AKSONA

The Effect of Simvastatin on Acute Phase Functional Outcome of Ischemic Stroke

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Article info	ABSTRACT
	Introduction: Stroke is one of the leading causes of death and disability worldwide, and especially in Indonesia. Several studies showed the pleiotropic and neuroprotective effect of simvastatin in addition to lowering blood cholesterol levels. **Objective:** This trial was conducted to investigate if the administration of simvastatin in acute ischemic stroke management can improve functional outcomes. **Methods:** This randomized, double-blind, placebo-controlled trial of simvastatin was conducted in patients with acute ischemic stroke with an NIHSS score of 4-14. Participants were randomly assigned to receive 40 mg of simvastatin or placebo for seven days. The NIHSS scale was compared on admission day, 4th and 8th day after administration of simvastatin between the two groups. **Results:** 52 individuals were randomized: 28 to simvastatin and 24 to placebo. There was no significant improvement of functional outcome between the two groups ($p > 0.05$). **Conclusion:** Administration of simvastatin had no significant effect on outcome (measured by NIHSS) in patients with acute ischemic stroke.

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INTRODUCTION

Stroke is the second leading cause of death and the number one cause of disability worldwide and in Indonesia. According to estimates of the Global Burden of Disease (GBD), there were 11.9 million strokes worldwide, 104.2 million prevalent, and approximately 6.2 million deaths in 2017. Stroke incidence, prevalence, and mortality have all decreased between 1990 and 2017, but the number of new incidents, deaths, survival, or disabled has nearly doubled.[1,2]

Stroke is the leading cause of death among Indonesians over the age of five, accounting for 15.4% of all deaths and having a prevalence of 12.1 per 1000 population. Hypertension, previous stroke, diabetes, dyslipidemia, and smoking are frequent risk factors. Aside from causing disability and death, health care costs are also quite high.[3,4]

Large-scale clinical trials have shown that statins reduce the incidence of cerebrovascular events. It has since been demonstrated that statins have some pleiotropic effects, including antithrombotic, inhibiting inflammatory responses, antioxidant activities, stabilizing atherosclerotic plaque, improving endothelial function, increasing endothelial Nitric Oxide (NO) levels, immunomodulatory actions, and reducing cell apoptosis.[5–13]

Several studies, both experimental and clinical trials, have been conducted to investigate the effects of simvastatin and several other classes of statins on stroke. Statins were found to modulate endothelial Nitric Oxide Synthase (eNOS), reduce Nitric Oxide, and improve cerebral blood flow in the penumbra area in experiments. Another study in the ischemic stroke model showed that simvastatin-treated mice showed a more significant reduction in infarct volume, improved perfusion, and less neurological deficit. [14,15]

A clinical trial examining the use of simvastatin in the acute phase of stroke was conducted through the MISTICS (Marker of Inflammation after Simvastatin in Ischemic Cortical Stroke) study. In this study, patients were given simvastatin at 40 mg/day for the first week and continued at 20 mg/day until the 90th day. NIHSS measured significant neurological improvement at three days, but the 90-day mRS outcome was not better.[16] To seek optimal treatment and improve functional outcomes, it's necessary to investigate the effect of simvastatin in the acute phase of ischemic stroke.

OBJECTIVE

This trial was conducted to investigate if the administration of simvastatin in acute ischemic stroke management can improve the functional outcome measured by NIHSS.

METHODS

This study was a double-blind, randomized clinical trial. The control group included patients with acute thrombotic stroke who met the inclusion and exclusion criteria and received standard treatment plus a placebo. The treatment group included patients with acute thrombotic stroke who met the inclusion and exclusion criteria and received standard therapy plus simvastatin. The two groups were drawn from the same population. The division into two groups was done by randomization using a random table. The sampling method was conducted sequentially according to the patients who came until the predetermined sample size was reached (sampling from consecutive admissions). Placement of research subjects into the control or treatment group was done by randomization. The inclusion criteria were patients with the first attack of acute ischemic stroke, onset within 48 hours, GCS >13, NIHSS scale 4-14, willingness to participate in the study, and signing the consent form between January and April 2012.

Exclusion criteria were other neurologic abnormalities in the brain such as brain injury, tumor, infection, presence of aphasia, allergy to simvastatin, history of dyslipidemia or previous use of simvastatin, elevated liver enzyme levels, acute or chronic renal failure, sepsis, pneumonia, or urinary tract infection, taking itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, gemfibrozil, cyclosporine, danazol, verapamil, diltiazem, and amiodarone.

Simvastatin or placebo was administered at 40 mg per day for seven consecutive days. The NIHSS scale examination was carried out at the beginning of admission on the 4th and 8th days to measure the early improvement in functional outcomes.

