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Association Between Blood Pressure After Thrombolysis and Neurological Outcome in the Elderly Patients With Ischemic Stroke

Junsoo Seok, Jong-Seok Lee, Ki Young Jeong, Han Sung Choi, Hoon Pyo Hong, Young Gwan Ko

Department of Emergency Medicine, Kyung Hee University College of Medicine, Seoul, Korea

Corresponding Author:
Jong-Seok Lee, MD, PhD
Department of Emergency Medicine, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, 23 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Korea

Tel: +82-2-958-1637
Fax: +82-2-958-8746
E-mail: seok918@gmail.com

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Background: This study aimed to evaluate the relationship between systolic blood pressures (SBPs) within 10 hours after intravenous recombinant tissue plasminogen activator (rtPA) treatment and early neurological outcomes in geriatric and nongeriatric patients with acute ischemic stroke (AIS). **Methods:** This was a retrospective observational study of patients with AIS who received intravenous rtPA between January 2010 and May 2015. Clinical factors were compared between geriatric and nongeriatric patients. SBPs at the time of rtPA bolus and every hour thereafter were collected. The primary outcome was major neurological improvement (MNI) at 24 hours after thrombolysis. **Results:** Serial measures of SBP revealed different 10-hour courses between patients with and without MNI in the geriatric group. The difference in SBP tendency was statistically significant (p=0.049). In contrast, there was no significant difference in SBP change in the nongeriatric group (p=0.251). In univariate analysis, geriatric patients with MNI showed higher frequency of very early neurological improvement (VENI) at 1 hour after rtPA infusion (p=0.023) and lower level of SBP at 3 hours and 10 hours (p=0.037 and p=0.046, respectively). In multivariate analysis using a logistic regression model, VENI at 1 hour and SBP value after 10 hours were independently related to MNI. **Conclusion:** SBP level and its change during the first 10 hours after intravenous rtPA treatment are different between geriatric and nongeriatric patients. In the geriatric group, SBP decrease is predictive of neurological state at 24 hours after thrombolysis. In the nongeriatric group, SBP decrease is not associated with neurological outcome.

Key Words: Acute stroke, Blood pressure, Geriatrics, Prognosis

INTRODUCTION

Despite numerous attempts to reduce the risk of stroke in the last few decades, stroke is still the main cause of disabilities and death among adults worldwide. In Korea, the mortality rate of cerebrovascular diseases is approximately 10%, following closely behind that of cardiovascular diseases[1,2]. With the rapid population aging in Korea, the population of people aged 65 years or older is expected to occupy over 14% of the entire Korean populations by 2018, and accordingly, the social burden of stroke is predicted to increase[3]. The most widely accepted standard treatment of acute ischemic stroke is recombinant tissue plasminogen activator (rtPA) administration[4,5]. Supportive therapies such as oxygen therapy, posture correction, mechanical ventilation, control of body temperature, blood sugar, and blood pressure, and intravenous fluid therapy have been used as adjunct therapies for stroke[6-15]. However, the appropriate target blood pressure range for patients with acute stroke has not been established yet[16,17]. While a number of studies have reported that high systolic pressure is associated with short-term and long-term worsening of prognoses in patients with acute stroke[18,19], other studies have reported that acute hypotension is associated with poor prognoses in patients with stroke[20].

However, these contradicting results of the previous studies may be due to the different research designs used in those studies differed in the frequency and the duration of the period of blood pressure measurement, the duration of the monitoring period for prognosis evaluation, and the proportion of patients treated with thrombolytic agents. Some studies overlooked the possibility of differences in blood pressure variations over time in different age groups. A pre-

vious study found that as arterial stiffness and peripheral resistance increased, the risk of cerebrovascular and cardiovascular diseases increased in geriatric group, suggesting that different methods should be used to control blood pressure in geriatric and nongeriatric patients[21]. Therefore, when investigating the association between blood pressure and neurological outcomes after intravenous administration of thrombolytic agents in patients with acute ischemic stroke, more accurate results may be obtained by dividing the subjects into geriatric and nongeriatric groups. In this study, the blood pressure of pati- ents with acute ischemic stroke was measured hourly for 10 hours after they were administered thrombolytic agents in the Emergency Department (ED). Then, we compared the changes in blood pressure over time between the geriatric and nongeriatric groups, and investigated whether blood pre- ssure measured after administration of thrombolytic agents is associated with early neurological prognoses.

