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RELATIONSHIP BETWEEN SYSTOLIC BLOOD PRESSURE AFTER INTRAVENOUS ANTIHYPERTENSIVE THERAPY AND OUTCOME OF ACUTE HEMORRHAGIC STROKE

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Abstract
Background: High blood pressure often occurs in patients with hemorrhagic strokes and is associated with poor outcomes and recurrent stroke events. Higher and persistent systolic blood pressure is associated with edema around the bleeding.
Methods: Thirty acute hemorrhagic stroke patients who met the criteria were included in this study. All patients received intravenous antihypertensive therapy. The mean systolic blood pressure was obtained by calculating the average of the 30 measurements. Hemorrhagic stroke outcomes were assessed using the Modified Rankin Scale (mRS). Poor outcomes were expressed as mRS values ≥ 3. This study used the Spearman correlation test.
Results: There was a significant difference in systolic blood pressure before and after given significant intravenous antihypertensive therapy ($p < 0.001$), but no significant relationship was found between mean systolic blood pressure after receiving intravenous antihypertensive therapy with mRS on day 14 ($r = 0.216$, $p = 0.251$) and no significant relationship was found between systolic blood pressure difference before and after receiving intravenous antihypertensive therapy with mRS on day 14 ($r = 0.074$, $p = 0.699$).
Conclusion: There is no relationship between systolic blood pressure after receiving intravenous antihypertensive therapy with acute hemorrhagic stroke outcome.

Introduction
Stroke remains a major health problem and it is estimated that there are 700,000 stroke incidents that occur each year in the United States, which cause 160,000 deaths annually, with 4.8 million stroke survivors currently surviving[1.] High blood pressure is a major risk factor for stroke and other vascular diseases, where the risk for a first stroke increases by more than half for an increase in diastolic blood pressure of 10 mmHg. Evidence from experiments on the treatment of hypertension has shown that a relatively small decrease in blood pressure (6 mmHg in diastolic blood pressure) lowers the risk of more than a third for stroke and one fifth for coronary heart disease[2.]

One-third of patients with hemorrhagic strokes have expanded bleeding several hours after the attack. An initial systolic blood pressure (SBP) ≥ 200 mmHg is associated with extended bleeding and increased mortality in patients with hemorrhagic stroke. Persistent higher systolic blood pressure is associated with brain edema formation around bleeding. Lowering blood pressure is expected to reduce the rate of expansion of bleeding, although some important evidence regarding this is not available. Recent research supports that a decrease in blood pressure can be tolerated due to decreased metabolism and can maintain autoregulation in the area around the bleeding[3.]

Method

Study sample
Thirty hemorrhagic stroke sufferers in the acute phase that have been enforced by history taking, physical examination, neurological examination and computed tomography (CT) head scenarios treated at the Central General Hospital (RSUP) Haji Adam Malik Medan participated in this study, after which they were given intravenous antihypertensive therapy using nicardipine starts with a dose of 5 mg / hour and titrated 2.5 mg / hour every 15 minutes up to a maximum dose of 15 mg / hour, then blood pressure measurements are taken

where in the first 2 hours measurements are taken every 15 minutes and then 60 minute measurements were taken during the next 22 hours so that a total of 30 measurements were obtained in 1 day and then from the 30 measurements the average cytolic blood pressure was calculated by adding up the total systolic blood pressure and divided by the number of measurements. Then the functional outcome is assessed using the Modified Rankin Scale after passing through the acute phase.

Study design

This research is analytic descriptive with cross sectional data collection method with the source of data obtained is primary data from all patients with acute hemorrhagic stroke who were hospitalized in RSUP Haji Adam Malik Medan.

Statistical analysis

The research data will be analyzed statistically with the help of the Windows SPSS (Statistical Product and Science Service) computer program. Descriptive analysis is used to look at the characteristics of respondents in the acute phase of hemorrhagic stroke patients and know the mean distribution of systolic blood pressure after receiving intravenous antihypertensive therapy in patients with acute hemorrhagic stroke. To see the difference in mean systolic blood pressure before and after intravenous antihypertensive therapy is used t dependent test. To see the relationship between average systolic blood pressure after receiving intravenous antihypertensive therapy on the outcome of acute hemorrhagic stroke and to see the relationship between the difference in systolic blood pressure before and after intravenous antihypertensive therapy on the outcome of acute hemorrhagic stroke used the Spearman correlation test.

