Antithrombotic Drug Uses and Deep Intracerebral Hemorrhages in Stroke Patients With Deep Cerebral Microbleeds

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Background: It has been suggested that antiplatelet or anticoagulant drugs elevate the rate of intracerebral hemorrhage (ICH) in patients with cerebral microbleeds (MBs). To investigate the mechanism by which antiplatelet drugs or warfarin may contribute to deep ICH occurrences in patients with deep MBs, we prospectively analyzed deep ICH occurrences in 807 consecutive patients (351 females and 456 males; mean age ± standard deviation 69.8 ± 12.0 years) who were admitted to our hospital with strokes. *Methods:* Occurrence-free rate curves were generated using the Kaplan–Meier method; deep ICH occurrence–free rates were compared using the log-rank test. The follow-up period was 0.5 to 71 months (mean ± standard deviation 31.6 ± 22.2 months). *Results:* In patients with deep MBs, the rates (1.0%/year; 6 ICHs in 180 patients) of deep ICH occurrence associated with antiplatelet drugs were not significantly greater than that without the drugs (1.0%/year; 6 ICHs in 167 patients; $P = .977$). The incidence of deep ICHs associated with warfarin use was not significantly greater than that without warfarin use. *Conclusions:* Multivariate analysis revealed that the use of antiplatelet drugs or warfarin did not significantly influence the occurrence of deep ICH in patients with deep MBs. Antiplatelet drugs or warfarin did not significantly elevate the rate of deep ICHs in stroke patients with pre-existing deep MBs. **Key Words:** Antiplatelet drug—intracerebral hemorrhage—microbleeds—stroke—warfarin.

Cerebral microbleeds (MBs) are related to bleeding-prone microangiopathies, including lipohyalinosis[1,2] and amyloid angiopathy.[1,3] MBs also correlate with cerebral infarctions associated with microangiopathy, particularly lacunar infarction,[4-6] seen in other angiopathies.[7] MBs have been shown to be surrogate markers of stroke recurrence and severity of microangiopathy.[4,8-14]

Several studies have found that antiplatelet or anticoagulant drugs may induce intracerebral hemorrhage (ICH) and enlarge hemorrhage size.[15-18] Both pre-existing and nascent MBs are associated with ICH occurrence.[8-11] These findings have led to concerns over the safety of antiplatelet or anticoagulant drug use in patients with MBs. The presence of MBs increased the risk of aspirin-associated ICH.[19,20] A subset of clinicians already regard MBs as a relative contraindication to warfarin therapy.[21,22] There is no clear evidence, however, that MBs increase the risk of ICH associated with antiplatelet or anticoagulant drugs. Recently, Lovelock et al[23] concluded, in a systemic review, that anticoagulant drug use in patients with MBs elevated the rate of ICH. Therefore, MBs may be a marker of increased risk of ICH in patients taking antiplatelet or anticoagulant medications. Without the initiation of antiplatelet or anticoagulant therapy, however, patients, particularly those with histories of

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cerebral infarct, may develop infarctions. In this study, we sought to investigate the effects of antiplatelet or anticoagulant drugs on patients with MBs.

Methods

Subjects

We enrolled consecutive patients who were admitted to our hospital with strokes (index strokes) within 7 days after onset between April 2004 and October 2009 and followed them until January 2010. Stroke recurrences were evaluated in all patients. We excluded patients that died within 2 weeks of the first admission, patients for whom we had follow-up of <2 weeks, and patients with unclear findings on magnetic resonance imaging (MRI) scans because of motion or metal artifact. All study procedures were approved by the ethics committee of our hospital (Institutional Review Board 2004-1 for Kushiro City General Hospital).

Radiologic Examination

More than 2 physicians with Japanese Board Certification in neurosurgery and stroke diagnosed the type of stroke based on the radiologic findings. We divided strokes into subtype of ICH (subcortical and deep), subarachnoid hemorrhage, and cerebral infarction (lacunar infarction, atherothrombotic infarction, cardioembolic infarction, and infarction of unknown origin). All strokes were verified by computed tomography (CT) and MRI scans on admission. Gradient echo T_2*-weighted (T_2*-w) MRI scans, fluid-attenuated inversion recovery (FLAIR) images, diffusion-weighted images (DWIs), and magnetic resonance angiography scans were performed to differentiate stroke types. In addition to CTs and MRIs, stroke subtypes were diagnosed by electrocardiograms, including Holter electrocardiogram, echocardiogram, and/or digital subtraction angiography. ICHs associated with head traumas, arteriovenous malformations, venous malformations, moyamoya disease, ruptured cerebral aneurysms, angiomas, or tumors were excluded from this study.

Dot-like low intensity spots on T_2*-w MRI with diameters <10 mm were defined as MBs. Calcifications were excluded by CT. The total number of MBs was counted on the admission T_2*-w MRI, excluding MBs in areas surrounding the ICH and within the globus pallidus.[24] The locations of MBs and ICHs were divided according to the Microbleed Anatomical Rating Scale (MARS).[25] In this study, MBs were divided into lobar MBs and deep MBs, including MBs in territories of perforating arteries and posterior fossae.

T_2*-w MRI, FLAIR, and DWI imaging performed on a 1.5-T scanner (Sigma Excite 1.5, GE) were obtained in the axial plane with the following parameters: repetition time/echo time/excitations of 450/26/2, 8800/141/1, and 5000/84/2, respectively; a flip angle of 20°; a section thickness of 7.5 mm without a gap; and a matrix of 256 × 205.

Variables

Fasting blood samples were obtained the morning after initial admission. Diabetes mellitus was defined according to National Diabetes Data Group diagnostic criteria.[26] Smoking history categorized patients into cigarette smoking and nonsmoking on admission; the latter included former regular cigarette smokers who had quit >1 year earlier. Patients were considered to have habitual alcohol intake if alcohol consumption exceeded 100 g of ethanol per week. Subjects were considered hypertensive when their blood pressure repeatedly exceeded 140/85 mm Hg or if they were taking antihypertensive medications. At each follow-up visit, antihypertensive drug therapies were titrated to achieve a target BP < 140/85 mm Hg. Medications taken by patients were recorded 8 to 24 months after admission for the index stroke in patients. If the follow-up period was <8 months, medication usage was recorded at the last drug administration.

Statistics

The elicit the effect of antiplatelet drugs or warfarin on patients with MBs, we generated recurrence-free rate curves using the Kaplan–Meier method. ICH occurrence rates were compared by the log-rank test. The Student *t* test was used to compare age and number of MBs, considering each as a categorical variable. The overall frequency with which each categorical variable was associated with stroke recurrence was calculated in the form of hazard ratios and 95% confidence intervals (CI) using a Cox proportional hazard model. When not applicable for this analysis, categorical variables were analyzed with the Pearson Chi-square test.

Multivariate analyses were also performed using the Cox proportional hazard model, with the elimination of variables that did not contribute to the model ($P > .2$). The number of deep MBs was chosen as the cutoff to separate patients into groups by multivariate analyses were changed several times. $P < .05$ was considered statistically significant.

Results

Of the 1095 patients consecutively recorded during the study period, we excluded 190 patients who survived or who underwent follow-up in <2 weeks, and also excluded 27 patients with pacemakers. An additional 21 patients were excluded for unclear MRI findings because of motion or metal artifacts. Fifty patients were excluded because of insufficient information. After these exclusions, we followed and investigated 807 patients (351 females; 69.8 ± 12.0 years of age) with strokes. The stroke type (index stroke) at admission was ICH in 188 (23.3%)