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RELATIONSHIP BETWEEN PaCO₂ LEVELS AND CLINICAL OUTCOMES OF ACUTE ISCHEMIC STROKE PATIENTS WITH DECREASED OF CONSCIOUSNESS

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Abstract

Background: Stroke is a leading cause of mortality and disability worldwide. Changes in Partial Pressure of Carbon Dioxide (PaCO₂) in patients with acute ischemic stroke can worsen the ischemic condition in cerebral and clinical outcomes.

Objective: To determine the relationship between PaCO₂ levels and clinical outcomes of acute ischemic stroke patients with decreased awareness.

Research Methods: This study uses a cross-sectional design. Sampling was conducted at H. Adam Malik General Hospital Medan. Samples were taken as many as 46 subjects consecutively. The independent variable of the study is the level of PaCO₂ and the dependent variable is the clinical outcome. Data analysis using the Spearman correlation test.

Results: The characteristics of the study subjects consisted of men (43.5%) and women (56.5%) with an age range of 51-60 years, Batak ethnicity, high school education level, and decreased levels of PaCO₂. The level of PaCO₂ of research subjects had a mean of 37.39 mmHg ± 8.04. The median value of mRS in 7 treatment days was 4 (2-6). The most out of the disability mRS category was moderate disability of 28.3%. There is a significant relationship between PaCO₂ with an increase in the value of mRS within 7 days of treatment and the strength of the correlation is relatively moderate. (p = 0.001; r 0.499).

Conclusion: there is a significant relationship between PaCO₂ with an increase in the value of mRS within 7 days of treatment

Introduction

Stroke is a disease that is a major concern in public health and a major cause of mortality and disability throughout the world. As many as 15 million people suffer strokes in the world each year, of which as many as 5 million die and the rest have permanent disabilities that place a burden on families and communities.¹ The results of a systematic review conducted in 28 countries from 1990 to 2010 showed a reduction in the incidence of stroke from 250.55 per 100,000 people / year to 257.96 per 100,000 people / year.²

Pathophysiologically, complex changes occur at the cellular level and the microcirculation of stroke is interrelated.³ If regional Cerebral Blood Flow (CBF) is reduced, then in the area concerned will be found low perfusion pressure, partial pressure of oxygen (PaO₂) decreases, partial pressure of carbon dioxide (PaCO₂) increases and lactic acid accumulation.⁴ As a result of lack of oxygen, lactic acidosis occurs which causes impaired function of enzymes, due to high H⁺ ions. Furthermore lactic acidosis causes cerebral edema characterized by swelling of cells, especially glia tissue, and results in microcirculation.⁵ Lactate elevation is not only a marker of anaerobic metabolism in stroke, but also may be a cause of secondary injury with infarct volume expansion and poor clinical outcomes.⁴ According to Pollock et al.⁶ mention changes in PaCO₂ will affect CBF Cerebral Blood Flow (CBF). These conditions consist of hypercapnia/hypercapnia, an increase in CBF due to increased PaCO₂ and hypocapnia hypoperfusion, a decrease in CBF due to a decrease in blood PaCO₂ levels.⁶ According to Allyson⁷, a very low decrease in PaCO₂ in acute ischemic stroke patients can worsen the ischemic condition in the cerebral and clinical outcome.⁷



Method

Research sample

The study sample was taken from acute ischemic stroke patients with decreased consciousness who came to H. Adam Malik General Hospital Medan. The sampling technique used was consecutive sampling with 46 research subjects

Study design

This study is a cross-sectional design. Blood gas analysis was examined to see PaCO₂ in ischemic stroke patients with decreased consciousness. Examination of clinical outcome of stroke with mRS (Modified Rankin Scale) in ischemic stroke patients is first performed at admission and last day of treatment within 7 days.

Statistic analysis

Data from the study were statistically analyzed using the SPSS computer program version 22.0. To determine the relationship of PaCO₂ levels with clinical outcome were analyzed using the Spearman test.

