Blood Pressure Control and Recurrence of Hypertensive Brain Hemorrhage

Shuji Arakawa, MD; Yoshisuke Saku, MD; Setsuro Ibayashi, MD, PhD; Tetsuhiko Nagao, MD, PhD; Masatoshi Fujishima, MD, PhD

Background and Purpose—Recent studies have demonstrated that recurrence of hypertensive brain hemorrhage (HBH) is not uncommon. However, risk factors for the recurrence of HBH have not been evaluated systematically.

Methods—We analyzed 74 patients with HBH who were admitted to our clinic and followed up as outpatients for a mean of 2.8 years. Blood pressure (BP) and other clinical features were compared between the groups of patients with and without rebleeding. We determined the recurrence rate of HBH in relation to BP.

Results—Diastolic BP was significantly higher in the recurrence group than in the nonrecurrence group (82±7 mm Hg; P = 0.04). Systolic BP and other clinical variables were not different between the groups. The recurrence rate was 10.0% per patient-year in patients with diastolic BP > 90 mm Hg and < 1.5% in those with lower diastolic BP (P < 0.001). No patients with diastolic BP < 70 mm Hg experienced rebleeding.

Conclusions—Higher diastolic BP was related to an increased rate of rebleeding. Diastolic BP > 90 mm Hg may be regarded as a factor predictive of the recurrence of HBH. (Stroke. 1998;29:1806-1809.)

Key Words: blood pressure • cerebral hemorrhage • hypertension • stroke prevention

Although hypertensive brain hemorrhage (HBH) has been generally considered to be a one-time event,1-2 recent studies have demonstrated that recurrence of HBH is more common than believed. Reported recurrence rates are 1.8% to 5.3% for various follow-up periods.3-6 The higher recurrence rate is due, at least in part, to decreased mortality from brain hemorrhage7,8 and an increased number of survivors with high risks for recurrence. The incidence of recurrent HBH has been a subject of a number of studies, while risk factors for rebleeding have not been evaluated systematically. Although uncontrolled hypertension appears to be an important risk factor for recurrence,1-6,9,10 the level of blood pressure (BP) that may prevent rebleeding is uncertain.

In this study we evaluated the relationship between recurrence of HBH and other clinical variables, with special emphasis on postictal BP levels.

Subjects and Methods
From January 1995 to December 1996, 93 patients with HBH visited our clinic as outpatients. All patients experienced first-ever HBH between 1982 and 1996 and had been followed up monthly until the time of inclusion in this study. Nineteen patients with follow-up periods < 3 months were excluded. We analyzed 74 patients (51 men, 23 women; mean age, 59 years) with follow-up periods of 3 to 162 months (mean, 67 months).

The hypertensive nature of brain hemorrhage was determined by (1) location of hematoma in the putamen, thalamus, pons, cerebellum, or subcortical white matter; (2) documentation of hypertension by medical history or BP readings > 160/95 mm Hg (on at least 3 different days > 4 weeks after the onset of hemorrhage) or regular use of antihypertensive drugs for BP control; and (3) exclusion of known or suspected causes of hemorrhage such as aneurysm, arteriovenous malformation, head trauma, brain tumor, anticoagulant use, and cerebral amyloid angiopathy. The location of hemorrhage was as follows: 32 patients (43%) in putamen, 27 (36%) in thalamus, 7 (9%) in subcortical white matter, and 8 (11%) in pons or cerebellum.

Examination of the patients and measurements of BP were made every 4 weeks. At each follow-up examination, data were collected on neurological status, new cerebrovascular episodes, and BP levels. Sixty-one patients (82%) received antihypertensive drugs depending on physicians’ judgment.

Mean values of systolic BP (SBP) and diastolic BP (DBP) during follow-up periods were determined by averaging all values recorded in the outpatient clinic and were compared between the groups of patients with and without rebleeding. In patients with rebleeding, all BP readings before the recurrence were averaged. We also determined the recurrence rate of HBH in relation to mean values of BP during follow-up periods.

Other clinical profiles such as age, sex, location of hemorrhage, history of ischemic stroke, diabetes mellitus (determined by an oral glucose tolerance test, casual blood glucose levels > 200 mg/dL, or medical history of diabetes), hyperlipidemia (total cholesterol > 220 mg/dL and/or triglycerides > 160 mg/dL), liver cirrhosis (by blood tests and ultrasonography), chronic renal failure (those on maintenance hemodialysis), ischemic heart disease (history of angina pectoris or myocardial infarction), and antihypertensive and antiplatelet therapy after the first hemorrhage were also analyzed.

