The effect of long-term valproic acid treatment in the level of total cholesterol among adult

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Abstract:
Valproic acid (VA) is the antiepileptic, antimigraine and anti-mental disturbances agent. The use of VA is correlated to metabolic rearrangements including changes of lipoproteins; however, these effects still in debate. Herewith we analyze the effect of long-term VA treatment in the level of total cholesterol among adult. Sixty (30 case groups and 30 control groups) participants were asked for venous blood collection to examine the level of total cholesterol by enzymatic cholesterol oxidase phenol 4-aminoantipyrine peroxidase. The relationship of the long-term VA treatment and the level of total cholesterol was obtained from the analysis using the logistic regression analysis. Our analysis depicts that there is a relationship between the long-term VA treatment and the level of total cholesterol (P=0.024, odds ratio 0.272, 95% confidence interval 0.088–0.844). in conclusion, the long-term VA treatment reduces the level of total cholesterol in adult.

Keywords: Lipid profile, side effects, total cholesterol, valproic acid

Introduction
Valproic acid (VA) is a branched and short-chain fatty acid, which is widely used for the epilepsy, migraine, and mental problems.¹ Long-term VA treatment causes the increase of insulin and leptin levels resulting in hypercholesterolemia.²

Hypercholesterolemia is a risk factor for atherosclerosis.³ The total cholesterol multiply the risk of coronary heart disease by 2.52–3.20 in productive ages.⁴ Several studies also depicted that there is an elevation of mortality by atherosclerosis in people with epilepsy.⁵

The impact of VA on the level of total cholesterol is still in debate. Some studies demonstrated that there is a significant arrangement in cholesterol profiles, while others showed no impact of VA on cholesterol profiles.⁶ Regarding these controversies, we report the relationship of the long-term VA treatment and the level of total cholesterol among adult.

Materials and Methods
A Case-control study was performed among adult using VA for at least 1 month in the outpatient clinic Department of Neurology Dr. Soetomo Hospital Surabaya Indonesia period July-October 2018, with inclusion criteria: 18 years of age or more, and exclusion criteria: taking phenytoin and or carbamazepine, lipid-lowering drugs/statins and or gemfibrozil, and have a history of dyslipidemia before using VA accessed from interview and confirmed from medical record.

Sixty (30 case groups, level of total cholesterol more than 200mg/dL and 30 control groups,
level of total cholesterol 200mg/dL or less) subjects were obtained by consecutive admission sampling method, then asked for fasting at least 8 hours for venous blood collection for the level of total cholesterol examination.

The level of total cholesterol was examined in using the Cholesterol CHOD-PAP Method kit (Biolabo SAS, France) and sample preparation were performed according to insert kit from the manufacturer.

Data were analyzed as follow: categorical scale data such as sex, body mass index (BMI) category, history of smoking, other drug use, diabetes mellitus, and anti epileptic drugs combination were cross-tabulated using the Chi-square test, while for numerical scale data such as age, weight and height of body, BMI, and a daily dose of VA were analyzed using two-independent sample T-test because their data were normally distributed. The relationship of the long-term VA treatment and the level of total cholesterol was obtained from the analysis using the Chi-square test then continued with logistic regression.

This study was approved by The Local Research Ethics Committee with ethical clearance certificate number 0347/KEPK /VI/2018.

Results

The analysis of cross-tabulation for the confounding variables demonstrated that there were no significant association for sex, age, body height, body weight, BMI, history of other medication, diabetes mellitus, smoking and dose of VA, except the anti-epileptic drugs combination [Table 1].

At present, there is no study that shows a cutoff point of time-related to the association of the time of VA treatment and the level of total cholesterol, herewith we use cutoff points of time of 12 months, obtained from the Receiver Operating Characteristic (ROC) curve.

The magnitude of the effect of the long-term VA treatment in the level of total cholesterol is presented in Table 2. The result showed that there was a relationship between the long term VA treatment at the 12-month cutoff points with the level of total cholesterol ($p = 0.020$, OR 0.289, 95% CI 0.100-0.837).

Data analysis was then continued using logistic regression for the variable time of VA treatment, anti-epileptic drugs combination, and the level of total cholesterol. The result of the analysis still demonstrated that there was an association between the time of VA