RESULTS

This research was conducted in the Neurology ward of Dr. Soetomo Hospital Surabaya for four months, starting from January 2012 to April 2012. From this study, 52 research subjects were obtained, consisting of 24 subjects in the control group and 28 subjects in the treatment group. During this study, a research subject dropped out as much as one person from the treatment group. Dropout was caused by the subject experiencing side effects from the simvastatin given, namely nausea, and the administration of simvastatin was discontinued. Until the end of the study, 51 research subjects consisted of 24 subjects

from the control group and 27 from the treatment group.

Overall, 23 subjects were female, and 28 subjects were male. In the control group, 9 subjects were female, and 15 subjects were male. In the simvastatin group, 14 subjects were female and 13 subjects were male. In the control group, the sex difference was greater for men (62.5%) than for women (37.5%). In the treatment group, the comparison of men and women was balanced at 51.85% and 48.15%. The characteristics of the other basic data variables of the research subjects can be seen in Table 2, where the mean age of the control group was 54.12 years, while the simvastatin group was 57.89 years (p = 0.395). The mean onset of attacks until patients received treatment in the control group was 22.62 hours, while in the simvastatin group, it was 13.44 hours (p = 0.016). The mean systolic blood pressure in the control group was 163.75 mmHg, while the simvastatin group was 165.56 mmHg (p = 1.000).

The mean diastolic blood pressure in the control group was 97.50 mmHg, while the simvastatin group was 91.85 mmHg (p = 0.457). The mean random blood sugar in the control group was 154.33 mg/dl, while it was 175.81 mg/dl the simvastatin group (p = 0.509). The mean total cholesterol in the control group was 189.54, mg/dl while the simvastatin group was 188.62 mg/dl (p = 0.884). The mean triglycerides in the control group were 138.46 mg/dl, while the simvastatin group was 129.15 (p = 0.627). The mean LDL in the control group was 120.67 mg/dl, while the simvastatin group was 119.27 mg/dl (p = 0.946). The mean HDL in the control group was 37.46 mg/dl, while the simvastatin group was 40.19 mg/dl (p = 0.174). The mean albumin in the control group was 4.07 mg/dl, while the simvastatin group was 4.16 mg/dl (p = 0.390).

After testing the differences in distribution between the two groups using the t-test, it was found that there was a difference in the mean value of each variable between the control group and the simvastatin group, but this difference was not statistically significant with each p-value > 0.05, except for the mean onset of stroke (p < 0.05).

From the distribution difference test of two groups using the Mann-Whitney test on the median NIHSS scale at the time of hospital admission, the median in the control group was 5 with a minimum value of 4 and a maximum of 12, while in the simvastatin group, the median was 5 with a minimum value of 4 and a maximum of 12 (p = 0.249). Characteristics of research subjects based on the median NIHSS scale upon admission to the hospital can be seen in Table 3. On the 4th and 8th days after administering simvastatin or placebo, the NIHSS scale was reassessed. The results of the Mann-Whitney test for both groups can be seen in Table 4.

From Tables 3 and 4, it can be seen that the median NIHSS scale on the first, fourth, and eighth days in the control group was 5, 5, and 3.5 (sequentially), while in the simvastatin group it was 5, 5, and 4 (sequentially). From Table 4, it can be seen that there was a decrease in the median NIHSS scale in both groups on the 4th and 8th days. However, from the results of the Mann-Whitney test, there was no significant difference in the median of the NIHSS scale between the two groups on the 4th (p=0.856) and 8th (p = 0.568) days of observations after the administration of simvastatin or placebo (p > 0.05). The median difference in the NIHSS scale on day one and day 8 in the control and treatment groups was the same, namely 2 (p=0.230), and the median difference in the NIHSS scale on day 4 and day 8 in the control group was 0.5 and 1 in the treatment group (p=0.792). Thus, it can be concluded that there is no significant difference between the control group and the treatment group (p > 0.05).

Due to the differences in baseline data on the onset of attacks between the control group and the simvastatin group, further analysis of the NIHSS scale based on the onset of stroke was carried out to see the effect of the onset of stroke on changes in the degree of motor function that occurred. In this study, research subjects were divided based on the onset of stroke, so that there were two groups, namely the group of study subjects whose onset was before 12 hours and more than 12 hours in both the control group and the simvastatin group. This division is based on the MISTICS trial.[16]

There were 26 subjects who had a stroke onset of less than 12 hours and 25 subjects who had an attack onset of more than 12 hours. Table 5 shows the median characteristics of the NIHSS scale in study subjects who had a stroke onset of less than 12 hours. The median NIHSS scale on days 1, 4, and 8 in the control group was 5, 5, and 3 (sequentially), while in the simvastatin group it was 5, 4, and 4 (sequentially). From Table 5, it can be seen that there was a decrease in the median NIHSS scale in both groups on the 4th and 8th days.

