Risk Factors for Hemorrhagic and Cardioembolic Complications of Intracerebral Hemorrhage Associated with Anticoagulants

Sho Osawa, MD,* Tatsuya Shimizu, MD, PhD,† Tadashige Kano, MD, PhD,* Ryosuke Shintoku, MD, PhD,* Hiroya Fujimaki, MD,* and Ken Asakura, MD*

Background: Patients with intracerebral hemorrhage taking anticoagulants are increasingly common in Japan due to the aging population. The clinical benefit of restarting anticoagulants is established, but the optimal timing of resumption is controversial. Risk factors for hemorrhagic and cardioembolic events in the acute phase are also unknown. This study investigated hemorrhagic and cardioembolic events and risk factors in intracerebral hemorrhage patients taking anticoagulants. *Methods:* The clinical data of 65 consecutive intracerebral hemorrhage patients taking anticoagulants were retrospectively reviewed. Hemorrhagic and cardioembolic complications and risk factors were analyzed. *Results:* Lobar hemorrhage was the most frequent (21 of 65 cases, 32.3%). At discharge, 31 patients (47.7%) showed severe disability or had died. Eight (18.6%) of 43 patients who restarted anticoagulants after initial treatment developed hemorrhagic events, including recurrent intracerebral hemorrhage in 3. HAS-BLED score was 2-3 in these 3 patients. Six (15.8%) of 38 patients who took anticoagulants for cardiogenic factors suffered cardioembolism. Systemic inflammatory response syndrome was significantly more common in the cardioembolic group (66.7%) compared with the noncardioembolic group (21.9%, $P < .05$). CHA_2DS_2-VASc score was paradoxically high in the noncardioembolic group (3 versus 5, $P < .05$). *Conclusion:* HAS-BLED score and CHA_2DS_2-VASc score were not useful for risk assessment for hemorrhagic events, recurrent intracerebral hemorrhage, and cardioembolism in the acute phase. Inflammatory response might be important in the occurrence of cardioembolic events.

Key Words: Intracerebral hemorrhage—Hemorrhagic complications—Cardioembolic complications—anticoagulant—systemic inflammatory response syndrome

Introduction

Anticoagulants are often administered as prophylactic therapy for cardioembolism caused by atrial fibrillation (AF), which has high prevalence in elderly people.[1] Consequently, the number of patients presenting with intracerebral hemorrhage (ICH) who are taking anticoagulants is increasing due to aging of the population.[2] Temporary cessation and resumption of anticoagulants after the initial treatment is reported to have clinical benefits,[3–5] but the optimal timing for resumption is still controversial.[6] The timing for resumption should be determined based on the known risk factors for hemorrhagic and thrombotic events such as CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism-vascular disease, age 65-74 years, and sex category) score and HAS-BLED (hypertension, abnormal renal/liver function, stroke-bleeding history or predisposition, labile international normalized ratio, elderly [>65 years], and drugs/alcohol concomitantly) score.[7] However, the actual predictive effectiveness of these factors remains unclear.

From the *Department of Neurosurgery, Maebashi Red Cross Hospital, Maebashi, Gunma, Japan; and †Department of Neurosurgery, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan.

Received June 10, 2018; revision received September 19, 2018; accepted September 30, 2018.

Address correspondence to Sho Osawa, MD, Department of Neurosurgery, Maebashi Red Cross Hospital, 389-1 Asakura-cho, Maebashi, Gunma 371-0811, Japan. E-mail: m1620004@gunma-u.ac.jp.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.09.054

This study analyzed the occurrence and risk factors of hemorrhagic and cardioembolic complications in ICH patients taking anticoagulants, especially focusing on the complications occurring after resumption of anticoagulants.

Methods

This study included 65 patients (9.0%) who were taking anticoagulants among 722 patients with ICH admitted to Maebashi Red Cross Hospital from April 2013 to October 2017. Patients who met the following criteria were excluded: ICH related to brain tumor; cerebral artery aneurysm; cerebral arteriovenous malformation; traumatic ICH; and vasculitis. The clinical characteristics of the 65 patients who met the inclusion criteria were analyzed.

The occurrence of hemorrhagic complications and possible risk factors were analyzed in 43 patients taking anticoagulants for cardiogenic factors, or prevention of deep venous thrombosis (DVT) or pulmonary embolism (PE), and who resumed anticoagulant therapy after initial treatment. Twenty-two patients were excluded from the above 65 patients because they did not resume anticoagulants due to poor general condition or severity of ICH. The occurrence of cardioembolic complications and possible risk factors were analyzed in 38 patients taking anticoagulants for cardiogenic factors and who resumed anticoagulant therapy after initial treatment. Five patients were excluded from above 43 patients because they were taking anticoagulants for prevention of DVT or PE.

