Effect of propranolol with and without rosuvastatin on migraine attacks: a triple blind randomized clinical trial

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Aim: To investigate the effect of rosuvastatin in combination with propranolol in reducing migraine attacks. **Patients & methods:** In a clinical trial study with census method, 120 patients with migraine headache were included. Patients were randomly assigned (using block randomization) to either propranolol (10 mg twice a day) with rosuvastatin (10 mg daily; intervention group [n = 60]) or propranolol (10 mg twice a day) with placebo (control [n = 60]). **Results:** The numbers of attacks were significantly decreased in the intervention group at the end of second, third and fourth weeks from the beginning of the intervention ($p < 0.05$). **Conclusion:** In patients with migraine, concomitant administration of propranolol (10 mg twice a day) and rosuvastatin (10 mg daily) is effective in reducing migraine attacks.

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Migraine is one of the most frequent disorders and an important source of disability. This neurological condition has imposed an extensive clinical and financial burden on both the patient and society [1]. Migraine attacks are characterized by a wide range of sensory processing abnormalities leading to headaches, photophobia, phonophobia, osmophobia and nausea [2]. While previous investigations have detected a vascular origin for migraine [3], more recent studies have highlighted the role of cortical spreading depression, extravasation of neurogenic plasma protein and dysfunction of the brainstem in the pathogenesis of migraine or the associated symptoms [2]. Yet, the most accepted theory about migraine is the activation of the trigeminovascular system [4]. Several different medications have been suggested to alter the migraine attacks underlying pathogenic events to prevent or treat these attacks [5]. Beta-blockers have been frequently used as the first choice for the prevention of migraines [6]. While the exact mechanism of function of β -blockers in migraine prophylaxis is not clear, their influence on the catecholaminergic system and serotonin receptors in the CNS could be a possible function [7]. Propranolol is one of the most frequently prescribed β -blockers for migraine attack prevention [8,9]. A recent meta-analysis of randomized controlled trials has shown the efficacy of propranolol in controlling the episodic migraine headaches [10]. Statins have been also recently tested for the prevention of migraine attacks. This group of cholesterol-lowering drugs exhibits some cholesterol-independent functions such as amending endothelial dysfunction [11], decreasing inflammatory responses in vessels [12], reduction of platelet aggregation [13] and improvement of the function of the autonomic nervous system [14]. Administration of simvastatin in conjunction with vitamin D has been proven to effectively prevent migraine attacks in adult patients [15]. Statins have been suggested as a useful medication in migraine management since they could decrease the elevated cardiovascular risk in migraineurs, hence reducing the migraine attacks [16]. Moreover, a recent study has suggested atorvastatin as an alternative for sodium valproate in the

prevention of migraine attacks with similar efficacy and lower complications [17]. Besides, results of animal studies have introduced atorvastatin as a promising candidate for migraine treatment or prevention via decreasing NF- κ B signaling in trigeminal nucleus caudalis [18]. Additionally, statins can suppress potassium channels that according to recent studies are linked to migraine pathophysiology [19].

The aim of the present study is to assess the efficacy of combination therapy including rosuvastatin and propranolol to prevent migraine attacks through a randomized, triple-blind, placebo-controlled study design.

Patients & methods

The study was conducted in Imam Khomeini Clinic and Sina hospital, Hamadan, Iran, from January 2018 to September 2019. Vitamin D levels were assessed in all the studied participants at the baseline using the Euroimmun ELISA (the enzyme-linked immunosorbent assay) kit (Germany).

Eligibility criteria

The convenience nonprobability method was used for sampling. Sampling was continued for 8 months. During this time period, 120 patients who met the criteria entered the study. The inclusion criteria were as follow: age ≥ 18 years, more than 3 years history of migraine, presence of migraine attacks ≥ 4 days/month, total cholesterol levels between 150 and 190 mg/dl. The diagnosis of migraine was accomplished according to the International Headache Society for headache classification (ICHD-III) criteria [20]. Exclusion criteria were pregnancy, breastfeeding, hepatic or renal failure, memory defects, sensitivity to statins and presence of atherosclerotic disorders.

