

Mechanism of neurological

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Mechanism of neurological deficit improvement through analysis in cerebral artery stenosis, Endothelial Progenitor Cells (EPC), Asymmetric Dimethylarginine (ADMA), Malondialdehyde (MDA), and Superoxide Dismutase (SOD) after balloon angioplasty procedure in ischemic stroke patients

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ABSTRACT

Backgrounds: Balloon angioplasty is one of the endovascular procedures which aims to open atherosclerotic stenosis or occlusion of the cerebral blood vessels. Balloon angioplasty has been performed on ischemic stroke patients with arteriosclerotic stenosis. However, the procedure's outcomes vary, and no microcellular indicator has become a standard for balloon angioplasty.

Methods: NIHSS examination and *Digital Subtraction Angiography* (DSA) were performed on 35 ischemic stroke patients. NIHSS examination is used to determine the severity of neurological deficits. At the same time, *Digital Subtraction Angiography* (DSA) is a diagnostic procedure to determine the location and size of the stenotic lesion in the arteries. Patients underwent several laboratory biomarker analyses, including EPC, ADMA, MDA and SOD, followed by balloon angioplasty. Afterward, repeat the DSA procedure. EPC, ADMA, MDA and SOD were re-analysed seven days later and NIHSS was re-examined thirty days after balloon angioplasty.

Results: Stenosis, EPC ($p < 0.001$), MDA ($p = 0.001$), SOD ($p = 0.001$), and NIHSS ($p < 0.001$) have significant output before and after balloon angioplasty ($p < 0.001$). EPC and SOD significantly correlate with neurological deficits alteration ($p < 0.05$). EPC and SOD have a cut-off value of 50% improvement in neurological deficits. EPC and SOD significantly improve neurological deficit ($p = 0.008$ and $p < 0.001$).

Conclusion: The mechanism of neurological deficit improvement in balloon angioplasty procedure happened through the elevation of EPC and SOD levels. The outcomes of balloon angioplasty could be estimated by measuring the EPC and SOD values as the standard for indicators adjustment to measure clinical progress after balloon angioplasty in ischemic stroke patients.

Keywords: ADMA, Balloon Angioplasty, EPC, MDA, NIHSS, SOD, Stenosis.

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INTRODUCTION

Stroke is a syndrome with quickly developed signs and symptoms, disruption of the focal and global function of the brain that happened more than 24 hours, caused by disruption of the brain vascularization.¹ Two main types of stroke are ischemic and hemorrhagic. Ischemic

stroke happens due to the blockade or occlusion of the cerebral blood vessel, while the rupture of the cerebral blood vessel causes hemorrhagic stroke.² Cerebral artery stenosis is a narrowing of the cerebral blood vessel due to the accumulation of atherosclerotic plaque in the arterial wall.³

Balloon angioplasty is a procedure to

open atherosclerotic stenosis or occlusion in arterial or venous blood vessels by inserting a tiny balloon using a catheter into the artery until reaching the stenosis location.⁴⁻⁶ Balloon filled with contrast and slowly inflated; the contrast is expelled until deflated. Pressure must be applied as the balloon inflates to stretch the atherosclerotic plaque and push it to

the blood vessel's wall.⁷ This technique will allow the blood vessel to expand and increase blood flow (recanalization).⁸

Maintaining integrity and function of the blood vessel endothelial would have a massive effect on avoiding restenosis after the angioplasty procedure.⁹ Mature endothelial cells possess a precursor known as Endothelial Progenitor Cell (EPC), included in a stem cell population with regenerative capacity that can differentiate itself into mature endothelial cells.^{10,11} When endothelial damage occurs, EPC can increase its number in circulation and mobilize itself to the lesion site.^{9,12} Distribution of EPC does not only illustrate regenerative capacity, but it also illustrates the well-being of the endothelial condition.⁹ However, the endothelial injury does not only bring up EPC but also Asymmetric dimethylarginine (ADMA), which is an endogen that inhibits Nitrite Oxide Synthase (NOS).¹³ Disruption of the nitric oxide production caused by NOS disruption by ADMA causes vascular inflammation that causes endothelial dysfunction and atherosclerosis.¹⁴ The lumen diameter shrinks after the coronary angioplasty related to increased pro-inflammation mediators.¹⁵ Additionally, endothelial inflammation causes oxidative stress, a disruptive process to balance prooxidative and antioxidants.¹⁶ In oxidative stress condition, there is a group of antioxidant that acts to suppress or prevents the formation of free radicals by neutralizing any molecules with the potential to grow; one of them is Superoxide dismutase (SOD).¹⁷ In cardiovascular diseases, SOD plays a role in illustrating the effectiveness of the antioxidant defense system against oxidative stress.¹⁸

