Secular Trends in the Background of Intracerebral Hemorrhage from 2010 to 2015

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Objective: Direct oral anticoagulants (DOACs) were recently introduced for the clinical use in stroke prevention, and they are reported to show a lower risk of intracerebral hemorrhage (ICH) compared to warfarin. We were interested to know whether there is any change in clinical backgrounds of ICH patients to date. *Methods:* From 2010 to 2015, ICH patients admitted to our hospital were consecutively screened (n = 658). Hematoma size was assessed by brain computed tomography images on admission. Outcome was measured by the modified Rankin Scale, and favorable outcome was defined as modified Rankin Scale 0-2. Biennial trends were compared in 3 periods, P1: 2010-2011, P2: 2012-2013, and P3: 2014-2015. *Results:* The percentage of ICH patients taking antithrombotics had been slightly decreasing ($P = .245$: [P1] 33.0%, [P2] 27.4%, and [P3] 26.2%). The frequency of patients taking antiplatelets had significantly decreased ($P = .001$: [P1] 50.7%, [P2] 44.3%, and [P3] 22.8%), and those taking DOACs had significantly increased ($P = .001$: [P1] 1.4%, [P2] 4.9%, and [P3] 19.3%). Frequency of favorable outcomes in patients taking antithrombotics was slightly increased in P3 compared to P1 and P2 (23.3%, 21.1%, and 21.3%, respectively). There was no significant difference in hematoma size between patients taking warfarin and DOACs. *Conclusions:* Number of ICH patients taking antithrombotics has been slightly decreasing and the percentage taking DOACs among ICH has been increasing for 6 years.

Key Words: Hemorrhage—stroke—medicine—prognosis—antithrombotic

Introduction

Intracerebral hemorrhage (ICH) is one of the high mortality intracranial diseases. As the background of ICH, atherosclerosis and chronic hypertension can often be observed.[1,2] However, these atherosclerosis and chronic hypertension are also risk factors of brain infarction. For preventing ischemic stroke, antithrombotic medicines are generally prescribed. Based on the pharmacological features of medicines, the antiplatelet agents are used for the prevention of atherothrombotic stroke, and the anticoagulation agents are prescribed for the prevention of embolic stroke. Meanwhile, these antithrombotic medicines might have an influence on the increase of the risk of hemorrhagic complications.[3,4] Moreover, brain hemorrhagic stroke can be observed as recurrent stroke in ischemic stroke patients, and vice versa.[5,6] Warfarin is a fundamental anticoagulation agent, however, it is sometimes discussed as a major problem in hemorrhagic stroke.[7-9] In this context, direct oral anticoagulants (DOACs) have been recently introduced for the clinical use along with warfarin. The data from the clinical trials demonstrated their lower risk of hemorrhagic complications and the same effect of reducing embolic incidence, when compared to warfarin.[10-13] Therefore, it can be expected that the incidence rate of brain hemorrhage might be going to be reduced hereafter.

Herein, we conducted a study in which acute ICH patients were retrospectively, but consecutively investigated in a single institution between 2010 and 2015 which covers the year before DOAC became available

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Table 1. *Patients' characteristics*

	Total	2010-2011	2012-2013	2014-2015
N	658	216	223	219
Sex (male %)	56.2	55.6	54.3	58.9
Age (mean ± SD yo)	69.1 ± 12.4	68.6 ± 12.8	69.8 ± 12.7	69.4 ± 11.7
Risk factors (%)				
Hypertension	84.9	80.6	86.9	87.1
Dyslipidemia	32.7	35.9	28.6	34.1
DM	19.0	19.2	18.3	19.4
AF	13.1	12.0	12.4	14.8
Smoking	42.3	43.1	42.5	41.5
Previous stroke	25.6	25.5	28.7	22.6
Previous antithrombotics use	28.7	33.0	27.4	26.2
Clinical data				
Hematoma volume (mean ± SD m**L**)	24.9 ± 34.4	24.6 ± 31.2	25.4 ± 38.9	24.8 ± 32.7
NIHSS on admission (mean ± SD)	12.3 ± 9.9	12.6 ± 9.5	12.1 ± 9.7	12.3 ± 10.5
NIHSS for 1 month (mean ± SD)	11.0 ± 12.8	10.6 ± 12.1	11.1 ± 12.9	11.3 ± 13.3
mRS for 1 month (mean ± SD)	3.4 ± 1.7	3.7 ± 1.6	3.4 ± 1.7	3.1 ± 1.9
Mortality (%)	10.3	9.3	10.3	11.4

Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; SD, standard deviation.

and the year after 4 different DOACs have been on the clinical use. The alteration of the background of ICH patients in recent years was assessed. Then, we chronologically investigated the alteration of the outcome of ICH patients as well as the transition of the clinical characteristics of ICH patients.