MATERIALS AND METHODS

1. Subjects

A retrospective study was conducted in patients who were intravenously administered thrombolytic agents for acute ischemic stroke between January 2010 and May 2015 in an emergency medical center (20 wards, 30,000 patients/yr) of a university hospital (850 wards) in a major city. After emergency physicians examined patients who had exhibited neurological deficits within 4 hours and 30 minutes before visiting the ED, and activated the "rapid treatment protocol for strokes," neurologists evaluated the neurological state of patients while blood tests and computed tomography of the head were being performed. Patients selected for rtPA administration by neurologists according to the guidelines published by the American Heart Association (AHA)/ American Stroke Association (ASA)[16] were admitted to the stroke unit after they were intravenously administered rTPA in the ED. Patients were intravenously administered 10% of the total dose of rtPA (0.9 mg/kg) over 1 minute, and the remaining 90% was intravenously infused over 60 minutes. Blood pressure was measured before administration, at the moment of administration, and every 30 minutes after administration for all patients. The neurologists decided to use antihypertensive drugs in patients whose systolic pressure or diastolic pressure increased to over 180 and 105 mmHg, respectively, according to the AHA/ASA guidelines[16]. Patients who were less than 20 years old, had previously undergone arterial blood clot removal surgery, had been hospitalized in an intensive care unit for comorbidities other than stroke, had disabilities that scored over 3 points on the modified Rankin Scale (mRS), and had no clinical information for the primary endpoint were excluded. The protocol used in this study was approved by the Institutional Review Board of Kyung Hee University Hospital (KHUH 2015-07-108).

2. Data Collection

The patients were divided into the geriatric group (65 years or older) and nongeriatric group (20–64 years). We investigated the age, sex, underlying diseases, disabilities prior to stroke, severity of stroke, length of rtPA administration, blood test result, systolic pressure by time, presence of hemorrhagic transformation, neurological outcomes, and functional outcomes of the patients by reviewing their medical records. The underlying diseases included hypertension, diabetes, and atrial fibrillation, which are cardiovascular risk factors for stroke. A patient was considered to have hypertension if he/she was currently taking antihypertensive drugs, or had systolic pressure greater than 140 mmHg, or diastolic pressure greater than 90 mmHg[22]. A patient was considered diabetic if he/she was currently taking hypoglycemic agents or had a fasting blood glucose level greater than 126 mg/dL[22]. History of disabilities prior to stroke and the severity of stroke were evaluated based on the mRS scores and the National Institutes of Stroke Scale (NIHSS) scores. The time from the onset of symptoms to rtPA administration (onset-to-rtPA) and the time from the arrival at the ED to rtPA administration (door-to-rtPA) were calculated. In the blood test, the number of white blood cells, neutrophils, and lymphocytes, and the blood levels of hemoglobin, C-reactive proteins, albumin, creatinine, blood urea nitrogen, glucose, and glycated hemoglobin were measured in the venous blood samples collected before computed tomography. Systolic pressure was measured at the time of rtPA administration (T0) and every hour thereafter. Hemorrhagic transformation was defined as bleeding around the site of cerebral infarction. For neurological outcomes, very early neurological improvement (VENI) and major neurological improvement (MNI) were evaluated using the NIHSS scores. VENI was defined as an NIHSS score of 0 point 1 h after rtPA administration, or a decrease in the NIHSS score by 5 or more points relative to the score prior to rtPA administration[23]. MNI was defined as an NIHSS score of 0–1 point 24 hours after rtPA administration or a decrease in the NIHSS score by 8 or more points relative to the score prior to rtPA administration[24]. Functional outcomes were evaluated using mRS scores at the time of discharge. Neurologists evaluated NIHSS and mRS scores of all patients.