Lipid is the most active biomolecule from various biological targets of oxidative stress. Malondialdehyde (MDA) is an end product of lipid peroxidation¹⁹ and a toxic substance caused by the interaction between oxidative stress with the membrane system. MDA is a marker to evaluate the oxidative stress level.²⁰

Balloon angioplasty procedure can cause the release of EPC and ADMA after the balloon inflation due to the endothelial injury and risk of reperfusion injury^{10,12,13} that may cause inflammation

and oxidative stress.²¹ Those inflammation and oxidative stress state would bring up SOD and MDA that illustrates the balance of the oxidative stress process. Significant mobilization of EPC depends on the extent of the endothelial injury itself and the extent of the endothelial injury caused by the inflation pressure applied.²²

Nowadays, the indications that influence balloon angioplasty outcomes in ischemic stroke are still being discussed. The Stenting Versus Aggressive Medical Management Therapy for Intracranial Stenosis (SAMMPRIS) study has shown that the therapy using medical treatment is better than endovascular, including balloon use,²³ but criticized as the failure of the endovascular procedures (including balloon) were caused by the patient who was in acute phase.²⁴ In India, balloon angioplasty was performed on 39 patients, 23 of them were in the acute phase. No patient experienced restenosis after balloon angioplasty.²⁵ Patient with acute phase ischemic stroke (onset 5 hours 45 minutes) was able to move, eat and get dressed independently one month after balloon angioplasty.²⁶ In a study with 74 stroke patients with a mean stenosis rate of 79%, the mean value of recurrent stroke in 30 days and 3 months after the intervention were 5% and 8.5%, respectively.²⁷ Despite the procedure success rate to reduce stenosis being under 50% in more than 80% of patients, the recurrent stroke or mortality rate in 30 days varies between 4%-40% while the restenosis rate reaches 24-40%.²⁸

According to the descriptions above, it is known that reperfusion with balloon angioplasty can be used as a treatment option for ischemic stroke patients. Therefore new studies are required to determine the relation between cerebral artery stenosis alteration, EPC, ADMA, SOD and MDA levels before and after balloon angioplasty and analyze its relation to neurological deficits in ischemic stroke patients.

26 METHODS

This study was conducted with a group pre-test and post-test design. Data were collected before and after balloon angioplasty in RSUP Fatmawati Jakarta and RS Pelni Jakarta. The duration of

sampling occurred from February 2021 until November 2022. The sampling technique used was Consecutive sampling

The sample in this research is an ischemic stroke patient that receives a balloon angioplasty procedure. Inclusion criteria are a first-timer stroke patient without allergic reaction to contrast, experiencing neurological deficit symptoms and the presence of cerebral artery stenosis from Digital Subtraction Angiography (DSA) result, and never receiving any therapy: thrombolytics, mechanical endovascularization and brain vascular stenosis lesion surgery. Meanwhile, exclusion criteria in this research are patients who experience other brain vascularization abnormalities and those who opted to non-participating in this research. Patients who failed balloon angioplasty procedures, neurologic deficit examination, and laboratory were excluded from the study.

The percentage change in cerebral artery stenosis was measured from the difference in the narrowing of the cerebral artery lumen percentage; before and after balloon angioplasty. EPC levels were obtained from the CD34⁺ biomarker examination in cells/ μ L. ADMA levels were obtained from the examination of ADMA with units of ng/mL. SOD levels were obtained by examining SOD levels in units of U/mL. MDA levels were obtained by investigating MDA levels within μ mol/L. Neurological deficit was measured by neurological physical examination and National Institutes of Health Stroke Scale (NIHSS) score.

