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The Relationship of Blood Parameter Routine, serum level of homocysteine and Long Term Ischaemic Stroke Outcome

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Abstract : *Background and Purpose*: Homocysteine (Hcy) is considered as one of the factors affecting the prognosis of ischaemic stroke. Homocysteine is an amino acid containing sulfydril and needs vitamin B6, B12, folic acid and betaine for the metabolism This amino acid has a pre-oxidative and pre-inflammatory effect and induces the progression of vasoconstriction, disturbance of structure and function of endothelium and atherosclerosis. It also acts as a prethrombotic factor with increasing coagulability and platelets aggregation. Hyperhomocysteinemia (HHcy) is an acquired metabolic anomaly and leads to cardiovascular and cerebrovascular complications like atherosclerosis, thrombosis, stroke, Alzheimer's disease, dementia and declining memory.The aim of this study is to determine the relationship between Blood Parameter Routine, homocysteine level and ischemic stroke outcome.
***Method*:** This cross-sectional study was conducted between July 2016 and October 2016 on 36 patients with ischemic stroke, after approval by Medical Faculty Science's Ethics Committee at University Sumatera Utara. Patients with a history of ischemic stroke recurrent , brain lesion malignancy, Hemoragic stroke at the beginning or during hospitalization were excluded. Uncontrolled diabetes, anemia and dramatic blood pressure reduction in admission were defined as confounding factors. In the first week, serum level of homocysteine was measured and modified Rankin Scale (mRS) and status of patients were measured with Barthel index (BI) in the first week and three month after stroke. Data were analyzed by Chi Square, Student t-test, and ANOVA. Patients were followed for a median of 90 days.
Results: Thirty six patients were recruited in the present study (52.8% men and 47.2% women). The abnormal cut off point of plama homocysteine was > 10.3 umol/L. The routine blood tests done at the beginning of hospital admission compared blood homocysteine examination found no significant difference ($p>0.05$). There was no significant difference between systolic and diastolic blood pressure against homocysteine ($p>0.05$). Further subgroup analysis showed that this correlation was significantly between 90 days homocysteine on outcome stroke MRS ($p< 0.003$) and BI ($p<0.005$).
Conclusion : Abnormal plasma homocysteine level is an independent risk factor of ischemic stroke and more correlated with 90 days outcome stroke.
Key words : homocysteine, hypertension, long term stroke ischemic.

1. Introduction

Homocysteine (Hcy) is a naturally occurring nonproteogenic sulfur-containing amino acid produced as a part of the body"s methylation process.[1-4] The Hcy accumulated either in inherited disorders, that alters enzyme activity in metabolic transsulfuration and remethylation pathways or alternatively, in nutritional

deficiencies od essential cofactors or enzyme substrates, inckuding cobalamine (vitamin B_{12}), folate and pyridoxine (vitamin B_6), thus results in blockage of homocysteine metabolic pathways..[5-10] Homocysteine levels can range from a low level of 14 umol $L^{-1}$to a devastating level of 100 umol L^{-1} in severe cases.[5]

Hyperhomocysteinemia (HHy) is an acquired metabolic anomaly was first identified by McCully. The HHy may leads to cardiovascular and cerebrovascular complications. High levels of homocysteine may lead to increased production of oxidation products, homocysteine mixed disulfides which may damage endothelium by excessive sulfation of connective tissue.[11,12] First hours after acute ischemic stroke is crucial, which is a time period that is particularly useful for intervention. So it is very important to determine prognostic factors as soon as possible. Several studies have underscored the prognostic importance of various laboratory parameters such as blood sugar, total leukocyte count and erythrocyte sedimentation rate (ESR) in the case of ischemic stroke.[4,7,10] In ischemic stroke, major hemodynamic factors that determine blood flow velocity in basal cerebral arteries is the length and cross-sectional area of the blood vessels, the degree of pressure throughout the blood vessels and blood viscosity. Other factors associated with blood flow velocity is age and gender, the partial pressure of oxygen and carbon dioxide, body temperature and some physiological changes such as waking or sleeping, and exercise.[6-8]