3. Statistical Analysis

The categorical variables were indicated as frequency and percentage. The continuous variables were expressed as

mean and standard deviation if they had a normal distribution and as median and interquartile range if they did not have a normal distribution. For the univariate analysis, a chi-square test or Fisher exact test was used for the categorical variables, and a Student t-test or Mann-Whitney U test was used for the continuous variables depending on whether they were normally distributed or not. The systolic pressure measurements during the 10 hours after the intravenous administration of rtPA were plotted on a graph, and changes in blood pressure were compared between the geriatric and non-geriatric groups. Next, to investigate whether blood pressure is associated with MNI, the patients were divided into those who had neurological improvement and those that did not, and their systolic blood pressure (SBP) measurements during the 10 hours after the intravenous administration of rtPA were plotted on a graph and compared. A subgroup analysis was performed in each of these groups to account for differences between the geriatric and nongeriatric group. For the statistical comparison of changes in blood pressure, a repeated measures analysis of variance (RM ANOVA) was performed. A logistic regression model was created by including variables whose p-values were less than 0.10 in the univariate analysis in the multivariate analysis. For variable selection, the forward stepwise selection method was used. A Hosmer-Lemeshow goodness-of-fit test was performed on the final regression model. All statistical analyses were performed using IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA). Statistical significance was set at $p<0.05$.

RESULTS

1. General Characteristics

A total of 1,347 patients visited the emergency medical center for acute (within 4 hours and 30 minutes) neurological deficits between January 2010 and May 2015, and 537 patients (39.9%) were diagnosed with acute ischemic stroke. Of these, 194 patients (36.1%) were intravenously administered rtPA and monitored after discharge. Among the 194 patients, 29 were excluded due to medical history of undergoing arterial blood clot removal surgery in the past, 9 were excluded due to history of disabilities prior to stroke that scored over 3 points on the mRS, and 1 was excluded for history of admission in an intensive care unit for ST-elevation myocardial infarction. In the end, 155 patients were selected as the study subjects (Fig. 1).

Of the 155 patients, 94 (60.6%) were male and 61 (39.4%) were female subjects. The mean age of the patients was 70 years (interquartile range [IQR], 63–76 years). In regards to the number of patients with underlying diseases, 111 patients (71.6%) had hypertension, 43 patients (27.7%) had diabetes, and 61 patients (39.4%) had atrial fibrillation. A total of 121 patients (78.1%) never had a disability prior to stroke, and 34 patients (21.9%) had mild disabilities that still allowed them to perform daily tasks. The mean NIHSS score at the time of the visit to the ED was 9 points (IQR, 6–14 points). The time from the onset of symptoms to rtPA administration, and from the arrival at the ED to rtPA administration were 126 minutes (IQR, 90–165 minutes) and 49 minutes (IQR, 40–59 minutes), respectively. Nineteen patients (12.3%) had hemorrhagic transformation, one of whom died later, and 5 of whom had an increase in the NIHSS scores by 4 or more points. Thirty-four patients (21.9%) showed VENI at 1 hour after rtPA administration, and 43 patients (27.7%) showed MNI at 24 hours after rtPA administration. At the time of discharge, 40 patients (25.8%) had mRS scores of 0–1 point, and 36 patients (23.2%) had mRS scores of 5–6 points.

2. Comparison Between the Geriatric and Nongeriatric Patients

No differences in the early NIHSS scores, length of administration time, and rate of hemorrhagic transformation and of VENI were found between the geriatric and nongeriatric groups. In the blood tests, the white blood cell count and lymphocyte count were statistically significantly lower in the geriatric group compared to the nongeriatric group; however, the difference was within the range of normal reference values. In the geriatric group, the rate of hypertension was higher in the geriatric group than in the nongeriatric group, but not to a statistically significant degree. While the non-geriatric group had a higher proportion of men (80.4%) than women, there was no difference in the proportions of men and women in the geriatric group (Table 1).

Systolic pressure of the patients in the geriatric and the non-geriatric groups was measured every hour for 10 hours after the intravenous administration of rtPA and was plotted on a graph for comparison. While systolic pressure decreased consistently for the first 4 hours in the nongeriatric group, there was barely any decrease in systolic pressure in the

