ORIGINAL ARTICLE

Headache as a Predictive Factor of Severe Systolic Hypertension in Acute Ischemic Stroke

Yoon-Ho Hong, Yong-Seok Lee, Seong-Ho Park

ABSTRACT: ***Background:*** Elevation of blood pressure (BP) is common in acute cerebral infarction, with several studies reporting a high plasma catecholamine level or previous hypertension as a contributory factor. However, more comprehensive studies on associated clinical parameters are lacking. Our main aim in undertaking this study was to correlate clinical variables associated with a BPelevation in acute ischemic stroke. ***Methods:*** Consecutive patients who were admitted to the emergency room and diagnosed with an acute cerebral infarction within 24 hours after the onset of symptoms were investigated. A BP elevation was defined as a high systolic (≥200mmHg) or diastolic (≥110 mmHg) pressure. The mean systolic and diastolic BP were compared between the different stroke subtypes, lesion locations (carotid vs. vertebrobasilar), and hemispheric sides. The frequency of symptoms, risk factors, location of the infarct, stroke severity, vascular status and laboratory abnormalities were analyzed in order to build a regression model. ***Results:*** One hundred thirty-one patients were recruited (M:F=60:71, mean age 66±12 years) and an elevated BP was identified in 33 patients (25.2%). The mean systolic and diastolic BP did not differ significantly between the stroke subtypes, lesion locations, and hemispheric sides. According to univariate logistic regression, an elevated systolic BP correlated with headache (p=0.01) and underlying hypertension (p=0.02) while an elevated diastolic BP correlated with underlying hypertension (p=0.01). Multivariate logistic regression analysis revealed previous hypertension (OR 5.21, 95% CI 1.40-19.37) and headache (OR 4.09, 95% CI 1.44-11.66) to be independent predictors of an elevated systolic BP. ***Conclusions:*** Headache itself is closely associated with severe systolic BP elevation in acute ischemic stroke. Whether treatment of elevated BP improves headache and clinical outcome is not yet known, necessitating future controlled studies.

RÉSUMÉ: La céphalée comme signe avant coureur de l'hypertension systolique sévère dans l'accident vasculaire cérébral aigu. ***Introduction***: Il est fréquent d'observer une tension artérielle (TA) élevée dans l'infarctus cérébral aigu et plusieurs études rapportent un niveau élevé de catécholamines plasmatiqus ou une hypertension préexistante comme facteur contributif. Cependant, il n'existe pas d'études plus exhaustives sur les paramètres cliniques qui y sont associés. Le but principal de cette étude était d'établir des corrélations entre des variables cliniques et une élévation de la TA dans l'accident vasculaire cérébral (AVC) ischémique. ***Méthodes***: Une série de patients admis consécutivement à l'urgence et chez qui on a posé un diagnostic d'infarctus cérébral aigu dans les 24 heures du début des symptômes ont été évalués. Une TA élevée était définie comme suit: une tension systolique 3 200 mmHg ou diastolique 3 110 mmHg. Les tensions systolique et diastolique moyenne ont été comparées entre les différents sous-types d'AVC, le site des lésions (territoire carotidien et vertébro-basilaire) et l'hémisphère droit et gauche. La fréquence des symptômes, les facteurs de risque, le site de l'infarctus, la sévérité de l'AVC, le statut vasculaire et les anomalies de laboratoire ont été analysés afin d'établir un modèle de régression. ***Résultats***: Cent trente et un patients ont été recrutés, 60 hommes et 71 femmes, dont l'âge moyen était de 66 ± 12 ans. Une TA élevée a été observée chez 33 patients (25,2%). Les TA systolique et diastolique n'étaient pas significativement différentes selon le sous-type d'AVC, le site de la lésion et l'hémisphère touché. L'analyse de régression univariée a montré qu'il existait une corrélation entre une TA systolique élevée et la céphalée (p = 0,01) et une hypertension sous-jacente (p = 0,01). L'analyse de régression multivariée a montré que l'hypertension préexistante (RR 5,21; IC 95% 1,40-19,37) et la céphalée (RR 4,09; IC 95% 1,44-11,66) étaient des facteurs prédisant une TA systolique élevée. ***Conclusions***: La céphalée est étroitement associée à une TA systolique très élevée dans l'AVC ischémique aigu. Il faudrait réaliser des études contrôlées, car on ne sait pas encore si le traitement de l'hypertension améliore la céphalée et l'évolution clinique.

