Blood Pressure Management in Acute Intracerebral Hemorrhage: Relationship Between Elevated Blood Pressure and Hematoma Enlargement

Kazuhiro Ohwaki, MD; Eiji Yano, MD; Hiroshi Nagashima, MD; Masafumi Hirata, MD; Tadayoshi Nakagomi, MD; Akira Tamura, MD

Background and Purpose—The association between elevated blood pressure (BP) and hematoma enlargement in acute intracerebral hemorrhage (ICH) has not been clarified. We investigated the association between maximum systolic BP (SBP) and hematoma enlargement, measuring SBP between a baseline and a second CT scan in patients with hypertensive ICH.

Methods—We assessed 76 consecutive patients with hypertensive ICH retrospectively. We usually attempted to lower SBP below targets of 140, 150, or 160 mm Hg. Recordings of serial BP from admission until the second CT scan were assessed. A neuroradiologist, who was not informed of the aim of this study, reviewed CT films. Hematoma enlargement was defined as an increase in volume of ≥140% or 12.5 cm³.

Results—Hematoma enlargement occurred in 16 patients. Maximum SBP was significantly associated with hematoma enlargement (P=0.0074). A logistic regression model for predicting hematoma enlargement was constructed with the use of maximum SBP, hematoma volume, and Glasgow Coma Scale score at admission. After adjustment for these factors, maximum SBP was independently associated with hematoma enlargement (odds ratio per mm Hg, 1.04; 95% CI, 1.01 to 1.07). Target SBPs of ≥160 mm Hg were significantly associated with hematoma enlargement compared with those of ≥150 mm Hg (P=0.025).

Conclusions—Our findings suggest that elevated BP increases the risk of hematoma enlargement. Efforts to lower SBP below 150 mm Hg may prevent this risk. (Stroke. 2004;35:000-000.)

Key Words: intracerebral hemorrhage  ■ hematoma  ■ blood pressure

Lowering blood pressure (BP) is commonly practiced to prevent hematoma enlargement in patients with intracerebral hemorrhage (ICH). However, the association between elevated BP and hematoma enlargement remains unclear.1–3 Persistent marked elevation of BP can predispose patients to hematoma enlargement. On the other hand, there may be areas of focal ischemia adjacent to a hematoma, and reduction of BP has been assumed to promote further ischemia. Elevated BP can also be a protective response (referred to as the Cushing-Kocher response) to preserve cerebral perfusion. There has therefore been considerable controversy regarding the initial control of BP after the onset of ICH.4–9 The American Heart Association recommends that patients with systolic BP (SBP) >180 mm Hg or diastolic BP (DBP) >105 mm Hg should receive intravenous antihypertensive agents. Supporting evidence for this guideline is extremely weak.10

We investigated 76 consecutive patients with hypertensive ICH to determine whether elevated BP is related to hematoma enlargement and, if so, to estimate an appropriate target BP.
Routine care of these patients at the unit included the following: when ICH was diagnosed by CT scan, we set a “target SBP” and tried to lower BP below the target SBP. We might have intended to set a relatively high target SBP in patients of advanced age or with a large volume of hematoma to preserve cerebral perfusion, but no clear rules existed. The target was usually set at 140, 150, or 160 mm Hg. BP was continuously monitored with alarm settings, and a nurse usually attended each patient. Although antihypertensive therapy was not standardized, most of the patients received intravenous nicardipine or diltiazem. The vast majority of patients initially received intravenous nicardipine; more nicardipine was used if a rapid reduction in BP was not observed within 5 to 10 minutes. Most of the patients were subsequently controlled by continuous intravenous nicardipine or diltiazem. All uses of antihypertensive agents or sedatives after admission were recorded.

