



Physiological Aspects of Plasma Osmolarity and its Association with the Clinical Severity of Ischemic Stroke Evaluated with the NIHSS: A Cross-sectional Study

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Abstract

BACKGROUND: Ischemic stroke is one of the leading causes of mortality and disability worldwide. Recent studies have observed that some physiological factors play a pivotal role in determining stroke severity, which can be assessed using the National Institutes of Health Stroke Scale (NIHSS) score. Hydration status is one of the most frequently studied physiological factors and can be evaluated by measuring plasma osmolarity levels. However, studies regarding the association between plasma osmolarity and stroke severity remain scarce.

AIM: This study aimed to investigate the association between increased blood plasma osmolarity levels and the NIHSS scores in patients with acute ischemic stroke.

METHODS: This cross-sectional study obtained medical records of subjects aged 18–80 years old who were diagnosed with their first acute ischemic stroke from January to March 2021 at the Siloam Hospitals Lippo Village Tangerang in Indonesia.

RESULTS: The NIHSS scores of patients with acute ischemic stroke were observed to have a moderate positive correlation with plasma osmolarity ($p = 0.004$, $r = 0.309$). Patients with an elevated plasma osmolarity had higher NIHSS scores than those with normal levels of plasma osmolarity (8.52 ± 5.01 vs. 6.03 ± 3.72).

CONCLUSIONS: Higher levels of plasma osmolarity among acute ischemic stroke subjects correlated positively with increased NIHSS scores on admission.

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Introduction

Stroke is a neurological disease with the highest prevalence worldwide, based on the World Health Organization (WHO) survey. At present, stroke is the second leading cause of death, with an annual mortality rate of 5.5 million people [1], [2]. Stroke is one of the most disability-causing diseases globally. It was found that 50% of patients with stroke experience permanent disability with varying degrees of severity [2]. With increasing progress in healthcare quality, the global life expectancy continues to increase, thus shifting the prevalence of diseases toward metabolic and degenerative diseases, along with an increase in global stroke prevalence, including Indonesia [1], [2], [3], [4].

As stroke research progresses, multiple scales have been developed to measure the severity of stroke. The National Institutes of Health Stroke

Scale (NIHSS) is one of the best scoring systems for assessing the severity of stroke symptoms [5], [6]. In addition to the NIHSS, several other parameters that are potentially correlated to the clinical severity of stroke have also been studied, including plasma osmolarity levels. Increased plasma osmolarity is associated with dehydration, and some studies have shown its relation to increased mortality in patients with severe clinical disorders such as cardiac, cerebral, vascular, and gastrointestinal disorders. It is also particularly associated with prolonged admission and increased mortality rates in intensive care patients [7], [8], [9].

Comprehensive management of stroke is essential for better patient outcomes. We hypothesized that the hydration state, which is determined by patients' plasma osmolarity levels, correlates with the outcome of patients with acute ischemic stroke, and that it can act as a new indicator to treat stroke patients for a better outcome. Therefore, the present study was conducted.

Methods

This was a hospital-based cross-sectional study conducted between January and March 2021 at the Siloam Hospitals Lippo Village. The research data collected are secondary data from the medical records of patients suffering from acute ischemic stroke for the 1 time. Data were gathered using consecutive sampling based on the inclusion criteria of patients between the ages of 18 and 80 years diagnosed with the first ischemic stroke attack. Patients with an altered level of consciousness, systemic infection, chronic kidney disease, prior history of head trauma within 3 months, and incomplete medical records were excluded from the study.

The NIHSS score was measured at admission, while plasma osmolarity was calculated using the formula: $2 [\text{serum sodium level, Na}^+] + [\text{glucose}]/18 + [\text{blood urea nitrogen, BUN}]/2.8$. Plasma osmolarity was considered a dichotomous variable, with an upper limit of 295 mOsm/L. Diagnosis of ischemic stroke was made by neurologists based on physical examination and was confirmed with computed tomography to rule out other acute brain disorders.