Patients and Methods

Patients

Following approval of the ethical committee of the Research Institute for Brain and Blood Vessels—Akita, acute phase ICH patients admitted to our hospital were consecutively screened between 2010 and 2015 (n = 658). Our institutional review board waived the need for patient consent, as this is a retrospective study and all data were deidentified. Patients with intraventricular hemorrhage, ICH caused by arterial aneurysm, caused by vascular malformation and with brain tumor were excluded from this study. All patients were diagnosed using a computer-assisted tomography (CT) scanner (Aquilion ONE, Toshiba Medical Systems Inc., Tokyo, Japan) on admission. The hematoma volume was calculated from the CT images using the formula: ABC/2 × 1000 mL (A is the largest cross-sectional diameter of the hematoma [mm], B is the largest diameter of the perpendicular to A [mm], and C is the number of CT slices with hematoma multiplied by the slice thickness [mm]).[14]

The stroke risk factors were defined as follows: hypertension (currently prescribed antihypertensive medication), dyslipidemia (>220 mg/dL total cholesterol or >150 mg/dL triglyceride or currently prescribed antidyslipidemia medication), diabetes mellitus (spontaneous blood sugar level >200 mg/dL or currently prescribed antidiabetic medication), and smoking (current or previous smoker). Atrial fibrillation (AF) was defined when patients reported AF history or AF was detected by the electrocardiogram on admission. The antithrombotic medication use was confirmed by the patient's prescription history.

The neurological severity was assessed on admission by the National Institutes of Health stroke scale (NIHSS). The neurological deficit assessed by NIHSS and the outcome measured by the modified Rankin Scale (mRS) were analyzed for 1 month. A favorable outcome was defined as mRS 0-2. In-hospital mortality was calculated from the number of mRS6 within 1 month.

Statistical Analysis

Data were presented as mean ± standard deviation or as a number and percentage. For analyzing the biennial trend, the observation period was divided into 3 groups, i.e., 2010-2011, 2012-2013, and 2014-2015. The clinical characteristics were compared among the 3 groups by the t test for the mean variable and by the χ^2 test for the percentage variable. The comparison of hematoma volumes was performed by the nonparametric one-way ANOVA test. The analysis of categorical variables, such as NIHSS and mRS, was calculated by the Pearson χ^2 test. All statistical analysis were performed by JMP13 software (SAS Institute Inc, Cary, NC). Values of $P < .05$ were considered as significant.

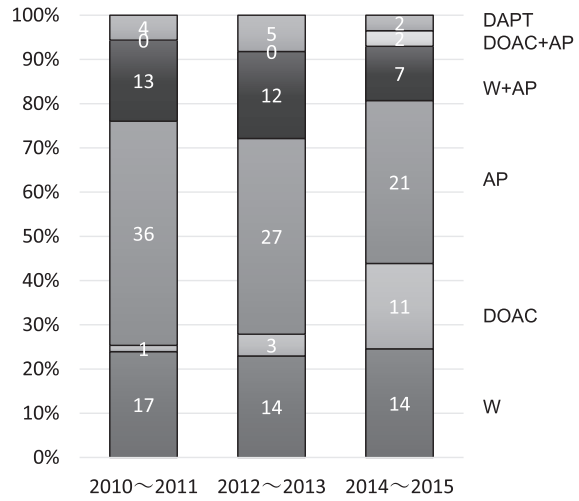

Figure 1. *Bar graphs of the types of antithromobitcs among ICH patients taking antithrombotics. The percentages of patients taking warfarin + antiplatelet agents and dual antiplatelet use are lower in 2014-2015 compared with 2010-2011 and 2012-2013. The number in each sector indicate the percentage. Abbreviations: AP, antiplatelet; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; W, warfarin.*

Results

Secular Change of the Patients' Background

Clinical characteristics of all patients, as well as the data divided into the 3 chronological groups, are shown in Table 1. The total number of patients in each period was nearly the same. The sex distribution, average onset age, and the distribution of stroke risk factors showed similar trends in these periods. The average hematoma volume was 24.9 mL, and this amount was almost the same among the 3 periods. There was no significant difference in NIHSS on admission and for 1 month in these periods. Although, mortality slightly increased, the average score of mRS for 1 month was slightly decreased for the 3 periods (not statistically significant). Regarding the biennial trend of the percentage of ICH patients who had taken antithrombotic medicines, the percentage was slightly decreasing for the 3 periods, but there was no significant difference.