Result

Of the 30 patients who suffered hemorrhagic strokes analyzed, consisting of 19 men (63.30%) and 11 women (36.70%). The mean age of the subjects was 55.4 years. Of the 30 study samples, the most ethnic groups were Javanese with 11 people (36.70%), the most bleeding locations in the basal ganglia were 15 people (50.00%). Based on the medical history of the research subjects 24 subjects (80.00%) had a history of hypertension, 24 subjects (80.00%) had a history of taking antihypertensive medication but were not routinely consumed, 3 subjects (10%) had a history of diabetes mellitus, 3 subjects (10 %) had a history of high cholesterol and no subject (0%) had a history of heart disease. The mean systolic blood pressure at admission was 213.67 ± 17.12 mmHg. The mean initial mRS value was 4.83 ± 0.46 and the final mRS value was 5.43 ± 1.19. The mean onset of hospital admission was 27.73 hours in which 4 people arrived over 24 hours after experiencing symptoms of a hemorrhagic stroke and the mean bleeding volume at admission was 41.6 ml. Complete data on the research subject is presented in table 1 below.

Table 1. Demographic Characteristics of Research Subjects

Characteristics	n = 30
Age, mean ± SD (year)	55,40 ± 7,96
Gender, n (%)	
- Male	19 (63,30)
- Female	11 (36,70)
Race, n (%)	
- Jawa	11 (36,70)
- Batak	9 (30,00)
- Karo	5 (16,70)
- Melayu	3 (10,00)
- Aceh	2 (6,70)
Location of Bleeding, n (%)	
- Basal Ganglia	15 (50,00)
- Lobar	12 (40,00)
- Thalamus	3 (10,00)
Medical History, n (%)	

- Hypertension	24 (80,00)
- Hyperlipidemia	3 (10,00)
- Diabetes Mellitus	3 (10,00)
- Heart Disease	0 (0,00)
Onset, n (%)	
- < 3 hours	3 (10,00)
- 3 – 24 hours	23 (76,70)
- > 24 hours	4 (13,30)
Mean mean ± SD (hour)	27,73 ± 31,26
History of taking antihypertensive medication, n (%)	
- Irregular	24 (80,00)
- No medication	6 (20,00)
Mean systolic blood pressure mean ± SD (mmHg)	213,67 ± 17,12
Early mRS Value mean ± SD	4,83 ± 0,46
Final mRS Value mean ± SD	5,43 ± 1,19
Bleeding Volume, mean ± SD (mL)	41,60 ± 22,78

Table 2 shows complete data on the distribution of systolic blood pressure after receiving intravenous antihypertensive therapy based on the demographic characteristics of the subjects and the study variables.

Table 2. Average Distribution of Systolic Blood Pressure After Intravenous Antihypertensive Therapy Based on Characteristics of Research Variables

Characteristics of Research Variables	Mean Systolic Blood Pressure After Medication	
	n	Mean ± SD
Gender		
- Male	19	172,67 ± 4,61
- Female	11	164,84 ± 6,15
Age (year)		
- ≤ 45	3	182,23 ± 8,77
- 46-64	24	169,24 ± 4,23
- > 64	3	161,73 ± 11,96
Location of Bleeding		
- Basal ganglia	15	166,20 ± 4,78
- Lobar	12	174,66 ± 6,90
- Thalamus	3	168,32 ± 7,08
Bleeding Volume		
- < 15 ml	2	162,65 ± 7,35
- 15-30 ml	8	164,89 ± 9,03
- > 30 ml	20	172,47 ± 4,21
Onset		
- < 3 hours	3	158,18 ± 11,08
- 3 – 24 hours	23	172,54 ± 4,18
- > 24 hours	4	162,74 ± 11,12
History of taking antihypertensive medication		
- Irregular	24	172,46 ± 4,15
- No Medication	6	159,11 ± 7,11
Hypertension		

- Yes	24	172,46 ± 4,15
- No	6	159,11 ± 7,11
Diabetes Mellitus		
- Yes	3	174,15 ± 15,80
- No	27	169,31 ± 3,83
Hyperlipidemia		
- Yes	3	179,63 ± 19,51
- No	27	168,70 ± 3,63

Table 3 shows that the mean systolic blood pressure before administration of intravenous antihypertension was 213.67 ± 17.11 and decreased to 169.79 ± 20.23 after intravenous antihypertension was given.

Table 3. Differences in Mean Systolic Blood Pressure Before and After Intravenous Antihypertensive Therapy

	n	Mean ± SD	Difference	p
SBP on admission	30	213,67 ± 17,11		
			43,86	<0,001
SBP after medication	30	169,79 ± 20,23		

T-dependent test, the difference between after and before

Based on statistical analysis, there was a decrease in mean systolic blood pressure after being given significant intravenous antihypertensive therapy with a p value <0.001 compared to before giving intravenous antihypertensive therapy.