Information collected for demographic data and the NIHSS score at first hospital admission included history of hypertension, diabetes mellitus (DM), dyslipidemia, heart disease, smoking, and metabolic panels (sodium, glucose, and BUN levels).

Data analysis

Data were collected using provided research form. Data were then edited, coded and organized using SPSS version 24.0 software. Statistical analysis was performed using statistic test which appropriate with research variables measurement scale. Tests of normality were carried out using the Kolmogorov test, as the samples included were more than 50. The data were considered to have a normal distribution if the p-value was > 0.05 . Statistical analyses were performed using Pearson's correlation for data with a normal distribution. The Spearman rank correlation method was used to assess the association of increased plasma osmolarity level and NIHSS scores ($p < 0.05$).

Ethical clearance

Ethical clearance was obtained from The Ethics Committee of Pelita Harapan University with ethical review number: 041VK-LKJ/ETI/2021.

Results

A total of 73 subjects were included in this study, with a predominance of males (57.53%). Most

patients were aged between 51 and 60 years old (34.25%, $n = 25$). Most of the patients had a history of hypertension (83.56%), followed by dyslipidemia (52.05%), DM (32.88%), and heart disease (12.33%). The mean plasma osmolarity level of this patient cohort was 296.67 ± 7.80 mOsm/L, while the mean NIHSS score was 7.47 ± 4.68 (Table 1).

Table 1: Baseline characteristics of subjects (n = 73)

Characteristics	Frequency (%)
Gender	
Male	42 (57.53)
Female	31 (42.47)
Age, n (%)	
41–50 years old	18 (24.66)
51–60 years old	25 (34.25)
61–70 years old	20 (27.40)
71–80 years old	10 (13.70)
Occupation, n (%)	
Working	38 (52.05)
Not working	35 (47.95)
Smoking, n (%)	
Yes	39 (53.42)
No	34 (46.58)
Medical history, n (%)	
Hypertension	61 (83.56)
Dyslipidemia	38 (52.05)
Diabetes mellitus	24 (32.88)
Heart diseases	9 (12.33)
Mean NIHSS score (SD)	7.47 (\pm 4.68)
Mean plasma osmolarity (mOsm/L) (SD)	296.67 (\pm 7.80)

SD: Standard deviation.

The Pearson's correlation test revealed a moderately significant positive correlation between plasma osmolarity level and NIHSS score, with a positive tendency ($p = 0.004$, $r = 0.309$). These results suggest that elevated plasma osmolarity is significantly associated with worse clinical symptoms of ischemic stroke patient which is showed by an increase in the NIHSS score.

Table 2: Analysis of risk factors to NIHSS score in patients with normal and elevated plasma osmolarity

Variable	Mean NIHSS score \pm SD	Minimum - Maximum	p-value
NIHSS score (n=73)			
Normal plasma osmolarity	6.03 \pm 3.72	0–12	
Elevated plasma osmolarity	8.52 \pm 5.01	2–29	0.023*
Male (n=42)			
Normal plasma osmolarity	5.16 \pm 3.27	0–11	
Elevated plasma osmolarity	10.00 \pm 5.47	3–29	0.002*
Female (n=31)			
Normal plasma osmolarity	7.42 \pm 4.10	0–12	
Elevated plasma osmolarity	6.74 \pm 3.96	2–14	0.653
Smoking (n=39)			
Normal plasma osmolarity	8.54 \pm 2.93	4–12	
Elevated plasma osmolarity	10.35 \pm 5.18	2–29	0.252
Not smoking (n=34)			
Normal plasma osmolarity	4.35 \pm 3.22	0–10	
Elevated plasma osmolarity	5.35 \pm 3.22	2–12	0.372
Diabetes mellitus (n=24)			
Normal plasma osmolarity	6.36 \pm 2.80	3–8	
Elevated plasma osmolarity	9.08 \pm 4.56	3–16	0.100
Non-diabetes mellitus (n=49)			
Normal plasma osmolarity	6.05 \pm 4.21	0–12	
Elevated plasma osmolarity	8.07 \pm 5.36	2–29	0.172
Hypertension (n=61)			
Normal plasma osmolarity	6.27 \pm 3.37	0–12	
Elevated plasma osmolarity	8.44 \pm 5.25	2–29	0.087
Non-hypertension (n=12)			
Normal plasma osmolarity	5.88 \pm 4.76	0–12	
Elevated plasma osmolarity	7.75 \pm 3.86	4–12	0.513
Dyslipidemia (n=38)			
Normal plasma osmolarity	7.69 \pm 3.56	3–12	
Elevated plasma osmolarity	10.96 \pm 5.06	2–29	0.028*
Non-dyslipidemia (n=35)			
Normal plasma osmolarity	5.00 \pm 3.45	0–12	
Elevated plasma osmolarity	4.78 \pm 2.13	2–9	0.820
Heart diseases (n=9)			
Normal plasma osmolarity	7.50 \pm 0.70	3–12	
Elevated plasma osmolarity	7.83 \pm 5.08	2–29	0.728
Non-heart diseases (n=64)			
Normal plasma osmolarity	6.07 \pm 3.82	0–12	
Elevated plasma osmolarity	8.35 \pm 5.17	2–9	0.063

