EXAMINATION OF OxLDL SERUM LEVEL AS THE PROGNOSIS OF ACUTE THROMBOTIC ISCHEMIC STROKE

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ABSTRACT

A serum level of Oxidized Low Density Lipoprotein (oxLDL) has recently been proposed as a biochemic marker of cardiovascular disease in association with atherosclerotic process. Study of oxLDL mechanism and its influence in cerebrovascular disease has not been commonly done and needs more identification. The goal of this study was to examine the serum level of oxLDL as acute ischemic thrombotic stroke prognostic. This study was performed as an analytic observational research, using longitudinal observational study design, from September 2005 to February 2006 in Dr. Soetomo Hospital Surabaya. This study found 40 samples who complied with inclusion and exclusion criteria, which consisted of two groups. Twenty-five samples were stroke group, who were taken twice for oxLDL and National Institute of Health Stroke Scale (NIHSS) examination. The first was performed on arrival to the hospital (= 48 hours after onset) and the second on the tenth day of hospitalization. Fifteen samples were non stroke group whose their vein blood was taken for oxLDL level examination once they came to the hospital. There was positive correlation between oxLDL and NIHSS, proven by Spearman statistical analysis, with correlation coefficient of 0.635 and significance of 0.001 ($p < 0.05$). There was significant different mean between oxLDL stroke group and non-stroke group, as proved with t test ($0.00 < 0.05$). However, the different mean test between oxLDL1 and oxLDL2 was not significant ($0.47 > 0.05$).

Keywords: *oxLDL, atherosclerosis, stroke, NIHSS*

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INTRODUCTION

Stroke is a common disease with a high mortality rate. It is the primary cause of disability among adults. Ischemic stroke constitutes the major part of stroke cases (± 85%), which results from thrombosis or emboli in cerebral blood vessel. The underlying process of thrombosis is atherosclerosis (Gusev 2003; Wijaya 2002). In western countries, atherosclerosis generally represents most of death cases since it is the main contributor in the pathogenesis of heart attack, cerebral infarct, and peripheral vascular diseases (Fisher 2001; Meilhac 1999). Oxidized Low-Density Lipoprotein, from then on designated as oxLDL, presents in atherosclerotic plaque, and some facts support the concept that oxLDL is the key antigen in atherosclerosis (Brown 2004). The objective of this study was to prove the role of oxLDL serum level as the prognosis of acute thrombotic ischemic stroke, with the particular objective to prove the difference of oxLDL level in admission (=48 hour) (oxLDL1) and 10 day (oxLDL2) treatment, the difference of NIHSS (National Institute of Health Stroke Scale) values in admission (=48 hour) (NIHSS1) and 10 day (NIHSS2) treatment, to prove the difference of oxLDL serum level in stroke and non-stroke patients, and to prove the correlation between oxLDL serum level and NIHSS.

MATERIALS AND METHODS

This was an observational analytic study using longitudinal observation design, by which thrombotic ischemic stroke patients group were observed twice for the scores of NIHSS and oxLDL serum level soon after the admission (= 48 hours) and at day 10 during treatment in Neurology Wards, Dr Soetomo Hospital, Surabaya. In this study the oxLDL serum level in non-stroke groups was also examined by taking the examination once during the admission. Samples comprised 40 persons, 25 of which were stroke patients from whom vein blood was taken for oxLDL level

examination twice, the first in admission (=48 hours) and the second at day 10 of treatment, while 15 others were non-stroke samples from whom vein blood was taken for oxLDL level only once, during the admission to the hospital.

RESULTS

Results of differential test of oxLDL mean in stroke and non-stroke groups showed significant value (0.00 < 0.05), indicating difference mean between both groups. The result of differential test of NIHSS1 (mild and moderate) oxLDL1 mean in stroke group showed non-significant difference (0.674 > 0.05), indicating no difference in oxLDL mean between mild and moderate NIHSS1 category. None of the total score of NIHSS1 belonged to severe category.

Table 1. Results of differential test between the mean of oxLDL level in stroke and non-stroke groups

Variables	Sample types	Sig. (2-tailed)
OxLDL1	Stroke Non stroke	0.00

Table 2. Results of differential test of the mean of oxLDL level in NIHSS category

	NIHSS1 Category	Sample size	Mean	SD	Sig. (2-tailed)
OxLDL1	Mild	3	86.33	65.41	0.674
	Moderate	22	95.53	30.75	

Table 3. Results of differential test of the mean of oxLDL level in NIHSS category among stroke group

	NIHSS2 Category	Sample Size	Mean	SD	Sig. (2-tailed)
OxLDL2	Mild	10	83.54	44.29	0.138
	Moderate	15	108.22	35.84	

The results of differential test of the mean of NIHSS2 category (mild and moderate) oxLDL in stroke group revealed insignificant value (0.138 > 0.05), indicating no difference in oxLDL mean between mild and moderate NIHSS2. Total score of NIHSS2 did not belong to severe category. The results of differential test of oxLDL1 and oxLDL2 means in stroke group showed no significant value (0.47 > 0.05), indicating there was no difference in both means. Pearson's correlation test between oxLDL1 and NIHSS1 data revealed correlation coefficient of 0.479 with significance level of 0.015 < 0.05, showing significant correlation between both variables. Similarly, Pearson's correlation test between oxLDL2 and NIHSS2 data revealed correlation coefficient of 0.460 with significance level of 0.021 < 0.05, so that with confidence level of 95%, the correlation between both variables was significant.

