Do the Antithrombotic Therapy at the Time of Intracerebral Hemorrhage Influence Clinical Outcome? Analysis between the Difference of Antiplatelet and Anticoagulant Agents and Clinical Course

Takeshi Okada, MD,* Taizen Nakase, MD,† Masahiro Sasaki, MD,† and Tatsuya Ishikawa, MD*

Background: It is controversial whether taking antiplatelet agents (APs) or anticoagulant agents (ACs) could influence clinical outcome after intracerebral hemorrhage (ICH). *Methods:* We retrospectively investigated 557 ICH patients between September 2008 and August 2013. We reviewed patients' characteristics, hematoma volume, deterioration (hematoma expansion, surgical hematoma evacuation, or death), and clinical outcome in modified Rankin Scale. *Results:* A total of 397 were classified as neither AP nor AC ("Nothing"), 81 as single AP (44 as aspirin [ASA], 22 as clopidogrel or ticlopidine [CLP/TIC], 7 as cilostazol, 8 as dual antiplatelet therapy), 43 as single AC (40 as warfarin, 2 as rivaroxaban, 1 as dabigatran), and 36 as both AP and AC (AP + AC). The clinical outcome was worse in APs than in "Nothing" ($P = .021$). Among APs, CLP/TIC showed poorer clinical outcome than ASA ($P = .020$). Deterioration was observed more frequently in AC than in "Nothing" ($P < .001$) and the clinical outcome was also worse in AC than in "Nothing" ($P < .001$). AP + AC use resulted in deterioration more frequently than "Nothing" ($P < .001$) and in poorer outcome than in "Nothing" ($P < .001$). *Conclusions:* The use of antithrombotic agents could be associated with the deterioration after admission and the poor clinical outcome. CLP/TIC use may affect the poor outcome compared with ASA use. **Key Words:** Intracerebral hemorrhage—antiplatelet—anticoagulant—clinical outcome.

Owing to the increase in the number of patients with thrombotic disease, the number of patients taking antithrombotic agents is also increasing.[1] Although antithrombotic therapy effectively prevents thrombotic events,[2] some studies show that antithrombotic therapy influenced on an increased risk of bleeding complications including intracerebral hemorrhage (ICH).[1,3] Meanwhile, the influence of the antiplatelet agents (APs) and/or anticoagulant agents (ACs) at the time of ICH has not yet been elucidated. Some studies show that the use of APs and/or ACs at the time of ICH contributed to initial hematoma volume on admission, hematoma expansion after admission, and a worse clinical course in the acute stage.[4-10] Others show that antithrombotic therapy was not significantly associated with any deterioration.[11-13] Also, no study has shown the correlation between the difference of antithrombotic agents that the patients were taking and clinical outcome following ICH. Moreover, novel oral anticoagulants (NOACs) have been introduced for

From the *Department of Surgical Neurology; and †Department of Stroke Science, Research Institute for Brain and Blood Vessels Akita, Akita, Japan.

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Address correspondence to Takeshi Okada, MD, Department of Surgical Neurology, Research Institute for Brain and Blood Vessels Akita, 6-10 Senshu-Kubota-machi, Akita 010-0874, Japan. E-mail: t-okada@akita-noken.jp.

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stroke prevention in nonvalvular atrial fibrillation and the choice of antithrombotic agents have expanded accordingly. Some studies show that NOACs had a significantly smaller risk of ICH.[14,15] In this study, we evaluated the relationship between the use of antithrombotic agents at the time of ICH and clinical outcome in the acute ICH patients.

Methods

Patients and In-hospital Treatments

We reviewed 729 consecutive patients with ICH admitted to the hospital between September 2008 and August 2013. Of those, 172 were ineligible for ICH attributable to underlying aneurysm, hemorrhage transformation of ischemic infarction, or venous thrombosis. All patients were diagnosed as having ICH by a computed tomography (CT) scan (Aquilion ONE; Toshiba medical system, Tochigi, Japan) on admission. Efforts were made to keep the systolic blood pressure below 160 mm Hg by giving intravenous calcium channel blockers during 24 hours after admission followed by oral antihypertensive agents. All the patients except for those dead and undergoing surgical hematoma evacuation received a follow-up CT scan at 6 and 24 hours after the initial CT scan. Patients who underwent surgical hematoma evacuation before the first follow-up CT scan were assessed by a follow-up CT scan on the next day after the operation. Rehabilitation was performed on all available patients from the second hospital day.

Data Collection

We retrospectively obtained the medical records to assess clinical characteristics and outcome for the patients. We reviewed sex, age, and cerebrovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, previous stroke, alcohol, and smoking). The patients were classified into 4 groups taking AP alone, AC alone, combination use of AP and AC (AP + AC), or neither AP nor AC ("Nothing"). In addition, the medication of APs was classified into the following groups: aspirin (ASA), clopidogrel or ticlopidine (CLP/TIC), cilostazol (CIL), and dual antiplatelet therapy (DAPT). Drug dosages were 81 or 100 mg a day in ASA, 75 mg a day in CLP, 200 mg a day in TIC, and 200 mg a day in CIL. The medication of ACs was classified into the following groups: warfarin (WF), dabigatran, and rivaroxaban. Regarding the prothrombin time (PT) international normalized ratio (INR) value of the patients who had taken WF alone or WF and AP, optimal dose was set in 2.0 to 3.0 for those less than 70 years of age, or 1.6 to 2.6 for those 70 years of age or older following the Japanese guidelines for the management of stroke.[16] The following categories among these groups were assessed: an initial hematoma volume, deterioration after admission, and a modified Rankin Scale (mRS) score at discharge or transfer to a rehabilitation unit. The deterioration after admission was defined as follows: hematoma expansion at a follow-up CT scan, undergoing surgical hematoma evacuation after admission, or death.

Table 1. *Patients' characteristics*

Variable	All
Patients, N	557
Sex, male/female	310/247
Age, y, (mean ± SD)	68.5 ± 12.7
Time to hospital visiting, n	
≤1h	142
>1 h-≤2 h	119
>2 h-≤3 h	41
>3 h-≤6 h	83
>6 h-≤12 h	38
>12 h-≤24 h	33
≥24 h	67
Unknown	34
Cerebrovascular risk factor, n	
Hypertension	421
Alcohol	231
Hyperlipidemia	153
Smoking (current)	103
Smoking (ever)	117
Diabetes mellitus	91
Previous cerebral infarction	80
Previous intracranial hemorrhage	51
Chronic kidney disease	16
Previous subarachnoid hemorrhage	9
Cause of hemorrhage, n	
Hypertension	477
Amyloid angiopathy	56
Vascular malformation*	21
Tumor	2
Trauma	1
Site of hemorrhage, n	
Putamen	205
Thalamus	164
Lobar	98
Brain stem	36
Cerebellum	35
Caudate nucleus	10
Cerebral ventricle	9
Length of hospital stay, d, median (quartile)	22 (13.0-37.5)

Abbreviation: SD, standard deviation.
*Vascular malformation shows arteriovenous malformation, arteriovenous fistula, or moyamoya disease.

Image Analysis

Hematoma volume was measured on the CT images using the standard formula: ABC/2 (where A is the largest