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Correlation between HbA1C and Infarct Volume in Acute Ischemic Stroke

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Abstract

BACKGROUND: Stroke is second leading cause of death worldwide. Chronic hyperglycemia can promote neuronal toxicity. The previous study shows that acute hyperglycemia is correlated with infarct volume of ischemic stroke.

AIM: This study aims to investigate the correlation between hemoglobin A1C (HbA1C) and infarct volume on acute ischemic stroke.

METHODS: This is a cross-sectional study in acute ischemic stroke patient in Dr. Moewardi General Hospital, Surakarta, Indonesia. Data of infarct volume were collected from head computed tomography (CT)-scan and calculated with A × B × C/2 formula. We also collected lipid and patients' glycemic profile from patients' blood laboratory result. Head CT-scan and laboratory data of participants analyzed with Pearson and Spearman's rho test for parametric and non-parametric data, respectively. We also performed multivariate analysis to evaluate confounding covariates. $p < 0.05$ was considered as statistically significant.

RESULTS: A total of 38 participants were included in this study, with mean infarct volume was 0.46 ± 0.64cc and mean HbA1C was 6.96 ± 2.69%. Bivariate analysis shows strong positive correlation between infarct volume and HbA1C with $r = 0.898$ ($p < 0.001$). Other variable that showed a significant correlation with infarct volume were diabetes mellitus history ($r = 0.671$; $p < 0.001$), random blood su gar ($r = 0.466$; $p = 0.003$), fasting blood sugar ($r = 0.636$; $p < 0.001$), 2-h postprandial glucose level ($r = 0.646$; $p \leq 0.001$), high density lipoprotein ($r = -0.354$; $p = 0.029$), and triglyceride ($r = 0.429$; $p = 0.007$). Based on multivariate analysis, HbA1C regression coefficient on infarct volume was $B = 0.222$ ($p < 0.001$), indicating that HbA1C as one of the variables contributing to volume of infarct.

CONCLUSIONS: There is a strong positive correlation between infarct volume and HbA1C, and HbA1C is variable contribute to the volume of infarct.

Introduction

Stroke is an acute focal or general neurological dysfunction as a result of underlying cerebrovascular disease. Stroke can be broadly classified into ischemic and hemorrhagic stroke. Ischemic stroke, which contribute around 71% of all strokes, results from infarction of artery in the brain, spinal cord, or retina [1]. Stroke is a second leading cause of death worldwide which account for around 11% of total deaths annually. In 2019, stroke account for more than 6 million death worldwide, increasing from around 5 million death in 2000 [2]. Stroke is also a major cause of long-term disability. Around 45% post-stroke patient had some degree of disability [3].

Diabetes mellitus is a well-known risk factor for ischemic stroke. Chronic hyperglycemia in diabetes mellitus can promote pro-oxidative and pro-inflammatory cytokines which can cause neuronal toxicity. Hyperglycemia could increase matrix metalloproteinase-9, which can cause nerve damage and cerebral edema. Furthermore, hyperglycemia may be responsible for the pro-coagulant state, which can further compromise the blood supply to the penumbral area in acute ischemic stroke [4]. Uncontrolled hyperglycemia is related to worse functional outcome, higher risk of mortality, and increasing cost of care in stroke cases [5].

One of the most important predictors for functional outcomes in ischemic stroke is infarct volume. Larger infarct had worse overall clinical outcome and higher rate of transformation into intracranial hemorrhage [6]. Several studies reveal that infarct volume is associated with glucose level in ischemic stroke. Watila *et al*. (2014) demonstrated that patients with blood glucose level >126 mg/dL had larger infarct, more severe clinical manifestation at presentation, and worse clinical outcome. However, this study only assessed blood glucose levels at admission, which may not captured the effect of chronic hyperglycemia on infarct volume and functional outcome [7]. This study aims to investigate the correlation between long-term

glycemic control, assessed with hemoglobin A1C (HbA1C) and infarct volume on acute ischemic stroke in Dr. Moewardi General Hospital, Surakarta, Indonesia.