Intervention

Patients were randomly assigned to intervention and control groups. As we wanted to increase compliance of patients to the prescribed drugs and avoid self-prescribed medications, we did not include the third arm with placebo and placebo 'nothing arm'. A block randomization method was utilized to randomize the patients into two groups with equal sizes. Random allocation sequence, enrollment of participants and assignment of participants to groups were performed by trained staff. The patients, the physicians who assessed the patients, and the staff who analyzed the data were not aware of patients' status until the end of the study as they were separated from those involved in the patients' allocation process. The study was designed as a triple-blind study. The intervention group ($n = 60$) received propranolol (10 mg film-coated tablets, twice a day, dosage form: 10 mg tablet) and rosuvastatin (10 mg film-coated tablets, daily, dosage form: 10 mg tablet); while the control group ($n = 60$) were treated with propranolol (10 mg film-coated tablets, twice a day, dosage form: 10 mg tablet) and placebo. Special diets and aerobic exercise were recommended for both groups and the number of migraine attacks was monitored for 4 weeks. No rescue medications were used for acute migraine attacks. No concomitant medication was allowed during the study period. Questionnaires (Supplementary Data) were designed by the research team and filled by the trained staff via telephone contacts with patients at the end of each week during the study period (4 weeks). The numbers of migraine attacks were calculated by asking from patients. All patients had pain-free intervals. The frequency of attacks was assessed accordingly. Compliance with medications was checked by the staff during telephone contacts. The patients were on a migraine diary. Yet, patients were not on prophylactic migraine medication at baseline. Patients were contacted at the end of each week to assess their possible complications, number of migraine attacks and compliance to medications. The study protocol was approved by ethical committee of Hamadan University of Medical Sciences. Written consent forms were signed by study participants and permission to use human data was obtained. The clinical trial number was IRCT20120215009014N267. Figure 1 shows the study flowchart.

Primary outcome

Numbers of migraine attacks per month were obtained through an interview with the patients.

Secondary outcomes

Secondary outcome was assessment of the side effects such as hepatic failure, gastrointestinal complications, memory defects, myopathy and hypersensitivity to statins. Safety was described by occurrence of clinically observable side effects.

Figure 1. Study flowchart. Assessment of patients' eligibility was a stepwise process including assessments through phone calls, interview and laboratory tests. Then, the 120 eligible persons were randomly assigned to intervention and control groups, respectively.

Statistical methods

Data analysis was conducted using SPSS v. 21 (IBM Corp., IL, USA). All the analyses were estimated at 95% CIs. *p*-values below 0.05 were regarded as significant. Categorical variables were described as ratios or percentages and shown in tables and diagrams. The normality of the frequency of migraine attacks was assessed using the Kolmogorov–Smirnov test. Mean values of the frequency of migraine attacks were compared using the Mann–Whitney test. Mean values of migraine attacks per month based on the vitamin D levels were also compared using the Kruskal–Wallis test and Tukey *post hoc* test.

Results

Baseline characteristics of study participants

Each of the intervention and control groups included 60 individuals with similar sex ratios (female/male: 56 [93.3%]/4 [6.7%]). The study groups were also matched in terms of age (mean age $\pm$ standard deviation [SD] values: 36.27 ± 10.58 and 33.72 ± 10.16 in the control and intervention groups, respectively; $p = 0.185$). Besides, the participants showed no difference in their serum levels of vitamin D ($p = 0.125$). Table 1 shows baseline characteristics of patients in each group. There was no dropout during the study period.

Table 1. Baseline serum levels of vitamin D in intervention and control groups of the study.

Parameters	Control group	Intervention group
Age (mean $\pm$ SD)	36.27 $\pm$ 10.58	33.72 $\pm$ 10.16
Sex ratio (female/male)	56 (93.3%)/4 (6.7%)	56 (93.3%)/4 (6.7%)
Vitamin D levels:		
– Deficient	23 (38.3%)	34 (56.7%)
– Insufficient	10 (16.7%)	6 (10.0%)
– Sufficient	27 (45.0%)	20 (33.3%)
– Sum	60 (100%)	60 (100%)

Deficient: <20 ng/ml; insufficient: 20–30 ng/ml and sufficient: $\geq$ 30 ng/ml.**Table 2. Comparison in number of migraine attacks between intervention and control groups.**