However, from the results of the Mann-Whitney test, there was no significant difference in the median of the NIHSS scale between the two groups on the 4th (p = 1.000) and 8th (p = 0.778) observations after administration of simvastatin or placebo with p > 0.05. In contrast, the median difference in the NIHSS scale on day 1 and day 8 in the control and treatment groups was the same, namely 2 (p = 0.461), and the median difference in the NIHSS scale on day 4 and day 8 in the control group was 0, and 1 in the treatment group (p=0.910). Thus, it can be concluded that there is no significant difference between the control group and the treatment group (p > 0.05).

Table 6 shows the median characteristics of the NIHSS scale in study subjects who had a stroke onset of more than 12 hours. The median NIHSS scale on days 1, 4, and 8 in the control group was 5, 5, and 4 (sequentially), while in the simvastatin group it was 4, 3, and 1 (sequentially). From Table 6, it can be seen that the median NIHSS scale was decreased in both groups on the 4th and 8th days. However, from the results of the Mann-Whitney test, there was no significant difference in the median NIHSS scale between the two groups on the 4th day of observation (p = 0.628) and the 8th day (p = 0.588) after administration of simvastatin or placebo, p > 0.05, while the median difference in the NIHSS scale on day 1 and day 8 in the control and treatment groups was the same, namely 2 (p = 0.549), and the median difference in the NIHSS scale on day 4 and day 8 in the control group 1, and 0 in the treatment group (p = 0.511). Thus, it can be concluded that there is no significant difference between the control group and the treatment group (p > 0.05).

From the results of the Mann-Whitney test, it can be concluded that there was no difference in the improvement of functional output, which was known through the median delta of the NIHSS scale, either in the group with stroke onset of less than 12 hours or more than 12 hours (p > 0.05).

DISCUSSION

The primary data collected is tested for normality first with the Kolmogorov-Smirnov test (KS test) to see whether the data distribution follows the normal distribution. From the results of the KS test, it was found that the distribution of the data was normal. For the data group that follows a normal distribution, analysis can be carried out using a parametric test, namely the t-test, to find the difference between the two control and treatment groups. Of all the basic data variables that were analyzed, there were indeed differences between the control and treatment groups, but in general, the differences were not statistically significant (p > 0.05), except for data on the onset of stroke (p < 0.05).

Several variables that are thought to affect the outcome of a thrombotic stroke can be overcome by the randomization technique that we have used when allocating research subjects into the control and treatment groups. By using this randomization technique, it is hoped that the factors that can affect the output, both known and unknown, can be divided equally into the treatment and control groups. The imbalance of stroke onset in the two groups is still possible in the randomization process. If this is the case, it is necessary to adjust the analysis to exclude

confounders not excluded from randomization. In this study, the onset of stroke was divided into two groups, namely, the group of subjects who had stroke onset in less than twelve hours and those who had more than twelve hours. The basis for selecting the twelve-hour limit was the MISTICS trial. From this division, 26 subjects (7 from the control group and 19 from the treatment group) had stroke onsets of less than twelve hours, and 25 subjects (17 from the control group and 8 from the treatment group) had stroke onsets of more than twelve hours.

From the data analysis, it was found that, although the median NIHSS scale of the treatment group was lower than the control group on both the 4th and 8th day of observations, the distribution difference test using the Mann-Whitney method showed that there was no statistically significant difference (p > 0.05). These results indicate a difference with the results of the study of the MISTICS trial, which reported that there was a significant difference in the improvement of the NIHSS scale between the control group and simvastatin, which began to appear on the third day of observation.

This may be because the inclusion criteria in our study were patients who came within 48 hours after the onset of the attack, whereas in the MISTICS trial, a period of 12 hours after the onset of the attack was used, and simvastatin was given up to 90 days post-stroke, whereas in this study, simvastatin was given up to 7 days only. The results of this study are inconsistent with the MISTICS trial, which showed that administration of simvastatin treatment in acute thrombotic stroke was associated with improved stroke functional outcomes. However, the results of this study are in line with an experimental study by Balduini et al., who compared histology between mice given simvastatin before and after cerebral ischemia. This study found that the group of experimental rats given simvastatin before cerebral ischemia had a much better functional outcome than those receiving simvastatin after cerebral ischemia.[13,16]

The time difference in simvastatin administration significantly affects the functional outcome of stroke and the extent of infarct size in experimental animals. The effect of simvastatin on ischemic brain tissue is mainly through an anti-inflammatory mechanism (NFκB inhibition), thereby inhibiting the release of inflammatory mediators (TNF-α, IL-1β), inhibiting leukocyte infiltration, and increasing neuroprotective eNOS regulation.[18,19,20]

