Comparison of Clinical Severity Improvement Degree between Acute Thrombotic Stroke Patients with Low and High Matrix Metalloproteinase-9 Levels

Muhamad Hamdan[1], Hendro Susilo, Paulus Sugianto[1], A. Firdaus Sami[1], Mohammad Saiful Ardhi[1], Sita Setyowatie[1]

[1]Department of Neurology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital Surabaya, 60285 Indonesia

Abstract

Background: Stroke is a cause of disability and dependency in both humanity and economic. Studies on the association of Matrix metallopeptidase 9 (MMP-9) levels with improved clinical severity are currently limited.

Objectives: To determine the improvement of clinical severity in acute thrombotic stroke patients with high and low MMP-9 levels.

Methods: Patients acute thrombotic stroke were grouped into low and high MMP-9 levels. MMP-9 levels were considered low when <840 ng/mL and high when ≥840 ng/mL. Clinical severity improvement was assessed using the ΔNIHSS scale.

Results: Eighty subjects were enrolled that consists of clinical severity improved patients with lower MMP-9 (37.9%) that higher than high MMP-9 (21.6%). This difference was not statistically significant (p = 0.115).

Conclusion: There was no difference in clinical severity improvement in patients with acute thrombotic stroke with low MMP-9 levels in blood serum compared to high MMP-9 levels.

***Keywords**: Acute thrombotic stroke, MMP-9, NIHSS Level*

Introduction

Stroke is the main cause of death and disabilities in Indonesia and the world [1]. Stroke has enormous clinical, social, and economic implications and demands a significant effort [2]. The average mortality in 30 days for stroke is about 7.6%. There are currently four million people in the United States living with physical limitations due to stroke and about 15-30% of them suffer from the permanent disability. In 1990 the death rate caused by the stroke was 4.5 million worldwide [3].

Corresponding Author:
Muhamad Hamdan
Department of Neurology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital Surabaya, 60285 Indonesia
E-mail: muhamadhamdanppjpi@gmail.com

Elderly with hypertension have a greater risk for ischemic stroke [4]. The number of stroke patients will increase every year, it is estimated that the number of stroke patients will increase to 7.7 million by 2020. Todays, strokes not only affect the elderly population but also young adults and productive. Stroke could cause disability and dependency in both human and economic, impaired cognition and death function. Stroke survivors who could survive up to 30 days after the attack were about 20% and it requires further treatment. The cost of stroke treatment during acute phase treatment to long-term care in the United States is approximately US $ 51.2 billion every year [3,5–7]. Several studies have demonstrated an inflammatory process that involved in the pathogenesis of stroke. Brain blood flow that stops could cause death in nerve cells that trigger an immune response that causes inflammation, cell activation, and infiltration.

Once activated, inflammatory cells release various cytotoxic agents including the Metalloproteinase Matrix (MMP) which, if in the active state it could cause further cell damage and disturbances in the blood-brain barrier. Among some MMP, MMP-9 has a more dominant role in stroke [8].

MMP levels in circulating plasma could be used as a marker of stroke in predicting bleeding in embolic stroke, predicting clinical outcomes and the magnitude of infarct volume. The elevated MMP-9 levels after the occurrence of brain ischemia in the plasma were positively correlated with the severity of stroke as measured by the National Institutes of Health Stroke Scale (NIHSS) scores [9]. However, until now there has been no study in Indonesia that observed the correlation between the magnitude of clinical severity improvement with low and high MMP-9 levels in patients with acute thrombotic stroke. Then, if this study proves the existence of such linkage, then the MMP-9 examination could be used as an alternative examination that helps explain the prognosis of healing stroke thrombotic acute in patients.

Method

An observational analytic study using case-control design was used, which was implemented in January to August 2015 in Seruni room, in Emergency Unit, Seruni A, Seruni B of Dr. Soetomo General Hospital Surabaya. The samples used in this study were those with acute thrombotic stroke as well as meeting the inclusion and exclusion criteria. Sampling technique used was consecutive sampling.

The inclusion criteria were; Patients with acute thrombotic stroke with onset of attack between 24 to 72 hours, age over 18 years, willing to participated the research (signed informed consent). Patients with acute thrombotic stroke who have sepsis, liver disorder or renal failure were exclude from study. The independent variables were MMP-9 in serum and the dependent variables were Clinical severity measured by NIHSS, while confounding variables were Smoking, hyperglycemia and hypertension.

This study used venous blood research material from patients with acute thrombotic stroke that needed to determine the MMP-9 level in serum. The research started by taking data of all subjects included in the inclusion and exclusion criteria and the responsible family of the patient (spouse, child, parent, close relative or another family part) briefed on the purpose, usefulness, and risk of the study, then the subject was requested to follow the research without coercion.

