

Hypoxia Inducible Factor 1- α in Acute Ischemic Stroke: Good Predictor for Clinical Outcome

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Abstract

Background. Stroke is the third leading causes of death and can cause severe disability. Ischemic stroke has a higher prevalence compared to hemorrhage stroke. Hypoxia-inducible factor-1 α (HIF-1 α) is a transcription factor which maintains cellular homeostasis in response to hypoxia. It can trigger apoptosis while stimulating angiogenesis process and decrease neurological deficit after an ischemic stroke. However, this protein complex has not been widely investigated. Objective. Here, we examined the potential of HIF-1 α as a marker for neuroplasticity process after ischemic stroke. Methods. Serum HIF-1 α were measured in acute ischemic stroke patients. National Institute of Health Stroke Scale (NIHSS) were assessed on the admission and discharge day (between days 7 and 14). To classify the ischemic stroke, we used (Trial of Org 10172 in Acute Stroke Treatment) TOAST criteria. Statistical significances were calculated with Spearman rank test. Results. A total of 58 patients, 31 with large artery atherosclerosis LVD and 27 with small vessel disease (SVD) were included in this study. HIF-1 α level in LVD group was (mean \pm SD) 0.5225 \pm 0.2459 mg/L and in SVD group was 0.3815 \pm 0.121 mg/L. HIF-1 α was higher ($p = 0.004$) in LVD group than in SVD group. The initial NIHSS score in LVD group was (mean \pm SD) 15.46 \pm 2.61 and discharge NIHSS score was 13.31 \pm 3.449. Initial NIHSS score in SVD group was 6.07 \pm 1.82 and the discharge NIHSS was 5.703 \pm 1.7055. In LVD group, HIF-1 α was correlated significantly with initial NIHSS ($p = 0.0000$) and discharge NIHSS ($p = 0.0000$, $r = 0.93$). This was also the case for SVD. We found a significant correlation between the level of HIF-1 α with initial NIHSS ($p = 0.0000$) and discharge NIHSS ($p = 0.0383$) in SVD group ($r = 0.94$). Conclusion. HIF-1 α has a strong correlation with NIHSS and it may be used as the predictor of acute ischemic stroke outcome.

Introduction

Stroke is the third leading causes of mortality and severe disability worldwide. Ischemic stroke is responsible for around eighty percent of strokes. It occurs as the arteries narrow or become blocked, leading to severe reduction in the blood flow or ischemia. It is a medical emergency and timely management is crucial to minimize neuronal damage and potential complications.^{1,2} Following a hypoxic condition, brain responses it by initiating gene expressions that function in preconditioning hypoxia. One of the transcription factors involved is the Hypoxia-inducible factor-1 α (HIF-1 α).^{3,4,5}

HIF-1 α is a transcription activator that plays an integral role to maintain homeostasis after a hypoxic insult. A disproportion in the supply and oxygen demand in cerebral tissue promotes a sequence of biochemical and molecular events that leads in neuron cell death. In response to such a detrimental situation, the tissue adopt several cellular mechanisms. One of recently studied mechanism is the induction of HIF-1 α .^{4,6,7,11} It is a transcriptional regulator of oxygen stability and a main stimulator of adaptive response by upregulating several target genes which are important in erythropoiesis, angiogenesis, glucose transport and metabolism.^{7,8,9,13} However, studies also suggested the role HIF-1 α in the apoptotic cascade by stimulating pro-apoptotic molecules namely Nix, IL 20 and Bnip30 which results in mitochondrial dysfunction and leads to neuronal cell death.^{7,12,13} Therefore, deeper understanding regarding the role of HIF-1 α , specifically in ischemic stroke, is required to improve recovery

and brain repair process after stroke. To date, studies regarding the relationship of HIF-1 α and ischemic stroke were all conducted in animal model. To our knowledge, our study was the first study to determine the association between HIF-1 α , the severity of stroke ischemia, and its outcome in human.

Methods

This was a cross-sectional study on acute ischemic stroke patients which was confirmed by non-contrast brain computerized tomography (CT) less than 24 hours onset and we collected HIF-1 α level from blood serum on admission. We assessed the neurological deficit using the National Institute of Health Stroke Scale (NIHSS) in the admission and discharge day (between days 7 and 14). Ischemic stroke classification were established using Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. We classified acute ischemic stroke patients into two groups according to TOAST stroke classification: large vessel disease (large atherosclerosis and cardioembolic stroke) or LVD and small vessel disease (lacunar stroke) or SVD. We excluded patients with chronic renal failure, acute myocardial infarction, severe respiratory failure, severe anemia, dementia, acute limb ischemia and history of brain injury. To determine statistical significances, Spearman rank test were performed. P value (p) below 0.001 is considered significant. R coefficient was calculated to establish the correlation.