CT Findings
A CT brain scan at admission was obtained for all patients, except those who were referred from other hospitals. Of the 12 referred patients, a CT scan at the admission to our unit was obtained for 8 patients and used as the baseline CT. The second CT scan was usually obtained on the day after admission as a routine procedure or when the patient demonstrated neurological deterioration. The interval from admission to the second CT scan was recorded for each patient. CT scans were performed with the use of a 512 × 512 matrix with 5- to 10-mm slices. A neuroradiologist with 20 years of experience, who was not informed of the aim of this study, reviewed the CT films. CT images were then copied as computer files, concealing all personal identification. Hematoma sizes in the initial and second CT scans were measured. In the slice with the largest area of ICH, the longest diameter (A) of the hematoma and the second diameter (B) on the perpendicular line were measured. The height of the hematoma was calculated by the number of 10-mm interval slices intersected to obtain the third diameter (C). The 3 diameters were multiplied and then divided by 2 (A × B × C/2) to obtain the volume of ICH. Enlargement of hematoma was defined as an increase in the volume of ≥140% or ≥12.5 cm³ between baseline and second CT scans, as in a previous study.11 The neuroradiologist, taking different conditions at scanning into account, also determined the presence or absence of hematoma enlargement. Blood in the ventricles was recorded if present but was not included in the hematoma volume. The shape of each hematoma was recorded as regular or irregular. The site of hematoma was recorded as putamen, thalamus, brain stem, cerebellum, lobes, or mixed (putamen and thalamus).

Data Collection
Recordings of serial BP readings from the arrival in the unit to the time of the second CT scan after admission were assessed. BP recordings were extracted from the critical care nursing records. In most cases, BP recordings were made every 10 to 15 minutes until SBP was stabilized (for 1 to 2 hours). After that, BPs were recorded every 2 hours or at any time that BP changed markedly. All BP recordings were cuff measurements.

Time of onset was defined on the basis of initial symptoms observed by the patient or by a witness. In some cases, the precise time of onset could not be identified because the patient was found unconscious. When the interval between the time the patient was last known to be normal and was discovered was <12 hours, we used the midpoint of the interval as the time of onset. The median interval of these cases was 3.5 hours (n=9).

We defined “maximum SBP” as the highest value of SBP between the baseline and second CTs. In referred patients whose CT scans were not obtained at admission to our unit (n=4), maximum SBP was defined as the highest value between the time of admission and the second CT. In addition to maximum SBP, the following clinical information was abstracted from the hospital records: sex, age, presence or absence of risk factors associated with cerebrovascular disease, antiplatelet and anticoagulant drug use, date and time of hemorrhage onset, Glasgow Coma Scale (GCS) score at admission, SBP at admission, target SBP, and surgical interventions (if any).

Liver function tests, as well as platelet count and total protein, were also collected, and liver dysfunction was defined on the basis of a preceding study.13

Statistical Analysis
When target SBP was not set (n=6), it was included in the 200-mm Hg target SBP group since antihypertensive therapy was deferred in most of those patients. Target SBP was usually set at 140, 150, or 160 mm Hg, in 10-mm Hg intervals; for analysis it was reclassified as either 150 mm Hg (140 or 150) or 160 mm Hg (160, 170, 180, or 200).

We used χ² tests were used to compare patients with and without hematoma enlargement for the categorical variables. We performed t tests or Wilcoxon rank sum tests for the continuous variables. Those with probability values <0.10 were eligible to be included as predictor variables in the logistic regression analysis for hematoma enlargement. Values of P<0.05 were considered significant. All analyses were performed with the use of the Statistical Analysis System (SAS Institute Inc).

Results
The study group was composed of 53% men and 47% women. Age of the patients ranged from 37 to 91 years, with a mean of 63 years. The location of hematomas was as follows: putamen in 20 patients (26%), thalamus in 17 (22%), brain stem in 13 (17%), cerebellum in 4 (5%), lobes in 11 (14%), and mixed in 11 (14%). Two patients were dependent on dialysis (3%). We documented antiplatelet and anticoagulant drug use in 6 patients (8%) and in 1 patient (1%), respectively. The mean GCS score at admission was 7.7, and nearly half of the patients were deeply comatose (GCS score 3 to 6, 49%; GCS score 7 to 12, 34%; GCS score 13 to 14, 14%; GCS score 15, 3%). Mean SBPs and DBPs at admission were 193 and 104 mm Hg, respectively. Mean maximum SBPs and DBPs were 180 and 95 mm Hg, respectively. The mean interval between the baseline and second CTs was 15.7 hours.

Hematoma enlargement, as determined from measurement of CT scan copies, occurred in 16 patients. Table 1 illustrates the statistical relationship between hematoma enlargement and clinical variables. Maximum SBP between the baseline and second CTs was the factor most significantly associated with hematoma enlargement (P=0.0074).