Methods

This was an observational, and quantitative study with cross-sectional design in Dr. Moewardi General Hospital, Surakarta, Indonesia from. Participant was acute ischemic stroke inpatient, which recruited with purposive sampling method. Inclusion criteria for this study were (1) patient aged over 18 years old; (2) diagnosis of acute ischemic stroke is confirmed with head computed tomography (CT)-scan; and (3) normal hemoglobin level. Exclusion criteria of this study were patient with; (1) unmeasurable ischemic lesion volume; (2) arrhythmia; (3) acute bleeding; (4) patients receiving blood transfusion in the past 1 week; (5) increasing creatinine serum >3 folds of normal range; (6) chronic liver disease; (7) chronic hemolytic anemia; (8) patients receiving immunosuppressant, anti-psychotic, and/or corticosteroid; and (9) history of alcohol consumption. Written informed consent had been signed by all participants included in this study and this study design had been approved by the local institutional review board, Dr. Moewardi General Hospital Health Research Ethics Committee through ethical clearance number 709/VI/HREC/2020.

A 64-slice head CT-scan and laboratory data of participants who met both inclusion and exclusion criteria then analyzed to find correlation between infarct volume and laboratory parameter. Infarct volume was measured by certified radiologist with formula of A × B × C/2, with (A) being the largest diameter of the infarct; (B) being perpendicular diameter of (A); and (C) being number of slices, represent infarct thickness [8]. Laboratory parameter analyzed in this study were lipid and glycemic profile. Laboratory result was issued by certified pathologist.

Data distribution then analyzed with Shapiro–Wilk test. Correlation test between infarct volume and laboratory parameter was analyzed with Pearson and Spearman's rho test for parametric and non-parametric data, respectively. We also performed multivariate analysis to evaluate correlation between HbA1C, infarct volume, and its covariate. $p < 0.05$ was considered as statistically significant. All analysis was done with SPSS v.22 software.

Results

This study was conducted in Dr. Moewardi General Hospital, Surakarta, Indonesia from June to August 2020. A total of 38 participants met the inclusion and exclusion criteria were included in this study. Mean age of participant was 58.37 ± 11.49 years and 55.3% were male. Mean infarct volume was 0.46 ± 0.6cc and mean HbA1C was 6.96 ± 2.69%. We analyzed distribution of numeric data using Shapiro–Wilk test. $p > 0.05$ indicates normal distribution of data. Characteristics of participant and data distribution test are detailed in Table 1.

Table 1: Characteristics of participant and data distribution

Variable	Mean ± SD	Median (Min-Max)	n (%)	p
Demography				
Age (years)	58.37 ± 11.49	55 (39–82)		0.172*
Sex				
Male			21 (55.3)	
Female			17 (44.7)	
Risk Factors				
Hypertension history				
Yes			17 (44.7)	
No			21 (55.3)	
Heart Disease History				
Yes			2 (5.3)	
No			36 (94.7)	
Diabetes Mellitus History				
Yes			9 (23.7)	
No			29 (76.3)	
Dyslipidemia History				
Yes			9 (23.7)	
No			29 (76.3)	
Smoking History				
Yes			9 (23.7)	
No			29 (76.3)	
BMI (kg/m^2)	23.01 ± 2.56	23 (18.7–2.76)		0.256*
Infarct				
Location				
Internal capsule			7 (18.4)	
Corona radiata			12 (31.6)	
Ganglia basalis			2 (5.3)	
Nucleus caudatus			6 (15.8)	
Nucleus lentiformis			1 (2.6)	
Parietal			7 (18.4)	
Thalamus			3 (7.9)	
Volume (cc)	0.46 ± 0.64	0.14 (0.02–1.98)		0.000
Blood Pressure				
Systole (mmHg)	168.13 ± 35.34	173 (103–254)		0.213*
Diastole (mmHg)	92.21 ± 15.77	92 (63–112)		0.245*
Lipid Profile				
Cholesterol (mg/dL)	170.79 ± 50.40	173 (20–265)		0.536*
HDL (mg/dL)	35.61 ± 13.35	34.5 (9–85)		0.006
LDL (mg/dL)	129.97 ± 49.00	130 (25–245)		0.385*
Triglyceride (mg/dL)	159.53 ± 94.95	148.5 (34–429)		0.001
Glycemic Profile				
RBS level (mg/dL)	137.39 ± 91.57	102 (68–465)		0.000
FBS level (mg/dL)	117.76 ± 72.11	95 (47–363)		0.000
2HPP glucose level (mg/dL)	149.66 ± 86.88	114.5 (71–419)		0.000
HbA1C (%)	6.96 ± 2.69	5.75 (5–14.8)		0.000

*Normal distribution, BMI: Body mass index, HDL: High density lipoprotein, LDL: Low density lipoprotein, RBS: Random blood sugar, FBS: Fasting blood sugar, 2HPP: 2 h post prandial, HbA1C: Hemoglobin A1C.