Data analysis was conducted using the SPSS application. Hypothesis testing was performed using statistical inferential tests with a confidence interval of 95%. Analysis of changes in biological inflammatory markers (AMDA, EPC, MDA, SOD) before and after balloon angioplasty intervention was performed using the Paired Sample T Test. Data that were not normally distributed using the Shapiro-Wilk test were analyzed using the non-parametric Wilcoxon Rank test. Correlation analysis of variable changes was done with Spearman's correlation test. Determination of predictive significance and marker cut-off points for changes of 50% in neurological deficits was

determined based on Area Under Curve (AUC) using Received Operating Curve (ROC). Inter-variable effect test analysis was then conducted to assess the effect of each item using linear regression.

RESULTS

Thirty-five respondents were included in this research. The characteristics of said respondents are presented in Table 1. According to the degrees of neurological deficit measured with NIHSS scoring, ischemic stroke patients are divided into two groups, NIHSS >50% and NIHSS<50%. It can be seen that the average age of ischemic stroke patients that suffers a neurological deficit of more than 50% is 50.35 years old, while 54.39 years old for those who suffer a deficit below 50%. From sex, those who scored more than 50% in NIHSS were mostly females, while males were more common in NIHSS scores of less than 50%. Overall, males suffer more strokes than women. From the location of the lesion, both NIHSS groups had LICA as the most common site of stroke compared to the other sites and overall, left circulation sites (LCCA, LICA, LVA) were more common to stenosis than the right arteries. From risk factors, hypertension is the highest risk factor for stroke. From onset time, patients from stroke attack until balloon angioplasty obtained NIHSS scores above 50% averaged at 24.12 days, while those who scored below 50% averaged at 29.02 days (Table 1).

Next, we observe the changes in stenosis, EPC, ADMA, MDA, SOD and NIHSS. It can be inferred that there is a significant change in stenosis, EPC, MDA, SOD, and NIHSS variables with $p<0.001$, $p=0.001$, $p=0.001$, $p<0.001$ and $p<0.001$, respectively. Meanwhile, the ADMA variable did not significantly change before and after the balloon angioplasty procedure ($p=0.790$). For neurological deficit, there is a significant clinical improvement from 9 to 4 or averaging 45.15%, as shown in Table 2.

Table 3 shows no significant correlation between stenosis changes and neurological deficits ($p=0.459$). As shown in Table 4, it can be inferred there is a significant correlation between EPC changes and neurological deficit

Table 1. Characteristics of Research Respondents

Variables	NIHSS \geq 50% (n = 17)	NIHSS < 50% (n = 18)	p
Age (years) (Mean \pm SD)	50.35 \pm 7.78	54.39 \pm 9.52	0.125
Sex, n (%)			
Male	8 (47.10)	13 (72.20)	0.129
Female	9 (52.90)	5 (27.80)	
Location of the lesion, n (%)			
RCCA	1 (5.90)	0 (0.00)	
RICA	5 (29.40)	3 (16.70)	
LICA	3 (17.60)	9 (50.00)	
LCCA	3 (17.60)	3 (16.70)	
LVA	2 (11.80)	1 (6.60)	
Post Bifurcatio RCCA/RICA	1 (5.90)	1 (5.60)	
Post Bifurcatio LCCA/LICA	2 (11.80)	1 (5.60)	
Hypertension, n (%)			
Yes	14 (82.40)	16 (88.90)	0.658
No	3 (17.60)	2 (11.10)	
Diabetes, n (%)			
Yes	4 (23.50)	11 (61.10)	0.025*
No	13 (76.50)	7 (38.90)	
Cholesterol, n (%)			
Yes	6 (35.30)	9 (50.00)	0.380
No	11 (64.70)	9 (50.00)	
Smoking, n (%)			
Yes	5 (29.40)	3 (16.70)	0.433
No	12 (70.60)	15 (83.30)	
Obesity, n (%)			
Yes	1 (5.90)	0 (0.00)	0.486
No	16 (94.10)	18 (100.00)	
Coronary heart syndrome, n (%)			
Yes	1 (5.90)	7 (38.90)	0.041*
No	16 (94.10)	11 (61.10)	
Alcohol consumption, n (%)			
Yes	2 (11.80)	1 (5.60)	0.603
No	15 (88.20)	17 (94.40)	
Onset to balloon time (days) (Mean \pm SD)	24.12 \pm 6.70	29.06 \pm 11.15	0.181

RCCA: Right Common Carotid Artery; RICA: Right Internal Carotid Artery; LICA: Left Internal Carotid Artery; LCCA: Left Common Carotid Artery; LVA: Left Vertebral Artery; *Statistically significant if p-value less than 0.05