Statistical comparisons between the groups were performed with Student’s t test or the Mann-Whitney U test for the comparison of two groups and Fisher’s exact probability test for the analysis of proportion. Recurrence-free rates were analyzed with a log-rank test.
TABLE 1. Clinical Characteristics of 8 Patients With Recurrence of HBH

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at 1st BH/Sex</th>
<th>Site of 1st BH</th>
<th>Site of 2nd BH</th>
<th>Interval Between 1st and 2nd BH, y</th>
<th>Risk Factors</th>
<th>Antihypertensive Agents</th>
<th>Mean SBP, mm Hg</th>
<th>Mean DBP, mm Hg</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59/M</td>
<td>Thalamus, B</td>
<td>Thalamus, R</td>
<td>2.0</td>
<td>HT</td>
<td>Ca, ACE</td>
<td>149</td>
<td>96</td>
<td>GR</td>
</tr>
<tr>
<td>2</td>
<td>51/M</td>
<td>Thalamus, R</td>
<td>Thalamus, L</td>
<td>12.3</td>
<td>HT</td>
<td>Ca</td>
<td>144</td>
<td>94</td>
<td>Death</td>
</tr>
<tr>
<td>3</td>
<td>38/M</td>
<td>Putamen, R</td>
<td>Thalamus, L</td>
<td>3.5</td>
<td>HT</td>
<td>Ca, ACE, β</td>
<td>132</td>
<td>94</td>
<td>SD</td>
</tr>
<tr>
<td>4</td>
<td>47/F</td>
<td>Putamen, R</td>
<td>Cerebellum, R</td>
<td>4.3</td>
<td>HT</td>
<td>None</td>
<td>141</td>
<td>92</td>
<td>VS</td>
</tr>
<tr>
<td>5</td>
<td>39/M</td>
<td>Putamen, R</td>
<td>Putamen, L</td>
<td>4.4</td>
<td>HT, HLP</td>
<td>Ca, ACE</td>
<td>127</td>
<td>90</td>
<td>GR</td>
</tr>
<tr>
<td>6</td>
<td>60/M</td>
<td>Putamen, L</td>
<td>Pons</td>
<td>1.9</td>
<td>HT, HLP</td>
<td>Ca</td>
<td>140</td>
<td>87</td>
<td>VS</td>
</tr>
<tr>
<td>7</td>
<td>70/F</td>
<td>Thalamus, L</td>
<td>Thalamus, L</td>
<td>1.3</td>
<td>HT</td>
<td>Ca</td>
<td>132</td>
<td>75</td>
<td>SD</td>
</tr>
<tr>
<td>8</td>
<td>66/M</td>
<td>Thalamus, L</td>
<td>Putamen, L</td>
<td>4.2</td>
<td>HT</td>
<td>None</td>
<td>125</td>
<td>75</td>
<td>MD</td>
</tr>
</tbody>
</table>

B indicates bilateral; R, right; L, left; HT, hypertension; HLP, hyperlipidemia; Ca, calcium antagonist; ACE, angiotensin-converting enzyme inhibitor; β, β-blocker; GR, good recovery; SD, severely disabled; VS, vegetative state; and MD, moderately disabled.

TABLE 2. Univariate Correlation Between Baseline Variables and Rebleeding After HBH in 74 Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Recurrence (n=8)</th>
<th>Nonrecurrence (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.0±12.3</td>
<td>59.8±8.6</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>6/2</td>
<td>45/21</td>
</tr>
<tr>
<td>Follow-up period, y</td>
<td>4.3±3.5</td>
<td>5.7±4.0</td>
</tr>
<tr>
<td>Site of 1st hemorrhage (Put/Thl/other)</td>
<td>4/3/1</td>
<td>28/23/15</td>
</tr>
<tr>
<td>Old ischemic stroke</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0%</td>
<td>11%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>25%</td>
<td>26%</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td>Antihypertensive agents</td>
<td>75%</td>
<td>85%</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Mean SBP, mm Hg</td>
<td>136±8</td>
<td>135±10</td>
</tr>
<tr>
<td>Mean DBP, mm Hg</td>
<td>88±8</td>
<td>82±7</td>
</tr>
</tbody>
</table>

Put indicates putamen; Thl, thalamus. Values are mean±SD.