A logistic regression model for predicting hematoma enlargement was constructed with the use of the factors with a significance level of P<0.10. Although SBP at admission reached that level (P=0.0631), we did not include it in the logistic regression model because SBPs at admission may vary depending on variations in delay from onset to admission. By logistic regression analysis, maximum SBP was independently associated with hematoma enlargement (odds ratio [OR] per mm Hg, 1.041; 95% CI, 1.010 to 1.074) (Table 2). Hematoma volume was negatively associated with hematoma enlargement. A nonsignificant increase in the incidence of hematoma enlargement was observed in patients with poor GCS score at admission.

Hematoma enlargement, as determined by the neuroradiologist, occurred in 35 patients. A logistic regression model for predicting hematoma enlargement, according to the neuroradiologist’s determination, was also constructed with the use of the same factors (maximum SBP, hematoma volume, and GCS score at admission). Again, positive association of
TABLE 1. Differences in Clinical Factors Between Patients With and Without Hematoma Enlargement

<table>
<thead>
<tr>
<th>Factors</th>
<th>Patients Without Hematoma Enlargement</th>
<th>Patients With Hematoma Enlargement</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=60</td>
<td>n=16</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (50)</td>
<td>6 (38)</td>
<td>0.374</td>
</tr>
<tr>
<td>Liver dysfunction, n (%)</td>
<td>17 (28)</td>
<td>8 (50)</td>
<td>0.101</td>
</tr>
<tr>
<td>Irregular pattern, n (%)</td>
<td>41 (68)</td>
<td>8 (50)</td>
<td>0.173</td>
</tr>
<tr>
<td>Intraventricular hemorrhage, n (%)</td>
<td>42 (70)</td>
<td>9 (56)</td>
<td>0.298</td>
</tr>
<tr>
<td>Age (y), mean</td>
<td>63.5</td>
<td>61.8</td>
<td>0.642</td>
</tr>
<tr>
<td>Mean of Time from onset to admission (h)*, median</td>
<td>7</td>
<td>6</td>
<td>0.083</td>
</tr>
<tr>
<td>SBP at admission (mm Hg), mean</td>
<td>197.2</td>
<td>175.7</td>
<td>0.063</td>
</tr>
<tr>
<td>Maximum SBP (mm Hg), mean</td>
<td>175.9</td>
<td>194.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Time from admission to 2nd CT (h), mean</td>
<td>15.6</td>
<td>16.1</td>
<td>0.841</td>
</tr>
<tr>
<td>Total protein (g/dl), mean</td>
<td>7.1</td>
<td>7.3</td>
<td>0.472</td>
</tr>
<tr>
<td>Platelet count (10^4/mm³), mean</td>
<td>20.7</td>
<td>20.8</td>
<td>0.944</td>
</tr>
<tr>
<td>Hematoma volume (cm³), median</td>
<td>30.1</td>
<td>13.8</td>
<td>0.051</td>
</tr>
</tbody>
</table>

GCS indicates Glasgow Coma Scale; and SBP, systolic blood pressure.
*Not including 15 patients with unknown onset time.

TABLE 2. Odds Ratio of Hematoma Enlargement According to the Cutoff Point*

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum SBP (per mm Hg)</td>
<td>1.041</td>
<td>1.010–1.074</td>
</tr>
<tr>
<td>Hematoma volume (cm³)</td>
<td>0.975</td>
<td>0.956–0.995</td>
</tr>
<tr>
<td>GCS at admission</td>
<td>0.845</td>
<td>0.695–1.028</td>
</tr>
</tbody>
</table>

GCS indicates Glasgow Coma Scale; SBP, systolic blood pressure.
*Cutoff point: ≥1.4 times or ≥12.5 cm³.

Discussion

In this study we observed a significant association between high maximum SBP between baseline and second CT scans and the occurrence of hematoma enlargement. After we controlled for hematoma volume and GCS at admission, a significant positive association between maximum SBP and hematoma enlargement persisted. The analysis of target SBP indicated that hematoma enlargement occurred more often in patients with a target SBP of ≥160 mm Hg.