Table 4. Results of differential test of the mean of oxLDL1 and oxLDL2 level

Variable	Sample Size	Sig. (2-tailed)
OxLDL	OxLDL1 OxLDL2	0.47

Table 5. Correlation between NIHSS and oxLDL in stroke group

Group	Variable			Corel. Coeff. (r)	Sig. (2-tailed)
Stroke	NIHSS1	><	oxLDL1	0.479	0.015
	NIHSS2	><	oxLDL2	0.460	0.021

Table 6. Correlation between lipid profile and oxLDL in stroke and non-stroke groups

Group	Variables			Corel. Coeff. (r)	Sig. (2-tailed)
Stroke	Cholesterol	><	oxLDL	0.472	0.002
	LDL Choles.	><	oxLDL	0.574	0.000
	HDL Choles.	><	oxLDL	0.097	0.552
	Triglyceride	><	oxLDL	0.385	0.014
Non Stroke	Cholesterol	><	oxLDL	0.779	0.001
	LDL Choles.	><	oxLDL	0.564	0.028
	HDL Choles.	><	oxLDL	0.157	0.576
	Triglyceride	><	oxLDL	0.536	0.040

Results of correlation test between oxLDL and lipid profile in stroke patients using Pearson's correlation with confidence level of 95% (significance 0.05) showed that total cholesterol had correlation coefficient of 0.472 and significance level of 0.002; LDL cholesterol had correlation coefficient of 0.574 and significance level of 0.000; HDL cholesterol had correlation coefficient of 0.097 and significance level of

0.552; and triglyceride had correlation coefficient of 0.385 and significance level of 0.014. Therefore, only HDL cholesterol from lipid profile that did not have significant correlation with oxLDL in stroke group, while the others had significant correlation.

Similar findings were also found in the significance level of correlation between lipid profile and oxLDL in non-stroke group. Using Spearman's correlation test with confidence level of 95% (significance 0.05), the results were as follows: total cholesterol had correlation coefficient of 0.779 and significance level of 0.001; LDL cholesterol had correlation coefficient of 0.564 and significance level of 0.028; HDL cholesterol had correlation coefficient of 0.157 and significance level of 0.576; and triglyceride had correlation coefficient of 0.536 and significance level of 0.040. Conclusively, only HDL cholesterol from lipid profile that did not have significant correlation with oxLDL in non-stroke group, while the others had significant correlation.

DISCUSSION

In this study, there were 25 patients who met the inclusion criteria. Those patients had mean age of 58.36 years. According to its characteristics, the highest occurrence rate of thrombotic ischemic stroke is found in those aged more than 50 years. Age is a one important risk factor since stroke incidence may rise exponentially two- or three-times each decade in those of more than 50 years old (Susilo 2000). In view of the age and sex of stroke and non-stroke groups, it is apparent that male is in higher number than female, where there were 14 males (56%) and 11 females (44%). This confirmed the finding of Machfoed and Neurona (2004) who intended to identify the stroke risk factor in patients admitted in a hospital in Surabaya, where the stroke incidence among males was higher than that in female.

For conventional risk factors, hypertension, particularly stage II hypertension, was found in 15 persons or about 60%. This is in line with the statement in the literature that hypertension is one of stroke risk factors playing a substantial role in stroke incidence. Therefore hypertension was regarded as confounding variable in this study. The degree of hypertension was referred to JNC VII. None of 25 samples belonged to normal group, 16% had a category of prehypertension, 24% stage I hypertension and 60% stage II hypertension (=160/100). Results of correlation test between NIHSS and oxLDL was strong and significant. This indicated that the higher the oxLDL value, the higher the functional degree. This also confirms the study by Holvoet and Ehara in cardiology. They found that oxLDL level in the plasma had positive correlation with the degree of severity of coronary artery disease, while Ehara et al. showed that oxLDL level had positive correlation with the degree of severity of post-transplantation coronary artery stenosis (Wijaya 2001).

The result of differential test between oxLDL1 and oxLDL2 revealed a value of 0.47 > 0.05, indicating no significant different mean. The absence of significant difference between oxLDL1 and oxLDL2 remains hard to explain since presently oxLDL is studied as an indicator, not as a prognostic, so that there is no supporting reference. However, if we refer to the literatures (Suryohudoyo 1996; Wijaya 2001), we find that oxLDL is produced by high LDL, oxidized by macrophage and smooth-muscle-produced oxidant, and that oxLDL increases along with the severity of atherosclerosis and plaque instability in atherosclerotic lesion. It is possible that high oxLDL2 level related with several factors, one of which was LDL cholesterol level that remained high. However, this study did not carry out the second/serial LDL cholesterol examination, so that it has not been proved definitively. Other possibility causing high oxLDL2 is related to long-term outcomes (death and repeated stroke) (Wong 2003), so that to obtain its confirmation follow-up to the stroke patients is required.

