

Original Research Article

The effect of hyperglycemia and troponin I levels on the prognosis of acute ischemic stroke in non-diabetic and diabetic patients

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ABSTRACT

Background: Acute hyperglycaemia may predict a higher risk of hospitalization mortality after ischemic stroke in non-diabetic patients and a higher risk of poor functional improvement in non-diabetic stroke patients. It is thought that insula involvement in right cerebral hemispheres has a role in autonomic control of the heart. Troponin is a sensitive marker that is widely used in the diagnosis and risk stratification of acute coronary syndrome. High troponin I is found in acute stroke patients and is associated with a poorer prognosis.

Methods: The study was cross-sectional, 30 patients diagnosed with acute ischemic stroke at Haji Adam Malik General Hospital Medan from June 16, 2017 to March 31, 2018. All participants were taken blood to measure blood glucose levels at the time of admission >140 mg/dL with a history of previous or not diabetes. Troponin I levels was checked when acute ischemic stroke patients had entered the inpatient room. The patient's prognosis is determined by National Institute of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS). The calculation of NIHSS and MRS scores was performed on the first day of admission and the fourteenth day after being admitted to the hospital. Statistical test using Fisher exact test.

Results: Of the 30 samples consisted of 19 men and 11 women. The significant effect between hyperglycaemia in acute ischemic stroke patients with diabetes and non-diabetes on the fourteenth day NIHSS (PR 2.8; 95% CI, 1.184-6,622; p=0.045).

Conclusions: There was an effect between hyperglycaemia in non-diabetic and diabetic on the poor prognosis of acute ischemic stroke patients.

Keywords: Acute ischemic stroke, Hyperglycemia, Prognosis of acute ischemic stroke, Troponin I

INTRODUCTION

Globally, stroke is the first cause of long-term disability, the second leading cause of dementia and the third largest cause of death after ischemic heart disease and cancer.¹⁻³ In 2001, it was estimated that strokes caused the deaths of 5.5 million people in the world, around 9.6% of total global deaths. Two-thirds of these deaths occur in those living in developing countries and 40% of sufferers are under 70 years of age.⁴

Stroke is the leading cause of death among Indonesians above five years of age, comprising 15.4% of all deaths, age-gender-standardised death rate 99/100000, and age-gender-standardised disability-adjusted life years lost 685/100000. Stroke prevalence is 0.0017% in rural Indonesia, 0.022% in urban Indonesia, 0.5% among urban Jakarta adults, and 0.8% overall.⁵ The American Heart Association, according to a report on the updating of heart disease and stroke statistics, states that strokes ranked second in 2013 as the biggest cause of death in the United States.⁶

Stroke is defined by the World Health Organization (WHO) as a rapid clinical sign of focal (or global) disorders of cerebral function, with symptoms lasting 24 hours or more or causing death, without other causes than vascular.⁴ As a non-traumatic cerebrovascular disease that interferes with local and/or global nerve function, stroke appears sudden, progressive, and rapid.^{1,4}

Stroke can be categorized as ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. About 80% of strokes are ischemic, 10-15% are intracerebral haemorrhage and 5% are subarachnoid haemorrhage.^{4,7}

Acute stroke also has a relationship with the stress of hyperglycemia. Hyperglycemia occurs in 60% of acute stroke cases and in 12-53% of cases without a previous diagnosis of diabetes.^{1,7,8} The presence of hyperglycemia that occurs in ischemic stroke patients during hospital admission will extend the treatment period, worsen functional improvement and increase mortality.^{1,8}

Hyperglycemia stress is defined as hyperglycemia that occurs in patients who were previously euglycemic which improves if the acute process is overcome.^{1,7} By triggering anaerobic metabolism, lactic acidosis, and free radical production, hyperglycemia causes membrane lipid peroxidation, interferes with mitochondrial function and causes metabolic cells to be lysed.^{7,9} This will encourage and accelerate cerebral injury in the penumbra area and will further increase the size of cerebral infarction.¹⁰