Patient's age, sex, comorbidity, disease requiring anticoagulant therapy, types of anticoagulant agent, antiplatelet agent, duration from onset to resumption (day of onset defined as day 1), laboratory findings of creatinine, aspartate aminotransferase, alanine aminotransferase, platelet count, location of hematoma, and type of anticoagulant used after resumption were analyzed. Location of hematoma was classified as the putamen, thalamus, lobar, cerebellum, brain stem, intraventricular, and multiple sites. The usefulness of CHA_2DS_2-VASc score[8] and HAS-BLED score[9] was evaluated as risk factors for cardioembolic and hemorrhagic events, respectively. CHA_2DS_2-VASc score is a risk stratification score to estimate the 1-year risk of cardioembolic events in a patient with nonvalvular AF without anticoagulant therapy. HAS-BLED score is a risk stratification score to estimate the 1-year risk of hemorrhagic events in patients taking anticoagulants. The relationship between inflammatory response and acute hypercoagulopathy was also investigated. To evaluate the involvement of inflammatory response in the occurrence of complications, the relationship between diagnosis of systemic inflammatory response syndrome (SIRS) on admission and cardioembolic/hemorrhagic complications was analyzed. SIRS was diagnosed based on 2 or more of the following criteria: Body temperature less than 36°C or greater than 38°C; heart rate greater than 90/minute; tachypnea greater than 20/minute or arterial partial pressure of carbon dioxide less than 32 mmHg; and white blood cell count of less than 4000 cells/mm^3 or greater than 12,000 cells/mm^3.[10]

Statistical analysis was performed using free statistical software EZR.[11] Fisher's exact and chi-square tests were used for categorical data comparisons as appropriate. Differences in the means and medians of continuous measurements were tested by Student's *t* test and by the Mann-Whitney U test, respectively. *P* values of less than .05 were considered significant.

Results

Clinical Characteristics of ICH Patients Taking Anticoagulants

Clinical characteristics of the 65 ICH patients taking anticoagulants are shown in Table 1. In particular, 39 patients (60.0%) were male, mean age was 77.0 ± 8.8 (standard deviation) years, and 48 patients (73.8%) had

Table 1. *Clinical characteristics of ICH patients taking anticoagulants*

	All patients (N = 65)	
Men (%)	39	(60.0)
Age, years, average (±SD)	77	(±8.8)
Hypertension (%)	48	(73.8)
Diabetes (%)	11	(16.9)
Dyslipidemia (%)	19	(29.2)
Causative diseases		
Cardiogenic factors (%)	57	(87.7)
DVT/PE (%)	8	(12.3)
Types of anticoagulants		
Warfarin (%)	49	(75.4)
DOAC (%)	16	(24.6)
Rivaroxaban (%)	8	(12.3)
Apixaban (%)	6	(9.2)
Edoxaban (%)	1	(1.5)
Dabigatran (%)	1	(1.5)
Antiplatelets (%)	23	(35.4)
Aspirin (%)	19	(29.2)
Clopidogrel (%)	2	(3.1)
Aspirin + Clopidogrel (%)	1	(1.5)
Cilostazol (%)	1	(1.5)
Location of hematoma		
Lobar (%)	21	(32.3)
Thalamus (%)	11	(16.9)
Putamen (%)	10	(15.4)
Cerebellum (%)	10	(15.4)
Brainstem (%)	4	(6.2)
Intraventricular (%)	3	(4.6)
Multiple (%)	6	(9.2)
mRS at discharge, median (IQR)	4	(4-5)

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism; DOAC, direct oral anticoagulants; mRS, modified Rankin Scale.

hypertension. Anticoagulant therapy had been instituted for AF in 46 patients (70.8%), mechanical valve replacement in 7 (10.8%), ventricular aneurysm in 4 (6.2%), PE in 5 (7.7%), and DVT in 3 (4.6%). Anticoagulant therapy on admission was based on warfarin in 49 patients (75.4%) and direct oral anticoagulants in 16 (24.6%). In addition, 23 patients (35.4%) were taking antiplatelet agents. Hematoma site was classified as lobar in 21 patients (32.3%), thalamus in 11 (16.9%), putamen in 10 (15.4%), cerebellum in 10 (15.4%), brain stem in 4 (6.2%), intraventricular in 3 (4.6%), and multiple sites in 6 (9.2%). Median modified Rankin Scale (mRS) at discharge was 4, and 31 patients (47.7%) were mRS greater than or equal to 5.