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Elevated blood pressure (BP) is common in acute stroke with a frequency of up to 84%.[1] This elevated BP usually declines during the first few days even without hypotensive medication.[1-4] The precise causes or related factors of the transient elevation of BP have not been entirely clarified, although a high plasma catecholamine level, previous hypertension, mental stress on hospital admission, pontine lesions, or alcohol intake before the

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stroke have all been suggested as contributory or correlating factors.[1-3,5-9]

The pathophysiology of transient BP elevation has also been investigated during focal cerebral ischemia. In the acute stroke period, there is a loss of autoregulation of the cerebral blood flow causing pressure-dependent cerebral perfusion to the ischemic brain.[10] In this regard, the initial BP elevation has been considered to reflect a physiological compensatory response for the reduced cerebral blood flow to the ischemic portion of the brain. Aggressive lowering of the elevated BP may lead to an extension of the infarcted area leading to worse neurologic outcome.[11] The hazards of hypotensive therapy, as well as some beneficial aspects of an initial elevation in BP, have led most clinicians to apply hypotensive drugs conservatively in the acute period.[11-14]

A waiting strategy, however, may not be advocated in severe hypertension as an excessive BP elevation may be detrimental.[15,16] Hemorrhagic transformation of an ischemic lesion, especially with the use of anticoagulants or thrombolytics, has been associated with severe hypertension. Moreover, there is a fear that high perfusion pressures in the infarcted area may increase cerebral edema, although this has yet to be proven. For optimal management of severe hypertension in the acute ischemic stroke, it is crucial to determine treatable causes or associated factors.

In this study, we investigated the association between BP elevation, severe rises, and several symptoms, risk factors, and clinical variables. Consecutive patients with acute cerebral infarction admitted within 24 hours of initial symptoms were assessed. A regression model with the comprehensive variables was constructed to identify predicting factors of an excessive BP elevation.

Methods

One hundred and thirty-one consecutive ischemic stroke patients who were admitted to the emergency room (ER) of Seoul Boramae Municipal Hospital within 24 hours from the onset of symptoms were assessed (May 1999 - July 2000). All the variables investigated in this exploratory study were recruited from a prospective database of the Boramae Stroke Registry. The variables included age, sex, stroke symptoms, risk factors, location of the lesions (carotid vs. vertebrobasilar), vascular status (intracranial or extracranial stenosis or occlusion), severity of stroke based on the National Institute of Health Stroke Scale (NIHSS), laboratory abnormalities. Both systolic and diastolic (Korotkoff phase V) BPs were repeatedly measured in the ER immediately upon arrival and taken in the supine position with a calibrated mercury sphygmomanometer by nursing staff. An elevated admission BPwas defined as either being a high systolic (≥200mmHg) or diastolic (≥110mmHg) pressure.

A history of arterial hypertension was applied to patients who were taking antihypertensive drugs regularly or if there was evidence of target organ damage including hypertensive retinopathy or definite left ventricular hypertrophy on transthoracic echocardiography. History of diabetes or coronary heart disease was defined according to standard criteria. Ex-smokers (n=6) were not considered having a risk factor of smoking. Heavy alcohol drinking was noted as present if mentioned by family members or caregivers. Information about risk factors such as prior transient ischemic attack, previous stroke, or family history of stroke, were obtained from self-reports or, if not possible, from the family members or medical records. Headache was considered present only if it was novel or worsened, as self-reported at the time of admission. The location of the ischemic lesions was determined by magnetic resonance imaging (MRI), and an intracranial or extracranial arterial stenosis was defined by magnetic resonance angiography (narrowing more than 50%). A neuroradiologist and neurologists were involved in determining the radiological findings. The NIHSS was calculated by neurologists including the authors, one of whom is a stroke neurologist. The stroke subtype was classified using the criteria of Trial of Org 10172 in Acute Stroke Treatment classification.[17] Additional diagnostic tests, if necessary, were performed to document causes of the stroke.