Preliminary data were obtained by taking anamnesis, physical examination and neurology, examination of MMP-9 level in *prodia* laboratory Surabaya, examination of clinical severity degree were assessed 2x, at the same time with blood taking for MMP-9 (onset 24 to 72 hours) examination and at day 5 onset by using the NIHSS method. All recording results are collected for further data tabulation and statistical analysis then, the collected categorical data were analyzed by using odd ratio test. This research have been proposed of ethical clearance in the Research Ethics Committee of Dr. Soetomo General Hospital.

Results

Basic data

The means age in the group with the improvement of clinical severity was 51.23 ± 10.708 years and with no improvement was 57.02 ± 10.838 years. The mean age difference in both groups was not statistically significant with p = 0.35 (Table 1).

In the group with clinical severity correlation, the male subject was 10 (24.4%), it smaller than the female gender subject by 12 (30.8%). This difference was not statistically significant with p = 0.523 (Table 1).

Improvement of the severity in subjects group with normotension was 9 (64.3%), it bigger in a group of subjects with hypertension by 13 (19.7%). This was statistically differenced with p = 0.001 (Table 1).

Improvement of clinical severity in group of subjects with normoglycemia was obtained by 14 (32.6%) subject, it higher than in the subjects group with hyperglycemia by 8 (21.6%). This difference was not statistically significant with p = 0.275 (Table 1).

The improvement of clinical severity in the non-smoking subjects group was 17 (29.8%), it higher than in the subjects who smoked as 5 (21.7%) was found. The differences in both groups were not statistically significant with p = 0.464 (Table 2).

The improvement of clinical severity in the subjects group with low MMP-9 levels was 11 (37.9%) subject,

it higher than in the subjects group with high MMP-9 levels by 11 (21.6%). The differences in both groups were not statistically significant with p = 0.115. It also obtained the odds ratio by 2.222 (CI 95% 0.814-6.064) with the β error was 38% (Table 3).

Table 1. Basic Characteristics of Subject

	Δ NIHSS			
	Improved n = 22	**Constantly n = 58**	**Total n = 80**	**P**
Age (years old)	51.23±10.708	57.02±10.838		0.35
Sex				0.523
Male	10 (24.4.0%)	31 (75.6%)	41	
Female	12 (30.8%)	27 (69.2%)	38	
Blood pressure				
Normotension	9 (64.3%)	5 (35.7%)	14	
Hypertension	13(19.7%)	53(80.3%)	66	
Random Blood Sugar				
Normoglycemia	14 (32.6%)	29 (67.4%)	43	
Hyperglycemia	8 (21.6%)	29 (78.4%)	37	
Smoking Status				
Un-smoking			57	
Smoking			23	

Table 2. Comparison of Smoking and Clinical Severity Improvement (ΔNIHSS)

	ΔNIHSS		**Total**	**p**	**RO (CI 95%)**
	Improved n = 22	**Constantly n = 58**			
Smoking status					
Un-smoking Smoking	17 (29.8%) 5 (70.2%)	40 (70.2%) 18 (29.8%)	57 23	0.464	1.530 (0.488-4.793)

Table 3. Comparison of MMP-9 Levels by Clinical Severity Improvement (ΔNIHSS)

MMP-9	**ΔNIHSS**		**Total**	**P**	**RO (CI 95%)**
	Improved n = 22	**Constantly n = 58**			
Low-MMP-9 High-MMP-9	11 (37.9%) 11 (21.6%)	18 (62.1%) 40 (78.4%)	29 (100%) 51 (100%)	0.115	2.222 (0.814-6.064)

Discussion

The mean age in the group with the improvement of clinical severity was 51.23 ± 10.708 years and in the group of no improvement was 57.02 ± 10.838 years. In accordance with literature that the highest incidence of ischemic stroke was at the age of 20-54 years and tended to decrease in the older age group [10]. The incidence of stroke every 10,000 population increased from 22% (age group 45-55 years) to 32% (age group 55-64 years) and 83% (age group 65-74 years) [11]. The difference between each group was not significant (p = 0.35).

The sex ratio of the men subjects was 41, it higher than women by 39. It was in accordance with epidemiological studies that men have a higher risk of stroke than women, especially in the age group less than 65 years [10–12]. Murphy et al also revealed that the incidence of stroke in men was 1.25 times higher than for women [13]. Several studies have also reported that men were more likely to suffer a stroke caused by a disruption of large or small blood vessels [6,14]. In this study, there was no difference in sex proportion between the two groups (p = 0.523).

Hypertension is a major risk factor for stroke and an increase in blood pressure often occurs in acute stroke. 50% of thrombotic stroke patients have hypertensive risk factors [15]. The response of acute hypertension is an increase in blood pressure above normal and usually occurs within the first 24 hours in stroke patients #16. Increased blood pressure reaches 75-80% in acute stroke patients and will decrease spontaneously within a few days [16]. Increased blood pressure in the acute phase of thrombotic stroke will provide severe output. Studies conducted on experimental animals with acute thrombotic stroke showed that autoregulation of cerebral blood flow in the penumbral area was impaired. Increased blood pressure is a natural response to increased perfusion and collateral blood flow in the penumbra to prevent ischemic damage.