The risk factors of stroke, such as sex, hypertension, DM, dyslipidemia, and heart disease, were all considered confounding factors. From the bivariate analysis, there was a significant difference in the NIHSS scores among subjects with dyslipidemia and increased plasma osmolarity levels compared to those with normal plasma osmolarity levels (10.96 ± 5.06 vs. 7.69 ± 3.56 , $p = 0.028$) (Table 2). A significant difference in the NIHSS score was also observed among male subjects with increased plasma osmolarity levels compared to males with normal plasma osmolarity levels (10.00 ± 5.47 vs. 5.16 ± 3.27 ; $p = 0.002$). The plasma osmolarity levels of other confounding factors such as smoking, hypertension, diabetes mellitus, and heart disease were not significantly associated with the NIHSS score.

Discussion

Our study reported a moderately significant positive association between elevated plasma osmolarity levels and increased NIHSS scores in patients with acute ischemic stroke which is confirmed from Pearson's correlation test ($p = 0.004$, $r = 0.309$). This finding signifies that increased plasma osmolarity corresponds with worse clinical symptoms of ischemic stroke. Subsequently, a study by Riana *et al.* reported similar findings and stated a significant and moderate positive correlation between plasma osmolarity levels and clinical outcomes in acute stroke patients measured using the NIHSS score ($r = 0.304$, $p = 0.011$) [10]. Another study by Brahmana also reported a significant and moderate relationship between plasma osmolarity and the NIHSS score ($p = 0.0001$, $r = 0.564$) [11].

An increase in plasma osmolarity is often found in patients who suffer from acute stroke [12], [13]. Several theories have been proposed to explain the high occurrence of elevated plasma osmolarity levels in acute stroke patients and the changes that occur in the body [14], [15], [16]. The first condition is dehydration, which is common in acute ischemic stroke, especially in elderly patients. A study by Rowat *et al.* found that 62% of all patients with acute stroke were dehydrated [17]. This dehydration is a result of decreased water intake caused by impaired consciousness and debilitated swallowing function (dysphagia), a complication of stroke. In addition, imbalance of electrolytes due to syndrome of inappropriate antidiuretic hormone (SIADH) can also cause disturbances in osmolarity component balance, which ultimately increases osmolarity levels [16], [17], [18], [19], [20]. Dehydration has been known to cause increased blood viscosity. Depending on at what rate it is measured, blood viscosity may be further divided into systolic blood viscosity which is measured at high shear rate and diastolic blood viscosity (DBV) which is measured

at low shear rate. An elevated DBV in particular, can aggravate blood flow disturbance which is important to limit further tissue damage in ischemic stroke. It is also hypothesized that an elevated DBV may trigger novel acute lacunar infarct through endothelial remodeling and luminal occlusion in small vessels. Moreover, a study by Chang *et al.* reported that increased blood viscosity from dehydration also directly has a negative impact on development of collaterals in stroke patients particularly in patients with middle cerebral artery occlusion. Dehydration may cause decreased cerebral blood volume, blood velocity and intravascular volume thus resulting in a lower pressure gradient and ability to stimulate collateral recruitment which is pivotal to maintain perfusion in penumbral region to limit further injury in stroke [21], [22].