In this study, admission BPs were compared between the different stroke subtypes, location, and the hemispheric sides of the lesion to investigate correlating factors associated with a BP elevation in acute ischemic stroke. A student's t test or ANOVA was used as appropriate. Frequencies of the variables including symptoms, risk factors, vascular status, and location of infarct were analyzed by Chi-square tests or Fisher's exact tests to investigate the difference between elevated and nonelevated admission BP groups. To identify predictive factors of severe hypertension in acute ischemic stroke, forward conditional step-wise multiple logistic regression analyses were performed. A p-value of 0.05 was used for entering and 0.10 for removing. Variables entered into the multivariate analysis were selected by the univariate logistic regression, in which the probable variables with a p value no more than 0.05 were chosen for further analysis. Continuous variables were converted to categorical ones before the logistic regression analyses according to the criteria depicted in the corresponding table. $P<0.05$ was considered statistically significant.

Results

One hundred thirty-one patients (male:female = 60:71, age 66, SD ± 12 years) were enrolled in this study. The mean systolic and diastolic BPwas 170.1 ± 32.2 mmHg and 95.4 ± 15.5mmHg, respectively. Thirty-three patients (25.2%) showed either a high systolic (≥200) or diastolic (≥110) BP. High systolic BP was observed in 25 patients and high diastolic BP in 24 patients, while 16 patients showed both high systolic and diastolic BP. The mean age (67 ± 11 years) and female sex ratio (42%) in the elevated admission BP group were comparable with those of the nonelevated group (65 ± 13 years, 47%).

Both the systolic and diastolic BPwere significantly higher in patients with previous hypertension; 177.7 ± 32.2/97.4 ± 16.6 with previous hypertension and 154.5 ± 26.3/91.4 ± 12.1 without previous hypertension ($p<0.01$ and $p=0.02$ respectively, student's t-tests). While the diastolic BP was not significantly different among the three stroke subtypes, the mean systolic BP was significantly higher in patients with a small-vessel occlusion than in the other two stroke subtypes (Table 1). However, the difference disappeared if the BP was compared after stratification by previous hypertension. Stratified by previous

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Table 1: Mean systolic and diastolic blood pressure according to the stroke subtype, location, and hemispheric side

Variables (n)	Systolic BP (mean ± SD in mmHg)	Diastolic BP (mean ± SD in mmHg)
Stroke subtype		
LAA(39)	168.3 ± 35.5*	93.9 ± 17.0
CE (18)	158.6 ± 28.3*	95.5 ± 15.6
SVO (44)	179.2 ± 28.7*	99.3 ± 14.4
Location of stroke		
Carotid (87)	169.7 ± 33.6	95.7 ± 16.6
Vertebrobasilar (44)	170.2 ± 29.7	95.0 ± 13.4
Side of hemispheric stroke		
Right (34)	173.5 ± 29.9	98.3 ± 14.8
Left (53)	167.6 ± 36.1	94.4 ± 17.6

*p=0.05 (ANOVA).
LAA = large-artery atherosclerosis; CE = cardiac embolism; SVO = small-vessel occlusion.

Table 2: Frequency (%) of the variables in the elevated and nonelevated admission BP groups

Variables	Admission BP	
	Elevated n=33 (%)	Nonelevated n=98 (%)
Symptoms		
Weakness	23 (69.7)	70 (71.4)
Aphasia	5 (15.2)	21 (21.4)
Headache*	10 (30.3)	14 (14.3)
Altered mentation	3 (9.1)	17 (17.3)
Vertigo	5 (15.2)	9 (9.2)
Vomiting	4 (12.1)	4 (4.1)
Seizure	0	3 (3.1)
Risk factors		
Previous hypertension§	29 (87.9)	59 (60.2)
Diabetes	8 (24.2)	25 (25.5)
Smoking	11 (34.4)	38 (41.3)
Excessive ethanol	7 (24.1)	11 (13.8)
Previous transient ischemic attack	0	10 (10.2)
Family history of stroke	6 (18.2)	10 (10.2)
Heart disease	8 (24.2)	21 (21.6)
Previous stroke	9 (27.3)	22 (22.9)
Vascular status		
Intracranial stenosis/occlusion	18 (54.5)	56 (60.2)
Extracranial stenosis/occlusion	2 (6.1)	12 (12.2)
Location of infarct		
Carotid	23 (69.7)	64 (65.3)
Vertebrobasilar	10 (30.3)	34 (34.7)

*p=0.04, §p<0.01, Chi-square tests

Table 3: NIHSS and laboratory findings in the elevated and nonelevated admission BP groups*

