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Serum Homocysteine Level and Lipid Profile in Migraine Patients Treated with Sodium Valproate

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Abstract

Background: Long-term treatment with sodium valproate affects the lipid profile and serum homocysteine level. Studies have revealed different results in epileptic patients and there is very little data available regarding the effects of sodium valproate in serum homocysteine level and lipid profile in migraine patients.
Objectives: The present study investigated the serum homocysteine level and lipid profile of migraine patients before and after sodium valproate prophylactic therapy.
Methods: This study included 52 adult patients with migraines who were candidates for prophylactic migraine treatment by sodium valproate. None of the patients were affected by hyperlipidemia syndromes, cardiovascular disease, stroke, diabetes, gout, carotid stenosis, hypertension, and thyroid, metabolic, or hepatic disorders. The initial peripheral venous blood sample was collected before receiving sodium valproate. Patients received sodium valproate 500 mg daily. The second venous blood sample was taken 3 months later, during the treatment period. Serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL), triglyceride (TG), high-density lipoprotein cholesterol (HDL), and homocysteine were measured by standard methods.
Results: The mean serum levels of TC, HDL, TG, and homocysteine increased significantly three months after treatment with sodium valproate. The mean serum level of LDL increased after treatment, however, the difference was not significant.
Conclusions: Sodium valproate increases the level of serum lipids in patients with migraines; therefore, the risk of cardiovascular diseases may increase by the long-term use of this drug as a prophylactic treatment in migraine patients. Consequently, in patients with other risk factors of cardiovascular disease, sodium valproate should be prescribed with caution.

Keywords: Homocysteine, Lipids, Migraine Disorders

1. Background

Migraine is a common, recurrent, and chronic primary headache disorder, which has been shown to have a global prevalence of 14.7%, 18.8% among women and 10.7% among men, worldwide (1). Generally, a migraine affects middle-aged patients and has a female-to-male ratio ranging from 3:1 to 4:1 (2). The pathophysiology of migraine is not yet completely clear, however, pathological vascular disorders are evidently involved in the pathophysiology of migraine (3-5). The results of recent studies have shown a consistent relationship between migraine and vascular disorders, including myocardial infarction, ischemic stroke, hemorrhagic stroke, and venous thromboembolism (2, 6).

Sodium valproate is an important drug frequently used for migraine prophylaxis. There are considerable evidences supporting the efficacy of sodium valproate in preventing migraine attacks and reducing headache frequency (7).

Despite the growing evidence that long-term treatment with sodium valproate in epileptic patients affects the lipid profile and serum homocysteine level, various studies have revealed different results (8, 9). These conflicting results were established in epileptic patients and based on our knowledge, there is very little data available regarding the effects of sodium valproate in serum homocysteine level and lipid profile in migraine patients (10).

In the present study, we investigated the serum homocysteine level and lipid profile of migraine patients before and after sodium valproate prophylactic therapy.

2. Methods

This study included 52 adult patients with aura free migraines (35 women, 17 men; mean age 35.8 $\pm$ 11.3 years)

who were candidates for prophylactic migraine treatment. The diagnosis of a migraine was made by two neurologists based on the International Classification of Headache Disorders (3 beta version) (11). This study was conducted in the Department of Neurology at Imam Khomeini General Hospital, which was affiliated to Tehran University of Medical Sciences (TUMS) from April 2016 to December 2017. None of the patients were on any drugs known to alter plasma lipids and homocysteine level in the last 12 months prior to study entrance; they were also not affected by hyperlipidemia syndromes, cardiovascular disease, stroke, diabetes, gout, carotid stenosis, hypertension, and thyroid, metabolic, or hepatic disorders. They had no history of cigarette smoking, substance abuse, and no family history of atherosclerosis or hyperlipidemia. In addition, pregnant or breast-feeding women were excluded from the study.

Characteristics of migraine attacks including frequency of attacks in month and duration of each attack in hours were collected at baseline and at the end of the study.

The initial peripheral venous blood sample was collected after overnight fasting before receiving sodium valproate. Patients received sodium valproate 500 mg daily. The second venous blood sample was taken 3 months later, during the treatment period.

Serum levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), and homocysteine were measured by standard methods. The serum level of low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald formula.

The present study conformed to the Helsinki Declaration guidelines and was approved by the Research Ethics Committee of TUMS. The study protocol was also fully explained to the patients and an informed consent was obtained from each participant.

The collected data was evaluated by the Kolmogorov-Smirnov test of normality. For within-group comparisons, the normal data were analyzed by paired sample *t*-test. Wilcoxon test was used for non-normally distributed data. Data analysis was performed using the Statistical Package of Social Sciences (SPSS) for Windows, version 19 and $P < 0.05$ was considered as statistically significant.