Result

Table 1. Overview of Characteristics of Research Subjects

Characteristics of respondents	Average	n (46)	Percentage (%)
Age (year)	56,2(±6,92)*		
• ≥40 – 50 year		10	21,7
• ≥51 – 60 year		23	50
• ≥61 – 70 year		13	28,3
Gender			
• Male		20	43,5
• Female		26	56,5
Educations			
• Elementary school		5	10,9
• Junior high school		9	19,6
• Senior high school		20	43,5
• Diploma		6	13
• Bachelor		6	13
Ethnics			
• Bataknese		33	71,7
• Javanese		8	17,4
• Acehnese		5	10,9
PaCO ₂	37,39(±8,04)*		
• Decrease		21	45,7
• Normal		15	32,6
• Increase		10	21,7

Based on table 1 above, obtained the characteristics of 46 research subjects obtained the age of all research subjects has an average of about 56.2 years ± 6.92 with the most age range at age 51-60 years as many as 23 subjects (50%), large research subjects are sex female (56.5%) and male (43.5%) with the highest level of education is high school (43.5%), the respondent is Batak (71.7%). The level of PaCO₂ of research subjects had



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a mean value of 37.39 mmHg \pm 8.04 which was classified as normal. Whereas the most PaCO₂ content category was with PaCO₂ levels decreased by (45.7%).

Descriptive analysis of the characteristics of the mRS score in this study uses median values with minimum and maximum values because the data distribution of the mRS score is not normally distributed. The mRS value within 7 days of treatment has a median of 4 (2-6). The characteristics of disability based on mRS in 7 days of treatment the most was severe disability in 13 subjects (28.3%). This can be seen in table 2 below.

Table 2. Characteristics of Modified Rankin Scale (mRS)

Characteristics of score	Average (minimum-maximum)	n (46)	Percentage (%)
mRS score within 7 days of treatment	4(2-6)		
• mild disability		11	23,9
• moderate disability		10	21,7
• moderate severe disability		13	28,3
• severe disability		6	13
• death		6	13

In this study clinical outcomes were assessed and grouped based on the Modified Rankin Scale (mRS) score within 7 days of treatment, while for PaCO₂ levels were also grouped into decreased, normal and increased. Clinical outcome of acute ischemic stroke patients within 7 days of treatment with decreased levels of PaCO₂ with mild disability was 8 patients (38.1%), normal PaCO₂ group had the most moderate to severe disability, 7 patients (46.7%) and the PaCO₂ group increased the most died, as many as 5 patients (50%). The proportion of clinical outcomes within 7 days of treatment based on a complete grouping of PaCO₂ levels can be seen in table 3 below.

Table 4. Proportion of Clinical Outcomes Based on PaCO₂ Levels

PaCO ₂ Levels	mRS score 7 days of treatment(n/%)					Total
	Mild disability	Moderate disability	Moderate to severe disability	Severe disability	Death	
Decrease	8(38,1)	7(33,3)	4(19)	1(4,8)	1(4,8)	21(100)
Normal	3(20)	3(20)	7(46,7)	2(13)	0(0)	15(100)
Increase	0(0)	0(0)	2(20)	3(30)	5(50)	10(100)

In this study clinical outcomes were assessed based on a Modified Rankin Scale (mRS) score within 7 days of treatment). The statistical analysis used was the Spearman correlation test due to abnormal data distribution. Based on the Spearman correlation test on 46 research samples, it was found that there was a relationship between PaCO₂ and mRS within 7 days of treatment, a significant relationship with p value <0.001 was obtained. The correlation r value obtained at 0.499 indicates the direction of the positive correlation with the strength of the moderate correlation. This can be seen in table 4 below.

Table 4. Relationship between PCO₂ levels and Modified Rankin Scale scores (mRS)

PaCO ₂ levels	Modified Rankin Scale within 7 days of treatment
	r = 0,499
	p < 0,001
	n = 46

Spearman correlation test



Discussion

Based on the characteristics of the 46 research subjects, the average age of all research subjects was around 56.2 years \pm 6.92 with the largest age range being 51 - 60 years (50%). The results of this study are relevant to previous studies conducted by Rambe et al (2013) which mention the average age of stroke patients is 59 years (age range 20-95 years) and the highest number of subjects at the age of 40-59 years. The cumulative effect of aging on the cardiovascular system and the progressive development of stroke risk factors over a period of time increases the risk of stroke. The risk of stroke has doubled after the age of 55 years.⁸ Age as one of the characteristics of a person, in epidemiological studies of age is an important variable because many diseases are found with a variety of frequencies caused by age. The increase in the frequency of strokes with increasing age is related to the aging process, where all organs of the body experience deterioration of function including the blood vessels of the brain. The blood vessels become inelastic, especially the endothelial area which thickens the in time a, resulting in narrowed lumen of the blood vessels and an impact on decreased cerebral blood flow⁹