Preventing hematoma enlargement is an important issue in patients with acute ICH. Although there have been numerous studies of BP after acute ICH, the appropriate control of BP is still controversial.6,9,13 Preceding studies have focused mainly on BP at admission. Kazui et al reported that poorly controlled diabetic patients with high SBP at admission (>200 mm Hg) were at high risk of hematoma enlargement. In a few studies, however, it appears that SBP at admission is not a predictive factor.6,13 While we did not use BP at admission in the regression analysis, including it in the logistic regression did not alter the significance of the other variables: SBP at admission (OR, 0.967; 95% CI, 0.943 to 0.992), maximum SBP (OR, 1.063; 95% CI, 1.021 to 1.108), hematoma volume (OR, 0.986; 95% CI, 0.943 to 0.993), and GCS score at admission (OR, 0.807; 95% CI, 0.645 to 1.010). This model demonstrated poor fit (P<0.0001, Hosmer–Lemeshow test). Fujii et al reviewed several measurements of SBP 1 hour after admission and used the mean of those values. They reported a significant association between hematoma enlargement and high SBP after admission. However, they speculated that the relationship between elevated BP after admission and hematoma enlargement was more likely caused by the increased intracranial pressure. If elevated BP causes hematoma enlargement, maximum BP after admission may have a greater influence on the occurrence of hematoma enlargement. When BP reached a target SBP, we used antihypertensive agents to lower BP below the target SBP. Therefore, maximum SBP may be a key factor for BP control. Few data are available about maximum BP after admission and target BP.

We defined hematoma enlargement according to the study by Kazui et al. They proposed a cutoff value for the diagnosis of increased hematoma size on CT based on an analysis of receiver operating characteristic curves. Hematoma enlargement occurred in 21% of the patients in our study, which constitutes a result comparable to that reported by Kazui et al (20%). In addition, we adopted another criterion for hematoma enlargement, the neuroradiologist’s determination. Patients with hematoma enlargement, as determined by the neuroradiologist (n=35), included all those determined by the cutoff point according to the study by Kazui et al (n=16). The neuroradiologist tended to include lesser enlargements. Hematoma size was assessed by an
experienced neuroradiologist who was not informed about the aim of this study, thus eliminating a possible bias in the design of a retrospective study. Some misclassification of hematoma size seems likely, but any misclassification would be nondifferential for maximum SBP. We used 2 criteria to define hematoma enlargement and confirmed that maximum SBP was significantly associated with hematoma enlargement in logistic regression analysis with either criterion.

Small hematoma volume was also related to hematoma enlargement. The incidence of hematoma enlargement was reported to decrease as the time interval from onset increased.\textsuperscript{6,11–13} When a hematoma is scanned during its initial volume increase, there may be a greater chance of detecting enlarging hematoma. Thus, hematoma enlargement is more likely to be observed by early CT scanning. In our study, however, time from onset was not associated with hematoma enlargement. A short interval from onset to admission does not seem to entirely explain the association between small hematoma and enlargement. Besides, hematoma volume is closely associated with location. In our study the incidence of hematoma enlargement in the brain stem was higher than at any other site (44%). Although the association between small hematomas and enlargement may indicate characteristics of location rather than of volume, a significant positive association between maximum SBP and hematoma enlargement remained in a logistic regression, constructed as above, that included only patients with hematomas in the putamen, thalamus, and mixed locations: maximum SBP (OR, 1.075; 95% CI, 1.013 to 1.141), hematoma volume (OR, 0.941; 95% CI, 0.892 to 0.993), and GCS score at admission (OR, 0.719; 95% CI, 0.490 to 1.053).

Our study was observational in design; thus, we cannot conclude definitively that increased BP caused hematoma enlargement. However, our results show that target SBPs of \(\geq 160\) mm Hg, set before hematoma enlargement was evaluated, were significantly associated with hematoma enlargement. They suggest that insufficient lowering of BP increases the risk of hematoma enlargement, although maximum SBP may not always be kept below the target SBP. This indicates that hematoma enlargement can occur unless target BP is set at levels well below those recommended in current guidelines.\textsuperscript{10}

There are some limitations to this study. In a retrospective study with a small population selected by a tertiary care unit, we cannot rule out the presence of unknown, confounding variables, not accounted for in the final analysis. However, it is unlikely that such undetected, residual confounding would completely eliminate the effect seen. Although target SBP might have tended to be set high in patients of advanced age or with a large volume of hematoma, hematoma enlargement occurred more often in younger patients with smaller hematomas. Thus, this bias probably does not weaken the association between elevated BP and hematoma enlargement. Our exclusion of patients who missed a second CT scan is also not expected to have meaningfully biased our results because most of these patients suffered brain death shortly after admission.

In conclusion, our findings suggest that high SBP is independently associated with an increased risk of hematoma enlargement after adjustment for other prognostic factors. Efforts to lower SBP below 150 mm Hg may prevent hematoma enlargement. A well-designed, large, randomized, controlled trial is urgently needed to confirm our results.

References

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Stroke. published online April 29, 2004;

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