Uncontrolled blood pressure and acute intracerebral hemorrhage in patients with hypertension

ORIGINAL ARTICLE

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Paramee Trakulkajornsak, M.D.[1]; Teeraphan Khamjaroen, M.D.[2]; Phumin Pharaveth, M.D.[3];Nutruja Boontor, M.D.[4]

[1]Ban Fang Hospital, Thailand; [2]Kantharawichai Hospital, Thailand; [3]Samrong Hospital, Thailand; [4]Si Chomphu Hospital, Thailand

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Correspondence to: Paramee Trakulkajornsak; paramee2535@gmail.com

ABSTRACT

OBJECTIVE

To identify the association between the blood pressure (BP) control and the first episode of intracerebral hemorrhage (ICH) in patients with hypertension.

METHODS

We conducted a case-control study among patients with hypertension to identify the risk of acute ICH in patients with uncontrolled hypertension. The cases were included if there were admitted at Khon Kaen Hospital (KKH) with acute ICH with underlying of hypertension from January 2013 to September 2015. The controls were matched by age and gender in the ratio 1:2. BP in each patient was recorded in relation to mean of the last 3 recorded in the patient records during the year before the in the admission date of the cases or visit date of the matched controls. Classification of blood pressure control was based on the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 8 criteria (JNC8).

RESULTS

A total of 225 medical records were included and reviewed (75 patients were the cases and 150 patients were the controls). Patients with uncontrolled hypertension increased the risk of the first episode of ICH were classified regarding JNC8; comparing to those with controlled BP, the patients with hypertension stage 2 were associated with highest rate of intracerebral hemorrhage (adjusted odds ratio (AOR), 4.20; 95% confidence interval (CI), 1.82 to 9.79); the patients with hypertension stage 1 who had underlying diabetes mellitus or chronic kidney disease and the age younger than 60 year-old were also associated with higher rate of intracerebral hemorrhage (AOR, 2.96; 95% CI, 1.33 to 6.57) as well as those who were older than 60 (AOR, 2.16; 95% CI, 0.56 to 8.33).

CONCLUSION

Our findings suggested that in patients with hypertension, inadequate BP control could increase the risk of ICH especially BP in the range of stage 2 hypertension. Randomized controlled trials stating the risks and benefits of tight BP control are suitable to generate high-quality data that can guide recommendation about BP control in patients with hypertension.

INTRODUCTION

Acute intracerebral hemorrhage (ICH), the least treatable form of stroke, affects more than 1 million people worldwide annually.[1,2] Thai Epidemiological Stroke Study in 2014 found that the proportion of hemorrhagic stroke is higher when compared to Caucasian population.[3] Treatment of hypertension has been demonstrated to be the most important factor in reducing the incidence of stroke.[4] The study from the American Stroke Association suggested that treatment of hypertension might prevent 17-28% of all hemorrhagic stroke and this effect did not vary by type of treatment.[5] In the study from the United States, blood pressure (BP) control during follow-up was associated with a higher risk of both lobar and non-lobar ICH recurrence.[6] The BP control is also one of the best ways to prevent recurrent ICH as hypertension is a well-known cause of ICH.[6] Moreover, studies in the United Kingdom and the Netherlands have demonstrated that the quality of control of hypertension is strongly related to the occurrence of stroke in the population.[7,8] However, the role of BP control in the first episode of ICH remains poorly defined. Thus, we conducted a study to assess the relationship between uncontrolled BP and risk of acute ICH among patients with hypertension.

METHODS

STUDY DESIGN

A case-control study was conducted using medical records of the patients with hypertension treated at Khon Kaen Hospital, Thailand to identify risk factors of acute ICH in patients with uncontrolled BP.