Hemorrhagic Complications and Risk Factors

Clinical characteristics of the 43 ICH patients who resumed anticoagulant therapy after initial treatment are shown in Table 2. Hemorrhagic complications occurred in 8 patients (18.6%), including recurrent ICH in 3, hemorrhage from malignant tumor in 2, gastrointestinal bleeding in 2, and hemorrhage from tracheostomy in 1. Age, sex, antiplatelet use, laboratory data on admission, HAS-BLED score, and SIRS showed no significant differences between the hemorrhagic group and nonhemorrhagic group. Warfarin use for resumption was more common in the hemorrhagic group, but with no significant difference (75.0% versus 37.1%, $P = .11$). Duration from onset to resumption was 7.5 days in the hemorrhagic group and 9 days in the nonhemorrhagic group with no significant difference. The median duration from onset to hemorrhagic events was 26.5 days.

Recurrent ICH was found in 3 patients (7.0%), with rebleeding at the same site in 1 patient who underwent hematoma evacuation surgery before the recurrent ICH and HAS-BLED score of 2 points. The other 2 cases of recurrent ICH were intraventricular hemorrhage after lobar hemorrhage with HAS-BLED score of 2 and 3.

Cardioembolic Complications and Risk Factors

Clinical characteristics of the 38 patients taking anticoagulants for cardiogenic factors and who resumed anticoagulant therapy after initial treatment are shown in Table 3. Cardioembolic complications occurred in 6 patients (15.8%). Causative diseases, such as ventricular aneurysm and mechanical valve, showed no significant difference between the cardioembolic group and noncardioembolic group. CHA_2DS_2-VASc score in patients with AF was paradoxically high in the noncardioembolic group (5 versus 3, $P < .05$). SIRS was significantly more common in the cardioembolic group (4 of 6 patients [66.7%] versus 7 of 32 [21.9%], $P < .05$). Duration from onset to resumption was 8 days in the cardioembolic group and 9 days in the noncardioembolic group with no significant difference. The median duration from onset to cardioembolic events was 7.5 days.

Discussion

Clinical Characteristics of ICH Patients Taking Anticoagulants

In the present study, the mean age of ICH patients taking anticoagulants was 77 years and the most frequent bleeding site was lobar. In the Japanese cohort study of ICH, the average age was 59 years, more than half of the bleeding sites were putamen and thalamus, and only 19% were lobar.[12] AF is the most common causative disease treated by anticoagulants and the prevalence is known to

Table 2. *Hemorrhagic complications and risk factors*

	All patients (N = 43)				
	Hemorrhagic events (−)		Hemorrhagic events (+)		*P* value
	(N = 35)		(N = 8)		
Men (%)	21	(60.0)	5	(62.5)	1
Age, years, median (IQR)	76	(70.5-82.5)	76.5	(72.8-80.0)	.95
Hypertension (%)	25	(71.4)	7	(87.5)	.66
Dyslipidemia (%)	13	(37.1)	3	(37.5)	1
Antiplatelet (%)	16	(45.7)	1	(12.5)	.12
Laboratory data on admission					
Cr, mg/dl, median (IQR)	.8	(.63-.93)	.83	(.67-.96)	.66
AST, IU/L, median (IQR)	22	(19.5-35.5)	25.5	(22.5-29.3)	.62
ALT, IU/L, median (IQR)	15	(13-19.5)	14	(12-23.5)	.8
Plt, $\times 10^4/\mu$l, median (IQR)	17.8	(14.6-21.2)	18.9	(16.8-23.1)	.48
HAS-BLED score, median (IQR)	3	(2-5)	2.5	(2-5)	.48
SIRS (%)	9	(25.7)	2	(25.0)	1
Warfarin use for resumption (%)	13	(37.1)	6	(75.0)	.11
Onset to restarting anticoagulation, days, median (IQR)	9	(5-15.5)	7.5	(5-10.8)	.62
Onset to hemorrhagic events, days, median (IQR)	-	-	26.5	(8-32.3)	-

Abbreviations: Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Plt, platelet count; SIRS, systemic inflammatory response syndrome.