We performed bivariate analysis to determine the correlation between infarct volume and laboratory parameters using non-parametric test. Numeric data were analyzed with Spearman correlation test, while categoric data were analyzed using Eta correlation test. Bivariate analysis shows a strong positive correlation between infarct volume and HbA1C with $r = 0.898$ ($p < 0.001$). Several confounding variable had a significant correlation with infarct volume, particularly diabetes mellitus history ($r = 0.671$; $p < 0.001$), random blood sugar (RBS) ($r = 0.466$; $p = 0.003$), fasting blood sugar (FBS) ($r = 0.636$; $p < 0.001$), 2 h postprandial (2HPP) glucose level ($r = 0.646$; $p = <0.001$), high density lipoprotein (HDL) ($r = -0.354$; $p = 0.029$), and triglyceride (TG) ($r = 0.429$; $p = 0.007$). Result of Spearman and Eta correlation test are summarized in Table 2.

We also performed multivariate analysis to find correlation between HbA1C, infarct volume, and other confounding variables. We use multiple linear regression on variable with $p < 0.250$ on bivariate analysis. Based on multivariate analysis, we discovered constant of

Table 2: Result of bivariate analysis

Variable	Infarct volume	
	Correlation Coefficient (r)	p-value
HbA1C	0.898	<0.001*
Other Variable		
Age	0.202	0.225
Sex	0.119	0.475
Systolic	−0.044	0.795
Diastolic	−0.136	0.328
BMI	0.127	0.446
Diabetes mellitus history	0.671	<0.001*
Hypertension history	0.025	0.880
Heart disease history	0.143	0.391
Dyslipidemia history	0.261	0.113
Smoking	0.033	0.845
RBS level	0.466	0.003*
FBS level	0.636	<0.001*
2HPP glucose level	0.646	<0.001*
Total cholesterol	−0.119	0.475
HDL	−0.354	0.029*
LDL	0.054	0.747
Triglyceride	0.429	0.007*

*Statistically significant, HbA1C: Hemoglobin A1C, BMI: Body mass index, RBS: Random blood sugar, FBS: Fasting blood sugar, 2HPP: 2 h post prandial, HDL: High density lipoprotein, LDL: Low density lipoprotein.

−1.190 and HbA1C regression coefficient of B = 0.222 ($p < 0.001$), indicating that HbA1C as dominant variable to affect infarct volume. Other confounding factors, with $p > 0.05$, were not predictor of infarct volume. Result of multivariate analysis are detailed in Table 3 and Figure 1.

Table 3: Result of multivariate analysis

Variable	Infarct volume		
	Regression Coefficient (B)	95% CI	p-value
Constant	−1.190	−1.591–−0.789	
HbA1C	0.222	0.187–0.257	<0.001*
Confounding Variable			
Age	−0.002	−0.006–0.002	0.378
Diabetes mellitus history	0.105	−0.042–0.253	0.155
Dyslipidemia history	−0.031	−0.155–0.092	0.607
RBS level	0.000	−0.002–0.001	0.556
FBS level	0.000	−0.002–0.002	0.944
2HPP glucose level	0.001	−0.001–0.002	0.580
HDL	0.003	−0.001–0.007	0.181
Triglyceride	0.000	−0.000–0.001	0.396

*Statistically significant, HbA1C: Hemoglobin A1C, RBS: Random blood sugar, FBS: Fasting blood sugar, 2HPP: 2 h post prandial, HDL: High density lipoprotein.

Discussion

The most participants of this study (55.3%) were male, consistent with epidemiological studies which showed higher prevalence of stroke in male. Wang *et al*. (2019) found that incidences of stroke were 1652.51 and 920.80/100.000 per year in men and women,