Table 2. Stenosis, EPC, ADMA, SOD, MDA, and NIHSS changes

Variables	Before-balloon	After-balloon	P-value
Stenosis (%)	65 (40-75)	30 (20-34)	<0.001 ^a
EPC/CD34+ (cells/ μ l)	2.13 (0.55-27.45)	3.24 (0.18-22.60)	0.001 ^a
ADMA (ng/mL)	73.57 \pm 11.42	74.20 \pm 11.12	0.790 ^b
MDA (μ mol/mL)	2.20 (1.48-3.71)	1.75 (1.33-4.56)	0.001 ^a
SOD (U/mL)	1.12 (0.46-3.22)	2.36 (0.32-3.86)	<0.001 ^a
NIHSS	9 (3-15)	4 (1-12)	<0.001 ^a

EPC: Endothelial Progenitor Cells; ADMA: Asymmetric Dimethylarginine; SOD: Superoxide Dismutase; MDA: Malondialdehyde; NIHSS: National Institutes of Health Stroke Scale ^aWilcoxon Rank Test; ^bPaired sample T-Test; *Statistically significant if p-value less than 0.05

($p=0.001$). This study has no significant correlation between ADMA changes and neurological deficit ($p=0.063$) (Table 5). Table 6 shows no significant correlation between MDA changes and neurological deficit ($p=0.561$) in this study. In addition, there is a significant correlation between SOD changes and neurological deficit ($p<0,001$) (Table 7).

According to Table 8 and Figure 1, the predictive cut-off value of EPC (CD34⁺) for the 50% neurological function improvement is 1.07 cells/ μ l (sensitivity 52.9%; specificity 61.1%). Then, the predictive cut-off value of SOD for the 50% neurological function improvement is 0.71 U/mL (sensitivity 76.5%; specificity 83.3%). From these results, the

differentiation level of SOD is better than EPC in predicting neurological function improvement in balloon angioplasty procedures with AUC values of 86.9% and 62.6%, respectively.

Based on Table 9 and Figure 2, it can be seen that the ones that have an inter-variable effect are EPC changes directly to the neurological deficit changes, EPC changes to SOD changes, and SOD changes to neurological deficit changes.

Table 3. Correlation between stenosis and NIHSS changes

Variables	Median	Min-Max	r	P
Stenosis changes (n=35)	-32	(-45) – (-15)	-0.129	0.459
NIHSS changes (n=35)	-3	(-10) - 0		

NIHSS: National Institutes of Health Stroke Scale; Min: Minimum; Max: Maximum; r=Coefficient Correlation; *Spearman correlation test: Statistically significant if p-value less than 0.05

Table 4. Correlation between EPC and NIHSS changes

Variables	Median	Min-Max	r	P
EPC changes (n=35)	1	(-8.74) – 4.60	-0.527	0.001*
NIHSS changes (n=35)	-3	(-10) - 0		

EPC: Endothelial Progenitor Cells; NIHSS: National Institutes of Health Stroke Scale; Min: Minimum; Max: Maximum; r=Coefficient Correlation; *Spearman correlation test: Statistically significant if p-value less than 0.05

Table 5. Correlation between ADMA and NIHSS changes

Variables	Median	Min-Max	r	P
ADMA changes (n=35)	3	(-28) – 29	0.318	0.063
NIHSS changes (n=35)	-3	(-10) - 0		

NIHSS: National Institutes of Health Stroke Scale; ADMA: Asymmetric Dimethylarginine; Min: Minimum; Max: Maximum; r=Coefficient Correlation; *Spearman correlation test: Statistically significant if p-value less than 0.05

Table 6. Correlation between MDA and NIHSS changes

Variables	Median	Min-Max	r	P
MDA changes (n=35)	-0,54	(-2.11)– 2.81	0.102	0.561
NIHSS changes (n=35)	-3	(-10) - 0		

NIHSS: National Institutes of Health Stroke Scale; MDA: Malondialdehyde; Min: Minimum; Max: Maximum; r=Coefficient Correlation; *Spearman correlation test: Statistically significant if p-value less than 0.05

Table 7. Correlation between SOD and NIHSS changes

Variables	Median	Min-Max	r	P
SOD changes (n=35)	0.42	(-0.19) – 2.67	-0,845	<0.001
NIHSS changes (n=35)	-3	(-10) - 0		