Variables	Elevated admission BP (n=33)	Nonelevated admission BP (n=98)
NIHSS	5.3 ± 4.8	6.5 ± 5.8
Laboratory results		
Hematocrit	0.40 ± 0.05	0.38 ± 0.05
White blood cell ($x10^9$/L)	7.8 ± 3.1	7.7 ± 2.7
Glucose (mmol/L)	7.2 ± 2.8	6.8 ± 3.1
Cholesterol (mmol/L)	4.6 ± 1.3	4.7 ± 1.1
Fibrinogen(g/L)	3.4 ± 0.8	3.6 ± 1.1

*No significant differences among admission BPgroups were found for any of the variables (student's t tests).

hypertension, no significant differences among the stroke subtypes were found in each group. In the group with previous hypertension, mean systolic BPs were 173.4 ± 34.7, 175.0 ± 29.0 and 186.6 ± 27.2 in large artery atherosclerosis (LAA) (n=30), cardiac embolism (CE) (n=8) and small vessel occlusion (SVO) (n=28), respectively (p>0.05, ANOVA). Without previous hypertension, mean systolic BPs were 151.3 ± 34.5, 145.4 ± 20.7 and 166.1 ± 27.3 in LAA (n=9), CE (n=10) and SVO (n=16), respectively (p>0.05, ANOVA). The location and side of the hemispheric stroke did not have any significant influence on either the systolic or the diastolic BP.

Among the symptoms, headache was more frequent in the elevated admission BP group (30.3% vs. 14.3%, p<0.05) (Table 2). Previous hypertension was also common in the elevated admission BPgroup (87.9% vs. 60.2%, p<0.01), while other risk factors showed no significant disparity. The stroke severity based on the NIHSS and laboratory results were not different between the admission BP groups (Table 3). In the univariate logistic regression analyses, the factors associated with high systolic BP were headache (p=0.01, OR=3.41) and underlying hypertension (p=0.02, OR=4.44), while high diastolic BP showed the significant association only with underlying hypertension (p=0.01, OR=6.82) (Table 4). With step-wise multiple logistic regression with the two variables, independent predictors for high systolic BP were headache (OR=4.09, 95% CI 1.44-11.66) and underlying hypertension (R=5.21, 95% CI 1.40-19.37) (Table 5).

Discussion

Compared with previous studies, this study was a relatively homogenous group in both the diagnosis and timing of the BP measurement. The time delay from the appearance of the initial symptoms may be one of the critical confounding factors in this type of study as an elevated BP tends to decline over a few days after admission. Therefore, only patients whose symptoms appeared within 24 hours were included to minimize such bias.

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Table 4: Univariate logistic regression*

variables	High SBP		High DBP	
	Odds Ratio	P	Odds Ratio	P
Age (≥65 yrs or lower)	1.11	0.82	0.67	0.38
Sex (female or male)	1.34	0.52	1.23	0.65
Symptom (presence or absence)				
Weakness	0.84	0.71	1.28	0.63
Aphasia	0.73	0.59	1.08	0.89
Headache	3.41	0.01	2.18	0.14
Altered mentation	0.43	0.27	0.76	0.68
Vertigo	1.83	0.35	1.25	0.75
Vomiting	2.75	0.19	2.91	0.16
Risk factors (presence or absence)				
Previous hypertension	4.44	0.02	6.82	0.01
Diabetes	1.2	0.72	0.74	0.59
Current smoking	0.59	0.28	0.64	0.36
Excessive ethanol	1.79	0.32	1.9	0.27
Family history of stroke	2.16	0.19	2.3	0.16
Heart disease	1.14	0.8	1.22	0.71
Previous stroke	1.02	0.97	1.83	0.22
Vascular status (presence or absence)				
Intracranial stenosis/occlusion	1.2	0.69	0.59	0.25
Extracranial stenosis/occlusion	0.68	0.63	0.31	0.28
NIHSS (≥9 or lower)	0.59	0.37	0.62	0.43
Laboratory results				
Hematocrit (≤0.35 or higher)	0.59	0.37	0.86	0.79
White blood cell (≥10^{10}/Lor lower)	1.65	0.43	0.66	0.6
Glucose (≥11mmol/Lor lower)	1.18	0.81	1.25	0.75
Fibrinogen (≥4g/Lor lower)	0.73	0.57	0.78	0.65
Cholesterol (≥5.7mmol/Lor lower)	0.59	0.42	1.76	0.29
Location of infarct				
Vertebrobasilar or carotid	0.73	0.51	0.78	0.61

*Continuous variables were converted to categorical ones based on the criteria in parentheses.
The variables seizure and transient ischemic attack are excluded in the analysis as no patient was found in the elevated admission BPgroup.
§Univariate logistic regression analysis where the odds ratios and p-values were estimated with a model using the method of a block entry of variables.
SBP: systolic BP; DBP: diastolic BP

Table 5: Multiple logistic regression

variable	p-value*	Adjusted OR	95% CI
Headache	0.008	4.09	1.44-11.66
Hypertension	0.014	5.21	1.40-19.37

*From logistic regression analysis adjusting for headache and hypertension to investigate independent predictors of high SBP.