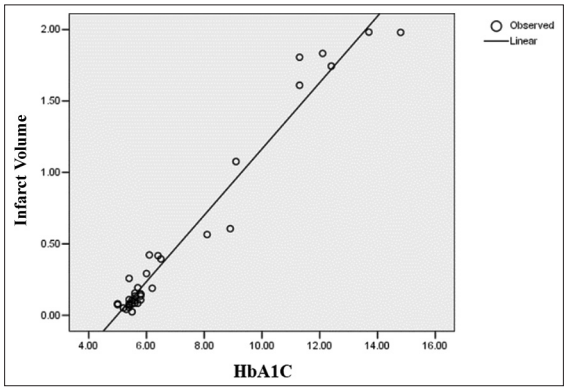

Figure 1: Correlation curve between hemoglobin A1C and infarction volume

respectively [9]. Mean age of our participant was 58.37 ± 11.49, similar to study by Misbach and Wendra (2011), which shows mean age of 58.8 ± 13.3 years in stroke patient [10]. In this study, there is no correlation between age and infarct volume. However, studies show that age is an important independent risk factor, where stroke rates doubling every decade after age of 55. Furthermore, age is a significant predictor of stroke clinical outcome, regardless of stroke severity, etiology, thrombolysis efficacy, gender, and other vascular risk factors. Older patients tend to have higher mortality rates and worse functional outcomes [11].

In this study, we calculate infarct volume from head CT-scan slides with formula of A × B × C/2. CT-scan is rapid and inexpensive imaging modality which makes it ideal for emergency cases and becomes gold standard imaging to diagnose stroke. In contrast to CT-scan, magnetic resonance imaging (MRI) produces images with better resolution, thus make it more sensitive than CT-scan to diagnosed ischemic stroke. However, MRI is relatively expensive and requires longer examination time [12]. In Indonesia, CT-scan, unlike MRI, is done to all patient suspected with stroke, make it as an abundant resource for radiological studies. Routine and A × B × C/2 is a simple, rapid, and reproducible method to measure [13]. However, a study discovered that this formula may overestimated infarct volume in acute stroke. Calculation of infarct volume by Od-value formula of 1.1 (A × B) + 0.03 $(A \times B)^2$ has higher specificity compared to A × B × C/2 formula [14].

Twenty-nine patients (76.3%) had no previous history of diabetes mellitus, the average value of HbA1C in this study was 6.96 ± 2.69, and 26.3% of patients had HbA1C >6.5%. The American Diabetes Association recommends HbA1C cutoff value of 6.5% to diagnose diabetes. Based on epidemiological studies, HbA1C >6.5% is more prone to vascular complications [5]. In this study, we discovered a statistically significant positive correlation between HbA1C and infarct volume ($p < 0.001$). Correlation coefficient of r = 0.898 indicates a very strong positive correlation between two variables. Similar result observed in study by Mostafa and Mohamed (2015) which examined the correlation between HbA1C and severity of ischemic stroke. They showed a significant moderate positive relationship (r = 0.489) between HbA1C and infarct size. A strong relationship between pre-stroke glycemic control and functional outcomes was also observed in this study. A poor HbA1C before cerebrovascular accident is adversely correlated with Barthel index score with r = −0.350. It indicates that HbA1C is a reliable independent predictor of stroke severity and functional outcome [15]. Another study also showed that HbA1C had a positive correlation with infarction volume assessed by diffusion weighted imaging MRI in the internal carotid artery region. Sun *et al*. (2016) found that infarct volume was larger in patients with HbA1c ≥6.36% (mean volume of 16.38 ± 10.48cc) compared

to patients with HbA1c <6.36% (mean volume of 5.24 ± 5.15cc) [16]. Another study by Lee *et al*. (2020) also supports this finding. Poor glycemic control, represented by glycated albumin, also correlated with more severe stroke and larger infarct volume. This study found that patient with higher level of glycated albumin had a median infarct volume of around 1.77cm^3, compared to median of 0.46 cm^3 on patients with lower glycated albumin. Furthermore, higher National Institute Health Stroke Scale score is found on 15.7% of patient with higher value of glycated albumin, compare to only 3.8% of patient with lower glycated albumin [17]. Those finding shows that glycemic control, either assessed with HbA1C or glycated albumin, is correlated with infarct volume and clinical outcome.

Chronic hyperglycemia promotes oxidative stress and mitochondrial superoxide overproduction. Furthermore, it can also leads to the formation of glycation end products of various proteins, which contribute to plaque and atherosclerosis formation [18]. Poor long-term glycemic control also altered the structure and function of the vascular bed in both small and large cerebral blood vessels, as well as acidotic and inflammatory state. These conditions could reduce blood supply to the penumbra area in acute ischemic stroke, thereby increasing area of infarction [4], [5].

