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Malondialdehyde levels and clinical outcomes assessed by the modified Rankin scale in patients with acute intracerebral hemorrhagic stroke

Niveles de malondialdehído y resultados clínicos evaluados por la escala de Rankin modificada en pacientes con accidente cerebrovascular hemorrágico intracerebral agudo

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SUMMARY

Background: *Oxidative stress plays an important role in secondary brain injury after a stroke of intracerebral hemorrhage. This study aimed to determine the association between malondialdehyde (MDA) levels with clinical outcomes assessed using the modified Rankin Scale (mRS) in patients with acute intracerebral hemorrhagic stroke.*
Methods: *A cohort study was enrolled in patients with intracerebral hemorrhagic stroke in Dr. Soetomo General Hospital Surabaya, Indonesia. The study subjects were blood drawn for the examination of MDA levels at hospital admission, and the examination of clinical outcomes was assessed using the mRS when the patient was discharged from the hospital.*
Results: *In 34 study subjects, 23 subjects with poor mRS and 11 subjects with good mRS were obtained. The results of the study analysis showed that subjects who had MDA levels >494.95 ng/mL with poor mRS were 17 subjects (73.9 %), higher than those with good mRS, 3 subjects (27.3 %). There were not statistically significant differences between age, GCS, bleeding volume, and MDA with clinical outcomes (p>0.06). However, there was an association between MDA levels clinical outcomes with p = 0.023 and relative risk (RR) of 1.983 (95 % CI 1.054-3.732).*
Conclusion: *There was a significant association between MDA levels and clinical outcomes assessed using the mRS in patients with acute intracerebral hemorrhagic stroke.*

Keywords: *Levels of malondialdehyde, modified Rankin Scale, cardiovascular disease.*

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RESUMEN

Antecedentes: *El estrés oxidativo juega un papel importante en la lesión cerebral secundaria después de un accidente cerebrovascular de hemorragia intracerebral. Este estudio tuvo como objetivo determinar la asociación entre los niveles de malondialdehído (MDA) y los resultados clínicos evaluados mediante la escala de Rankin modificada (mRS) en pacientes con accidente cerebrovascular hemorrágico intracerebral agudo.*
Métodos: *Se realizó un estudio de cohorte en pacientes con accidente cerebrovascular hemorrágico intracerebral en el Hospital General Dr. Soetomo de Surabaya, Indonesia. A los sujetos del estudio se les extrajo sangre para el examen de los niveles de MDA en el momento de la admisión al hospital, y el examen de los resultados clínicos se evaluó mediante la mRS cuando el paciente fue dado de alta del hospital.*
Resultados: *En 34 sujetos de estudio, se obtuvieron 23 sujetos con mRS pobre y 11 sujetos con mRS buena. Los resultados del análisis del estudio mostraron que 17 sujetos (73,9 %), presentaban niveles de MDA> 494,95 ng/mL con mRS pobre, y 3 sujetos (27,3 %) más altos que aquellos con mRS buena. No hubo diferencia estadísticamente significativa entre la edad, la GCS, el volumen de sangrado y la MDA con los resultados clínicos (p> 0,06). Sin embargo, hubo una asociación entre los resultados clínicos de los niveles de MDA con p= 0,023 y el riesgo relativo (RR) de 1,983 (IC del 95 %: 1,054-3,732).*
Conclusión: *Hubo una asociación significativa entre los niveles de MDA y los resultados clínicos evaluados mediante la mRS en pacientes con accidente cerebrovascular hemorrágico intracerebral agudo.*

Palabras clave: *Niveles de malondialdehído, escala de Rankin modificada, resultados clínicos.*

INTRODUCTION

Stroke is the second leading cause of death in the world and the highest cause of disability in the world, with intracerebral hemorrhagic strokes having an incidence of 10-20 cases per 100 000 population and reaching 10-15 % of all strokes worldwide each year (1,2). Indonesian stroke registry data in 2014 reported that the number of hemorrhagic strokes was 32.9 % of all strokes in Indonesia. The highest mortality rate was recorded in hemorrhagic stroke, which was 20.3 % after 48 hours and 18.3 % in less than 48 hours. This amount is higher than the mortality rate in ischemic stroke. As many as 52 % of patients die within the first month, and only 20 % will live independently within six months (3).