Results

Eight patients (11%) had recurrent HBH (Table 1), and the overall recurrence rate was 2.0% per patient-year. The interval between the first and recurrent hemorrhage ranged from 1.3 to 12.3 years. All patients but 2 were on antihypertensive medication. Common antihypertensive agents were calcium antagonists and angiotensin-converting enzyme inhibitors. Systolic BP after the first HBH was not different between groups (recurrence group versus nonrecurrence group: 136±8 versus 135±10 mm Hg [mean±SD]; P=0.7). In contrast, DBP was significantly higher in the recurrence group than in the nonrecurrence group (88±7 versus 82±7 mm Hg; P=0.04) (Table 2). In the patients with recurrence, 2 showed good functional recovery, 1 was moderately disabled, 2 were severely disabled, 2 were in a vegetative state, and 1 died.

When we analyzed the recurrence rate of HBH in terms of the level of DBP and SBP, recurrence was more common in patients with higher DBP during the follow-up. Five of 10 patients (50%) with DBP >90 mm Hg had rebleeding. We examined the relationship between BP control after the first HBH and its recurrence in terms of SBP and DBP levels. Although elevated DBP might only be a reflection of advanced hypertensive arteriopathy in HBH patients, DBP >90 mm Hg may be regarded as one of the factors predictive of recurrent HBH. It must be determined whether the control of DBP <90 mm Hg can reduce the recurrence in a prospective randomized intervention study.

Discussion

In this study we showed that recurrence of HBH was more frequent in patients with higher poststroke DBP. The recurrence rate in patients with DBP >90 mm Hg was 10.0% per patient-year, and this was significantly higher than the rate in those with lower DBP (Figures 2 and 3) (P<0.001). The other 3 patients with rebleeding had DBP between 70 and 90 mm Hg (Figure 1). No patients with DBP <70 mm Hg (n=5) had rebleeding. The recurrence rate of HBH appeared to elevate with increasing SBP, but the difference was not significant (Figure 2).

Other clinical variables were not different between the groups of patients with and without rebleeding. Although patients in the recurrence group were younger than those in the nonrecurrence group, the difference did not reach statistical significance (Table 2). Higher DBP was associated with increased recurrence rate even after correction for age (P=0.05).
158 mm Hg (mean, 135 mm Hg), and patients with severe hypertension were not present in this study. The threshold levels of SBP may be 160 mm Hg in terms of the recurrence of HBH. Alternatively, DBP plays a more important role than does SBP in the recurrence of HBH. The predominant importance of DBP over SBP on the incidence of initial brain hemorrhage has been reported in some epidemiological studies.11,12 The incidence of the first brain hemorrhage was markedly dependent on recent DBP levels11 and highest in those with diastolic hypertension in a prospective population survey.12 Similarly, DBP might also be a critical factor for recurrent HBH. However, concerning the importance of SBP, we must be aware that a relatively small number of samples might have resulted in a type II error in the present study.

We could not find any difference in variables other than BP between the groups of patients with and without rebleeding. Younger age at the first HBH10 and the presence of liver cirrhosis13 were reported to increase the risk of subsequent brain hemorrhage. However, these were not regarded as significant risks for recurrence in the present study. The lack of relationship between the recurrence of HBH and liver cirrhosis may be due to the small number of patients with liver cirrhosis in our analysis.

The recurrence rate in this study is higher than that reported in most previous studies (Hirohata et al, 3 1.8%; Lee et al,4 2.7%; Chen et al,5 5.3%; Misra and Kalita,6 4.7%; Passero et al,7 24%; Maruish et al,14 5.9%; and Neau et al,10 6.4%). This is due, at least in part, to different follow-up periods. A relatively longer follow-up period in this study may have resulted in the higher cumulative recurrence rate. Furthermore, in the present series patients with a previous HBH were recruited selectively. In the studies by Passero et al7 and Neau et al,10 a majority of cases with recurrent brain hemorrhage exhibited a “lobar-lobar” type recurrence, which is suggestive of the presence of cerebral amyloid angiopathy as an etiology of brain hemorrhage.

In conclusion, higher DBP after HBH was related to an increase in rebleeding, and DBP >90 mm Hg may be a factor predictive of recurrent HBH. Well-programmed prospective intervention studies are needed to determine the benefits of DBP control after HBH.

References

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**Figure 1.** Mean values of poststroke BP and clinical outcome.

**Figure 2.** Poststroke BP and recurrence rate of HBH. Patients with DBP >90 mm Hg had a significantly higher recurrence rate than those with lower DBP (*P*<0.001, log-rank test).

**Figure 3.** Kaplan-Meier curve for probability of rebleeding-free survival according to stratified poststroke DBP. The differences between the group of patients with DBP >90 mm Hg and the other two groups were statistically significant (*P*<0.001, log-rank test).
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