NIHSS: National Institutes of Health Stroke Scale; SOD: Superoxide Dismutase; Min: Minimum; Max: Maximum; r=Coefficient Correlation; *Spearman correlation test: Statistically significant if p-value less than 0.05

Table 8. Variables cut-off to the neurological deficit changes

Variables	Cut-off	Sensitivity	Specificity	AUC
EPC	1.07	0.529	0.611	0.626
SOD	0.71	0.765	0.833	0.869

DISCUSSION

In this study, out of 35 ischemic stroke patients who underwent balloon angioplasty, male was more common than female and the average age of ischemic stroke patients who underwent balloon angioplasty ranged from 50.35 - 54.39 years. The difference between males and females in this research cannot fully represent the stroke incidence rate between the two genders; this research focuses on balloon angioplasty in ischemic stroke patients. As a relatively new procedure in Indonesia, endovascular surgery in the cerebral vasculature, including balloon angioplasty, is not fully familiar to the public, unlike similar surgery in the cardiac vasculature, which is well known. So that some ischemic stroke patients are still hesitant when advised to proceed with balloon angioplasty and it is mostly of the female.²⁹ Kadooka et al., in a meta-analysis study (data from 1980 to 2017), presented the results that the average age of ischemic stroke patients who performed balloon angioplasty was around 61.8 years (range 48-68) and 62.1 years (range 53-66.6).³⁰

Interference with changes in arterial stenosis in balloon angioplasty can be influenced by several things, such as arterial dissection, embolism, elastic recoil and residual stenosis, which can lead to acute recurrent stenosis.²⁸ Previous studies have shown the success of balloon angioplasty which can reduce stenosis to below 50%, achieved in more than 80% of patients. According to Wabnitz and Chimowitz in 2017, using a single balloon angioplasty procedure is associated with rapid elastic recoil of the artery, acute vessel closure, and residual stenosis above 50% immediately after the procedure.³¹ Wojak and Hoppe also explained that recurrent stenosis could occur immediately after

balloon angioplasty. This is a peri- and post-procedure complication of balloon angioplasty, reducing the success rate.²⁸ Previous studies conducted repeat angiography follow-up within 6-12 months after the procedure, some undertaken even after 6 to 182 months after the procedure, but this study has limitations; the measurement of arterial stenosis (repeat angiography) through DSA can only be done within 30 minutes after balloon angioplasty, so it cannot show the presence or absence of restenosis for a long time after the procedure.^{32,33} There is no direct relationship between

changes in stenosis and changes in neurological deficits, as shown by the results in Table 3. This means that the change or widening of the lumen of the blood vessel (recanalization) after previously experiencing blockage does not necessarily restore the clinical condition of ischemic stroke patients. Many other factors influence this condition. This is consistent with Zhanget al., who stated that not all patients benefit from recanalization due to post-stroke cerebral hemodynamic disturbances.³⁴ This relates to the “no-reflow phenomenon” and arterial reocclusion/restenosis. This mechanism

involves microvascular obstruction.³⁵ This study successfully showed a significant change between cerebral artery stenosis before and after balloon angioplasty, where the mean reduction in stenosis was from 65% with a minimum of 40% and a maximum of 75% to 30% (minimum of 20% and maximum of 34%).

EPC values in stroke patients before balloon angioplasty in this study illustrate the state of vascular endothelial injury after experiencing vascular injury and ischemia due to stroke. Various risk factors, stroke onset, and the occurrence of vascular self-repair ability are represented in the EPC values taken before balloon angioplasty. Then the vascular injury by balloon angioplasty can trigger the release of EPC and CD34⁺ values. This study was carried out 7 (seven) days after balloon angioplasty describing the state of vascular endothelial repair due to stroke and coupled with balloon angioplasty. After balloon angioplasty, recanalization (which is also influenced by the presence or absence of restenosis after balloon angioplasty) contributes to endothelial repair. The lack of restenosis also indicates the absence of reperfusion injury, as shown by the EPC results, which relates to the clinical improvement of stroke patients who received balloon angioplasty in this study. The Correlation between changes in EPC values and NIHSS, as shown in the analysis results in Table 4, illustrates that endothelial injury (which cannot be avoided) due to balloon inflation pressure on atherosclerotic plaques in balloon angioplasty triggers the release of EPC into the blood plasma. EPCs have the self-renewal capacity and the ability to differentiate into mature endothelial cells. Thus, EPCs are important in vascular (arterial) repair by promoting re-endothelialization after injury.³⁶ Endothelial damage describes the balance between the magnitude of the injured blood vessel and the ability to repair it.³⁶ In this study, it is evident that the process of endothelial injury after balloon angioplasty can be repaired with the release of EPCs into the tissue. EPCs also act in angiogenesis and vasculogenesis and increase the repair of endothelial injury after ischemic stroke and the magnitude of the increase in EPCs