Results

A total of 58 patients (31 with LVD and 27 with SVD) were eligible in this study. The mean age of our subjects were (mean \pm SD) 59.52 \pm 11.52 years. We collected laboratory data such as blood glucose, uric acid, renal and lipid profile (table 1).

HIF-1 α level in LVD group was (mean \pm SD) 0.5225 \pm 0.2459 mg/L and SVD group was 0.3815 \pm 0.121 mg/L. The level of HIF-1 α was significantly higher (p = 0.004) in the LVD group than in the SVD group (table 2 and figure 1).

LVD or SVD type were found to correspond with the size of ischemic lesions identified from our non-contrast brain CT results (supplementary data). Wide ischemic changes were found in the LVD group. The initial NIHSS score in LVD group was (mean \pm SD) 15.46 \pm 2.61 and discharge NIHSS score was 13.31 \pm 3.449. Initial NIHSS score in SVD group was 6.07 \pm 1.82 and the discharge NIHSS was 5.703 \pm 1.7055 (table 3).

In the LVD group, the level of HIF-1 α was significantly correlated with initial NIHSS (p = 0.0000) and discharge NIHSS (p = 0.0000). In the SVD group we identified a similar result, the level of HIF-1 α significantly correlated with initial NIHSS (p = 0.0000) and discharge NIHSS (p = 0.0383).

Table 4 showed the correlation between HIF-1 α level and NIHSS in both groups. Here, we identified a strong correlation between the two variables in both groups.

Discussion

Our study include 58 acute ischemic stroke subjects who were divided into LVD and SVD groups according to TOAST criteria. For the first time in human study, we identified an association between HIF-1 α level and the subtypes of ischemic stroke. The level of HIF-1 α (table 2 and figure 1) was significantly higher in the LVD group than in the SVD group ($p = 0.004$). This result was similar with previous studies conducted in animal model of cerebral ischemia.³

In addition, from our non-contrast brain CT results, we identified a relation between the groups with the size of ischemic lesions (supplementary data). Wide ischemic changes were found in the LVD group. This finding showed the extent of neuronal brain damage after ischemic stroke.

This result was in accordance to previous studies which suggest that a wide brain damage is associated with an increase of HIF-1 α production. The production of HIF-1 α is initiated in the preconditioning-hypoxia sequence induced by neuronal damage.^{7,8,9,11,12,13}

A wide brain damage also correlates with worsening of neurological deficit in acute ischemic stroke patients.⁴ In this study we found that the initial NIHSS score in the LVD group was 15.46 ± 2.61 and discharge NIHSS score was 13.31 ± 3.449 . Initial NIHSS score in SVD group was 6.07 ± 1.82 and the discharge NIHSS was 5.703 ± 1.7055 (table 3).

In this study, we established an association between HIF-1 α and NIHSS (table 4). There were strong correlations between HIF-1 α and on admission and discharge NIHSS in both groups. In previous studies in mice and rats, HIF-1 α was activated in a biphasic manner lasting up to ten days after a hypoxic stimulation³, stimulates pro-angiogenic factors⁴, promototes neuronal viability⁷, and ameliorates brain injury¹³. We examined the HIF-1 α level only on admission but as it correlated significantly with the NIHSS, we may suggest that its level would reduce on discharge day and is associated with the improvement of clinical outcome, as occurs in mice model. Future study examining serial HIF-1 α level needs to be performed to prove this hypothesis.

From this study we conclude that HIF-1 α may be used to predict the clinical outcome in acute ischemic stroke patients. Further study to established its precise predictive value needs to be conducted.

In addition, drug and molecule which activate HIF-1 α *in vitro* and *in vivo* was proved to own a neuroprotective effect in mice cerebral ischemia model.^{3,8,9} Therefore the long run, development of molecule regulator for HIF-1 α stability and signalling in human is needed to produce a therapeutic option which enhance recovery and repair after ischemic stroke.

Conclusion

HIF-1 α level was associated with severity of ischemic lesion, large vessel disease had a higher level of HIF-1 α compared with small vessel disease. HIF-1 α had a strong correlation with NIHSS, both on admission and patients' discharge. From our findings, we can conclude that HIF-1 α may be a good predictor for a better clinical outcome in acute ischemic stroke patients.

