Impact of Antiplatelets and Anticoagulants on the Prognosis of Intracerebral Hemorrhage

Masaaki Hokari, MD, PhD, Daisuke Shimbo, MD, PhD, Katsuyuki Asaoka, MD, PhD, Kazuki Uchida, PhD, and Koji Itamoto, PhD

Background: Intracerebral hemorrhage (ICH) associated with antithrombotic therapy (AT) is becoming more common as the use of those medications increases in the aging population. *Methods:* This study included 490 consecutive patients hospitalized for nontraumatic ICH in a single center during an 8-year period, which was subdivided into former (2008-2011) and latter (2012-2015). Patients were classified into those with no antithrombotic drugs (NATs) and those with AT. The AT group was divided into 4 subgroups according to medications: antiplatelet (AP1), multiple antiplatelets (AP2), anticoagulant (AC), and antiplatelet and anticoagulant (APC). We evaluated the clinical characteristics and prognosis and compared the number of patients on AT between the former and latter groups. *Results:* There were 125 patients treated with AT (25.5%), including 50 (10.2%) on AP1, 14 (2.9%) on AP2, 32 (6.5%) on ACs, and 29 (5.9%) on APCs. Compared with the former group, the latter group had a higher number of patients on AT (19.3% versus 31.7%), AP1 (9.8% versus 10.6%), AP2 (1.6% versus 4.1%), ACs (4.9% versus 8.1%), and APCs (2.90% versus 8.9%). Compared with the NAT group, the patients in the AT group had a larger ICH volume, more frequent hematoma expansion, and higher rate of poor outcome, particularly for those on APCs. *Conclusion:* The number of ICH patients on AT has increased; these patients were more likely to have a poor prognosis than those who were not on AT. Care should be taken when giving a combination of antiplatelets and anticoagulants in ICH. **Key Words:** Intracerebral hemorrhage—antithrombotic drugs—antiplatelets—anticoagulants—prognosis.

Introduction

The need for antithrombotic therapy (AT), which successfully prevents and treats vascular diseases,[1] has increased in recent years. However, one of the most serious complications of AT is intracerebral hemorrhage (ICH). In fact, several reports showed poor outcomes and increased mortality in patients treated with AT.[2-4] Some clinical trials on antiplatelets[5-7] and anticoagulants[8-12] reported that the annual incidence of ICH ranged from 0.23% to 0.84%. Furthermore, a prospective observational study on AT in Japan reported that the use of multiple antithrombotic drugs independently increased the risk for intracranial bleeding events.[13] In addition, ICH associated with AT has become more common in Japan as the use of those medications has increased in the aging population.[3] Therefore, we aimed to evaluate the impact of antiplatelets and anticoagulants on the prognosis of patients with ICH and to document the trend in the use of AT in the past years.

Patients and Methods

Patients

This study included 490 consecutive patients hospitalized with nontraumatic ICH in a single center during an 8-year period between January 2008 and December 2015.

From the Department of Neurosurgery, Teine Keijinkai Hospital, Sapporo, Japan.

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Address correspondence to Masaaki Hokari, MD, PhD, Department of Neurosurgery, Teine Keijinkai Hospital, Maeda 1-12, Teine-ku, Sapporo, 006-0811, Japan. E-mail: karimasa@med.hokudai.ac.jp.

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ICH patients who were hospitalized later than 24 hours of ICH onset were excluded. Patients were divided into a former group (from January 2008 to December 2011) and a latter group (from January 2012 to December 2015). The patients were classified into those with no antithrombotic drugs (NATs) and those with AT, which was subclassified into 4 groups according to drugs taken: 1 antiplatelet drug (AP1), multiple antiplatelets (AP2), anticoagulant (AC), and antiplatelet and anticoagulant (APC).