Bhatia et al (2004) conducted a prospective study of the role of the prognostic value of routine clinical, haematological and biochemical parameters including platelet aggregation to a 30-day case fatality of acute stroke. On univariate analysis obtained by total leukocyte count (TLC) (11614.44 ± 3789.52 / mm3), erythrocyte sedimentation rate (ESR) (32.20 ± 13.78 mm / h), urea (70.66 ± 72.47 mg / dl), creatinine (2.07 ± 2.25 mg / dl), AST (55.05 ± 83.46 IU / L), SGPT (39.58 ± 36.54 IU / L) and globulin levels (3.79 ± 0.70 g / dl) had a significant association with bad outcomes. From the logistic regression test conducted on a meaningful parameter, it is known that serum creatinine, SGPT, ESR and TLC are associated with mortality prognosis.[5]

Elevated serum homocysteine has been associated with an increased risk for vascular disease. Increased levels of homocysteine may cause neurotoxicity and be associated with other prothrombotic factors. Experimental evidence suggests that elevated plasma homocysteine levels may cause toxicity vy a variety of mechanism, which include direct toxicity and vascular endothelial injury.[6,11,12]

Some reports have also suggested that an elevated homocysteine is an independent predictor of poor outcome in patients with stable and acute coronary disease.[7,8]

Stroke is a medical emergency associated with a very high risk of death in the acute and subacute phases and with a continous excess risk of death.[9,10] The greatest predictors of long-term survival after stroke include age, pre-stroke functional level, and functional status at three month after stroke. Therefore, it is recommended that stroke patients reduce dependency by three until six months in order to improve chances of long-term survival.[11,12]There are also a few studies reporting arelationship between homocysteine and functional disability in the acute phase of stroke. However, whether high homocysteine levels are risk factor for acute stroke complications, such as early neurological deterioration, has not been well addreses.[13-16] Therefore, the purpose of this study was to investigate the possible relationship between blood routine parameter, homocysteine levels and outcome Ischemic Stroke.In the first week, The outcome ischemic stroke was measured modified Rankin Scale (mRS) and status of patients were measured with Barthel index (BI) in the first week and three month after stroke

2. Material and Methods

After study received ethical approval from the Health Research Ethical Committee, Medical School, University of North Sumatra, Indonesia, we undertook a prospective cross sectional study of 36 consecutive patients at General Adam Malik Hospital. Over the period August until Desember 2016, of the remaining with ischemic stroke consit of 19 (52.8%) man and 17 (42.7%) women. Patients with a history of stroke, previous brain lesion, liver or kidney disorders, pneumonia, sepsis and who were having a seizure at the beginning or during hospitalization were excluded. Uncontrolled diabetes, anemia, and dramayic blood pressure reduction in admission were defined as confounding factors. After fulfilling the informed consent by patients of their legal responders, in the first 7 days after stroke, fasting blood sample (after 8-10 hour of fasting) were teken from all patients to measure serum level of homocystein. The samples were spilled in tubes containing ethylenediaminetetraacetic acid and centrifuged immediately. The resulting plasma is kept in -20^{o} C and the

serum levels of homocysteine were measured ny high-performance liquid chromatography technique with fluorescence recording. Normal level of serum homocysteine was considered as 14 micro mol/L and the value higher than this were considered as high homocysteine level or hyperhomocysteinemia. Patients were examined at the end of the first week and 30 days. The patients outcome functional were measured by Modified Rankin Scale and Barthel Index

2.1. Stroke Outcome

Prior knowledge of the expected outcome of stroke and its predictors is important for the selection of appropriate instruments of analysis in clinical trials relevant to stroke research. In clinical trials, the modified Rankin Scale (mRS) is widely used. mRS is a global outcome rating scale with values ranging from 0 (no impairment) to 5 (bedridden; incontinent; requiring constant nursing, care and attention) and 6 (a fatal outcome). This study considered mRS scale values 1 and 2 to denote a good outcome, and scale values 3 until 6 to signify a bad outcome.[6]

The Barthel Index includes 10 personal activities: feeding, personal toileting, bathing, dressing and undressing, getting on and off a toilet, controlling bladder, controlling blower, moving from wheelchair to bed and returning, walking on level surface (or propelling a wheelchair if unable to walk) and ascending and descending stairs. This study considered BI scale values $\geq$ 60 as agood outcome and $\leq$ 60 signify a bad outcome.[6]

2.2. Data Analysis

All participants, that the blood was withdrawn to measure haemoglobine, haematocrit, leucocyte, thrombocyte, Blood Fasting Glucose and level homocysteine. Demographic data would be analyzed using descriptive statistics. To analyze association between systole and diastole level homocysteine and Outcome stroke good and bad outcone. This study would use student t test and ANOVA test. A p value $\leq$ 0.05 was considered statistically significant.