Table 3. *Cardioembolic complications and risk factors*

	All patients (N = 38)				
	Cardioembolic events (−)		Cardioembolic events (+)		*P* value
	(N = 32)		(N = 6)		
Men (%)	20	(62.5)	5	(83.3)	.64
Age, years, median (IQR)	76.5	(72.8-81.3)	68	(66.5-74.8)	.07
Hypertension (%)	27	(84.4)	3	(50.0)	.09
Diabetes mellitus (%)	9	(28.1)	0	(0.0)	.3
Antiplatelet use (%)	13	(40.6)	4	(66.7)	.38
Causative disease					
AF (N = 31) (%)	27	(84.4)	4	(66.7)	.3
CHA_2DS_2-VASc score, median (IQR)	5	(4-6)	3	(3-4)	<.05
Ventricular aneurysm (%)	3	(9.4)	1	(16.7)	.51
Mechanical valve (%)	2	(6.3)	1	(16.7)	.14
SIRS (%)	7	(21.9)	4	(66.7)	<.05
Warfarin use for resumption (%)	12	(37.5)	3	(50.0)	.48
Onset to restarting anticoagulation, days, median (IQR)	9	(5-13.5)	8	(4-10.5)	.5
Onset to cardioembolic events, days, median (IQR)	-	-	7.5	(6.3-14.8)	-

Abbreviation: SIRS, systemic inflammatory response syndrome.

increase with age.[1] This relationship between AF and aging is considered to be the main cause of the higher age in our series.

Our study found unfavorable prognosis with almost half of the patients suffering severe disability or death, similar to the previous finding of poor prognosis for ICH patients taking anticoagulants compared to that for ICH patients not taking anticoagulants.[13] Advanced age may affect the prognosis as well. The higher incidence of lobar hemorrhage may reflect the vascular vulnerability which is affected by the prevalence of amyloid angiopathy which increases with age.[14,15] Aging of the population in Japan is expected to cause further increases in the frequency of these patients.

Hemorrhagic Complications and Recurrent ICH

Hemorrhagic complications occurred in 8 (18.6%) of the 43 patients who resumed anticoagulant therapy after initial treatment. More patients took warfarin at resumption in the hemorrhagic group, but without significant difference. HAS-BLED score, which can predict the annual incidence of hemorrhagic events during taking anticoagulants,[9] also showed no significant difference between the 2 groups. Intracerebral rebleeding developed at the primary lesion or other site in 3 patients (7.0%). HAS-BLED score was 2 in the case of rebleeding at the primary lesion, and 2 and 3 in the cases of intraventricular hemorrhage after lobar hemorrhage, which were less than or equal to the median score of 3 in our series. HAS-BLED score has been proposed for hemorrhagic risk assessment when resuming anticoagulants.[7] However, our findings suggest that HAS-BLED score may not be useful for predicting hemorrhagic complications in the acute stage. It is important to evaluate the patient characteristics, general condition, and comorbidity before resuming anticoagulants.

Thrombotic complication rate is reported to increase when resuming anticoagulants after 72 hours from onset.[16] Therefore, it is important to elucidate the risk factors for hemorrhagic complication to resume anticoagulants safely and early. The Japanese guidelines recommend resuming anticoagulants after confirming the hemostat value,[6] although the optimal timing for resumption is controversial as some recommendations suggest that anticoagulants should be resumed at 7-8 weeks or even 10-30 weeks after the onset.[5,17] However, the former study was designed to determine when to resume in the chronic phase based on analysis of timing of resumption and complications 28 days after onset, and the latter study may overestimate hemorrhagic complications because of the inclusion of cases of traumatic intracranial hemorrhage which sometimes develop chronic subdural hematoma several weeks or months after onset. A recent study recommended that anticoagulants should be resumed within 72 hours after onset for patients with high risk for thrombotic complications.[16] Resumption of anticoagulants at 4 days after onset is also reported to be safe.[18] The European guidelines recommend resuming anticoagulants at 10-14 days after onset.[19] In our study, the median duration from onset to resumption of anticoagulants was 9 days, and the median duration from onset to cardioembolic events was 7.5 days. Therefore, resumption of anticoagulant therapy within a week seems to be reasonable to reduce the risk of cardioembolic complications. However, median duration from initial onset to hemorrhagic events was 26.5 days which was longer than the duration from initial onset to cardioembolic events. The variety of bleeding sites also makes it difficult to determine the optimal timing for resumption. Further study is needed.

Cardioembolic Complications and Risk Factors

Median CHA_2DS_2-VASc score was significantly lower in the cardioembolic group. Although this paradoxical result seemed to be affected by the small sample size, the CHA_2DS_2-VASc score may not detect cardioembolic events in the acute stage. Patients with high-risk conditions for cardioembolic events, such as mechanical valve and ventricular aneurysm, were more common in the cardioembolic group, but with no significant difference. The prevalence of SIRS was significantly greater in the cardioembolic group, but showed no significant difference between the hemorrhagic and nonhemorrhagic groups. Therefore, SIRS was the specific risk factor for cardioembolic events. Perioperative risk of cerebral infarction in patients with AF is reported as 1.8%/30 days, which is higher than the predicted value calculated from epidemiological data.[20] This difference is considered to result from the inflammatory response and activation of coagulation factors caused by surgical stress and general anesthesia. Therefore, acute inflammatory response and concomitant activation of coagulation factors may be involved in the occurrence of acute cardioembolism in patients with ICH. Detection of SIRS is useful for risk assessment of cardioembolism.