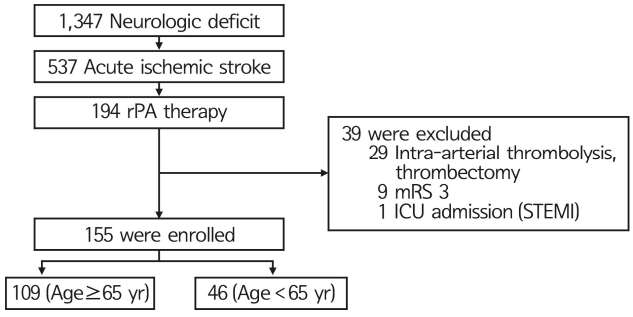

Fig. 1. Diagram of patient categories. rtPA, recombinant tissue plasminogen activator; mRS, modified Rankin Scale; ICU, intensive care unit; STEM1, ST-elevation myocardial infarction.

geriatric group. Starting from 4 hours after the administration, significant differences in systolic pressure were found between the geriatric and the nongeriatric groups (Fig. 2). In a graph that compared the systolic pressure of patients who showed neurological improvement at 24 hours after rtPA administration and of those who did not, significant differences in the decrease of systolic pressure were found between these 2 subgroups of patients within the geriatric group (p=0.049) (Fig. 3A). However, in the nongeriatric group, systolic pressure decreased consistently after rtPA administration regardless of neurological improvement, and no significant difference in the decrease of systolic pressure was found between the 2 subgroups (p=0.251) (Fig. 3B).

3. Predictor Factors of Neurological Prognoses in Geriatric Patients

A univariate analysis was performed to investigate clinical factors associated with neurological outcomes in the geriatric group that showed significant differences in the systolic pres-

Table 1. Baseline characteristics

Characteristic	Age≥65 yr (n=109)	Age<65 yr (n=46)	p-value
Age (yr)	73 (70-78)	56 (52-61)	<0.001
Male sex	57 (52.3)	37 (80.4)	0.001
Vascular risk factors			
Hypertension	83 (76.1)	28 (60.9)	0.054
Diabetes mellitus	31 (28.4)	12 (26.1)	0.765
Atrial fibrillation	47 (43.1)	14 (30.4)	0.140
Prestroke disability			0.082
mRS score 0	81 (74.3)	40 (87.0)	
mRS score 1	28 (25.7)	6 (13.0)	
Stroke severity			
NIHSS score (initial)	9.0 (6.0-14.0)	9.5 (6.0-13.0)	0.812
Time to rtPA administration (min)			
Onset-to-rtPA	132.0 (90.0-166.0)	118.0 (89.0-163.0)	0.578
Door-to-rtPA	51.0 (40.0-59.0)	45.5 (40.0-63.0)	0.813
Laboratory tests			
Hemoglobin (g/dL)	13.64±1.72	14.95±1.25	<0.001
Leukocytes (/mm^3)	7,790 (6,370-9,380)	9,250 (7,390-10,450)	0.021
Total neutrophil count (/mm^3)	4,312 (3,426-5,719)	5,253 (3,791-6,240)	0.059
Total lymphocyte count (/mm^3)	2,320 (1,696-2,918)	2,654 (2,134-3,272)	0.026
C-reactive protein (mg/dL)	0.3 (0.3-0.3)	0.3 (0.3-0.4)	0.073
Albumin (g/dL)	4.1 (3.9-4.3)	4.2 (4.1-4.3)	0.061
Creatinine (mg/dL)	0.8 (0.7-1.0)	0.8 (0.6-0.9)	0.164
Blood urea nitrogen (mg/dL)	17.0 (14.0-21.0)	14.0 (11.0-16.0)	0.193
Glucose	125 (111-170)	127 (106-179)	0.903
Total cholesterol (mg/dL)	173.49±35.24	178.02±40.84	0.486
Hemoglobin A1c (%)	6.0 (5.7-6.6)	5.7 (5.5-6.5)	0.164
Hemorrhagic transformation	13 (11.9)	6 (13.0)	0.846
Neurological outcome			
MNI at 24 hr	26 (23.9)	17 (37.0)	0.096
Functional outcome at discharge			0.893
mRS score 0-1	27 (24.8)	13 (28.3)	
mRS score 2-4	56 (51.4)	23 (50.0)	
mRS score 5-6	26 (23.9)	10 (21.7)	

Values are presented as median (interquartile range), number (%), or mean±standard deviation.
mRS, modified Rankin Scale; rtPA, recombinant tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; MNI, major neurological improvement.
p-values obtained by chi-square test or Fisher exact test for categorical variables, Student t-test or Mann-Whitney U test for continuous variable.

sure measurements depending on whether the patients had MNI or not (Table 2). The length of rtPA administration was shorter among the geriatric patients who showed MNI compared to the geriatric patients that did not show MNI (p=0.041). The rate of VENI 1 hour after rtPA administration was higher (p=0.023), and the systolic pressure at 3 hours and 10 hours after rtPA administration was lower in the geriatric group (p=0.037, p=0.046). Significant differences in the distribution of mRS scores at the time of discharge were found according to whether the patients had MNI (p<0.001).