3. Results

A total of 36 patients (52.8% men and the others women) with ischemic stroke were enrolled in present study. Their mean age was 54.42 $\pm$ 14.19 years old and their mean of the serum level of homocysteine was 11.97 + 5.2 micro mol/L. The serum level of homocysteine 30 days was high among 19% men and 17% women. Their was not difference from age and sex, p value > 0.05.

Table 1. Comparison of Blood Parameter Routine and homocysteine day-0

Variable	Homocysteine day 0		95% CI		p Value
	Low	High	Lower	Upper	
Haemoglobine	12.67$\pm$ 1,55	13.08 $\pm$ 1.88	-1.700	0.867	0.42
Haematocryte	41.62 $\pm$ 4.43	41.31 $\pm$ 5.60	-3.467	4.083	0.62
Leucocyte	9181.67$\pm$2500.87	10100.42 $\pm$ 2240.579	-2591.420	753.920	0.86
Trombocyte	254000$\pm$60595.53	264791.67$\pm$ 68402.25	-58197	36613	0.95
Blood Glucose	221.08 $\pm$ 71.658	195.08 $\pm$71.078	-25.511	77.511	0.89
ESR	32.75 $\pm$ 12.308	30.33$\pm$ 18.023	-9.362	14.196	0.53

Assessment of Blood Routine Check in the first week (Homocystiene day0) showed in Table 1, therefore comparing the status of haemoglobine, haematocryte, leucocyte, thrombocyte, blood glucose and erythrocyte sedimentation rate (ESR) and homocysteine day-0 were not significantly, p value> 0.05. The differences homocysteine was a low level $\leq$10.3 micromol/L and high level $\geq$ 10.3 micromol/L

Table 2. Comparison of Blood Parameter Routine and homocysteine day-30

Variable	Homocysteine day- 90		95% CI		p Value
	Low	High	Lower	Upper	
Haemoglobine	12.59± 1,59	13.50 ± 1.95	-2.117	0.299	0.47
Haematocryte	42.14 ± 4.57	40.27 ± 5.77	-1.728	5.458	0.67
Leucocyte	9517.27± 2246.23	10229.29 ± 2491.86	-2340.031	916.005	0.54
Trombocyte	257818±70915.53	266500 ± 57229.14	-54566	37203	0.52
Blood Glucose	226.41±68.04	168.14 ±64.31	11.947	104.585	0.62
ESR	31 ± 12.980	31.36 ± 20.839	-11.776	11.061	0.39

Assessment of Blood Routine Check in the three month (Homocystiene day-90) showed in Table 2, therefore comparing the status of haemoglobine, haematocryte, leucocyte, thrombocyte, blood glucose and erythrocyte sedimentation rate (ESR) and homocysteine day-90 were not significantly, p value> 0.05. The differences homocysteine was a low level ≤10.3 micromol/L and high level ≥ 10.3 micromol/L

Table 3. Blood Pressure Systolic and Diastolic and Homocysteine who different MRS day 0

Variable	MRS day 0		p Value
	Good	Bad	
Blood Pressure			
Systole	159.29 ± 25.25	164.32 ± 34.37	0.08
Dyastole	91.43 ± 9.493	95.00 ± 14.72	0.08
Homocysteine day 0	1.57 ± 0.51	1.72 ± 0.45	0.12
Homocysteine day 90	1.21 ± 0,42	1.50 ± 0.51	0.01

Table 4. Blood Pressure Systolic and Diastolic and Homocysteine who different MRS day 90.

Variable	MRS hari ke 0		p Value
	Good	Bad	
Blood Pressure			
Systole	163.86 ± 28.95	110 ± 00.000	0.08
Dyastole	94.00 ± 12.88	80.00 ± 00.00	0.29
Homocysteine day 0	1.65 ± 0.48	0	0.48
Homocysteine day 90	1.37 ± 0,49	1.50 ± 0.51	0.01

Furtheremore, on Table 3 and 4, showed Blood Pressure, Homocysteine and MRS day 0 and day 90. There was significant difference in Homocysteien day 90 between MRS day 0 and day 90 with using ANOVA test.