Research subjects with female sex (56.5%) more than men (43.5%). The results of this study are in line with research conducted by Rambe et al¹⁰ showing the demographic characteristics of women are 52.7% more than men.¹⁰ Women have several different factors than men, including coagulation factors, hormonal reproductive factors, including pregnancy and childbirth, as well as social factors that can influence the risk of stroke and stroke outcome.¹¹ The incidence of stroke in women is said to increase in postmenopausal age, because before menopause women are protected by the hormone estrogen which plays a role in increasing HDL, where HDL plays an important role in preventing the process of atherosclerosis.¹² Characteristics of the education level of the most research subjects in this study were high schools (43.5%). The results of this study are relevant to previous research conducted by Kusumawardani¹³ at the RSUP dr. Kariadi Semarang who received the most education for stroke sufferers was high school by 52.4%. According to Riskesdas in 2013 the prevalence of stroke tended to be higher in people with low levels of education based on a diagnosis of health services or symptoms as much as 32.8 %. Prevalence is higher in people who do not work based on diagnosis of health services or symptoms of 18 %. Economic status (education and income) is related to the incidence of stroke. This is due to the low level of economic status related to the utilization of health access and low health costs so that the quality of health is also low.¹⁴

The respondents are divided into Batak (71.7%), Java (17.4%) and Aceh (10.9%), so that it can be concluded that the majority of respondents with ischemic strokes are from the Batak tribe. This is consistent with the research of Rambe et al¹⁰ in the ischemic stroke group as many as 40.7% of the Batak tribe. Other relevant research results were also carried out by El Harizah¹⁵ on 100 stroke patients in the neurology clinic and inpatient rooms of FK USU / RSUP.H. Adam Malik Medan in the period December 2015 to April 2016 obtained the most tribes suffering from stroke was the 63 Batak tribe (63%), followed by the Javanese tribe of 22 patients (22%), the Aceh tribe of 8 patients (8%), the Malay tribe of 5 patients (5%), and 2 Chinese patients (2%).¹⁵ The cause of the high incidence of strokes in the Batak tribe compared to non-Batak tribes may be caused by risk factors that cannot be modified ie genetically and modifiable stroke risk factors.¹⁶ Batak tribe has more eating characteristics than other tribes so it is more likely to be obese.¹⁷ Typical Batak food also contains a lot of cholesterol levels.¹⁸

In this study, the PaCO₂ level of the study had an overall average value of 37.39 mmHg, the level was classified as normal. The results of this study are relevant to the research conducted by Salinet et al¹⁹ which stated the average value of PaCO₂ in acute ischemic stroke patients was 38.3. ¹⁹ The grouping of PaCO₂ levels was divided into decreased (45.7%), normal (32.6%) and increased by (21.7%), so it was concluded that some ischemic stroke patients with decreased consciousness in this study had PaCO₂ levels at partial admission relatively large decreased / hypokapnia. The results of this study are relevant to previous studies conducted by Salinet et al²⁰ which mention acute stroke patients having PaCO₂ levels that are lower than normal. In cerebral ischemia during acute stroke depression occurs in the CBF response to nerve activation and cerebrovascular reactivity to CO₂. This causes hypocapnia which aims to maintain auto regulation of brain pressure.²⁰

Ischemic stroke patients with decreased consciousness in this study had a median mRS value in 7 days of treatment of 4 (2-6). The disability category according to mRS within 7 days of treatment was divided into mild



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disabilities (23.9%), moderate disabilities (21.7%), moderate moderate disabilities (28.3%), severe disabilities (13%) and died as many as (13%). The results of this study are relevant to research conducted by Simorangkir²¹ which mentions clinical outcomes of good mRS stroke (≤ 2) obtained by 24% and bad mRS (3-6) by 76%. Calculation of stroke outcomes with mRS focuses more on the disabilities that patients will get after a stroke. Modified Rankin Scale (mRS) is a categorical scale that describes the functional outcomes of stroke patients with scores ranging from 0 to 6 and is recommended in studies of acute ischemic stroke. The value of mRS 0-2 is a measure of good outcomes and mRS 3-6 is a measure of bad outcomes.²²