Time point	Control group	Intervention group	p-value [†]
First week	2.56 $\pm$ 2.69	1.90 $\pm$ 2.06	0.356
Second week	2.27 $\pm$ 2.35	1.46 $\pm$ 1.96	0.022
Third week	2.24 $\pm$ 2.26	1.14 $\pm$ 1.69	0.008
Fourth week	2.53 $\pm$ 2.38	1.00 $\pm$ 1.80	<0.001

[†] p-value estimated from the Mann–Whitney test.**Table 3. Number of migraine attacks in the study period in intervention group based on vitamin D levels.**

Vitamin D levels	Number of attacks	p-value
Deficient	6.84 $\pm$ 7.24	0.002
Insufficient	8.33 $\pm$ 7.81	
Sufficient	2.35 $\pm$ 4.26	

Deficient: <20 ng/ml; insufficient: 20–30 ng/ml and sufficient: $\geq$ 30 ng/ml

Four individuals in the control group (6.7%) and one in the intervention group (1.7%) had aura. Based on the results of the Fisher exact test, no difference was detected between the studied groups in terms of this issue ($p = 0.171$).

At the beginning of the study, the mean ($\pm$ SD) values of migraine attacks per week were 4.38 ($\pm$ 2.39) and 4.05 ($\pm$ 2.09) in control and intervention groups, respectively. Based on the Mann–Whitney test results, there was a difference in the number of migraine attacks between the studied groups ($p = 0.872$).

Primary measures

Mean numbers of migraine attacks per week in the intervention and control groups were 1.90 versus 2.56 ($p = 0.356$), 1.46 versus 2.27, 1.14 versus 2.24 ($p = 0.008$) and 1.00 versus 2.53 ($p < 0.001$), at the end of the first to fourth weeks of the study, respectively. No significant difference was recorded in the number of migraine attacks between the two groups at the end of the first week following the intervention. However, the numbers of attacks were significantly declined in the intervention group at the end of the second, third and fourth weeks. Table 2 shows the results of comparisons.

Based on the results of repeated measures tests, numbers of migraine attacks were different between study groups after 4 weeks.

Based on the results obtained from Kruskal–Wallis and Tukey *post hoc* tests, the number of migraine attacks per month was significantly lower in the patients with sufficient vitamin D levels as compared with those suffering from deficient vitamin D levels ($p = 0.016$). However, ‘sufficient versus insufficient’ and ‘insufficient versus deficient’ comparisons showed no significant differences (p -values = 0.051 and 0.607, respectively). Rosuvastatin treatment did not significantly alter vitamin D levels in the intervention group ($p = 0.4$).

Table 3 shows the number of migraine attacks in the study period in intervention group based on vitamin D levels.

Secondary measures

Routine physical examinations and history taking were carried out to assess the possible side effects. There was no report of statin-associated side effects such as hepatic failure, gastrointestinal complications, memory defects, myopathy or hypersensitivity in patients.

Discussion

In the present triple-blind randomized clinical trial, the effect of rosuvastatin coadministration with propranolol on decreasing the number of migraine attacks was assessed. In this study, we used low-dose propranolol to prevent side effects such as hypotension. The study period was shorter than studies, which assess efficacy of medications in migraine prophylaxis. However, as there was no similar study in the literature, we aimed at identification of short time effects of rosuvastatin in migraine prophylaxis. In comparison with single propranolol therapy, rosuvastatin and propranolol coadministration significantly declined the number of migraine attacks. Moreover, migraine attacks were significantly more frequent in patients with insufficient vitamin D levels as compared with those having sufficient vitamin D highlighting the impact of adequate vitamin D on ameliorating migraines.