PATIENT RECORDS

The cases were verified and reviewed from In-Patient Department (IPD) records of KKH registry, Thailand from January 2013 through September 2015. The controls were verified and reviewed from Out Patient Department (OPD) records of the same hospital and study period. Case-patients were patients with hypertension with a history of first episode acute ICH and the control patients were patients with hypertension without a history of first episode acute ICH matched by age and gender with the ratio of 1:2 with the nearest follow-up date with the index date of the cases. Patients were excluded if they had a traumatic brain injury, bleeding tendencies such as hemophilia or those with a hemorrhagic transformation of ischemic stroke.

DATA COLLECTION

International Classification of Disease (ICD) 10; non-traumatic subarachnoid hemorrhage as I60, non-traumatic intracerebral hemorrhage as I61 and essential (primary) hypertension as I10. BP in each patient was recorded into the mean of the last three BP records in the medical record during the year before the admission date of the cases or visit date of the matched controls. If less than three records were available, we used either the mean of two to assess the level of BP achieved by treatment. Furthermore, following factors such as estimated glomerular filtration rate (eGFR), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride and coagulogram were also recorded by an average of the laboratory data within 1 years before the index date. The other characteristics regarding matched age-matched gender, body mass index (BMI) and

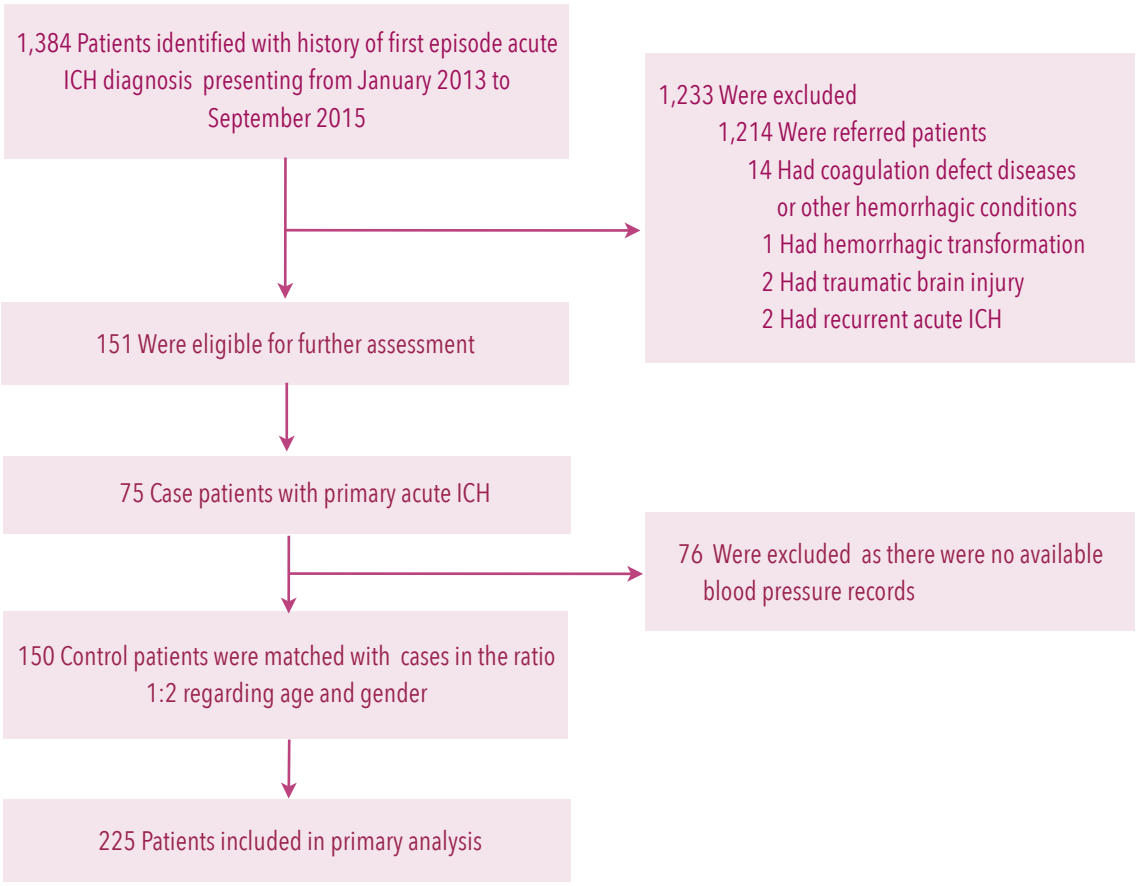

Figure 1. Case with sequential application of eligibility and exclusion criteria

past medical history diabetes mellitus (DM), dyslipidemia (DLD), ischemic stroke, chronic kidney disease (CKD), myocardial infarction (MI) were also recorded.

STATISTICAL ANALYSIS