A multivariate analysis was performed. Diabetes, length of rtPA administration time (from onset of symptoms to rtPA administration, from the arrival at the ED to rtPA administration), VENI, and systolic pressure at 3, 4, 5, 8, 9, and 10 hours after rtPA administration, all of which had p-values less than 0.10 in the univariate analysis, were used as the candidate predictor variables. A logistic regression analysis was performed using the forward stepwise selection method. The VENI and systolic pressure at 10 hours after rtPA administration were identified as the independent predictor variables of MNI (Table 3). In the Hosmer-Lemeshow goodness-of-fit test of the final regression model, the p-value was 0.940; therefore, the selected regression model was deemed appropriate.

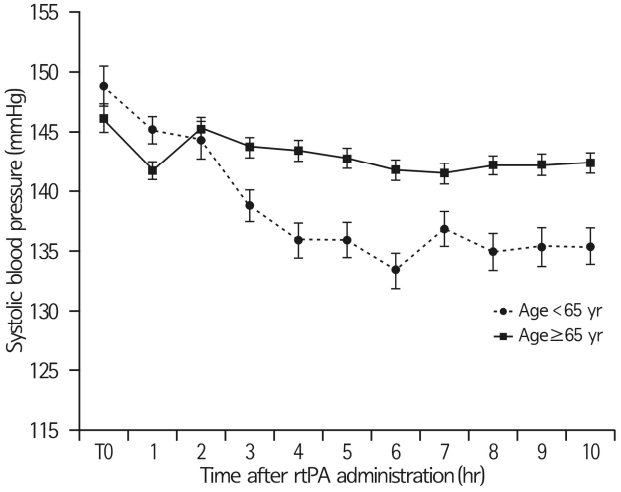

Fig. 2. Comparison of systolic blood pressure between geriatric (age≥65 years) and nongeriatric (age<65 years) patients during the first 10 hours after thrombolysis. rtPA, recombinant tissue plasminogen activator.

4. Predictor Factors of Neurological Outcomes in the Nongeriatric Patients

A multivariate analysis was performed using the same method as above to investigate clinical factors associated with neurological outcomes in the nongeriatric group that showed no changes in systolic pressure regardless of MNI. VENI, atrial fibrillation, hemorrhagic transformation, and systolic pressure at 9 hours after rtPA administration (p<0.10) were used as the candidate predictor variables. In the multiple logistic regression analysis, only VENI was identified as the independent predictor variable in the nongeriatric group (Table 4).

