)		0 (0/2)		0 (0/3)
Dabigatran		(1/1)	(1/1)				(0/1)
Rivaroxaban	(1/1)		(1/1)		(0/2)		(0/2)
Moderate							
Warfarin	0 (0/8)	25 (1/4)	0 (0/2)				0 (0/2)
DOAC	40 (2/5)	33.3 (1/3)	25 (1/4)	50 (1/2)			0 (0/3)
Dabigatran	(1/2)	(0/1)	(1/1)				(0/1)
Rivaroxaban	(1/3)	(1/2)	(0/3)	(1/2)			(0/2)
Small							
Warfarin	12.5 (1/8)	0(0/1)	50 (1/2)	0 (0/1)			
DOAC	9.1 (1/11)	9.1 (1/11)	0 (0/3)	0(0/2)	0 (0/1)	0 (0/1)	0 (0/4)
Dabigatran	(1/7)	(0/7)		(0/1)	(0/1)	(0/1)	
Rivaroxaban	(0/4)	(1/4)	(0/3)	(0/1)			(0/4)

In each cell, the percentage of hemorrhagic complication is noted. Bracket indicates the number of hemorrhagic complication patients / the number of all prescribed patients in each day.

and on the size of ischemic lesion. The hemorrhagic complication was observed, if the anticoagulation was started within 3days in the small infarction, 4 days in the moderate infarction and 5 days in the large infarction. Actually, the hemorrhagic transformation would be occurred in higher rate in the larger ischemic lesion, and it might relate to the worse outcome [8,20]. For reducing the risk of hemorrhagic complication, it would be ideal to start oral anticoagulation several days after the onset. According to the ESC guideline, the 1-3-6-12 rule has been proposed for the starting day of anticoagulation [18], supporting our findings from the real clinical world. Besides, in our findings, patients prescribed DOACs showed slightly higher percentage of newly emerged hemorrhagic complication compared with warfarin. One reason might be that DOACs can reach their optimal concentration immediately after institution, while warfarin will be gradually increased its dose to gain the optimal concentration. Therefore, DOACs might show higher frequency of hemorrhagic complication compared with warfarin during acute phase.

Meanwhile, we have reported that the hemorrhagic complication following thrombolysis with recombinant tissue plasminogen activator was associated to the existence of cerebral micro bleeds (CMBs) and leukoaraiosis [21]. However, there is a report which mentioned no correlation between hemorrhagic transformation and CMBs in ischemic stroke patients [22]. It is still controversial the relation of hemorrhagic transformation and CMBs or leukoaraiosis. Moreover, prior use of antiplatelet drug was reported to play a protective role against hemorrhagic transformation [22]. In this study, CMBs and leukoaraiosis were not evaluated regarding the hemorrhagic complication. It can be said that the participation of hemorrhagic risk factors, such as CMBs and leukoaraiosis, in the initiation timing of anticoagulation agents should be analyzed in acute ischemic stroke patients in the future.

This study contains some limitations. 1) Small number of cases caused the power of statistical analysis weak. It should need to increase the number of cases. 2) The prescription of anticoagulants was based on the decision of each attending doctor.

Actually, dabigatran was prescribed to patients with milder neurological deficits, and rivaroxaban and warfarin were prescribed to patients with severe deficits. It might be the reason that dabigatran cannot be prescribed to patients with impaired kidney function, and is difficult for patients with dysphasia. It is assumed that there was a bias for the selection of anticoagulants. However, because we have implemented a stroke care team and the data in this study came from single hospital, the stroke treatment can be considered to have consistency. None the less, this finding was a result of real clinical setting. Therefore, our data might be able to apply to the real world rather than clinical trial data.

CONCLUSION

At the acute phase treatment of anticoagulation, there was no recurrent ischemic stroke in patients treated with both warfarin and DOACs. Newly emerged hemorrhagic complication was observed, if anticoagulants were started within 3, 4 and 5 days of small, medium and large infarctions, respectively. Oral anticoagulation could be safely introduced in patients of acute phase stroke, depending on the ischemic lesion size.

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