RESEARCH ARTICLE

Comparing the Effect of Venlafaxine and the Combination of Nortriptyline and Propranolol in the Prevention of Migraine

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Abstract

Background: Migraine is a debilitating neurological condition, which can be categorized into episodic and chronic groups based on its clinical pattern. Avoiding the risk factors exacerbating migraine is not enough to reduce the frequency and severity of migraine headaches, and in the case of non-receiving proper drug treatment, episodic migraines have the potential to become chronic, which increases the risk of cardiovascular complications and leaves great impact on the quality of life of patients and increasing the health-care costs. The objective of this research was to compare the effects of venlafaxine (VFL) and nortriptyline and propranolol in preventing migraines. **Methods:** This research is an interventional study performed on 60 patients with migraine admitted to the neurological clinic. Patients were visited at 3 time intervals. In each stage, the variables of headache frequency, headache severity, nausea, vomiting, and drowsiness were recorded. Data were analyzed using SPSS 23 software. **Results:** VFL drug with a daily dose of 37.5 mg is not only more tolerable in the long term but also leaves better effect in reducing the frequency and severity of headaches compared to the combination of nortriptyline and propranolol. **Conclusion:** VFL is an appropriate, effective, and tolerable alternative to migraine treatment.

Key words: Migraine, nortriptyline, propranolol, venlafaxine

INTRODUCTION

Migraine is known as a common neurological disorder and causes many complications. Migraine headache is a painful and debilitating neurological condition resulting in poor quality of life and leaving high economic impact on the patient.[1,2] Based on its pattern, migraine can be divided into episodic and chronic groups.[3] Episodic migraine (EM) and chronic migraine (CM) are different from regular daily headaches. Episodic migraine has a headache <15 days/month, and CM refers to a headache of 15 days or more per month for at least 3 months.[4] Many risk factors such as age and ethnicity, obesity, nightly snoring, head trauma, stressful events, and uncontrolled consumption of opioids and barbiturates are involved in the transforming episodic migraine into a CM. The first step in preventing the transforming episodic migraine to CM is protecting against these risk factors. However, avoiding these risk factors has not shown reducing the effect on the incidence of CM.[5]

Patients with CM are less likely to have full-time job than patients with episodic type, and they are at risk of job incapacity, anxiety, chronic pain, and depression 2 times more than patients with episodic migraine. In addition, CM is associated with 40% more risk of heart diseases and angina and 70% more risk for stroke.[5] The main drugs used for migraine prophylaxis in different studies include some non-amitriptyline, flunarizine, oxetorone, pizotifen, methysergide topiramate, steroid anti-inflammatory drugs, and sodium valproate.[6] However, three drugs of amitriptyline, propranolol, and verapamil are the most commonly used drug for migraine prophylaxis among physicians and neurologists.[7] One of the drugs, drawn the attention of migraine prophylaxis studies, is venlafaxine (VFL). Different studies have investigated the impact of VFL on migraine prophylaxis. Studies conducted by Ozyalcin *et al*. have

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shown that VFL is more effective than placebo and is safer and better for migraine prophylaxis.[8]

Liu *et al*. examined the efficacy of VFL, flunarizine, and valproic acid in preventing migraine. Results confirmed the efficacy and safety of VFL, flunarizine, and valproic acid in migraine prevention.[9] The most commonly seen complications of VFL in different studies include nausea and vomiting, heartbeat, tachycardia, and drowsiness, and the moderate effect and relative prevalence of complications have caused that many patients not continue these drugs for long term. However, its significant positive response has been shown in a group of patients, and investigation to find the most appropriate drug for migraine prophylaxis provides an interesting area for research activities.[6] Several studies have been conducted on VFL to achieve a suitable dose with optimum effect and minimal side effects, but studies on the optimum dose of using it have not yet been concluded and the dose differences are seen in several studies.[10-12] In this research, VFL with a daily oral dose of 37.5 mg will be compared with the current treatment, i.e. combination of nortriptyline and propranolol, in terms of impact on reducing the frequency of headaches and common side effects.

METHODOLOGY

This research is an interventional study conducted on 60 patients with migraine admitted to the neurological clinic. Inclusion criteria of research included migraine patients without aura aged 18–70 years, having at least three headache attacks per month, discontinuation of previous prophylactic drug at least 2 weeks before, and non-pregnancy. The initial sample was randomly divided into two groups (each containing 30 people). Accordingly, the first patient referred to the clinic was included to the first group and the next patient was included the second group, and rest of the patients were included in these groups in the same way. For each group, a calendar record booklet was given, in which the number of headache, the severity of the headache (between 1 and 10), nausea, vomiting, and drowsiness were recorded per year of the treatment period.