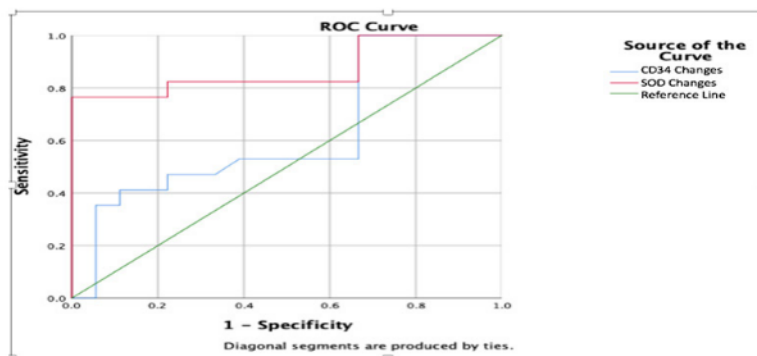


Figure 1. Predictive cut-off diagram of EPC dan SOD to 50% neurological deficit improvement.

Table 9. Inter-variables influence

Independent Variables	Dependent Variables	β	p	R ²	Description
Δ Stenosis	Δ Neurological Def.	-0.042	0.461	0.017	Insignificant
Δ Stenosis	Δ EPC	0.001	0.990	<0.001	Insignificant
Δ EPC	Δ Neurological Def.	-0.539	0.008*	0.193	Significant
Δ EPC	Δ SOD	0.175	0.014*	0.169	Significant
Δ SOD	Δ ADMA	-3.182	0.204	0.048	Insignificant
Δ SOD	Δ MDA	0.017	0.922	<0.001	Insignificant
Δ ADMA	Δ MDA	0.006	0.618	0.008	Insignificant
Δ MDA	Δ Neurological Def.	-0.343	0.506	0.014	Insignificant
Δ SOD	Δ Neurological Def.	-2.442	<0.001*	0.722	Significant

*Linear Regression: statistically significant if p-value less than 0.05

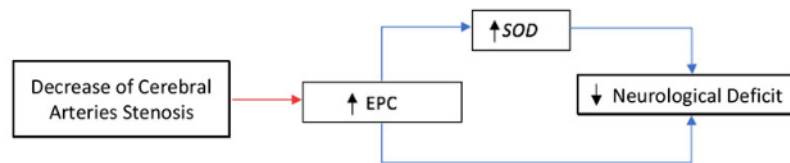


Figure 2. Inter-variables influence analysis

in the circulation is associated with better functional outcomes.³⁷ This study proves that EPCs have been able to act and repair endothelial damage during stroke attacks, which are then mediated by an increase in EPCs during balloon angioplasty. This is indicated by a significant improvement in neurological deficits in patients with ischemic stroke (Tables 2 and 4). In this study, changes in EPC showed a significant value before and after balloon angioplasty; where before the action, the mean CD34+ level was 2.13 cells/ μ l (minimum 0.55 cells/ μ l and maximum 27.45 (cells/ μ l) and after balloon angioplasty action changed to a mean of 3.24 cells/ μ l (minimum 0.18 cells/ μ l and maximum 22.6 cells/ μ l).