List Of Abbreviation

HIF 1- α : Hypoxia Inducible Factor-1 alfa; NIHSS: National Institute of Health Stroke Scale; SVD: Small Vessel Disease; LVD: Large Vessel Disease; CT: Computed Tomography; TOAST: Trial of Org 10172 in Acute Stroke Treatment; IL-20: Interleukin 20; Bnip 30: Bcl-²/E1B-19K-interacting protein 30

Declaration

Ethical approval of this study were obtained from Research Ethic Committee of Hasan Sadikin Hospital Bandung. All data or analysis during this study are provided by the corresponding author in this article supplementary files.

Competing Interest

There is no competing interest.

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Ethical Clearance

This research was granted approval by the ethical committee Dr. Hasan Sadikin Hospital Bandung, Indonesia (LB.04.01/A05/EC/069/II/2016).

Consent to Participate

Consent to participate was obtained from all participants. A consent form was written and signed by each participant. The ethics committee has approved this procedure.

Consent for Publication

This publication is one of the requirements to pursue doctoral title from Faculty of Medicine, University of Padjadjaran Bandung, Indonesia.

Availability of Data and Material

The full data are showed in supplementary material.

Authors' Contribution

Lisda Amalia : Preparation, collecting, analysis, making of manuscript, submission for publication

Yeremia Tatang : Preparation, collecting, analysis

Henny A. Sadeli : Analysis

Ida Parwati : Analysis

Ahmad Rizal : Analysis

Ramdan Panigoro : Analysis

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Tables

Table 1. Demographic and laboratory data

No	Variable	Mean	SD	Min	Max
Demographic					
1	Age	59.53	11.52	31	91
Risk factor					
2	Cholesterol	200.65	45.07	83	299
3	Triglyceride	123.15	60.13	49	366
4	HDL	46.63	16.99	17	99
5	LDL	141.09	38.36	60	224
6	Random Blood Glucose	141.17	60.02	77	363
7	Ureum	37.52	31.16	13	267
8	Kreatinin	0.93	0.32	0.38	2.4
9	Uric acid	6.23	2.13	2.1	12.4
10	HbA1C	7.61	2.58	4.5	13.3

Table 2. HIF-1 α level in LVD and SVD groups

HIF-1 α	Mean	SD	Min	Max	p
Large vessel disease	0.5225	0.2459	0.1	1.4	0.004
Small vessel disease	0.3815	0.121	0.1	0.6	

NIHSS	Mean	SD	Min	Max
Large vessel disease				
On admission	16.06	2.67	11	21
On discharge	15.13	3.15	6	20
Small vessel disease				
On admission	6.07	1.82	4	9
On discharge	5.73	1.71	4	9

Table 3. NIHSS During Admission and Discharge Time Points

NIHSS	Mean	SD	Min	Max
Large vessel disease				
On admission	16.06	2.67	11	21
On discharge	15.13	3.15	6	20
Small vessel disease				
On admission	6.07	1.82	4	9
On discharge	5.73	1.71	4	9

Table 4. Correlation of HIF-1 α level and NIHSS

HIF-1 α	NIHSS on admission	NIHSS on discharge	P	r
	(mean \pm SD)	(mean \pm SD)		
Large Vessel Disease	16.06 \pm 2.67	15.13 \pm 3.16	0.000	0.9299
Small Vessel Disease	6.07 \pm 1.82	5.7 \pm 1.7	0.00000	0.9394

Figures

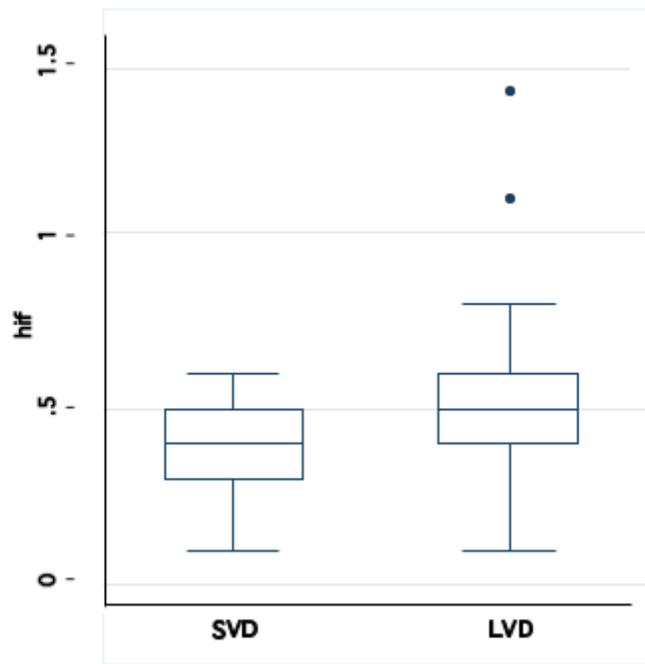


Figure 1

HIF-1 α level in SVD and LVD groups