In addition to neurological complications, patients with stroke can experience medical complications. Cardiac morbidity causes death in 20% of patients with ischemic stroke and is the second most common cause of death in acute stroke populations.^{11,12} This is estimated by the involvement of insula in the right cerebral hemisphere which may have a role in autonomic control of the heart.^{13,14} This autonomic dysfunction will cause myocytolysis and the release of cardiac enzymes, including the release of troponin into the blood in stroke patients.²

Increased cardiac troponin in the blood has been reported in all types of stroke (ischemic, intracerebral hemorrhage, and subarachnoid haemorrhage). In a meta-analysis study, it was found that about 18% of 2901 patients had elevated cardiac troponin values in the blood.¹⁵ Troponin is a sensitive marker that is widely used in the diagnosis and risk stratification of acute coronary syndrome. In stroke patients reported increased levels of blood troponin up to 60% of the patient population.¹⁶

This study aims to determine the effect of hyperglycemia on prognosis in acute ischemic stroke patients with diabetes and non-diabetes, and to determine the effect of troponin I levels on the prognosis in acute ischemic stroke patients.

METHODS

This was a cross-sectional study with a total number of 30 consecutive sampling non-random selected, clinically and computed tomography (CT) scan proven acute ischemic stroke patients were studied at Haji Adam Malik General Hospital Medan. The study was conducted from June 16, 2017 to March 31, 2018. All participants, that had fulfilled inclusion criteria and didn't have exclusion criteria, were taken blood to measure blood glucose levels at the time of admission >140 mg/dL and troponin I levels when acute ischemic stroke patients had entered the inpatient room. The patient's prognosis is determined by National Institute of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS). The calculation of NIHSS and MRS scores was performed on the first day of admission and the fourteenth day after being admitted to the hospital. Demographic data was analysed using descriptive statistics. Fisher's Exact test analyse the effect of hyperglycemia and troponin I levels on the prognosis of acute ischemic stroke in non-diabetic and diabetic. A p-value <0.05 was considered statistically significant.

Inclusion criteria

- All patients clinically proven to have acute ischemic stroke and have been confirmed by a head CT scan.
- Acute recurrent and non-recurrent ischemic stroke patients.
- Acute ischemic stroke patients who experience hyperglycemia.
- Acute ischemic stroke patients who also suffer from hypertension, dyslipidemia.
- Acute ischemic stroke patients who agree to participate in the study and are proven by informed consent.

Exclusion criteria

- All patients clinically proven to have hemorrhagic strokes and confirmed by head CT scan.
- Acute ischemic stroke patients with infarction in the brain stem
- Acute ischemic stroke patients with extensive infarction due to cardioembolism and infarction in large arteries.
- Acute ischemic stroke patients with a history of previous heart disease, namely: Ischemic Heart Disease, Congestive Heart Failure, Myocarditis, Pericarditis, Post heart surgery.
- Acute ischemic stroke patients with chronic renal failure.
- Acute ischemic stroke patients with pulmonary embolism.
- Acute ischemic stroke patients with chronic obstructive pulmonary disease.
- Acute ischemic stroke patients with sepsis or septicemia.

Statistical analysis

All statistical analyses were carried out using the SPSS statistical software, version 21.0. Descriptive analysis is used to see the demographic description of the research subject. The data were presented with Mean±SD and percentage. Categorical variables presented as percentage. Fisher's Exact test was used to determine the relationship of blood sugar levels with the prognosis of acute ischemic stroke and the relationship of troponin I sugar levels with the prognosis of acute ischemic stroke. The P value <0.05 was considered as statistically significant.

RESULTS

The research subjects consisted of 30 people who suffered from acute ischemic stroke, namely 19 male (63.3%) and 11 female (36.7%). Of all acute ischemic strokes, the mean age of 30 patients with acute ischemic stroke was 55.17±10.996 years with the highest range at the age of 50-64 years (50%) (Table 1).

Table 1: Baseline clinical characteristic of subject study.