Clinical Characteristics

The medical records were reviewed for clinical variables, including age and gender, location and volume of hematoma, current antithrombotic treatment status and reasons for taking antithrombotic drugs, hemorrhage expansion and need for hematoma evacuation by craniotomy, and clinical outcomes. For hematoma evacuation by craniotomy, we used fresh frozen plasma for patients taking ACs and platelet concentrate for those taking antiplatelets. Hemorrhage volume was estimated by the formula ABC/2, where A was the greatest hemorrhage diameter on computed tomography (CT), B was the diameter perpendicular to A, and C was the approximate number of CT slices with hemorrhage multiplied by the slice thickness.[14] We performed the second CT scan 2 hours after the initial CT in patients with relatively large ICH or those taking antithrombotic agents. However, in patients with small ICH, the second CT was performed the next day. Patients who had undergone emergent hematoma evacuations underwent a second CT immediately after the surgery. Hemorrhage expansion was defined as an increase of more than 33% in ICH volume.[2] One month after the onset of ICH, clinical outcomes were evaluated using the modified Rankin Scale (mRS); an mRS score of 5 or 6 was regarded as a poor outcome. In patients who were transferred to other hospitals or nursing care facilities before 30 days, the mRS was evaluated at discharge.

Statistical Analysis

All data were expressed as mean ± standard deviation. The study variables were compared by the χ^2 test or the unpaired *t*-test, as appropriate (Ekuseru-Toukei 2015; Social Survey Research Information Co., Ltd., Tokyo, Japan). Univariate analysis was performed to determine the association of poor outcome with the clinical variables and to compare the ratio of patients on AT between the former and latter groups. A *P* value lower than .05 was considered statistically significant.

Results

Characteristics of the Patients

The characteristics of the study population are presented in Table 1. The mean age was 69.2 ± 12.1 years for the entire study population, 68.1 ± 11.9 years for the former group, and 70.3 ± 12.3 for the latter group. There was no significant difference in age between the former and latter groups. The latter group had a tendency for

Table 1. *Clinical characteristic of the patients in this study*

	Total		2008-2011		2012-2015		*P*
Number of the patients	490		244		246		
M/F (% of M)	M291/F189	59.4%	M142/F102	58.2%	M149/F97	60.6%	.58
Age : AVERAGE ± SD (Y)	69.2 ± 12.1		68.1 ± 11.9		70.3 ± 12.3		.051
History of hypertension (%)	387	79.0%	188	77.1%	199	80.9%	.30
Hemodialysis (%)	32	6.5%	13	5.3%	19	7.7%	.28
Hematoma location							
Putamen	133 (M90/F43)	27.1%	67 (M43/F24)	27.4%	66 (M47/F19)	26.8%	.92
Thalamus	127 (M70/F57)	25.9%	68 (M37/F30)	27.9%	59 (M33/F27)	24.0%	.35
Combined	19 (M10/F9)	3.9%	7 (M5F2)	2.9%	12 (M5/F7)	4.9%	.24
Caudate	10 (M5/F5)	2.0%	3 (M1/F2)	1.2%	7 (M4/F3)	2.8%	.22
Subcortex	111 (M52/F59)	22.7%	56 (M26/F30)	22.9%	55 (M26/F29)	22.3%	.91
Brainstem	44 (M34/F10)	9.0%	22 (M18/F4)	9.0%	22 (M16/F6)	8.9%	1
Cerebellar	46 (M31/F15)	9.4%	21 (M13/F8)	8.6%	25 (M18/F7)	10.2%	.54
Hematoma volume (cm3 ± SD)	28.3 ± 40.1		30.3 ± 43.5		26.3 ± 36.5		.27
Hematoma enlargement	34	6.9%	14	5.7%	20	8.1%	.29
Patients treated with antithrombotic drugs (%)	125	25.5%	47	19.3%	78	31.7%	.001*
Patients performed hematoma removal (%)	87	17.8%	45	18.4%	42	17.1%	.72
mRS 5-6	184	37.6%	82	33.6%	102	41.5%	.060

Abbreviations: F, female; M, male; mRS, modified Rankin Scale; SD, standard deviation.