Compared with the same infarction size, intracerebral hemorrhage produces more inflammation and cell death. The pathophysiological process playing a role in inflammatory damage mediated by cellular and non-cellular components (4). Oxidative stress plays an important role in secondary brain injury after intracerebral hemorrhagic stroke because it causes permanent disruption in the cortex and subcortex components followed by impaired brain-blood barrier and brain edema with massive brain cell death (5). The lysis of red blood cells on the first day after intracerebral hemorrhagic stroke will release hemoglobin converted by the enzyme heme oxygenase-1 (HO-1) into neurotoxic components, such as heme and iron, that play a role in secondary brain injury (6). Early microglial activation, the release of pro-inflammatory mediators, and the influx of peripheral leukocytes will trigger neuroinflammation after intracerebral hemorrhagic stroke releasing large amounts of reactive oxygen species (ROS), causing excessive consumption of superoxide dismutase (SOD) and lipid peroxidation (5,6). Lipid hydroperoxide is the main product of the lipid peroxidation process. The structure of lipid hydroperoxides is very unstable and can easily change into malondialdehyde (MDA), 4-hydroxy-2-nonenal (4-HNE), and several other forms of aldehyde. MDA is the main secondary product in the lipid peroxidation process because it is more mutagenic than other aldehydes (7). Currently, MDA is more often used in biomedical research as a marker of oxidative stress, especially in various clinical conditions related to the lipid peroxidation process. The chemically stable nature of MDA makes it more often used as a marker of oxidative stress compared to 4-HNE (8).

A previous study showed that MDA levels increased in patients with both acute hemorrhagic and ischemic strokes compared to healthy controls (9). Another study also stated that serum MDA levels were significantly higher in patients with intracerebral hemorrhagic stroke compared to healthy controls and in patients who did not survive compared to patients who

survived. Furthermore, serum MDA levels were associated with 30-day mortality (OR= 6.279; 95 % CI= 1.940-20.319; p= 0.002) (10).

Modified Rankin Scale (mRS) is used to assess functional limitations after stroke, including aspects of daily personal life, such as eating, toileting, bathing, walking, preparing meals, traveling, shopping and social life of work, family responsibilities, social activities, and entertainment. mRS is a global measurement tool with good reliability and validity. This study aimed to prove the association between MDA levels and clinical outcomes assessed using the mRS in patients with acute intracerebral hemorrhagic stroke.

METHODS

The study design used in this study was a cohort. This study was conducted from August 2019 to November 2019 in Dr. Soetomo General Hospital, Surabaya. The inclusion criteria were patients aged 20 years and over, patients with the first attack of acute intracerebral hemorrhagic stroke that has been done clinical examination and head CT scan without contrast, patients' onset 24-72 hours, and patients who were willing to follow the study. Meanwhile, the exclusion criteria of this study were patients with acute intracerebral hemorrhagic stroke accompanied by intraventricular or subarachnoid hemorrhage, having an infection at the time of hospital admission, diabetes mellitus, acute coronary heart disease, history of malignancy, and Parkinson's disease.

The sample size was determined by the sample size formula for the unpaired categorical analytic study, the two-way hypothesis with a type I error of 5 %, and a type II error of 20 %. The value of the proportion of effects in groups with risk factors (P1) and groups without risk factors (P2) was determined based on a previous study, and the minimum sample size was 17 people for each group so that the sample size was 34 people. If a minimum of 10 % dropout was added, the total sample size was 38 people. The sampling method was conducted according to consecutive cases (sampling on consecutive admission) until a predetermined number of samples has been reached. There were 40 study subjects. Six subjects were dropped out of the study because of an infection during hospitalization in 2 subjects and blood lysis when storing in 4 subjects so that 34 (thirty-four) study subjects were collected.

The study subjects were blood drawn for examination of malondialdehyde levels at hospital admission and examination of clinical outcomes assessed using the mRs carried out when the patient was discharged from the hospital. Statistical analysis was performed with SPSS 21. The results of the study were analyzed using Chi-Square statistical tests, and Relative Risk (RR) calculations were performed.

RESULTS

Demographic data of study subjects, including age, sex, length of education, level of education, occupation, marital status, and ethnicity, can be seen in Table 1. Demographic characteristics include sex and age.

Table 1

Demographic characteristics of subjects

Variables	N (%)	Mean±SD
Sex		
Male	20 (58.8)	
Female	14 (41.2)	
Age		57.32±12.51
>75 years old	3 (8.8)	
≤75 years old	31 (91.2)	

Clinical characteristics include hypertension, smoking, location of stroke lesions, bleeding volume, GCS, MDA levels, and mRS. The clinical characteristics of study subjects can be seen in Table 2.

Table 2

Clinical characteristics of study subjects

Variables	N (%)	Mean±SD
Hypertension		
Grade I	12 (35.3)	
Grade II	22 (64.7)	
Smoking		
Yes	8 (23.5)	
No	26 (76.5)	
Location of Stroke lesions		
Right	16 (47.1)	
Left	18 (52.9)	
Bleeding Volume		16.41±12.30
<30 cc	30 (88.2)	
≥30 cc	4 (11.8)	
GCS		
Good (13-15)	23 (67.6)	
Poor (<13)	11 (32.4)	
MDA levels		1136.50±1042.78
<494.95	14 (41.2)	
>494.95	20 (58.8)	
mRS		
Good	11 (32.4)	
Poor	23 (67.6)	

MDA: malondialdehyde; mRS: Modified Rankin Scale

The results of the analysis of the association between age, GCS, bleeding volume, and MDA with clinical outcomes can be seen in Table 3. There was no statistically significant between age, GCS, bleeding volume, and MDA with clinical outcomes (p>0.06). However, there was an association between MDA levels clinical outcomes with p= 0.023 and relative risk (RR) of 1.983 (95 % CI 1.054-3.732).