During the 10-week period of treatment of the patients, the first group received VFL 37.5 mg daily and the second group received nortriptyline25 mg at nights and propranolol tablet 20 mg every 12 h. Each of the patients was visited 3 times during the 10-week treatment period. At each turn, the recorded data were taken, and the inclusion and exclusion criteria were reviewed. In project implementation, during the first, second, and third visits, three of the first group and five of the second group were excluded from the research and statistical analysis due to the lack of timely and accurate completion of the variables record booklet. At the end of research, and in the third visit, the latest data were collected for comparing, and statistical analysis and the repeated measure ANOVA test were performed on obtained data. The data were recorded daily by the patients in the calendar record booklet, and then, the data of three visits were collected and entered into SPSS 23 software to be analyzed.

RESULTS

Sample size of research began with 60 patients, and after 10 weeks of follow-up and three visits, it ended with 53 patients. Data of 7 people excluded from the research were considered in the statistical analysis. The first group included four males (13%) and the second group included six males (20%). Comparing two groups in terms of the effect on the frequency of headaches, the first group (VFL) with a mean of 3.62 ± 0.025 had a significant difference in terms of the frequency of headache, and it was better than the second group (with mean of 3.95 ± 0.026) ($P < 0.001$) [Table 1]. In addition, the reducing rate of frequency of headaches was higher in the first, second, and third visits and also in total in the VFL group [Table 2]. Comparing the two groups in terms of the effect on the headache severity, the VFL group with a mean of 6.18 ± 0.037 significantly performed better than the second group with a mean of 6.60 ± 0.037 ($P < 0.001$) [Table 1]. In addition, intragroup investigation in both groups in all three visits, significant difference was seen between two groups in the favor of VFL group in terms of the reduction in headache severity [Table 3]. Comparing the two groups in terms of the effect on the frequency of headaches, the first group (VFL) with a mean of 3.62 ± 0.025 showed significant difference with second group (with a mean of 3.95 ± 0.026) ($P < 0.001$) [Table 1]. Moreover, the rate of reduction on the frequency of headaches was also higher in the first, second, third, and also in total in the VFL group [Table 2]. Comparing the two groups in terms of the effect on headache severity, the VFL group with a mean of 6.18 ± 0.037 showed significantly better performance than the second group with a mean of 6.60 ± 0.037 ($P < 0.001$) [Table 1]. Intragroup investigation in both groups in both drug groups at three visits, the reduction was seen in headache severity, in which this significant difference was for the favor of VFL group

Table 1: The general comparison of two groups in terms of the effect of drugs on the five variables studied

Variable	Mean±SD		*P*
	Group 1	Group 2	
Headache frequency	3.62±0.025	3.95±0.026	<0.001
Headache severity	6.18±0.037	6.60±0.037	<0.001
Nausea	0.33±0.017	0.43±0.017	<0.001
Vomiting	0.056±0.009	0.13±0.009	<0.001
Drowsiness	0.57±0.006	0.35±0.007	<0.015

SD: Standard deviation

[Table 3]. Comparing the two groups in terms of rate of incidence of nausea showed that it was higher in the second group than that in the first group, with a mean of 0.43 ± 0.017, in which the difference was statistically significant ($P < 0.001$) [Table 1]. Moreover, intragroup comparison in both drug groups at the second group and the third visits, the nausea increased in both groups. In general, in all study period, the difference was statistically significant and the second group was more affected [Table 4]. Investigating the rate of incidence of vomiting showed that it was higher in the second group significantly than that in the first group with a mean of 0.13 ± 0.009 ($P < 0.001$) [Table 1], and this value showed significant increase in both groups during the second and third visits. In general, the first group patients were significantly affected less by vomiting [Table 5]. In comparing the rate of incidence of drowsiness between two groups, the first group with a mean of 0.57 ± 0.006 was statistically ($P = 0.015$) more affected by drowsiness [Table 1]. Drowsiness complication also increased significantly after the first visit. In general, the increase in the first group was more significant [Table 6].

Table 2: Comparison of the course of changes in the frequency of headaches between the groups at different measurement periods

Studied group	Group 1	Group 2
Measurement periods	**Mean±SD**	
First visit	3.82±0.821	4.11±0.740
Second visit	3.71±0.944	4.07±0.760
Third visit	3.33±0.863	3.65±0.698
Total	3.62±0.025	3.95±0.026

SD: Standard deviation

Table 3: Comparing the course of changes of headache severity between the groups at different measurement periods

Studied group	Group 1	Group 2
Measurement periods	**Mean±SD**	
First visit	0.230±0.06	0.274±0.08
Second visit	0.230±0.06	0.320±0.120
Third visit	0.230±0.06	0.382±0.18
Total	0.09±0.056	0.009±0.130

SD: Standard deviation

Table 4: Comparison of the course of changes in nausea changes between the groups at different measurement periods