Statistical analysis using the Spearman correlation test showed no significant relationship between the mean systolic blood pressure after being given intravenous antihypertensive therapy to the outcome of an acute hemorrhagic stroke (p = 0.251), where the relationship between the two showed an insignificant positive correlation with the strength of a weak relationship (r = 0,216) (Table 4) and the non-significant relationship between systolic blood pressure difference before and after receiving intravenous antihypertensive therapy to the outcome of acute hemorrhagic stroke (p = 0.699), where the relationship between the two showed a non-significant positive correlation with the strength of a very weak relationship (weak relationship) r = 0.074) (Table 5).

Table 4. Relationship of Mean Systolic Blood Pressure After Intravenous Antihypertensive Therapy to Acute Hemorrhagic Stroke Outcome

		Final mRS
Mean Systolic Blood Pressure After Intravenous Antihypertensive Therapy	**r**	0,216
	p	0,251
	n	30

Spearman Correlation Test

Table 5. Relationship Between Systolic Blood Pressure Difference Before and After Intravenous Antihypertensive Therapy and Outcome of Acute Hemorrhagic Stroke

		mRS Akhir
Systolic Blood Pressure Difference Before and After Intravenous Antihypertensive Therapy	**r**	0,074
	p	0,699
	n	30

Spearman Correlation Test

Discussion

This research is a descriptive analytic study with cross sectional data collection method that aims to determine the relationship of systolic blood pressure after receiving intravenous antihypertensive therapy to the outcome of acute hemorrhagic stroke so that it is useful to improve the quality of life of hemorrhagic stroke sufferers who receive intravenous antihypertensive therapy in its management. The research subjects consisted of 30 people, 19 men (63.30%) and 11 women (36.70%), with the average age of the subjects being 55.4 years, with an age range of 38-78 years, with classification subjects aged ≤ 45 years were 3 people (10.00%), 46-64 years were 24 people (80.00%), and> 64 years were 3 people (10.00%). This is consistent with the results of the Framingham study, the incidence of stroke in men is an average of 2.5 times more often than women. The average age of stroke from data from 28 hospitals in Indonesia is 58.8 years, with a range of 18-95 years. Age under 45 years as much as 12.90% and age> 65 years 35.80% [4].

In this study the mean systolic blood pressure of the study subjects at admission was 213.67 mmHg. High blood pressure has been reported in several previous studies as a major risk factor for hemorrhagic stroke. Sturgeon et al (2007) reported that individuals with systolic blood pressure> 160 mmHg and diastolic blood pressure> 110 mmHg were 5.55 times more likely to have a hemorrhagic stroke than those without hypertension.[5] Lepalla et al (1999) also reported that individuals with blood pressure systolic> 160 mmHg has a 3.78 times risk of having a hemorrhagic stroke compared to individuals without hypertension.[6] In this study, the mean decrease in systolic blood pressure after 24 hours of administration of intravenous antihypertensive therapy is nicardipine. The mean systolic blood pressure decreased to 169.79 ± 20.23 mmHg after being given intravenous antihypertensive therapy compared with the mean systolic blood pressure at hospital admission that was 213.67 ± 17.11 mmHg ($p < 0.001$). The results of this study are in accordance with research Yamada et al (2017) who found a decrease in mean systolic blood pressure at admission 180.00 ± 29.30 to 136.60 ± 16.90 after 24 hours of intravenous antihypertensive therapy ($p = 0.0061$). Nicardipine can cross the blood brain barrier and work as a vasorelax in the smooth muscle of blood vessels in the brain. At acidic pH from ischemic brain tissue, nicardipine is almost 100.00% protected, allowing rapid accumulation of ischemic tissue, local vasodilation, and a decrease in vasospasm that is seen in patients with acute subarachnoid hemorrhage. Although nicardipine is a vasodilator of cerebral blood vessels, it can also dilate arterioles that have little resistance, so there are no significant changes in intracranial volume and intracranial pressure[7,8]. In this study it was found that the mean systolic blood pressure after 24 hours of receiving intravenous antihypertensive therapy had an insignificant positive correlation with the strength of a weak association with acute hemorrhagic stroke outcome ($r = 0.216$, $p = 0.251$).