DISCUSSION

The results of the analysis of the association between MDA levels and clinical outcomes assessed using mRS showed statistically significant results. The subjects with high MDA levels >494.950 ng/mL had a 1.9 times higher risk of experiencing poor clinical outcomes of mRS compared to subjects who had low MDA levels <494.950 ng/mL. The results of this study are in accordance with a recent study showing that high MDA levels were associated with 30-day mortality with a p value=0.002 and an odds ratio value of 6.279 (95 % CI, 1.940-20.319) (10).

Table 3

The result of correlation test

Variables	mRS		Total	p
	Poor	Good		
Age				0.53
Age ≥ 75 y.o.	3 (13.0 %)	0 (0.0 %)	3	
Age < 75 y.o.	20 (87.0 %)	11 (100 %)	31	
GCS				1.000
Poor GCS (<13)	8 (34.8 %)	3 (27.3 %)	11	
Good GCS (13-15)	15 (65.2 %)	8 (72.7 %)	23	
Bleeding Volume				1.000
Volume ≥30cc	3 (13.0 %)	1 (9.1 %)	4	
Volume <30cc	20 (87.0 %)	10 (90.9 %)	30	
MDA				0.023
High MDA >494.95 ng/mL	17 (73.9 %)	3 (27.3 %)	20	
Low MDA <494.95 ng/mL	6 (26.1 %)	8 (72.7 %)	14	

MDA: malondialdehyde; mRS: Modified Rankin Scale

The basic characteristics of the study subjects include demographic characteristics and clinical data. Demographic characteristics include age and sex. Based on demographic data, most of the study subjects aged <75 years and were male. The results of the analysis for the association between confounding variables and clinical outcomes assessed using the mRS in this study showed no statistically significant differences for age, initial GCS, and bleeding volume variables.

In this study, we found that subjects who were >75 years old with poor mRS did not have a statistically significant difference when compared with subjects who were >75 years old with good mRS. This result differs from previous studies which stated that older age had poor mRS values (11). This difference in results could be due to the fact that in this study, most of the subjects had an age of <75 years. In addition, subjects who at the time of initial hospital admission had decreased consciousness with GCS <13 with poor mRS did not have a statistically significant difference when compared to subjects who at the time of initial hospital admission had decreased consciousness with GCS <13 with good mRS. These results are different from previous studies stating that subjects who entered with poor initial GCS had poor mRS outcomes (12). The difference in these results could be due to the fact that in this study, the majority of subjects at hospital admission had a good initial GCS.

In this study, subjects with bleeding volume ≥30 cc with poor mRS did not have a statistically significant difference compared to subjects with bleeding volume ≥30 cc with good mRS. These results are different from previous studies stating that bleeding volume ≥30 cc had poor mRS outcome (12). This difference in results could be caused by most subjects having a bleeding volume of <30 cc.

MDA levels increase in patients with both acute hemorrhagic and ischemic strokes compared to healthy controls (9). These findings are consistent with several previous studies that examined levels of oxidative stress using MDA and Total Antioxidant Capacity (TAC) in 24 hemorrhagic stroke patients and 24 ischemic stroke patients confirmed by head CT-Scan associated to awareness level and the National Institutes of Health Stroke Scale (NIHSS) in ischemic stroke, as well as the location and volume of the hematoma in hemorrhagic stroke. A significant positive correlation was obtained between MDA levels and bleeding volume in hemorrhagic stroke patients and a negative correlation between TAC levels and bleeding volume (13). This is different from another study that compared levels of Total Oxidant Status (TOS), Total Antioxidant Status (TAS), and MDA in patients with intracerebral hemorrhagic strokes with healthy controls. Compared to the control group, TOS, TAS, and MDA levels were significantly higher in patients with intracerebral hemorrhagic stroke. However, there was no correlation between TOS, TAS, and MDA levels with the Glasgow Coma Scale (GCS) total score and hematoma volume (14).

MDA is the main secondary product in the lipid peroxidation process often used as a marker of oxidative stress because it has a more stable chemical compound. Oxidative stress is involved not only in pathological processes but also at various important stages in the pathophysiological response during intracerebral hemorrhage, including causing brain cell death. Brain cell death will result in impairment of function and ADL that can be assessed with the mRS.

This study has advantages. This is the first study conducted in Indonesia, especially in Surabaya, focusing on the association between MDA levels and clinical outcomes assessed using the mRS in patients with acute intracerebral hemorrhagic stroke in Dr. Soetomo General Hospital, Surabaya. The limitation of this study is that this study was only conducted in one hospital and based on hospital data so that it cannot be generalized to the population. In addition, the mRS assessment was only done when the patient was discharged from the hospital regardless of the length of time of treatment.

CONCLUSION

There was a significant association between MDA levels and clinical outcomes assessed using the mRS in patients with acute intracerebral hemorrhagic stroke in Dr. Soetomo General Hospital, Surabaya.

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