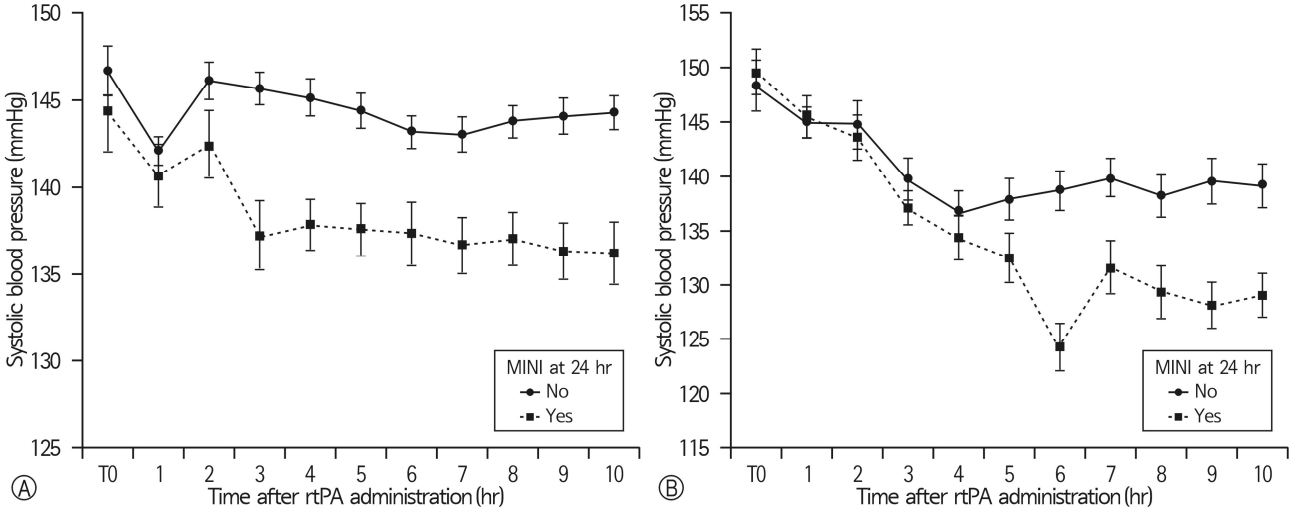

Fig. 3. Systolic blood pressure (SBP) during the first 10 hours after thrombolysis in patients with or without major neurological improvement (MNI). (**A**) In geriatric patients, changes in SBP after thrombolysis show a significant difference between patients with and without MNI (p=0.049, by 2-way repeated-measures analysis of variance [RM ANOVA]). (**B**) In nongeriatric patients, no significant difference is shown in SBP changes after thrombolysis (p=0.251, by RM ANOVA). rtPA, recombinant tissue plasminogen activator.

Table 2. Characteristics of geriatric patients according to the presence of major neurological improvement or not

Variable	Major neurological improvement		p-value
	Yes (n=26)	No (n=83)	
Age (yr)	73 (71-76)	73 (70-78)	0.892
Male sex	15 (57.7)	42 (50.6)	0.528
Vascular risk factors			
Hypertension	18 (69.2)	65 (78.3)	0.343
Diabetes mellitus	4 (15.4)	27 (32.5)	0.091
Atrial fibrillation	10 (38.5)	37 (44.6)	0.583
Prestroke disability			0.497
mRS score 0	18 (69.2)	63 (75.9)	
mRS score 1	8 (30.8)	20 (24.1)	
Stroke severity			
NIHSS score (initial)	9.5 (5.0-13.0)	9.0 (6.5-14.0)	0.348
Time to rtPA administration (min)			
Onset-to-rtPA	102.5 (87.0-153.0)	138.0 (97.0-171.5)	0.098
Door-to-rtPA	44.5 (33.0-57.0)	52.0 (42.0-62.5)	0.041
Laboratory tests			
Hemoglobin (g/dL)	13.95±1.60	13.55±1.76	0.303
Leukocytes (/mm^3)	7,800 (6,150-8,660)	7,790 (6,525-9,755)	0.325
Total neutrophil count (/mm^3)	4,002 (3,235-4,694)	4,369 (3,477-5,769)	0.216
Total lymphocyte count (/mm^3)	2,263 (1,703-3,101)	2,377 (1,686-2,909)	0.887
C-reactive protein (mg/dL)	0.3 (0.3-0.4)	0.3 (0.3-0.3)	0.821
Albumin (g/dL)	4.1 (3.8-4.3)	4.1 (3.9-4.3)	0.833
Creatinine (mg/dL)	0.85 (0.70-1.00)	0.80 (0.65-0.95)	0.903
Blood urea nitrogen (mg/dL)	16.0 (13.0-22.0)	18.0 (14.0-21.0)	0.659
Glucose	123 (105-158)	126 (111-170)	0.321
Total cholesterol (mg/dL)	171.19±37.93	174.20±34.57	0.706
Hemoglobin A1c (%)	6.0 (5.7-6.2)	6.0 (5.7-6.6)	0.463
Hemorrhagic transformation	2 (7.7)	11 (13.3)	0.730
VENI at 1 hr	9 (34.6)	12 (14.5)	0.023
Functional outcome at discharge			<0.001
mRS score 0-1	20 (76.9)	7 (8.4)	
mRS score 2-4	6 (23.1)	50 (60.2)	
mRS score 5-6	0 (0)	26 (31.3)	

Values are presented as median (interquartile range), number (%), or mean±standard deviation.
mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue plasminogen activator; VENI, very early neurological improvement.
p-values obtained by chi-square test or Fisher exact test for categorical variables, Student t-test or Mann-Whitney U test for continuous variable.