	Mean	Standard Deviation
Age (years)	55.17	10.99
Gender (n, %)		
Male	19	63.3
Female	11	36.7
Sistole (mmHg)	164.50	22.76
Diastole (mmHg)	94.17	17.72
Random blood glucose (mg/dL)	190.17	77.124
Fasting blood glucose (mg/dL)	132.17	58.79
Blood glucose 2 hours Prandial Post	166.43	80.13
HbA1c (%)	6.85	2.41
Total Kolesterol (mg/dL)	255.90	32.55
Trigliserida (mg/dL)	131.40	37.96
LDL (mg/dL)	153.23	45.41
HDL (mg/dL)	39.60	10.44
Troponin I	0.02	0.08
NIHSS- 1	5.30	2.84
NIHSS- 14	4.00	2.24
mRS- 1	2.33	0.96
mRS- 14	1.90	0.55

The statistical analysis of the study subjects found that the mean age of the study subjects was 55.17 years, with the mean systole of 164.50 mmHg, the mean diastole was 94.12 mmHg, with the mean ad random blood sugar levels of 190.17 mg/dl, the mean fasting blood sugar levels was 132.17 mg/dl, the mean blood sugar levels of 2

hours post prandial was 166.43 mg/dl, with the mean HbA1c of 6.85%, while the mean total cholesterol was 255.90 mg/dl, the mean triglyceride was 131.40 mg/dl, the mean LDL was 153.23 mg/dl, the mean HDL is 39.60 mg/dl and the mean troponin I level is 0.02. The statistic results obtained by the mean NIHSS of the first time the study subjects entered the hospital were 5.30 and the fourteenth day NIHSS mean was 4.00. The mean first-time mRS entered was 2.33 and the fourteenth day mRS was 1.90. See Table 1.

The group of patients with acute ischemic stroke with diabetes has an average age of 56.4±10.39 years. The group of acute non-diabetic ischemic stroke patients had a mean age of 52.7±12.29 years. Based on the results of the t-independent test, the p value was 0.616 (p>0.05), so it was concluded that there was no significant difference in the mean age between acute ischemic stroke patients with diabetes and non-diabetes. In the group of patients with acute ischemic stroke with diabetes, there were 20 people with 13 men (65%) and 7 women (35%) while the acute non-diabetic ischemic stroke amounted to 10 people with 6 men (60%) and 4 women (40%). Based on the Fisher's Exact test results, the p value is 1,000 (p>0.05), so it is concluded that there is no significant sex difference between acute ischemic stroke patients with diabetes and non-diabetes (see Table 2).

The group of acute ischemic stroke patients who examined troponin I levels had an increase in the average age of 60.5±13.435 years. The group of acute ischemic stroke patients with normal troponin I levels had an average age of 54.79±10.996 years. Based on the results of the t-independent test, a P value of 0.487 (P>0.05) was obtained, so it was concluded that there was no significant difference in mean age between acute ischemic stroke patients with troponin I levels increasing with normal ones.

In the group of acute ischemic stroke patients, troponin I levels increased by 2 people with 1 male (50%) and 1 female (50%) while acute ischemic stroke with normal troponin I levels were 28 people with 18 men (64.29 %) and 10 women (35.71%). Based on the Fisher's Exact test results, a p value of 1,000 was obtained (P>0.05), so it was concluded that there were no significant sex differences between acute ischemic stroke patients with troponin I levels increasing with normal ones. See Table 2.

Hyperglycemia in acute non-diabetic ischemic stroke patients will have a risk of 1,067 times more having the first day NIHSS 4-15 (moderate), compared with hyperglycemia in acute diabetic ischemic stroke patients (PR 1,067; 95% CI, 0,715-1,591; P=1,000). Based on the Fisher's Exact test results, the P value is 0.657 (p>0.05), so it is concluded that there is no significant relationship between hyperglycemia in acute ischemic stroke patients with diabetes and non-diabetes on the first day mRS (mRS H1).

Hyperglycemia in patients with acute non-diabetic ischemic stroke will have a 1.5 times greater risk of having mRS 3-6 (bad) the first day, compared to

hyperglycemia in acute ischemic stroke patients with diabetes (PR 1.5; 95% CI, 0.413- 5,450; P=0,657) (see Table 3).