3. Results

This study included 52 patients with migraines (35 women, 17 men; mean age 35.8 ± 11.3 years). The patients' mean weight was 68.5 ± 10.3 Kg and 70.2 ± 10.4 Kg before and after the treatment, respectively ($P = 0.001$). Frequency of migraine attacks decreased during treatment period significantly (7.5 ± 2.8 times in month at baseline compared with 4.2 ± 2.4 at the end of study $P = 0.001$). Sodium valproate reduced the duration of migraine attacks, significantly (12.1 ± 8.3 hours compared with 6.6 ± 3.6; $P = 0.000$).

Table 1. Mean Lipid Profile and Serum Homocysteine Level Before and After Treatment with Sodium Valproate

	Before Treatment	After Treatment	P Value
TC	152.2 ± 32.5	164.9 ± 39.5	0.001
LDL	94.5 ± 27.3	101.9 ± 24.8	0.051
HDL	43.3 ± 9.0	47.7 ± 13.2	0.036
TG	107.3 ± 50.4	119.4 ± 47.0	0.048
Homocysteine	10.6 ± 3.3	11.9 ± 4.3	0.022

Abbreviations: HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

The mean serum levels of TC, HDL, TG, and homocysteine increased significantly three months after treatment with sodium valproate (Table 1). As shown in Table 1, the mean serum level of LDL increased after treatment, however, the difference was not significant.

4. Discussion

In the previous decades, numerous studies were performed for assessing the effect of sodium valproate on the serum lipid profile in seizure cases; however, the results of these studies have been controversial. Eiris et al. reported a significant decrease in serum total cholesterol, HDL, and LDL levels in patients with seizure during treatment with sodium valproate (12). In addition, Green et al. found similar effects of sodium valproate on lipid profiles in patients with migraine (10), whereas Nikolaos et al. and Chuang et al. could not confirm a change in serum lipid levels after sodium valproate treatment (13, 14). Other researchers have reported a significant increase in total cholesterol and LDL levels after valproate therapy (15). The present study showed a significant increase in serum lipid levels in patients with migraines. The exact mechanism of effect of valproate on the lipid profile has not yet been fully understood. Some studies have reported endocrinologic and metabolic side effects of sodium valproate including changes in neurotransmitters such as insulin, leptin, neuropeptide, ghrelin, and adiponectin. Alterations in these neurotransmitters cause obesity and metabolic disturbance; this mechanism may subsequently alter the serum lipid profile (8, 16).

Furthermore, the present study showed that sodium valproate increases serum homocysteine levels in migraine patients. Homocysteine is a simple sulfur-containing molecule, which is actively synthesized in the human body (17). Previous studies demonstrated that the increase in serum homocysteine level is associated with a high risk of cardiovascular diseases and stroke (8,

11). In fact, homocysteine is an independent risk factor for atherosclerosis progression (18).

Some studies reported that migraines are associated with increased risk of cardiovascular diseases in both short and long term and the risk is stronger in female patients with aura (5, 6). For example, a systematic review demonstrated an increased risk of myocardial infarction among patients with migraines in relation to those without migraines (19). It is already known that high serum levels of total cholesterol, LDL, and homocysteine are associated with increased risk of cardiovascular diseases, especially coronary heart diseases. Based on the present study, sodium valproate results in high serum lipids level in patients with migraines; consequently the risk of atherosclerosis may increase with the long-term use of sodium valproate as a prophylactic treatment in migraine patients.

The results of the present study may introduce some implications for clinical practice and research in this field. Regarding the aspect of clinical practice, the results showed that sodium valproate increases some factors, which are known as cardiovascular risk factors. Based on these results, in patients with other risk factors of cardiovascular disease such as hypertension, diabetes, positive family history, and smoking, sodium valproate should be prescribed with caution. Although the present study is a preliminary study with a small sample size, the physician can still prescribe other prophylactic drugs for migraine in these patients. Secondly, in view of medical research, there is a need for further methodologically rigorous studies for assessing the effect of sodium valproate on the lipid profile. In addition, evaluation of the effect of sodium valproate on the incidence of cardiovascular disease and death in long term will be more reasonable.

Nevertheless, the present study showed that valproate induces significant weight gain in migraine patients. This finding is consistent with several previous studies (20, 21). Weight gain may cause some problems in patients including a decline of compliance and treatment discontinuation. There are various theories for explaining the effect of valproate on weight gain: Dysregulation of the hypothalamic system, affecting the adipokine levels, hyper insulinaemia, and insulin resistance (8, 21).

Taken together, the present study suffers from several limitations. The main problem was the small sample size and the short term follow up. Moreover, as the outcome of our study was the changes in the serum lipid profile, it is recommended to perform a cohort study in the future that assesses the risk of cardiovascular diseases and death in migraine patients treated with or without sodium valproate.

In conclusion, sodium valproate increases the level of serum lipids in patients with migraines, therefore the risk of cardiovascular diseases may increase by the long term use of this drug as a prophylactic treatment in migraine patients. Consequently, in patients with other risk factors of cardiovascular disease, sodium valproate should be prescribed with caution.

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