Asymmetric dimethylarginine is an endogenous inhibitor of NOS (nitric oxide synthase)³⁸ and is also known as a mediator of endothelial dysfunction and atherosclerosis.¹³ In cases of acute stroke, there is an increase in ADMA levels. It has an important role in brain injury due to the reduction of CBF, the emergence of oxidative stress and inflammatory reactions.¹³ Patients with a good outcome, ADMA levels increase from the first day after onset and decrease after day 3. Meanwhile, in patients with unfavorable outcomes, the ADMA level increased until day 3, remained stable until day 7 and decreased thereafter.¹³ In this study, as can be seen in Table 2, with an average time interval between stroke onset and balloon angioplasty action of 24.12 days and 29.06 days, ADMA levels decreased considerably when balloon angioplasty was performed. In coronary arterial disease (CAD) patients, ADMA significantly increases and is associated with restenosis after PCI. Elevated levels of ADMA before angioplasty and stenting in CAD patients may increase the occurrence of restenosis after the procedure and decreased nitric oxide (NO) production in patients with elevated levels of ADMA may accelerate the restenosis process. In addition, endothelial damage as a complication can occur in patients with PCI.³⁹ In this study, changes in ADMA before and after balloon angioplasty did not show significant changes ($p=0.790$) (Table 2). This illustrates that the ADMA value obtained during the stroke is not meaningful with the change after balloon angioplasty. The

correlation analysis between ADMA changes and clinical functional (NIHSS) was obtained, illustrating the absence of Correlation between ADMA changes and NIHSS (Table 5).

MDA is an end product of lipid peroxidation. This compound is a reactive aldehyde and one of several reactive electrophile species that cause cellular toxicity and is used as a biomarker to measure oxidative stress.¹⁹ Lipid peroxidation products are key mediators of neuronal apoptosis induced by oxidative stress.⁴⁰ As a biomarker of oxidative stress, MDA has a role in various diseases, including stroke. The brain is very sensitive to oxidative injury due to its high content of polyunsaturated fatty acids.⁴¹ There is strong evidence of the involvement of free radicals and lipids peroxidation in the pathophysiology of acute ischemic stroke.⁴⁰ Ischemic stroke induces the formation of ROS and RNS molecules. Furthermore, ROS has been implicated as important in reperfusion injury.⁴¹ The highest free radical damage occurs within 24 hours after the attack. Over the next 3 months, oxidative damage to lipids caused by free radicals is reduced due to activation of the antioxidant system.⁴² From the results in Table 5.2, it can be seen that the changes in MDA before and after balloon angioplasty have meaning with a value of $p=0.001$. However, in Table 6, changes in MDA did not correlate with changes in neurological deficits (NIHSS). The existence of significant changes in MDA before and after balloon angioplasty indicates the potential for oxidative and inflammatory stress due to inflation pressure after the procedure, but this is not enough for reperfusion injury to persist in blood vessels leading to the formation of ROS and free radicals; it is evident that these changes do not correlate with changes in neurological deficits in this study. In addition, the average ischemic stroke patients in this study were examined for MDA (initial), not in the acute phase. Also, the second examination was carried out on the 7th day after balloon angioplasty, after passing 24 hours as the peak period of free radical damage. In the next 3 months, antioxidants' role determines stroke patients' clinical condition.

A reactive oxygen synthesis is a group

of reactive oxygen-containing molecules ready to react with macromolecules to cause irreversible changes in function or even total damage.⁴³ Increased ROS production is an important feature in ischemic stroke and a mediator in ischemic damage.⁴³ Increased ROS after cerebral ischemia causes oxidative stress and neuronal damage.⁴⁴ ROS contain free radicals such as superoxide (O_2^-) and antioxidants such as hydrogen peroxide (H_2O_2). Both have a role in damaging pathogenic microbes; when the host cell is under oxidative stress, when the ratio of ROS is greater than anti-ROS, superoxide (O_2^-) and hydrogen peroxide (H_2O_2) can form hydroxyl radicals (OH^*) through Haber-Weish and Venton reactions that are highly reactive to host DNA.²⁰ Under conditions of oxidative stress, there is a set of antioxidants that act to suppress or prevent the formation of free radicals by neutralizing any molecules that have the potential to develop.¹⁷ This is a physiological attempt by the host cell to physiologically synthesize anti-ROS by forming a scavenger enzyme that secretes several enzymes.²⁰ One of them is superoxide dismutase (SOD).¹⁷ SOD plays a role in cardiovascular diseases and illustrates the effectiveness of the antioxidant protection system against oxidative stress.¹⁸ Studies have shown that SOD deficiency can exacerbate cerebral infarction after ischemia. This relationship between SOD and cerebral ischemia implies that SOD may be an effective therapeutic target for stroke treatment. Increased expression of SOD has been shown to function as a neuroprotective that can reduce ischemic and traumatic brain injury.⁴⁵ In this study, as shown in Table 2, changes in SOD before and after balloon angioplasty had a significant meaning with a p -value <0.001 . While Table 7 illustrates the Correlation of SOD changes with changes in neurological deficits (NIHSS). These results demonstrate that in this study, SOD gives significant meaning to changes in NIHSS of ischemic stroke patients. SOD can suppress superoxide free radicals (O_2^-) and is able to decompose more H_2O_2 into H_2O and O_2 and is useful for improving the condition of neurological deficits of ischemic stroke patients by inhibiting free radical activation. On