Table 3. Multiple logistic regression analysis of the relationship between clinical covariates and major neurological improvement in geriatric patients

	B	OR	95% CI	p-value
Very early neurological improvement at 1 hr	1.239	3.451	1.211-9.839	0.020
Systolic blood pressure at 10 hr (×10 mmHg)	-0.287	0.751	0.573-0.984	0.038

OR, odds ratio; CI, confidence interval.
Multivariate analysis was performed using the forward stepwise variable selection procedure.
The p-value of the Hosmer-Lemeshow goodness-of-fit test for final logistic regression model was 0.940.

Table 4. Multiple logistic regression analysis of the relationship between clinical covariates and major neurological improvement in non-geriatric patients

	B	OR	95% CI	p-value
Very early neurological improvement at 1 hr	1.950	7.031	1.697-29.137	0.007

OR, odds ratio; CI, confidence interval.
Multivariate analysis was performed using the forward stepwise variable selection procedure.

DISCUSSION

Intravenous administration of thrombolytic agents is the standard treatment for stroke[4,5]. However, for patients who are taking antihypertensive drugs, who are aged 80 years or older, or who have poor underlying neurological conditions (NIHSS scores>25 points) or comorbidities, the use of thrombolytic agents may be limited[16]. Airway management, mechanical ventilation, hyperbaric oxygen therapy, and controlling body temperature and level of blood glucose have been considered and proposed as adjunct therapies in the treatment guidelines for stroke[6-16]. However, with regard to blood pressure, only the upper limit of blood pressure has been suggested, and an adequate range of blood pressure within which the maximal therapeutic effects can be achieved has not been suggested yet[16,17]. Although numerous studies have investigated the relationship between blood pressure and prognoses in patients with acute ischemic stroke, they have not managed to establish a clear relationship, yet[18-20]. While there are reports that high systolic pressure is associated with short-term and long-term worsening of prognoses[18,19], Silver et al.[20] argued that acute hypotension is associated with poor prognoses.

In this study, we found that systolic pressure of patients with acute ischemic stroke changed over time after administration of thrombolytic agents, and that the changes appeared in a different pattern in the different age groups. According to previous studies, blood pressure rises in the early period after stroke and decreases over time[25,26], and the magnitude of the decrease in blood pressure changes depending on the degree of reperfusion after administration of thrombolytic agents[27]. When blood flow at the site of the ischemic stroke decreases locally, blood pressure rises as a result of autoregulation, which is activated to maintain the cerebral blood flow. When the blood flow is restored as a result of administration of thrombolytic agents, the local cerebral blood flow is restored and the initially elevated blood pressure decreases[27]. We hypothesized that this physiological response in which blood pressure rises and then returns to the same level again will appear in a different pattern in the geriatric and nongeriatric patients. Differences in this particular physiological response among different age groups have been confirmed in a previous study that compared the effects of antihypertensive drugs in different age groups[28]. These differences were attributed to the stiffening of arteries due to aging and endothelial cells' inability to perform autoregulation[28]. These may be the same reason why there was no significant decrease in the blood pressure of the geriatric patients in comparison with the nongeriatric patients after rtPA administration.

VENI is a marker of early reperfusion[27]. A previous study reported an association between VENI and prognoses of ischemic stroke[29]. The result of this study in which VENI was an independent predictor variable in both geriatric and the nongeriatric groups is consistent with that of previous studies. However, in the nongeriatric group, blood factors were not included as the independent predictor variables of neurological outcomes. In the nongeriatric group, the blood pressure elevated due to autoregulatory responses during the early period after ischemic stroke may have decreased as local cerebral blood flow was restored after reperfusion was performed, and also as the physiological responses were relatively reduced with increase of age[28]. They may be responsible for the differences in the influence of blood pressure on neurological outcomes between the nongeriatric and geriatric groups.