Previous studies have reported a higher prevalence of cardiovascular disorders among migraineurs. A large, prospective cohort study by Kurth *et al.* in female migraineurs showed a reliable association between migraine and cardiovascular disease and cardiovascular disease-induced mortalities [21]. Moreover, migraine has been recognized as an inflammatory condition caused by stimulation of the trigeminal neurovascular complex; therefore, statins could be beneficial in this disorder especially for patients with aura [22]. A recent meta-analysis of 16 cohort studies has verified the association between migraine and higher long-term risk of cardiovascular and cerebrovascular events [23]. In this regard, statins can be helpful in the treatment of migraine patients by decreasing the risk of cardiovascular events. In a randomized, double-blind, placebo-controlled trial, Buettner *et al.* reported the efficacy of simvastatin plus vitamin D3 in the prevention of headaches in adults with episodic migraines [15]. Moreover, a previous cross-sectional study revealed the association of statin with a lower incidence of severe headache or migraines, especially in those with higher serum vitamin D levels [24]. This observation is in line with our results regarding the higher efficacy of rosuvastatin in reducing migraine attacks in patients with sufficient vitamin D levels. According to these studies, patients' exposure to statins might decline migraine-associated cardiovascular events. Therefore, the increase in the cost and chances of statin-related adverse events could be compensated by the reduced risk of cardiovascular events. This note is highlighted by the observed higher frequency of dyslipidemia in migraineurs compared with controls as a recent study reported high cholesterol and LDL levels in 42 and 44% of migraineurs, respectively; whereas these values were 24% among the controls [25]. It is worth mentioning that statin are regarded as safe drugs as the risk of statin-induced serious muscle injury, serious hepatotoxicity and statin-induced newly diagnosed diabetes mellitus are negligible. Moreover, the great statin-associated decrease in the risk of atherothrombotic stroke, total stroke and other cardiovascular events is considerably more than possible side effects of these drugs [25]. Meanwhile, safety profile of propranolol in various conditions have been reported to be acceptable [26].

No significant change was observed in vitamin D levels of the intervention group. Some previous studies demonstrated the role of rosuvastatin in increasing the serum vitamin D levels [27], yet others challenged this observation and stated that these results need to be confirmed in well-designed prospective studies in which the effects of confounding factors such as ultraviolet-B irradiance and oral vitamin D supplementations are controlled [20]. Thus, there is no general consensus on this point. However, if effects of rosuvastatin on serum vitamin D levels are verifies, this drug can be regarded as a medication that ameliorates migraine via different mechanisms.

Our study had some limitations regarding the follow-up period and sample size. In this context, the verification of the obtained results by larger cohorts of patients and for longer periods is highly encouraged. Moreover, we have not reported data of mean migraine days and vitamin D levels at follow-up, which is recommended to be assessed in future studies.

Conclusion

Taken together, our results support the beneficial effects of a certain statin namely rosuvastatin in reducing migraine attacks in Iranian patients. As statins can amend endothelial dysfunction through different mechanisms [28], the administration of rosuvastatin might also decrease the elevated risk of vascular diseases among patients suffering from migraines. Based on the higher efficacy of rosuvastatin in reducing migraine attacks in patients with sufficient

vitamin D levels, further clinical trials are recommended to test the effects of rosuvastatin plus vitamin D in migraineurs.

Future perspective

Based on the extensive clinical and financial burden of migraine, future studies should focus on introduction of novel strategies for prevention of migraine headache. Moreover, safety of the prescribed medications should be assessed through laboratory tests.

Summary points

- We investigated the effect of rosuvastatin in combination with propranolol in reducing migraine attacks.
- Each of the intervention and control groups included 60 individuals with similar sex ratios.
- Baseline characteristics were matched between study groups at the beginning of the study.
- There was no significant difference in number of migraine attacks between two groups at the end of the first week following intervention.
- The numbers of attacks were significantly decreased in the intervention group at the end of second, third and fourth weeks from the beginning of the intervention.
- Numbers of migraine attacks were significantly higher in patients with insufficient vitamin D levels compared with those having sufficient vitamin D.
- In patients with migraine, concomitant administration of propranolol (10 mg twice a day) and rosuvastatin (10 mg daily) is effective in reducing migraine attacks.
- Based on the higher frequency of cardiovascular event among migraineurs, administration of statins might be beneficial in these patients.

Financial & competing interests disclosure

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Ethical conduct of research

The study protocol was approved by ethical committee of Hamadan University of Medical Sciences. Written consent forms were signed by study participants and permission to use human data was obtained. The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Data sharing statement

The authors certify that this manuscript reports original clinical trial data, IRCT20120215009014N267. Individual participant data that underlie the results reported in the article, after deidentification (text, tables, figures and supplement) are available along with the study protocol and statistical analysis. The data will be available from the publication date up until 5 years. Proposals to access data will be at the discretion of the corresponding author and to gain access, the data requestor will need to sign a data access agreement form.

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