Table 2. Correlation between subject’s baseline characteristic with diabetic, non-diabetic and troponin I levels.

Characteristic	Acute Ischemic Stroke		P	Acute Ischemic Stroke with Troponin I Level		P
	Diabetes (n=20)	Non-Diabetes (n=10)		Increased (n=2)	Normal (n=28)	
Age, mean±SD	56.4±10.399	52.7±12.293	0.616*	60.5±13.435	54.79±10.996	0.487*
Gender, n(%)						
Men	13 (65)	6 (60)	1.000**	1(50%)	18(64.29)	1.000**
Women	7 (35)	4 (40)		1(50%)	10(35.71)	

*t-independent Test, p<0.05, **Fisher’s Exact Test, p<0.05.

Table 3. The effect of hyperglycemia on the prognosis of acute ischemic stroke using NIHSS and mRS.

	Hyperglycemia		Total n(%)	P
	Non-Diabetic n (%)	Diabetic n (%)		
NIHSS H1				
Moderate (4-15)	8 (80)	15 (75)	23 (76.7)	1.000*
Mild (<4)	2 (20)	5 (25)	7 (23.3)	
NIHSS H14				
Moderate (4-15)	7 (70)	5 (25)	12 (40)	0.045*
Mild (<4)	3 (30)	15 (75)	18 (60)	
mRS H1				
Severe (3-6)	3 (30)	4 (20)	7 (23.3)	0.657*
Mild (0-2)	7 (70)	16 (80)	23 (76.7)	
mRS H14				
Severe (3-6)	1 (10)	0 (0)	1 (3.33)	NA
Mild (0-2)	9 (90)	20 (100)	29 (96.67)	

*Fisher’s Exact Test, p<0.05

Based on Fisher's Exact test results, the p value is 0.045 (P<0.05), so it is concluded that there is a significant relationship between hyperglycemia in acute ischemic stroke patients with diabetes and non-diabetes on the fourteenth day NIHSS (NIHSS H14). Hyperglycemia in acute non-diabetic ischemic stroke patients will have 2.8 times more risk of having NIHSS 4-15 (moderate) fourteenth days, compared with hyperglycemia in acute diabetic ischemic stroke patients (PR 2.8; 95% CI, 1,184 -6,622; P=0.045) (see Table 3).

Based on this study, it was found that NIHSS of acute ischemic stroke patients who had hyperglycemia, both those with diabetes and non-diabetes, entered the category of good and moderate, and for mRS included in the good and bad categories. So that it can be concluded, there is a significant effect between hyperglycemia in people with diabetes with non-diabetes on the prognosis

of acute ischemic stroke patients with the fourteenth day NIHSS.

Based on Fisher's Exact test results, the p value is 0.418 (p >0.05), so it is concluded that there is no significant relationship between troponin I levels that increase with normal in acute ischemic stroke patients on the first day mRS (mRS H1). Increased troponin I levels in acute ischemic stroke patients will have a risk of 2,333 times more having first day mRS 3-6, compared with acute ischemic stroke patients with normal troponin I levels (PR 2,333; 95% CI, 0,492-11,069 ; p = 0.418) (see Table 4).

Based on Fisher's Exact test results, the p value is 1,000 (p>0.05), so it is concluded that there is no significant relationship between elevated troponin I levels and normal in acute ischemic stroke patients to the fourteenth day NIHSS (NIHSS H14). Increased troponin I levels in patients with acute ischemic stroke will have a risk of

1,273 times more having NIHSS 4-15 (moderate) fourteenth days, compared with acute ischemic stroke patients with normal troponin I levels (PR 1,273; 95% CI, 0.295-5,482 ; p = 1,000) (see Table 4).

Based on this study, it was found that NIHSS of acute ischemic stroke patients who were examined for troponin I levels were in the good and moderate category and for mRS included in the good and bad categories.

So that it can be concluded, there is no significant effect between troponin I levels on the prognosis of acute ischemic stroke patients.