Complications that can occur in patients with hemorrhagic strokes include, hematoma expansion, perihematomic edema, intraventricular hemorrhage with hydrocephalus, convulsions, venous thromboembolism, hyperglycemia, increased blood pressure, fever and infection. Where, the expansion of the hematoma, the expansion of bleeding into intraventricular, and hyperglycemia are the main predictors for the increased risk of death and poor outcome during a hyperacute phase hemorrhagic stroke. Research conducted by Sakamoto et al (2013) states that the higher the mean systolic blood pressure after receiving intravenous antihypertensive therapy, the more likely the output will worsen and in groups with a higher mean systolic blood pressure can cause active bleeding, resulting in an expansion of the hematoma. Because the expansion of the hematoma can worsen neurological outcomes and worsening, the mean high systolic blood pressure is independently associated with poor outcomes and neurological deterioration. Edema around the hematoma can also have the potential to worsen the outcome, although in this study edema around the hematoma was not measured. The study states that patients with a mean systolic blood pressure <132.8 mmHg or a mean systolic blood pressure <130 mmHg have the lowest proportion to have a bad outcome[10].

In this study 29 subjects had poor outcomes and only 1 had a good outcome with an average final mRS of 5.43 ± 1.19 and no significant relationship was found. This was possible for a mean systolic blood pressure after receiving intravenous antihypertensive therapy in all subjects were 169.79 ± 20.23 mmHg and this is in accordance with the theory put forward by Hemphill et al (2015) that systolic blood pressure after being given intravenous antihypertensive therapy <135 mmHg has better outcomes than systolic blood pressure> 160 mmHg. In theory, increased blood pressure might increase the risk of bleeding due to rupture of the small

arteries and arterioles in the first hours. Blood pressure is correlated with increased intracranial pressure and bleeding volume. In a prospective observational study a reduction in cytolic blood pressure to a target of <160/90 mmHg was associated with neurological deterioration in 7% of patients and hematoma expansion in 9% of patients but was associated with a tendency towards good outcomes in patients whose systolic blood pressure was lowered within 6 hours after bleeding occurs.[11] In this study all the subjects studied entered the hospital with different onset of attack. From the descriptive analysis to see the average distribution of systolic blood pressure after receiving intravenous antihypertensive therapy based on hospital admission after the attack, the difference in mean systolic blood pressure showed that subjects who came <3 hours after onset had lower systolic blood pressure, namely 158, 18 ± 11.08 mmHg, compared with subjects who came between 3-24 hours with a higher mean systolic blood pressure of 172.54 ± 4.18 mmHg. This finding raises a suspicion whether the sooner to get intravenous antihypertensive therapy the response to antihypertensive treatment will also be faster and have better outcomes. In a study conducted by Inoue et al (2017) stated that patients with longer onset receiving intravenous antihypertensive therapy had worse outcomes and had a wider bleeding volume.[12]

Other complications that can occur in hemorrhagic stroke patients and especially with a decrease in consciousness and severe neurological deficits can cause pneumonia. Pneumonia often occurs in stroke patients who have been lying down for a long time and lack of mobilization which in this condition causes increased sputum secretion. Kaldor and Berlin stated that pneumonia often occurs on the side of the lung where motor weakness occurs, because on the side that experiences weakness also results in weakness in the muscles that move the chest cavity which causes lung circulation to be disrupted.[13] Alsumrain et al (2012) concluded that in hemorrhagic stroke patients with mechanical ventilation, nasogastric tube attached, dysphagia and tracheostomy which have been strongly associated with the development of pneumonia and obtained significant results (p = 0.001). In that study showed a higher mortality rate (25.60%) in patients accompanied by pneumonia compared to patients without pneumonia (12.00%). Hemorrhagic stroke patients who also have pneumonia have a lower GCS and a higher mRS value compared to those without pneumonia.[14] This study has several limitations. First, the characteristics of the study subjects such as onset of attack at hospital admission, bleeding volume and location of bleeding were not equated in all study subjects, so the possibility of a major bias arising in this study. Secondly, this study only monitored systolic blood pressure on the first day (24 hours) after receiving intravenous antihypertension so that the long-term effects due to nicardipine use and outcomes could not be analyzed. Third, in this study other conditions that could affect outcomes such as pneumonia were not excluded, because almost all subjects in this study experienced a decrease in consciousness that increased the risk for pneumonia that could affect the outcome of the study subjects.

Conclusion

There was a significant difference between the mean systolic blood pressure before and after the administration of intravenous antihypertensive therapy in patients with acute hemorrhagic stroke, but no significant relationship was found between systolic blood pressure after receiving intravenous antihypertensive therapy with the outcome of acute hemorrhagic stroke.

Suggestion

Future research needs to be done that exclude all acute hemorrhagic stroke patients with complications such as pneumonia, so as to minimize the bias of the results of the study.

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