Studied group	Group 1	Group 2
Measurement periods	**Mean±SD**	
First visit	0.573±0.270	0.600±0.290
Second visit	0.626±0.300	0.626±0.270
Third visit	0.633±0.330	0.838±0.230
Total	0.017±0.330	0.017±0.43

SD: Standard deviation

DISCUSSION

Given that none of the migraine prevention options has a 100% effect and does not completely treat the disease, it is practically impossible to introduce a drug as the first line of prophylaxis treatment, but one of the most commonly used clinic treatments is a combination of nortriptyline and propranolol.[13] These two compounds are not well tolerated in the long term due to complications such as nausea, vomiting, and drowsiness, and thus, many migraine patients are not covered with appropriate prophylactic drugs. As a result, not only their quality of life is not improved but also by discontinuation of prophylaxis, the risk of the transforming the episodic migraine to the chronic type increases, and subsequently, other major complications such as cardiovascular incidents increase.[14]

The objective of this research was to evaluate the use of VFL as an alternative to the combination of nortriptyline and propranolol, assuming that it has fewer side effects with similar or greater effects on the frequency or severity of headaches, and thus, it is more tolerable in the long term. Based on the results of this interventional study, the VFL drug used in Group 1 intervention acted significantly better than the combination of nortriptyline and propranolol in Group 2 in terms of the effect on the frequency of headaches and severity of headache.

Table 5: Comparison of the course of changes in vomiting between the groups at different measurement periods

Studied group	Group 1	Group 2
Measurement periods	**Mean±SD**	
First visit	0.573±0.270	0.600±0.290
Second visit	0.626±0.300	0.626±0.270
Third visit	0.633±0.330	0.838±0.230

SD: Standard deviation

Table 6: Comparison of the course of changes in drowsiness between groups in different measurement periods

Studied group	Group 1	Group 2
Measurement periods	**Mean±SD**	
First visit	0.164±0.03	0.183±0.03
Second visit	0.228±0.05	0.183±0.03
Third visit	0.285±0.09	0.183±0.03
Total	0.006±0.57	0.007±0.35

SD: Standard deviation

Moreover, two complications of nausea and vomiting were significantly lower in the first group than those in the second group. The second group showed better than the first group only in the case of drowsiness, in which this difference was statistically significant. The effect of amitriptyline (AMT) and VLF on patients was examined in a study by conducted by Bulut *et al*. It was reported that VLF side effects are low compared to AMT side effects. As a result, they recommended that VLF is to be considered for migraine prevention.[15] Some researchers use nortriptyline as the first line of treatment for migraine prophylaxis. In a research conducted by Krymchantowski *et al*., a combination of nortriptyline and topiramate was recommended for patients and they stated that this compound has advantages over other compounds.[16] In one of the first studies, in which the effect of nortriptyline was examined, this drug with low dose of 25 mg reduced the frequency of headaches by up to 50%, indicating the anti-migraine effect of the drug.[17]

The common nortriptyline side effects, including drowsiness, orthostatic hypotension, skin reactions, nausea, and constipation, have led researchers to seek less anti-depressant drug with less side effects.[5,18] VFL, as norepinephrine, also inhibits the reabsorption of serotonin and nortriptyline, but due to its different chemical structure, it has fewer side effects. Due to these characteristics, several studies have investigated the effect of VFL on migraine headaches, but a few of them have achieved satisfactory results.[12,18]

In a research conducted by Liu *et al*. in 2017, they reported that the obtained data confirmed the effectiveness and safety of VFL, flunarizine, and valproic acid in migraine prevention. Studies conducted by Liu *et al*. showed that VFL and valproic acid were more effective than flunarizine in reducing the severity of vertigo, but valproic acid showed less effect in reducing severity of vertigo compared with VFL and flunarizine.[9] In a study conducted by Ozyalcin *et al*., VFL was compared with placebo, which showed a significant difference. However, in this research, VFL was used in a dose of 75 mg.[8] In another research conducted by Tarlaci, 12 mg of escitalopram (ECLM) was compared to 70 mg of VFL in a 3-month period. In this research, VFL significantly reduced the frequency and severity of headaches, but in terms of tolerability, ECLM showed better performance, which it might be due to relatively high dose of vanliafoxin.[12]

CONCLUSION

The results of this research suggest that VFL with a daily dose of 37.5 mg is not only more tolerable in the long term but also seems to be effective in reducing frequency and severity of headaches than the combination of nortriptyline and propranolol. The results of this research could be considered by neurologists and physicians and researchers. VFL drug with low dose of 37.5 mg is an appropriate, effective, and tolerable alternative for migraine patients.

Recommendations

A significant effect of VFL with low dose of 37.3 mg on the reduction of the frequency of headaches and their severity along with its appropriate tolerability makes researchers interesting in conducting research with larger size and more complete randomization and research compare this drug with placebo.

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