the other hand, the increase in SOD results from the appearance of VEGF and stromal-derived factor (SDF-1 α), which are growth factors that help repair ischemic conditions by neovascularization and re-endothelialization by EPCs. This is also supported by the possibility of no reperfusion injury due to inflation pressure recanalization after stenosis dilation by balloon angioplasty so that the possibility of inflammation is minimal, and the appearance of Reactive oxygen species (ROS) becomes insignificant.

The results in Table 2 show a significant change in the NIHSS variable before and after balloon angioplasty ($p < 0.001$). This illustrates that balloon angioplasty is able to offer its success rate as a therapy to improve clinical conditions in ischemic stroke patients, of course, by paying attention to several variables that determine this success. While Tables 4 and 7 illustrate the significant Correlation between EPC and SOD to NIHSS, which indicates that in this study, EPC and SOD have a role in the clinical improvement of ischemic stroke patients who get balloon angioplasty. While Tables 3, 5 and 6 show no correlation between changes in stenosis, ADMA and MDA to changes in NIHSS. In this study, changes in NIHSS were measured based on the percentage change before and after balloon angioplasty. This percentage method is more effective and useful in calculating changes in neurological deficits over time than absolute scores.⁴⁶⁻⁴⁹ The results of this study illustrate that balloon angioplasty which causes injury to the endothelium of blood vessels can generate a more significant number of EPCs and SOD levels to cause clinical improvement in patients with ischemic stroke. While the absence of a significant role of ADMA and MDA on clinical changes in ischemic stroke patients also indicates that balloon angioplasty performed with good technique can avoid the occurrence of reperfusion injury.

The results in Table 8 and Figure 1 shows that for clinical improvement of 50% or more, the cut-off value for CD34+ is 1.07 cells/ μ l with a sensitivity of 0.539, specificity of 0.611 and AUC of 0.626. Meanwhile, SOD levels had a cut-off value of 0.71 U/ml with a sensitivity of 0.765, specificity of 0.833 and AUC of

0.869. From these results, when compared between EPC and SOD, SOD has a higher ability to predict the occurrence of clinical improvement in ischemic stroke patients if balloon angioplasty is performed.

The limitation of this study is cannot assess changes in arterial stenosis over a longer period of time since balloon angioplasty and did not analyze risk factors for stroke and medical treatment as variables. Further research is needed by imaging blood vessels in a longer post-balloon period, using risk factors for stroke and medical therapy as research variables and using a larger sample size to get deeper results than this study.

CONCLUSION

Balloon angioplasty procedures can reduce cerebral artery stenosis, elevate EPC numbers, not influence ADMA level, reduce MDA level, elevate SOD level and decrease NIHSS score. The outcomes of balloon angioplasty could be estimated by measuring the EPC and SOD values as the standard for indicators adjustment to measure clinical progress after balloon angioplasty in ischemic stroke patients. Mechanism of neurological deficit improvement in balloon angioplasty procedure happened through elevation numbers of EPC and SOD levels.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this article.

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ETHICAL STATEMENT

This research has obtained ethical clearance from the Ethics Review of Research and Development Committee of Fatmawati Central General Hospital No. 22/KPP/XII/2020.

AUTHOR CONTRIBUTION

Nasrul Musadir initiated the idea and basic concept of the research; responsible for data, statistical analysis, and draft report. Soetojo maintained the continuity

of the research and assisted in the research report. Syahrul added conceptual material, research flow, and a draft research report. Ketut Sudiana assisted in converting basic ideas and concepts into concepts and research flow and directed the research report. Budi Utomo and Siti Pariani assisted in statistical analysis and directed the report. Muhammad Hamdan, helped to add enrichment to research ideas and ideas. Fritz Sumantri Usman, helped and was responsible for overseeing the suitability of the sample according to the criteria and the flow of research runs properly.

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