Clinical outcome of acute ischemic stroke patients in 7 days of treatment with decreased PaCO₂ levels with mild disability was as much as (38.1%), normal PaCO₂ group experienced the most severe moderate disability, as many as (46.7%) and PaCO₂ group increased the most many experienced death as many as (50%). So it can be concluded that acute ischemic stroke patients with clinical outcomes in 7 bad care (died) most are groups with increased PaCO₂ levels. The results of this study are relevant to research conducted by Tiruviopati et al²³ which states the mortality rate (mortality) in stroke patients who have increased levels of PaCO₂ (hypercapnia) measured in the first 24 hours by 58.6%.²³ In ischemic stroke patients the condition of hypercapnia acidosis where an increase in PaCO₂ > 45 mmHg followed by a decrease in blood pH can increase the risk of death by 1.43 times greater than normal PaCO₂. In patients with ischemic stroke, acidosis due to hypercapnia is frequent and has been proven associated with the entry of toxic calcium into cells and causes programmed cell death and worse outcomes.²³ The mechanism of influx of calcium ions in neurons and the level of severe brain tissue damage caused by excitotoxic actions of glutamate release are triggered by high intracellular calcium levels.²⁴ In addition, according to Sidharta⁴ also mentioned when regional Cerebral Blood Flow (CBF) is reduced, then the area concerned will find low perfusion pressure, partial pressure of oxygen (PaO₂) decreases, Partial Pressure of Carbon dioxide (PaCO₂) increases and lactic acid buildup.⁴ As a result of lack of oxygen, lactic acidosis occurs which causes impaired function of enzymes, due to high H⁺ ions. Furthermore lactic acidosis causes cerebral edema characterized by swelling of cells, especially glia tissue, and results in microcirculation.⁵ Lactate elevation is not only a marker of the occurrence of anaerobic metabolism in stroke, but also may be a cause of secondary injury with expansion of infarct volume and poor clinical outcomes.⁴

In the group of patients with decreased PaCO₂ levels, they experienced the most mild disability, as many as 8 patients (38.1%). In this study both in number and percentage it can be said that the clinical outcome in the 7-day treatment of the PaCO₂ group has decreased better than the increase in PaCO₂. According to research conducted by Salinet et al¹⁹ mentions that in acute stroke patients changes in PaCO₂ levels are slightly lower than normal due to physiological effects aimed at maintaining autoregulation. The condition of hypocapnia is also mentioned as a key mediator in reducing intra-cranial pressure and the recovery process of the penumbra area around ischemic tissue. Hypocapnia is considered to be able to increase the ability of cerebral blood vessels to keep CBF constant when there is a change in perfusion pressure.¹⁹ According to Tsidal et al²⁵ states that when PaCO₂ decreases to 26 mmHg and continues to decrease to below 25 mmHg, through the mechanism of vasoconstriction will cause spasm in the blood vessels of the brain and threaten ischemia.²⁵ According to previous research conducted by Simorangkir²¹ which states that the condition of decreased consciousness in ischemic stroke patients is associated with poor mRS (score 3-6) with a p of 0.03. These results are supported by research conducted by Lie et al²⁶ states that acute ischemic stroke patients who experience awareness disorders will be at risk 3.3 times experiencing disability which will be associated with poor clinical outcomes in patients.²¹

In this study it was found that there was a significant relationship between PaCO₂ and mRS within 7 days of treatment with a p value of <0.001. The correlation r value obtained at 0.499 indicates the direction of the positive correlation with the strength of the moderate correlation. This shows that the higher the value of PaCO₂, the higher the mRS score will be. An increase in the mRS score in acute stroke patients illustrates the worsening of clinical outcomes (outcome). According to Pollock et al⁶ mentioned changes in PaCO₂ will affect CBF Cerebral Blood Flow (CBF). When PaCO₂ increases, vasodilatation of cerebral blood vessels will occur which causes an increase in the rate of blood flow to the brain, and eventually there will be an increase in intracranial pressure. Increased intracranial pressure with various implications is a factor that must be prevented because it will worsen the existing output (Clausen et al, 2005).²⁷ In addition to the rate of blood flow to the



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brain, PaCO₂ also influences brain perfusion pressure, because brain perfusion pressure is influenced by mean arterial blood pressure reduced by intracranial pressure. Changes in arterial PaO₂ do not have as much impact as changes in PaCO₂.²⁸

According to Maggio et al.²⁹, mentioning an increase in CO₂ levels in the blood during the acute phase of ischemic stroke causes disruption of the neurovascular coupling system and cerebral autoregulation so that it triggers neuronal injury. The mechanism underlying this is due to the release of extracellular H⁺ ions, decreased cell hydrogen potential (PH), and cellular metabolic failure.²⁹ Acidosis conditions caused by hypercapnia can increase the risk of death in cerebral injuries in hospitals.²³

Conclusion

There is a significant relationship between PaCO₂ with an increase in the value of MRS within 7 days of treatment and the magnitude of correlation strength is moderate. (p = 0.001; r 0.499).

Suggestion

Future studies can further analyze the factors that influence the clinical outcome of ischemic stroke, especially in patients with decreased consciousness.

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