The mean difference value of oxLDL in NIHSS1 and NIHSS2 category (mild and moderate) was not significant. However, sample size from moderate to mild category changed significantly. This indicated the presence of significant clinical improvement in stroke patients in a period of 10 days, but it was followed with significant change in oxLDL level. Clinical manifestation of stroke may present as the degree of severity of paralysis and the occurring numerous symptoms may result from the extent of stroke lesion itself and the extent of mass effect produced due to cerebral edema (Yatsu 1998). Symptoms resulting from the effect of edema generally relieves quickly, although it is not necessarily followed with the recovery of infarct area. Sign and symptoms of neurological deficit (NIHSS) may recover, but the occurring infarct lesion actually becomes more extensive. This is because collateral perfusion in a part of ischemic penumbra has been developed (Wong 2002). Wong, who studied intracranial atherosclerotic occlusion using TCD (Transcranial Doppler Ultrasound), and assessed the degree of stroke severity using NIHSS, found that there was no correlation between the progress of medial cerebral arterial lesion and clinical events. Thrombotic ischemic stroke patients who had experienced clinical improvement was followed after discharge, and after a period of 6 months repeated TCD examination revealed

that in most of the patients (71%) lesion area remained in abnormality (Wong 2002).

oxLDL level in most of the sample (>50%) remained high, even higher than that of oxLDL1. Referring Wong's study, a question arises: can the result of this oxLDL study be used as indicator to assess the long-term mortality and recurrent stroke? To answer this question, advanced study is needed since there have been no supporting references. The results of analysis of oxLDL correlation test with the components of lipid profile, i.e. cholesterol, triglyceride, and LDL, showed a positive correlation, particularly with LDL, with significance value of 0.000 < 0.05. The results of analysis of correlation test between oxLDL and HDL showed positive correlation of 0.097 with significance value of 0.552 > 0.05, so that with confidence level of 95%, the correlation of both variables was not significant. Correlation between circulating LDL and the risk of atherosclerotic disease manifestations has been undebatable. LDL can be trapped within collagenous tissue that fills subendothelial voids, where it may encounter oxidative stress which quickly depletes its antioxidant content. LDL particles will aggregate, phospholipide will be oxidized and a part of its protein will be glycated. These changes alter native LDL-cholesterol to become atherogenic and antigenic particle that stimulates cytokines and growth factor production and also alter the characteristics of arterial wall. Whereas, HDL can be regarded as giving protection to LDL against oxidation (Kaniawati 2001).

In non-stroke groups, the results of correlation test between lipid profile and oxLDL in non-stroke group with confidence level of 95% showed that cholesterol, triglyceride and LDL had significant correlation with oxLDL, while HDL had no significant correlation with oxLDL. LDL in non-stroke group had significant correlation, but not as strong as LDL, in stroke group (p = 0.000). Atherosclerosis is the increase of LDL level, besides the secretion of reactive oxygen compound by macrophage and smooth muscle in the subintima (Suryohudoyo 1996). Many epidemiological evidences support direct correlation between LDL-cholesterol level and the risk of coronary heart disease. The latest study showed that the statistically-significant reduction of LDL-cholesterol level may decrease mortality rate and inhibit plaque formation and disease process. Moreover, The Adult Treatment of The National Cholesterol Education Program (NCEP) has determined that the decision to control high cholesterol will be based on the value of LDL cholesterol (Kaniawati 2000). Although oxLDL showed no benefit as a short-time prognostic (insignificant difference of the mean of oxLDL1 and oxLDL2), oxLDL can be used as indicator or risk factor for stroke. This was also proved by other results of statistical test analysis showing that there was no significant difference in oxLDL level between stroke and non-stroke groups, and the presence of significant positive correlation between oxLDL and the degree of stroke severity as evaluated by using NIHSS.

CONCLUSION

oxLDL is not a short-time prognostic factor beneficial in acute thrombotic stroke, since during the treatment period for 10 days, clinical improvement is present, but the oxLDL level remains high. The fact that clinical improvement is present but not followed with oxLDL level reduction may be explained by the possibility that NIHSS is not accurate enough to assess the degree of stroke severity when brain damage remains present. Further studies are needed to stroke patients with high serial oxLDL level, so that the role of oxLDL level as long-term predictor of thrombotic ischemic stroke can be disclosed. The use of stroke severity measurement (NIHSS) should be accompanied by the use of other measurement tools, such as TCD (Transcranial Doppler Ultrasound) to find whether brain damage still exists or recovers.

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