We designed the study to have an alpha level of 0.05, 90% power to detect a difference, the resulting sample size was 213 participants; 71 cases and 142 controls. Comparing continuous data (e.g., age, mean of eGFR, mean of lipid profile, mean of coagulogram, BMI) between cases and controls were analyzed by using t-test and Mann-Whitney U test and presented as mean with standard deviation (SD) or median with interquartile range (IQR). In contrary, comparing categorical variable data (e.g., gender, lipid profile range, BMI, social history, past medical history and blood pressure) between study groups were analyzed by using chi-square test or Fisher's exact test where appropriate. We used binary logistic regression for univariable and multivariable analysis. Our results from the analysis are reported as crude odds ratio (COR). We also reported an adjusted odds ratio (AOR) to identify the risk association between the variables and ICH.

Table 1. Characteristics of the cases and controls

Characteristic	Patient with hemorrhagic stroke (n=75)	Controls (n=150)	P Value
Age-yr			0.979
Median	63.8	64.6	
Interquartile range	55.5-73.9	54.9-73.70	
Female sex-no. (%)	27 (36.0)	54 (36.0)	1.000
eGFR-ml/min/1.73m2	(n=74)	(n=120)	
Median	73.3	68.2	0.914
Interquartile range	46.4-93.3	51.0-94.9	
Lipid profile-mg/dl			
Total cholesterol12-no. (%)	(n=64)	(n=89)	0.905
<200	16 (41.0)	21 (43.8)	
200-239	16 (4.0)	18 (37.5)	
≥240	7 (17.9)	9 (18.8)	
Mean±SD	184.2±51.5	183.2±50.6	0.908
LDL-cholesterol-no. (%)	(n=55)	(n=89)	0.102
<130	32 (58.2)	65 (73)	
130-159	13 (23.6)	13 (14.6)	
≥160	10 (18.2)	11 (12.4)	
Median	116.5	109.0	0.504
Interquartile range	84.3-146.0	87.3-132.3	
HDL-cholesterol-no. (%)	(n=53)	(n=79)	0.965
<40	19 (35.8)	23 (29.1)	
40-59	24 (45.3)	46 (58.2)	
≥60	10 (18.9)	10 (12.7)	
Median	43.0	45.0	0.733
Interquartile range	37.0-57.5	38.0-54.0	
Triglyceride-no. (%)	(n=51)	(n=23)	0.676
<150	35 (63.6)	54 (66.7)	
150-199	12 (21.8)	8 (9.9)	
≥200	8 (14.5)	19 (23.5)	
Median	113.0	117.5	0.385
Interquartile range	81.5-175.0	89.1-191.5	