DISCUSSION

Hyperglycemia may be directly toxic to the ischemic brain. Accumulation of lactate and intracellular acidosis in the ischemic brain (produced through anaerobic cerebral glucose metabolism) promotes and accelerates ischemic injury by enhancing lipid peroxidation and free radical formation and impairing mitochondrial function. These neurotoxic effects may be particularly important in the ischemic penumbra where neurons are injured but still viable. Hyperglycemia facilitates the development of cellular acidosis in the ischemic penumbra and results in a greater infarct volume, thus promoting the recruitment of potentially salvageable neurons into the infarction. Hyperglycemic patients are relatively deficient in insulin. This leads to both reduced peripheral uptake of glucose (increasing the amount of glucose available to diffuse into brain) and increased circulating free fatty acids. Free fatty acids may impair endothelium-dependent vasodilation.⁷

Stress hyperglycemia patients are likely to have dysglycemia. These patients have a higher risk of vascular disease than patients with normal blood glucose level. These patients could sustain more ischemic damage at the time of infarction as a result of more extensive underlying cerebral vasculopathy compared with those who do not develop stress hyperglycemia. Hyperglycemia is an important determinant of the widespread changes in both small cerebral blood vessels and large extracranial vessels seen in diabetic patients. Hyperglycemia causes 24% reduction in regional blood flow, reduction in blood circulation to the marginal ischemic areas and converts ischemic penumbra to infarct. CO₂-induced increase in cerebral blood flow is decreased in diabetics. CO₂-induced cerebral vasodilatation is mediated through NO, and diabetics are known to have decreased endothelial NO production.⁷

In this study there was no significant effect between hyperglycemia in ischemic stroke patients with diabetes and non-diabetes patients on NIHSS H1 (PR 1.067; 95% CI, 0.715-1.591; P=1,000) but there was a significant effect between hyperglycemia in ischemic stroke patients people with diabetes and non-diabetes on NIHSS H14 (PR 2.8; 95% CI, 1.184-6,622;P=0.045). In the research

of Marulaiah et al, in 2017, there was a significant association between hyperglycemia in ischemic stroke patients with diabetes and non-diabetes in the NIHSS score (P <0.0001).¹⁷ In the Tziomalos et al, in 2016, there was a significant association between hyperglycemia in ischemic stroke patients with diabetes and non-diabetes in the NIHSS (P<0.001).¹⁸

In this study there was no significant difference between hyperglycemia in ischemic stroke patients with diabetes and non-diabetes in mRS H1 (PR 1.5; 95% CI, 0.413-5.450; P=0.657). In the study of Marulaiah et al, in 2017, there was no significant association between hyperglycemia in ischemic stroke patients with diabetes and non-diabetes in mRS (P=0.09).¹⁷

The involvement of the right insula in acute ischemic stroke is associated with a more relevant cardiac autonomic derangement and with a higher incidence of arrhythmias than any other stroke localization.¹⁹

In this study there was no significant relationship between troponin I levels which increased with normal in acute ischemic stroke patients to NIHSS H14 (PR 1,273; 95% CI, 0.295-5,482; P=1.000). In the study of Bustamante et al, in 2016, there was no significant relationship between troponin I levels that increased with normal in acute ischemic stroke patients with NIHSS (P=0.112).¹⁶ In the study of Atilla et al, in 2008, there was no significant relationship between troponin I levels increased with normal in acute ischemic stroke patients with NIHSS (P=0.098).¹³

In this study there was no significant relationship between elevated troponin I levels and normal in acute ischemic stroke patients to mRS H1 (P=0.418). In a study by Budincevic et al, in 2017, there was no significant relationship between troponin I levels which increased with normal in acute ischemic stroke patients to mRS (P=0.092).²⁰

Limitations of the study due to the relatively small number of study samples to provide representative results.

CONCLUSION

There was a significant effect between hyperglycemia in patients with acute ischemic stroke with diabetes and non-diabetes on the fourteenth day NIHSS. There was a significant effect between hyperglycemia on the prognosis of acute ischemic stroke patients with diabetes and non-diabetes.

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