The distribution of ICH patients taking antithrombotic agents were precisely sorted by the type of antithrombotics used (Fig 1). The rates of patients taking antiplatelet agents and those taking warfarin plus antiplatelet agents significantly declined for the 3 periods ($P = .015$: 50.7% and 18.3% in 2010-2011, 44.3% and 19.7% in 2012-2013 and 36.8% and 12.3% in 2014-2015, respectively). While the rates of patients taking DOAC and those taking DOAC plus antiplatelet agents significantly increased ($P < .001$: 1.4% and 0% in 2010-2011, 4.9% and 0% in 2012-2013 and 19.3% and 3.5% in 2014-2015, respectively). The frequency of patients taking warfarin did not change in these 3 periods.

The Alteration of the Outcome

As shown in Figure 2, although there were no statistical differences, the frequency of favorable outcome in patients not taking antithrombotic agents was slightly increasing, and that in patients taking antithrombotics was only increased in 2014-2015. The mortality was always higher in patients taking antithrombotics compared to patients not taking antithrombotics in these

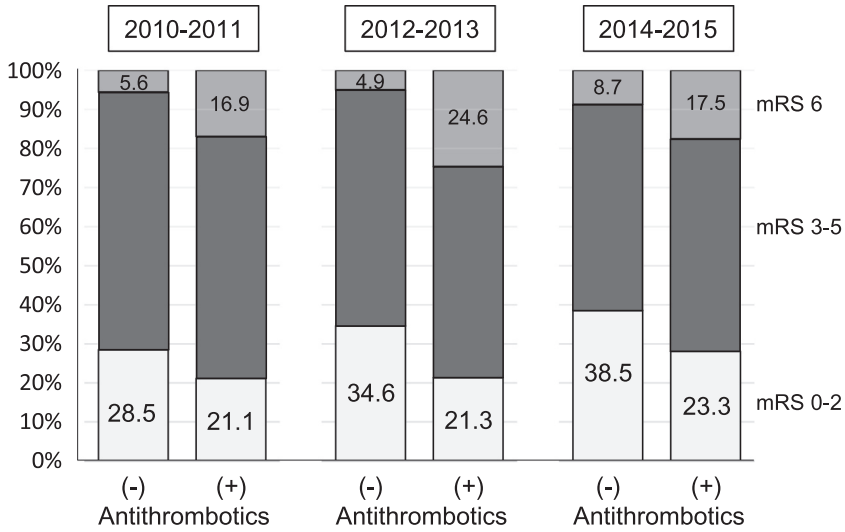

Figure 2. *Biennial trends of the percentage of outcome in patients taking and not taking antithrombotic agents. The percentage of better outcome (mRS 0-2) in patients not taking antithrombotics was increasing for 6 years. While, the percentage of better outcome in patients taking antithrombotics has slightly increased only in 2014-2015. The mortality (percentage of mRS 6) was not changed during these periods. The number in each column indicates the percentage. mRS 0-2 stands for the better outcome. Abbreviation: mRS, modified Rankin Scale.*

Table 2. *Clinical features in different types of antithrombotics*

	Warfarin	DOAC	Antiplatelet	W + AP	DOAC + AP	DAPT
N	45	15	84	32	2	11
Sex (male %)	55.6	60.0	63.1	81.3	50.0	36.4
Hematoma volume (mean ± SD mL)	30.1 ± 44.5	31.3 ± 39.0	32.1 ± 52.2	33.8 ± 37.9	15.5 ± 17.7	43.0 ± 48.4
NIHSS on admission (mean ± SD)	12.8 ± 9.9	11.1 ± 7.9	13.2 ± 10.6	15.4 ± 12.8	18.5 ± 0.7	18.7 ± 13.8
NIHSS for 1 month (mean ± SD)	14.3 ± 14.6	16.8 ± 15.7	13.3 ± 13.7	22.0 ± 17.6	10.0 ± 1.4	19.1 ± 18.7
mRS for 1 month (mean ± SD)	4.1 ± 1.7	4.1 ± 1.8	3.8 ± 1.6	4.5 ± 1.7	3.5 ± 0.7	4.1 ± 2.2
Mortality (%) *	15.6	20.0	13.1	37.5	0	36.4

Abbreviations: AP, antiplatelet; DAPT, dual antiplatelet therapy; DOAC, direct oral anti-coagulant; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

*There is a significant difference among the groups ($P = .025$).

periods. No significant trends of mortality were observed in these periods.