| Variables                                | Total cholesterol levels, mean±SD, n (%) | P       | OR (95% CI)   |
|------------------------------------------|----------------------------------------|---------|---------------|
| Gender                                   | High                                   | Normal   |               |
| Men                                      | 15 (50)                                | 11 (36.7)| 0.297         | 1.727 (0.616-4.845)|
| Women                                    | 15 (50)                                | 19 (63.3)|               |                        |
| Age (year old)                           | 44.40±10.71                            | 37.97±16.76| 0.083         |               |
| Body weight (kg)                         | 62.23±12.23                            | 59.37±10.17| 0.328         |               |
| Body height (cm)                         | 159.73±7.61                            | 159.57±8.55| 0.937         |               |
| BMI (kg/m²)                              | 24.35±4.36                             | 23.34±3.79| 0.341         |               |
| Category of BMI                          | Overweight                              | Normal   |               |
| Men                                      | 11 (36.7)                              | 11 (36.7)| 1.000         | 1.000 (0.350-2.858)|
| Women                                    | 19 (63.3)                              | 19 (63.3)|               |                        |
| History of other medication              | Yes                                    | No       |               |
| Men                                      | 6 (20)                                 | 24 (80)  | 0.103         | 7.250 (0.815-64.457)|
| Women                                    | 1 (3.3)                                | 28 (96.7)|               |                        |
| Diabetes mellitus                        | Yes                                    | No       |               |
| Men                                      | 5 (16.7)                               | 25 (83.3)| 0.424         | 2.800 (0.498-15.734)|
| Women                                    | 2 (6.7)                                | 28 (93.3)|               |                        |
| Smoking                                  | Yes                                    | No       |               |
| Men                                      | 4 (13.3)                               | 26 (86.7)| 0.671         | 2.154 (0.363-12.764)|
| Women                                    | 2 (6.7)                                | 28 (93.3)|               |                        |
| Antiepileptic drugs combination          | Yes                                    | No       |               |
| Men                                      | 1 (3.3)                                | 29 (96.7)| 0.026*        | 0.095 (0.011-0.815)|
| Women                                    | 8 (26.7)                               | 22 (73.3)|               |                        |
| Daily dosage of valproic acid (mg/KgBW)  | 12.39±6.90                             | 12.42±6.23| 0.569         |               |

*P<0.05. BMI=Body mass index, OR=Odds ratio, CI=Confidence interval, SD=Standard deviation, mg/KgBW=Milligrams/Kilogram body weight
Kusumastuti and Jaeri: Duration of valproic acid treatment and total cholesterol levels

**Table 2: Association between duration of valproic acid treatment and serum total cholesterol levels**

| Total cholesterol levels, n (%) | P   | OR (95% CI)  |
|---------------------------------|-----|-------------|
| High                            |     |             |
| Normal                          |     |             |
| Duration of valproic acid treatment (months) |     |             |
| >12 (33.3)                     | 0.020* | 0.289       |
| <12 (66.7)                      |     |             |
| Total                           | 30 (100) | 30 (100)   |

*P<0.05. OR=Odds ratio, CI=Confidence interval

The result of this study showed that people who used VA for more than 12 months had a risk of having a high level of total cholesterol, 3.68 times less than those who used VA 12 months or less. This shows that the use of VA for more than 12 months decreases the level of total cholesterol. In another word, it is hypothesized that VA inhibits oxidative stress in the endoplasmic reticulum via the pathway of glycogen synthase kinase 3/β which contributes to cholesterol metabolism and the pathogenesis of atherosclerosis.[9]

In addition, it is hypothesized that VA enhances the proliferation, differentiation, and function of pancreatic beta cells after pancreatitis, thereby improving the process of insulin secretion through an inhibitory mechanism in histone deacetylase (HDAC).[10] HDAC is a protein that contributes in the recovery process of pancreatic beta cell damage, thereby improving the insulin secretion process.[11]

**Table 3: Multivariate analysis association between duration of valproic acid treatment, combination of antiepileptic drugs, and serum total cholesterol levels**

|                  | P     | Adjusted OR | 95% CI        |
|------------------|-------|-------------|---------------|
| Duration of valproic acid treatment | 0.024* | 0.272       | 0.088-0.844   |
| Combination of antiepileptic drugs  | 0.031* | 0.088       | 0.010-0.799   |

*P<0.05. OR=Odds ratio, CI=Confidence interval

**Discussion**

The relationship of long-term VA treatment and the level of total cholesterol in this study was seen at the cut-off point of 12 months. At the cut-off point of 12 months use of VA, it was found that there was a significant relationship between the time of VA treatment and the level of total cholesterol, where people who used VA for more than 12 months had a risk of 3.68 times smaller to have high serum total cholesterol levels as compared to people who used VA 12 months or less.

Our results are similar to those of Nisha et al., 2018 that compared the level of total cholesterol in a newly diagnosed group of epilepsy and epilepsy patients who were treated with VA for more than 12 months. The study proves that the level of total cholesterol in the group of VA was lower than the group of the newly diagnosed group.[6]

The result of our study is also similar to those of Kantoush et al., which showed that the level of total cholesterol, triglycerides, and other cholesterols in children with epilepsy given VA was lower than in the control group.[7] In addition, Abidemi et al., using alloxan-induced Wistar rats showed that VA significantly reduced triglyceride, total cholesterol, and LDL cholesterol levels.[8]

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**Conclusion**

The use of VA for more than 12 months decreases the level of total cholesterol.

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**Conflicts of interest**

There are no conflicts of interest.

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