Table 5. Blood Pressure Systolic and Diastolic and Homocysteine who different BI day 0

Variable	BI day 0		p Value
	Good	Bad	
Blood Pressure			
Systole	160.91 ± 32.79	164.64 ± 28.58	0.93
Dyastole	91.82 ± 11.39	96.43 ± 14.99	0.27
Homocysteine day 0	1.55 ± 0.51	1.86 ± 0.36	0.01
Homocysteine day 90	1.31 ± 0,47	1.50 ± 0.51	0.01

Table 6. Blood Pressure Systolic and Diastolic and Homocysteine who different BI day 90.

Variable	BI day 90		p Value
	Good	Bad	
Blood Pressure			
Systole	163.33 ± 34.36	163.75 ± 28.04	0.64
Dyastole	92.00 ± 12.64	95.50 ± 13.16	0.79
Homocysteine day 0	1.60 ± 0.58	1.70 + 0.47	0.27
Homocysteine day 90	1.46 ± 0,51	1.35 ± 0.48	0.05

Furtheremore, on Table 5 and 6, showed Blood Pressure, Homocysteine and MRS day 0 and day 90. There was significant difference in Homocysteien day 90 between BI day 0 and day 90

4. Discussion

In the present study, of 36 patients (52.8% men and the others women) with ischemic stroke, the serum level of homocysteine more than 10.3 micro mol/L Their mean age was 54.42 ± 14.19 years old and their mean of the serum level of homocysteine was 11.97 + 5.2 micro mol/L. The serum level of homocysteine 30 days was high among 19% men and 17% women. Their was not difference from age and sex, p value > 0.05. There was significant difference in Homocysteien day 90 between BI and MRS day 0 and day 90 ($p < 0.05$).

Saberi et al reported, 145 patients ischemic stroke (55,9% men and 44.1% women) with mean age of 68.3 ± 13.8 years ols were evaluated. Serum level of homocysteine was determined as independent predictor for mortality in the first week (p=0.017, OR = 1.179, 95% CI 1.03-1.35. No significant correlation was found between serum homocysteine level and BI and FIM in the period of study ($p>0.05$).[13]

Ashjazadeh et al reported, 171 patients aged over 16 years within 5 days of their first Ischemic Stroke in Nemaxe Hospital, affiliated to Shiraz University of Medical Sciences. Their mean age was 67.9 ± 13.3 years old. The mean fasting hmocysteine level was significantly higjer in the cases (16.2 micro mol/L, 95% CI: 14.8 to 17.5) than in the controls (13.5 micro mol/L, 95% CI: 12.4 to 14.6) with p value =0.013.The mean homocysteine levels was elevated significantly in those with cardioembolic stroke compared with controls ($p=0.010$).[11]

Studies which have evakuated the relationship between homocysteine level and stroke subtypes have shown different results.[11-13] A Swedish study in 57 stroke patients with hiperhomocysteinemia reported significantly higher total homocysteine in all stroe subtypes. Other studies have shown a relation between increased total homocysteine and lacunar stroke and carotid stenosis.15

Saberi et al showed no significant correlation between serum homocysteine level and Barthel Index (BI) and Functional Indepedence measure (FIM) in fisrt month after ischemis stroke ($p>0.05$).[14] In our study was significant difference in Homocysteien day 90 between Barthel Index and Modified Rankin Scale at day 0 and day 90 ($p <0.05$). Saberi et al reported patients with normal homocysteine level had higher Functional Independence Measure score of first month than patients with higher homocysteine level but this association was not with absolute value of homocysteine and disappears after adjusting for confounding factors.[14] Howard et al in 2000 among 76 patients involved by ischemic stroke, serum level homocysteine in two groups with Rankin score above 2 and below 2 did not differ and it seems that it is congruent with our results. Also the above mentioned study used Rankin score that evaluates patients disability, wherever we assessed the functional outcome by FIM and BI.[11]

5. Conclusion:

Abnormal plasma homocysteine level is an independent risk factor of ischemic stroke and more correlated with 90 days outcome stroke

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Conflict of Interest

The authors state they have no conflict of interest.

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