Table 1. Characteristics of the cases and controls

Characteristic	Patient with hemorrhagic stroke (n=75)	Controls (n=150)	P Value
Coagulogram			
PT-sec	(n=71)	(n=42)	
Median	11.7	12.0	0.355
Interquartile range	11.1-12.4	11.1-13.1	
PTT-sec	(n=70)	(n=39)	
Median	32.2	33.6	0.099
Interquartile range	28.9-35.7	31.5-36.4	
INR13-sec	(n=71)	(n=43)	
Median	0.99	1.02	0.253
Interquartile range	0.94-1.06	0.95-1.10	
BMI (kg/m^2)-no. (%)	(n=65)	(n=131)	0.535
<18.5	1 (1.5)	6 (4.6)	
18.5-22.9	26 (40)	50 (38.2)	
23.0-24.9	19 (29.2)	28 (21.4)	
25.0–29.9	12 (18.5)	33 (25.2)	
≥30.0	7 (10.8)	14 (10.7)	
Median	23.43	23.88	0.825
Interquartile range	21.5-25.3	21.3-26.5	
Past medical history-no. (%)			
Myocardial infarction5	1 (1.3)	9 (6.0)	0.171
Diabetes mellitus12	22 (29.3)	66 (44.0)	0.034
Hyperlipidemia	10 (13.3)	38 (25.3)	0.038
Ischemic stroke	8 (10.7)	26 (17.3)	0.188
Chronic kidney disease	8 (10.7)	16 (10.7)	1.000

Plus-minus values are means ±SD; The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters

RESULTS

PATIENTS

From January 2013 through September 2015, we identified 1,384 patients with hemorrhagic stroke with underlying hypertension (Figure 1). We excluded 1,214 referred cases from other hospitals, 2 patients with recurrent intracerebral hemorrhage, 1 patient with a hemorrhagic transformation from ischemic stroke, 14 patients with coagulation defect diseases and hemorrhagic condition, 2 patients with traumatic intracerebral hemorrhage and 76 patients without a history of blood pressure in the period of one year before the

Table 2. Risk of acute intracerebral hemorrhage associated with uncontrolled blood pressure in hypertensive patients

Level of blood pressure control	Patients with acute intracerebral hemorrhage	Control patients	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)‡
	no. (%)			
Controlled Blood pressure			Reference	
DBP<90 and SBP<140 mm Hg*	11 (14.7)	56 (37.3)		
DBP<90 and SBP<150 mmHg†	17 (22.7)	35 (23.3)		
Uncontrolled Blood pressure				
Stage I				
DBP 90-99 or SBP 140-159 mmHg*	20 (26.7)	33 (22.0)	1.97 (0.92-4.18)	2.96 (1.33-6.57)
DBP 90-99 or SBP 150-159 mmHg†	5 (6.7)	7 (4.7)	2.32 (0.53-9.21)	2.16 (0.56-8.33)
Stage II (DBP≥100 or SBP≥160 mmHg)	22 (29.3)	19 (12.7)	3.76 (1.67-8.47)	4.20 (1.82-9.79)

*The range of controlled BP with general <60 year-old, diabetes mellitus, chronic kidney disease was defined as DBP<90 and SBP<140 mmHg
†The range of controlled BP with general ≥60 year-old without diabetes mellitus or chronic kidney disease.
‡The adjusted odds ratio were calculated by including blood pressure level, age, gender, eGFR and underlying diseases (DM, CKD). [16]

index date. After 95 patients were excluded, 75 cases were included in the total. The controls were matched by gender and age with ratio 1:2. Thus, 150 control patients with non-hemorrhagic stroke with underlying hypertension were included. Table 1 gives characteristics of the case and control patients. Two groups of patients were similar regarding age, gender, eGFR, lipid profiles, coagulogram, body mass index (BMI), past medical history of MI, ischemic stroke and CKD. However, a fewer proportion in DM (P=0.034) and dyslipidemia (P=0.038) in the group of case-patients.