Based on the analysis of clinical data obtained a significant result (p = 0.001). This was in accordance with research conducted by Kvistad CE et al. that there was a correlation between increased blood pressure and stroke severity when the patient was admitted to the hospital [17]. A study conducted by Ishitsuka K et al., against 1874 patients with acute thrombotic stroke performed blood pressure measurement in 24 hours onset of stroke, it has resulted in a correlation between hypertension with poor outcome and hypertension with the minor improvement of clinical severity [18].

IST (International Stroke Trial) conducted by Leonardi et al. performed randomly in 17,398 patients with thrombotic stroke that showed a correlation between systolic blood pressure at the onset of acute stroke with death and disability in U-shaped (U-shape relationship) [19,20]. American Diabetes Association and Clinical Endocrinological Consensus The American correlation define hyperglycemia in patients undergoing hospitalization as hyperglycemia stress in which blood glucose levels> 140 mg/dL without the prior history of diabetes. Patients with hyperglycemia stress were often found in acute thrombotic stroke because in the acute phase there was the release of cortisol and norepinephrine which will manifest the decrease in insulin (Lindesberg PJ, et al., 2004). Stress hyperglycemia might improve if the acute phase of a stroke was passed and 60% of hyperglycemia sufferers might become diabetic within a year (Farrokhi F, et al., 2011).

When comparing between normoglycemia and the improvement of clinical severity in this study, the results were not significant (p = 0.275). Not much research data suggests that lowering blood sugar levels could improve the outcome (Harm H et al., 2010). The largest study was a decrease in blood glucose levels with potassium-glucose-infusion infusion compared to standard saline infusion that showed no improvement in output and decreased mortality in patients (Harm H et al., 2010).

Based on cohort studies conducted by Ueshima H et al, there were several things that could increase the risk of stroke and the occurrence of intracranial also extracranial atherosclerosis, including the number of cigarettes smoked in one-day, how long a person smokes (in years) and current smoking conditions (Ueshima H, et al., 2004).

In this study, when comparing the non-smoking history and clinical severity improvement (ΔNIHSS), the results were not significant (0.464). This was in accordance with research conducted by Altafi D et al. that compared clinical outcomes (NIHSS) of thrombotic stroke smokers and non-smoking thrombotic stroke patients who resulted in a lack of correlation between thrombotic and non-smoking thrombotic stroke patients with clinical outcomes (Altafi D, et al., 2013).

MMP-9 is a zinc-dependent proteolytic enzyme that significantly increases its cadmium in patients with thrombotic stroke (Castellanos M, et al., 2003). Based on a study conducted by Lisovaya OA it was found that elevated MMP-9 levels were not only correlated with an increase in cardiovascular incidence but were also associated with long-term vascular remodeling phenomena (Lisovaya OA, 2014).

The final result showed that the improvement of clinical severity in subjects with low MMP-9 level was 37.9% higher than in the subjects group with the high MMP-9 level by 21.6%. The differences in both groups were not statistically significant with p = 0.115 and the odds ratio value was 2.222 (CI 95% 0.814-6.064). This was not in accordance with the proposed research hypothesis. Inappropriateness with the proposed research hypothesis could be due to several things.

First, this study did not consider the infarct volume into the subject. Montaner J et al., Conducted a study of 39 thrombotic stroke patients evaluated at onset of stroke, 12, 24, and 48 hours of onset, and found that MMP-9 values had a positive correlation with NIHSS and infarct volume also revealed that MMP-9 was a strong predictor in predicting infarct volume [9]. Ning et al., Through a study conducted on 52 thrombotic stroke patients, explained that MMP-9 has a correlation with infarct volume and clinical severity [21].

Second, in this study did not distinguish the location of the infarction that could affect the output of stroke in the study subjects. Montaner et al., Explains that there was a correlation between MMP-9 and the location of the infarct [9], it was similar to a study conducted by Lucivero et al., In 29 thrombotic stroke patients, explained that high MMP-9 levels had a correlation with partial anterior cerebral infarct compared to cerebral infarct lacunar [22].

Third, MMP-9 might be affected by the stiffness of arterial blood vessels. Arterial vascular stiffness could have an effect on hemodynamic disorders that trigger blood vessel remodeling and increase cardiovascular risk. Yasmin et al., Conducted a study of 116 patients with hypertension by measuring pulse wave velocity (PWV) in the aorta and brachial also measured MMP-9 levels and serum elastase activity (SEA) levels. From a study by Yasmin et al., Stated that arterial vascular stiffness was significantly correlated with MMP-9 levels (Yasmin et al., 2005).

Conclusion

There was no difference in clinical severity correlation in patients with acute thrombotic stroke with low MMP-9 levels in blood serum compared to the patients with acute thrombotic stroke with high MMP-9 levels in blood serum.

Conflict of Interest : There is no conflict of interest

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Ethical Clearance : This study was approved by Ethical Commission of Health Research Faculty of Medicine University of Airlangga

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