This study found a wide variation in the patients' NIHSS score, which may be due to age differences, location of the lesion, or other confounding risk factors. For example, several studies have found that lesions around the hypothalamus can specifically affect changes in osmolarity by over-secretion of the hormone vasopressin. Vasopressin can affect the hydro-mineral balance in cell membranes and the blood-brain barrier, which may cause brain edema. Increased vasopressin levels trigger an increase in the luminal activity of Na⁺/H⁺ exchange (NHE) receptors 1 and 2, the amount of NHE1 (Na⁺/H⁺ exchange receptors 1), and the action of Na⁺/K⁺/2Cl⁻ water co-transport [19], [20]. Fluid balance is quite difficult to manage, especially in elderly patients, as some symptoms and indications of dehydration are sometimes unclear and challenging to monitor. This condition can be exacerbated by several other disturbances, such as cortical dysfunction, which may lead to decreased thirst perception [23].

High plasma osmolarity levels are also associated with poor clinical outcomes of stroke because an increase in hematocrit levels can induce the release of erythrocyte-derived adenosine diphosphate (ADP), which worsens vascular occlusion [24], [25]. Furthermore, increased hematocrit levels may also harm endothelial cells due to the propagation of several mechanisms, such as lipid peroxidation, oxidative stress, and thrombin formation [25], [26]. These adverse effects can increase stroke severity, which is characterized by elevated NIHSS scores. Increased plasma osmolarity is also considered an inflammatory stimulus as it is accompanied by an increase in inflammatory cytokines such as tumor necrosis factor, interleukin-1 β , 6, and 8 (IL-1 β , IL-6, and IL-8), which are considered highly potent in precipitating the worsening of ischemic stroke [27]. A study by Dmitreva *et al.* reported that even an acute slight increase in sodium (from 135 to 145–150 mmol/L) in the presence of aldosterone stiffens endothelial cells and impairs nitric oxide release, thus increasing the risk of thrombotic event incidence [28]. This finding suggests that an increase in plasma osmolarity may exacerbate thrombotic event incidence, particularly in locations exposed to high shear stress, such as

curvatures, ostia, and bifurcations. Furthermore, chronic elevation of plasma sodium levels may further damage the endothelium of the microvasculature due to the inflammatory effect of sodium.

The plasma osmolarity level, which is associated with a patient's hydration status, was also found to influence the occurrence of early neurological deterioration (END) in stroke through various mechanisms depending on the severity of the stroke. In mild stroke, END occurs by extension of ischemia to the initially asymptomatic (penumbra) cluster of neurons surrounding the core ischemic tissue. In severe stroke, this clinical deterioration is likely to occur through vasogenic edema and hemorrhagic transformation. The increase in osmolarity ultimately worsens the ischemic process in stroke by increasing blood viscosity and decreasing blood pressure, resulting in decreased perfusion to the brain tissue. Impaired brain perfusion worsens the clinical condition of stroke patients and is further exacerbated by various complications, such as seizures or death [29], [30].

Conclusions

Our study demonstrates that elevated plasma osmolarity levels were significantly associated with an increase in the NIHSS scores of patients with acute ischemic stroke, which signifies a worse clinical condition. In the acute phase, the hydration status of patients with ischemic stroke should become an essential variable for the comprehensive management of stroke to ensure a better clinical outcome. Our study had several limitations. The cross-sectional nature of our study limited the evaluation of trends or changes in the initial NIHSS score at admission and the NIHSS score at discharge. Several confounding factors that were not excluded, such as history of hypertension, DM, dyslipidemia, heart disease, and smoking behavior, might also have affected the results. We would suggest further research with bigger sample size and multiple point of entry for both NIHSS and osmolarity level.

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