From our findings, patients with hypertension stage 2 were associated with the highest rate of acute ICH (AOR, 4.20; 95% CI, 1.82 to 9.79)(Table 2). In addition to this, patients with hypertension stage 1 who had underlying of DM or CKD and age younger than 60 year-old were also associated with higher rate of ICH (AOR, 2.96; 95% CI, 1.33 to 6.57) as well as patients who were older than 60 (AOR, 2.16; 95% CI, 0.56 to 8.33). Other variables included age (AOR, 1.00; 95% CI, 0.98 to 1.03), gender (AOR, 1.24; 95% CI, 0.64 to 2.39), mean eGFR (AOR, 0.997; 95% CI, 0.995 to 0.999) and past medical history of DM (AOR, 0.44; 95% CI, 0.21 to 0.89) and DLD (AOR, 0.49; 95% CI, 0.22 to 1.10) were found not to associated with the occurrence of acute ICH from the binary logistic regression analysis.

DISCUSSION

PRINCIPAL FINDINGS

Our findings suggested that in patients with hypertension, inadequate BP control increased the

risk of ICH especially patients with BP in the range of stage 2 hypertension. In addition to this, patients with hypertension stage 1 who had underlying of DM or CKD and age younger than 60 years old were also associated with higher rate of ICH as well as patients who were older than 60. Other variables included age, gender, mean eGFR and past medical history of DM and DLD were found not to associated with the occurrence of acute ICH from the binary logistic regression analysis.

STRENGTHS AND LIMITATIONS OF THE STUDY

Our findings suggested that in patients with hypertension, inadequate BP control increased the risk of ICH especially patients with BP in the range of stage 2 hypertension. This association appeared to become stronger with worsening severity of hypertension defining through the JNC8 severity stage.[17] To our knowledge, this is the first study to identify the relationship between the proper power between uncontrolled blood pressure and ICH in patients with hypertension. Eligibility criteria were carefully used to define the cases and the controls. However, our study has several limitations. As the selection bias is commonly found in the case-control study; missing of data such as a history of hypertension treatment and duration of underlying of hypertension that may also be the risk factors of ICH.

COMPARISON WITH PREVIOUS STUDIES

In the previous case-control study, they determined the risk of stroke in term of quality of hypertension control which they did not clarify case of a specific type of stroke such as ischemic or hemorrhagic stroke and studied the relationship between the incidence of all types of stroke and blood pressure control but not a hemorrhagic stroke.[7] We specified a case into hemorrhagic stroke patients. Another recently published study investigated the association between blood pressure after index ICH and risk of recurrent ICH. It found that poor BP control during follow-up was associated with higher rate of recurrent ICH.[18] This finding conforms to our study that uncontrolled blood pressure associated with increased the rate of first episode ICH diagnosis.

The JNC8 guideline recommends increasing the threshold of systolic BP to higher than 150 mmHg compared with >140 mmHg in the JNC7 guideline for starting BP-lowering therapy for the elderly.[16,19] However, this recommendation was lack of a clear balance between risks and benefits of less aggressive BP control in this population subgroup.[18] Our findings suggested that stage I hypertension in the patients 60 years or older according to JNC 8 who had the SBP between 150 to 159 mmHg might not be increased the risk of ICH when compared with stage I hypertension in patients younger than 60 years who had the SBP between 140 to 159 mmHg. Thus, it is coherent to the other research. But, Stage II hypertension in general patients exactly increased the incidence of ICH (SBP>160 mmHg). Furthermore, stage I hypertension in patients underlying DM or CKD might be associated increasing the risk of ICH when compared with other patients who no DM or CKD. At the end of our findings suggested that tight BP control could strongly reduce the risk of ICH in patients with hypertension; still, a recent cost-

effectiveness study recommends the benefit of BP control regarding JNC 8 guidelines for those with known cardiovascular and cerebrovascular conditions only.[20]

CONCLUSION AND IMPLICATION

Our findings suggested that in patients with hypertension, inadequate BP control increased the risk of ICH especially patients with BP in the range of stage 2 hypertension.

Multi-center randomized controlled trials with adequate sample size stating the risks and benefits of tight BP control are suggested to generate high-quality data that can guide recommendation about BP control in patients with hypertension.

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