We observed a significant relationship between RBS, FBS, and 2HPP glucose level with infarct volume on bivariate analysis. Watila *et al*. (2014) also observed that elevated RBS related to larger infarct. Acute ischemic stroke has reciprocal relation with hyperglycemia. Not only acute ischemic stroke could be worsened by hyperglycemia, it also can induce hyperglycemia. This condition, known as stress hyperglycemia, is caused by increased cortisol level [7]. Another study also highlights that FBP also shows significant relationship with functional outcomes in stroke patients. Lower FBG level is associated with better functional outcome in stroke patient [19]. We also observed a significant correlation between diabetes mellitus history and infarct volume. Our finding is in line with study done by Hjalmarsson *et al*. (2015), which stated that hyperglycemia as a marker for worse clinical outcome was observed on ischemic stroke with no diabetes mellitus history, but not with patient diagnosed with diabetes mellitus [5]. A systematic-review and meta-analysis on 23 studies evaluating correlation of hyperglycemia and infarct volume show conflicting result. Several studies show that hyperglycemia exacerbates infarct volume. However, greater increased of infarct volume was observed in studies using streptozotocin as diabetogenic agent compared to studies using dextrose infusion, which is more similar to real life pathophysiology of Type 2 diabetes mellitus [20].

We also found that HDL and TGs, but not cholesterol and low density lipoprotein (LDL), had a significant correlation with infarct volume. The study by Pikija *et al*. (2006) shows that higher serum TG is associated with lower infarct volume in brain CT-scan. Higher TG level also correlated with less severe stroke symptom on onset and lower mortality rate. However, further study is needed to understand the mechanism underlying this effect [21]. History of hyperlipidemia also reduces white matter hyperintensity, which could predict infarct progression and correlate with poor outcome of ischemic stroke [22]. Furthermore, high TG-glucose index, which is calculated with formula of log scale of (fasting TG × fasting glucose)/2, is associated with sooner recurrent ischemic stroke [23]. Hyperlipidemia is also a well-known risk factor for stroke. Hyperlipidemia has been shown to exacerbate ischemic damage through endothelial cell injury, oxidative stress, inflammation, and neuronal loss [24].

Consistent with study conducted by Bonardo *et al*. (2018), we found that both systolic and diastolic blood pressure did not correlate with infarct volume on ischemic stroke [25]. However, Cipolla *et al*. (2018) showed that a larger infarct was found in patients with hypertension. Chronic hypertension will result in increasing cerebrovascular resistance, causing cerebral hypoperfusion. Increased vascular tone and narrowed vessels occur could also be found due to chronic hypertension. Cipolla *et al*. hypothesized that hypertension create poor collateral flow, resulting in fewer tissue that could be revascularized [26].

On multivariate analysis, we observed HbA1C regression correlation of 0.222, which indicates that 22.2% infarct volume are determined by HbA1c. Other major determinant of infarct volume is location of blood vessel blockage in ischemic stroke. Infarction in blood vessel supplies large area in the brain will result in bigger infarct area. Infarction in large blood vessel also result in worse clinical outcome [27]. We did not find any confounding factors that affect infarct volume in ischemic stroke. This result may be caused by strong correlation between confounding factors, we analyzed with HbA1C as independent variable. HbA1C tends to have positive correlation with RBS, FBS, and 2HPP, since they all measure blood glucose level. HbA1C also has a strong correlation with total cholesterol, LDL, and LDL/HDL ratio. The latest study even evaluated HbA1C as a potential biomarker of dyslipidemia. Using HbA1C in Type 2 diabetic patient provides both early diagnostic assessment for dyslipidemia and glycemic control status with relatively inexpensive test [28].

To the best of our knowledge, this is the first study to analyzed correlation between glycemic control and infarct volume in Indonesian population. Our finding emphasizes the importance of blood glucose monitoring in routine clinical examinations to prevent large infarct volume and severe clinical outcome in stroke, particularly in patient with diabetes mellitus. This study also done multivariate analysis to understand correlation between HbA1C and infarct volume, and other confounding factors. Our study is a cross-sectional study which only evaluate correlation

between two variables. The study with serial HbA1C could provide causality information between glycemic control and infarct volume. More accurate imaging with MRI and analysis with Od-value are needed for better infarct volume estimation, as well as to assess the penumbra area in ischemic stroke. Larger number of participants is required to provide better data that can represent the population.

Conclusions

There is a strong positive correlation between infarct volume and HbA1C, and HbA1C is variable contribute to the volume of infarct.

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