The Involvement of Antithrombotics in the Outcome

Then, by summarizing all patients in the 6 years, the clinical background and outcome were analyzed among different antithrombotic agents. The precise data of patients taking different antithrombotic medicines were presented in Table 2. There were only 2 patients taking DOAC plus antiplatelet agents, and they were excluded from statistical analysis. Patient groups of both, dual antiplatelet therapy and warfarin plus antiplatelet tended to be worse on NIHSS on admission compared with warfarin and DOAC groups ($P = .256$: 18.7, 15.4, 12.8, and 11.1, respectively). The warfarin plus antiplatelet and the dual antiplatelet therapy patient groups exhibited significantly higher mortality compared with the warfarin, the DOAC and the antiplatelet groups ($P = .025$: 37.5%, 36.4%, 15.3%, 20.0%, and 13.1%, respectively).

Discussion

This study demonstrated the chronological change in the precise data of ICH patients for the recent 6 years divided into 3 periods. It was revealed that the total number of ICH patients did not changed, but the number of patients taking antithrombotic agents had decreased. Along with the increase of the percentage of DOAC use, the outcome became better. Although it is indirect, these observations might suggest that ICH related to antithrombotic medicines could be decreased because of the increase of DOAC use.

Atherosclerosis of brain arteries can be a risk of ICH as well as brain infarction.[2] Usually, patients with atherosclerotic risk are treated with antiplatelet medicines. While, patients with AF are mostly prescribed anticoagulation agent. The prevalence of AF becomes higher in older people compared with younger people, and elderly people often have atherosclerotic diseases along with AF. Therefore, these patients are sometimes prescribed not only antiplatelet agents but also anticoagulation agents, becoming a high risk group of ICH. It can be said that it is a critical issue to reduce the risk of hemorrhagic complication in these patients.

Among anticoagulation medicines, warfarin has been the main agent for a long time. However, DOACs have been released recently, and are getting more actively prescribed in routine clinical cases. It was reported that DOACs showed the same or better effect of preventing embolic incidences as compared to warfarin in their clinical trials.[10-13] Moreover, the risk of hemorrhagic complication was reported to be significantly reduced by DOACs compared with warfarin.[10-13] Recent real-world data have been accumulated for confirming these findings.[15,16] Meanwhile, the frequency of ICH has been reported to be higher in Asia than Western countries.[17,18] Moreover, ICH of elderly people is very critical in the super aged society like Japan. Therefore, it is of great interest to report whether ICH is decreasing due to the benefit of DOACs or not in the area where the population of elderly people has increased. Actually, according to the government annual statistics in the region where our institution is located, the total population was almost the same between 2010 and 2015 (the population was 323,600 and 315,800, respectively) but the number of people over 65 years old had increased from 77,000 to 88,000 (Ref.: www.pref.akita.lg.jp).

With this background, our results revealed that the percentage of ICH patients taking antithrombotic medicines has been declining among total ICH patients for 6 years. Particularly, the percentage of patients taking antiplatelet agents has decreased and that of DOAC has increased. Whereas, the mortality of patients taking DOAC was relatively lower than that of warfarin. The ratio of patients showing preferable outcome was higher in DOAC than warfarin. Therefore, it might be the reflection of this background that the percentage of preferable outcome became higher only in the 2014-2015 period than other periods.

There are some limitations in this study. The total number of this study was relatively small, leading to a weakness in statistical power. There might be a possibility of type II error, so our findings must be confirmed by larger studies. Moreover, the patient's enrollment was from a single institution. Nevertheless, this institution has been

functioning as a comprehensive stroke center in this region, and the medical circumstances in this region have not changed in these 6 years. Therefore, it can be considered that the data from this institution are suitable for estimating recent patient movement. Actually, the fundamental data were quite similar between this study and a previous study.[8]

Conclusions

Number of ICH patients taking antithrombotics has been slightly decreasing for 6 years. Among ICH patients, percentage of patients taking DOACs has been significantly increasing, while the hematoma size and prognosis has not been changed to date.

Author Contributions

TN conducted throughout the study, JM screened and advised the analysis and TI advised about scientific methods of this study.

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