In the study of Balduini et al., it was found that mRNA expression for the two pro-inflammatory cytokines, IL-1β and TNF-α was significantly increased in the hypoxic-ischemic group, but not in the group receiving statins 7 days earlier. In

experimental animals, it was found that the anti-inflammatory properties of statins play an essential role in their neuroprotective effects, thereby reducing leukocyte infiltration and pro-inflammatory cytokine production in degenerative tissues. Previous studies also found that simvastatin inhibits leukocyte and endothelial cell interactions only when receiving a previous statin, which may explain why post-hypoxic ischemic pharmacological therapy is not neuroprotective.[20]

Another study by Sironi et al. gave simvastatin therapy to mice at 3 hours after experiencing middle cerebral artery occlusion, significantly reduced infarct size compared to control. This proved that the neuroprotective effect of simvastatin is shown in earlier administration in an ischemic model.[10,18]

From these results, it was found that our study hypothesis was not proven. Thus, administering simvastatin in patients with acute thrombotic stroke with an attack onset of within 48 hours is not beneficial for improving functional outcomes as measured by the NIHSS scale. The strength of this study is the double-blind, randomized controlled clinical trial design, while the weaknesses of this study are: 1) inclusion criteria that simvastatin be given in a more extended period within 48 hours after the onset of a thrombotic stroke attack; 2) this study only observed outcomes within 8 days since the patient was admitted to the hospital.

CONCLUSION

Supplementary administration of simvastatin to standard treatment in patients with acute thrombotic stroke with an attack onset within 48 hours did not significantly improve stroke functional outcome as measured by NIHSS improvement on days 1, 4, and 8.

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ATTACHMENT

Table 1. Characteristics of research subjects by gender.

	Groups		Total	P
	Control	Simvastatin		
Women	9	14	23 (45%)	0,309
Men	15	13	28 (55%)	
Total	24 (47.6%)	27 (52.94%)	51 (100%	

Table 2. Characteristics of research variables in the control group and simvastatin

No	Variable	Control		Simvastatin		P
		Mean	SD	Mean	SD	
1	Age (years)	54.12	9.679	57.89	9.799	0.395
2	Stroke Onset (hours)	22.62	14.581	13.44	13.057	0.016
3	Blood Pressure Systolic (mmHg)	163.75	25.676	165.56	26.651	1.000
	Diastolic (mmHg)	97.50	19.393	91.85	15.941	0.457
4	Random Blood Sugar (mg/dl)	154.33	58.080	175.81	90.617	0.509
5	Total Cholesterol (mg/dl)	189.54	46.323	188.62	52.575	0.884
6	TG (mg/dl)	138.46	57.415	129.15	48.122	0.627
7	LDL (mg/dl)	120.67	41.664	119.27	34.613	0.946
8	HDL (mg/dl)	37.46	6.750	40.19		0.174
9	Albumin (mg/dl)	4.0700	0.32771	4.1626	0.30570	0.390

Table 3. NIHSS scale scores of subjects in the control group and simvastatin at the time of hospital admission

Variable	Control			Simvastatin			P
	Median	Minimum	Maximum	Median	Minimum	Maximum	
NIHSS day 1	5	4	12	5	4	12	0.249

Table 4. NIHSS scale scores of subjects in the control group and simvastatin on the first, fourth and 8th day after treatment

Variable	Control			Simvastatin			P
	Median	Minimum	Maximum	Median	Minimum	Maximum	
NIHSS day 4	5	1	12	5	1	11	0.856
NIHSS day 8	3.5	0	12	4	0	11	0.568
Δ NIHSS day 1-8	2	0	5	2	0	6	0.230
Δ NIHSS day 4-8	0.5	0	3	1	0	4	0.792

Table 5. The median characteristics of the NIHSS scale in subjects who had stroke onset less than 12 hours

Variable	Control			Simvastatin			P
	Median	Minimum	Maximum	Median	Minimum	Maximum	
NIHSS day 1	5	4	9	5	4	12	0.651
NIHSS day 4	5	2	9	4	1	10	1.000
NIHSS day 8	3	2	9	4	0	10	0.778
Δ NIHSS day 1-8	2	0	3	2	0	5	0.461
Δ NIHSS day 4-8	0	0	3	1	0	3	0.910

Table 6. Characteristics of the median delta of the NIHSS scale in study subjects who had a stroke onset of more than 12 hours

Variable	Control			Simvastatin			P
	Median	Minimum	Maximum	Median	Minimum	Maximum	
NIHSS day 1	5	4	12	6.5	4	11	0.238
NIHSS day 4	5	1	12	5	3	11	0.628
NIHSS day 8	4	0	12	4	1	1	0.588
Δ NIHSS day 1-8	2	0	5	2	0	6	0.549
Δ NIHSS day 4-8	1	0	3	0	0	4	0.511