The influence of acute hypertension on stroke treatment outcomes was a popular topic of research in the past decades. However, study results on this topic have been inconsistent, and the clinical importance of blood pressure on treatment of acute stroke has not been ascertained yet. Studies that have investigated whether blood pressure is associated with prognoses of patients with acute ischemic stroke used different blood pressure variables. Early studies aimed to investigate the influence of basal blood pressure measured at the time of admission into a hospital on stroke treatment outcomes[30-32]. Leonardi-Bee et al.[30] found a U-shaped relationship between basal systolic pressure and poor prognoses made 48 hours after the onset of stroke. However, the study overlooked the fact that blood pressure can change before and after the onset of stroke, and the blood pressure measured once at the time of admission into the hospital does not fully reflect basal blood pressure.

Studies have also attempted to reproduce the variability of blood pressure by repeatedly measuring blood pressure during a certain period of time, and finding mean and standard deviation, coefficient of variation, pulse pressure, and pulse

pressure index of the blood pressure measurements[18,33-36]. A study that analyzed VISTA data and measured blood pressure at 0, 1, 2, 16, 24, and 48 hours reported that the range of variations in blood pressure was associated with early neurological and functional outcomes[33]. Another study investigated the association between blood pressure and prognoses of stroke by calculating differences in blood pressure measured at two different times[20]. The NINDS tPA stroke research team analyzed 37 blood pressure measurements made during the first 24 hours, and found that a short-term decrease in SBP (the maximum difference of systolic pressure relative to the systolic pressure measured right before the analysis) and an overall decrease in SBP (the maximum difference of systolic pressure difference relative to the systolic pressure measured right before a certain time) were associated with neurological and functional outcomes 3 months later[20]. Although these studies overcame the limitations of earlier studies by investigating a wider variety of blood pressure variables, they did not use the course of blood pressure changes itself as a variable. Recently, Toyoda et al.[37] compared changes in blood pressure repeatedly measured over 36 hours in patients with acute ischemic stroke, and found that changes in systolic pressure during 12–36 hours can be predictive of neurological outcomes 3 weeks later. This was one of the few studies that performed statistical analyses using the course of changes in blood pressure as a variable. Our study used a similar method. We repeatedly measured blood pressure over 10 hours after the intravenous administration of rtPA, and evaluated short-term neurological outcomes to minimize the effects of confounding factors.

In this study, the length of evaluation of MNI, which was used as the major outcome variable, was 24 hours and tended to be short. Since blood pressure can exhibit wide variations within a short period unlike other clinical factors, increasing the length of outcome evaluation may reduce the influence of blood pressure, while increasing that of confounding factors associated with time. In this study, the MNI evaluated 24 hours after rtPA administration was highly associated with the mRS scores at the time of discharge. This finding is consistent with that of Nam et al.[38], which reported that neurological states 24 hours after administration of thrombolytic agents reflect prognoses after 3 months. By predicting neurological states of patients with acute stroke 24 hours after treatment with thrombolytic agents, we can predict long-term prognoses of stroke and make proper treatment plans for these patients.

This study had a number of limitations. First, this study was conducted retrospectively at a single institution. Second, systolic pressure only in the first 10 hours after rtPA administration was analyzed. Third, a subgroup analysis could not be performed due to the small sample size. Although the study has some limitations, our findings may be useful in establishing a clinical basis for predicting the target range of blood pressure, and prognoses of patients with stroke.

In conclusion, the course of changes in blood pressure in the first 10 hours after intravenous administration of thrombolytic agents in patients with acute ischemic stroke was different in the geriatric and nongeriatric groups. A smaller decrease in blood pressure was observed in the geriatric patients compared to the nongeriatric patients. Systolic pressure was higher among the geriatric patients who did not show neurological improvement than the geriatric patients who showed neurological improvement. Among the nongeriatric patients, systolic pressure decreased after rtPA administration regardless of whether they had neurological improvement or not. Independent predictor variables that were associated with neurological improvement 24 hours after rtPA administration in the geriatric patients with acute ischemic stroke were neurological improvement at 1 hour after the administration and systolic pressure at 10 hours after the administration. When investigating the association between prognoses of acute ischemic stroke and blood pressure, patients' age should be considered, or patients should be divided into a geriatric group and nongeriatric group.

Conflicts of Interest Disclosures: The researchers claim no conflicts of interest.

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