Conclusion

Many ICH patients taking anticoagulants are elderly, with lobar as the most frequent bleeding site, and poor prognosis. Resumption of anticoagulant therapy within a week might be reasonable for prevention of cardioembolism. However, the timing of resumption should be determined based on risk assessment for cardioembolic and hemorrhagic complications. Risk assessment scores such as CHA_2D2_S-VASc score and HAS-BLED score were not predictive of cardioembolism and hemorrhagic complications in the acute phase. Acute inflammatory response may contribute to acute cardioembolism, and detection of SIRS may be useful for risk assessment of cardiogenic embolism in the acute phase.

Disclosures

The authors have no conflicts of interest to report.

References

1. Inoue H, Fujiki A, Origasa H, et al. Prevalence of atrial fibrillation in the general population of Japan: an analysis based on periodic health examination. Int J Cardiol 2009;137:102-107.
2. Yamaguchi S, Kobayashi S. Epidemiology of acute stroke in Japan: Japan Standard Stroke Registry. No Sotchu 2014;36:378-384. (in Japanese).
3. Nielsen PB, Larsen TB, Skjùth F, et al. Restarting anticoagulant treatment after intracranial hemorrhage in patients with atrial fibrillation and the impact on recurrent stroke, mortality, and bleeding. A nationwide cohort study. Circulation 2015;132:517-525.
4. Yung D, Kapral MK, Asllani E, et al. Investigators of the Registry of the Canadian Stroke Network. Reinitiation of anticoagulation after warfarin-associated intracranial hemorrhage and mortality risk: the Best Practice for Reinitiating Anticoagulation Therapy After Intracranial Bleeding (BRAIN) study. Can J Cardiol 2012;28:33-39.
5. Pennlert J, Overholser R, Asplund K, et al. Optimal timing of anticoagulant treatment after intracerebral hemorrhage in patients with atrial fibrillation. Stroke 2017;48:314-320.
6. The Japan Stroke Society. The Joint Committee on Guidelines for the Management of Stroke. Japanese Guidelines for the Management of Stroke (Appendix 2017). http://www.jsts.gr.jp/img/guideline2015_tuiho2017.pdf; 2015.
7. da Silva IRF, Frontera JA. Resumption of anticoagulation after intracranial hemorrhage. Curr Treat Options Neurol 2017;19:39.
8. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. Chest 2010;137:263-272.
9. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093-1100.
10. Tsiotou AG, Sakorafas GH, Anagnostopoulos G, et al. Septic shock: current pathogenetic concepts from a clinical perspective. Med Sci Monit 2005;11:RA76-RA85.
11. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452-458.
12. Gotoh S, Hata J, Ninomiya T, et al. Trends in the incidence and survival of intracerebral hemorrhage by its location in a Japanese community. Circ J 2014;78:403-409.
13. Cucchiara B, Messe S, Sansing L, et al. CHANT Investigators. Hematoma growth in oral anticoagulant related intracerebral hemorrhage. Stroke 2008;39:2993-2996.
14. Kremer PH, Jolink WM, Kappelle LJ, et al. SMART and ESPRIT Study Groups. Risk factors for lobar and non-lobar intracerebral hemorrhage in patients with vascular disease. PLoS One 2015;10:e0142338.
15. Biffi A, Sonni A, Anderson CD, et al. Variants at APOE influence risk of deep and lobar intracerebral hemorrhage. Ann Neurol 2010;68:934-943.
16. Hawryluk GW, Austin JW, Furlan JC, et al. Management of anticoagulation following central nervous system hemorrhage in patients with high thromboembolic risk. J Thromb Haemost 2010;8:1500-1508.
17. Majeed A, Kim YK, Roberts RS, et al. Optimal timing of resumption of warfarin after intracranial hemorrhage. Stroke 2010;41:2860-2866.
18. Hasegawa S, Ohta K, Ueda Y, et al. The timing of the resumption of anticoagulants and its relationship to clinical outcomes in patients with intracerebral hemorrhage. No Sotchu 2017;39:339-343. (in Japanese).
19. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace 2015;17:1467-1507.
20. Kaatz S, Douketis JD, Zhou H, et al. Risk of stroke after surgery in patients with and without chronic atrial fibrillation. J Thromb Haemost 2010;8:884-890.