Patients with a hemorrhagic stroke, where the BP elevation is more severe and frequent than in ischemic stroke, were excluded. Generally, the intracranial pressure increment is more steep and rapid in hemorrhagic stroke, and the pathophysiologic process leading to the elevated BPmay differ from ischemic stroke.[7]

In this study, the ischemic stroke subtype itself was not directly related to elevated BP. This is in contrast to the previous report of Litsa et al,[18] in which 72 patients and 22 controls were included and the greatest rises of BP were observed in patients with lacunar infarct among ischemic stroke subtypes. Although the mean systolic BPwas significantly higher in the small vessel occlusion group in our study, stratified analyses according to previous hypertension revealed no significant difference. It is likely that this disappearance of association might be a consequence of the reduced numbers of observations for each comparison. However, previous hypertension, which is more prevalent in patients with small artery disease, could be a confounding factor, as the underlying pathology of small-artery disease is mainly lipohyalinosis resulting from long-standing hypertension. Further study may clarify this discrepancy.

Although a right hemispheric lesion has been suggested to disinhibit insular function resulting in increased sympathetic cardiovascular tone, severe hypertension was not correlated with the side of the hemispheric stroke in this study.[19] A highly elevated BPwas also not related to an altered mentation or stroke severity, in agreement with previous reports.[7,20] In extensive hemispheric or brainstem lesions, depression of the central nervous system from dysfunction of the ascending reticular activating system may result in the failure of the autonomic regulation of cardiovascular tone.[8] However, it might not be a sufficient condition to cause severe hypertension.

Previous hypertension was the most potent predictor for the initial high BP as reported in previous studies.[1,2,7] Despite the effective treatment of chronic hypertension, the upward shift of the autoregulatory window might not be normalized in some patients because of the irreversible vascular changes that have occurred.[21] Furthermore, there is a loss of autoregulation in the acute ischemic brain causing an alteration in cerebral perfusion that is directly proportional to the peripheral BP. Therefore, an increase in BP as a compensatory response for maintaining the cerebral blood flow in the ischemic penumbra might occur in a more exaggerated form in patients with chronic hypertension.

This study identified headache as an independent predictor of severe systolic BPelevation in acute ischemic stroke. Pain of any cause, including headache, may elevate BP through the increase of sympathetic activity. It is also possible that headache may be an epiphenomenon related to severe hypertension, particularly in view of the values used to define elevated BP in this study.[22-24] Although the causal relationship can not be determined with certainty, the results of this study indicate that patients who complain of headache after an acute ischemic stroke very likely will have elevated BP.

The biologic basis of headache in ischemic stroke is not well-known.[25] Whether or not a headache alters the neurological or general outcome in ischemic stroke also has not been extensively studied. Jörgensen et al[26] reported that the presence of headache has no relationship to the neurologic outcome and does not alter the overall outcome of an ischemic stroke. However, headache has not been considered from the perspective of severe

hypertension in the acute period of ischemic stroke. In this setting, complex ischemic and compensating processes are ongoing and physicians need make an urgent and correct clinical decision. In this regard, the strong association between headache and high systolic BP shown in this study may have important implications for the optimal management in acute ischemic stroke. Headache as a symptom of acute ischemic stroke could elevate BP, and adequate control with appropriate analgesics might help to avoid harmful effects of severe hypertension, especially in the use of anticoagulants or thrombolytics.[27-30] The opposite situation may be postulated as well, i.e., treatment of elevated BP in patients with high BP and headache could improve headache and clinical outcome. These issues, which could not be resolved in this observational study, should be clarified in future controlled studies.

In summary, we investigated the factors associated with elevated BP within 24 hours from the onset of acute ischemic stroke and found that previous hypertension and headache were independent predictors of high systolic BP, and previous hypertension of high diastolic BP. Further investigation into the relationship between the headache and BP elevation in acute ischemic stroke is warranted.

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