Original Article

A randomized clinical trial comparison of venlafaxine with gabapentin on reducing pain in patients with neuropathic diabetic pain

Ramin Atighi[1], Sourena Nazarbaghi[2], Rahim Zahedi[3], Rezvan Nourozzadeh[2*]

[1]Medical Doctor, Private Practice, Urmia university of Medical Sceicnes ,Urmia , Iran. [2]Department of Neurology, Imam Khomeini Hospital, Urmia University of Medcial Sceinces, Urmia, Iran. [3]Endocrinologist, Private Practice, Shahid Beheshti University of Medcial Sceinces, Tehran, Iran.

Correspondence: Rezvan Nourozzadeh, Department of Neurology, Imam Khomeini Hospital, Urmia University of Medcial Sceinces, Urmia, Iran. norouzzadeh.r@umsu.ac.ir

ABSTRACT

Distal Symmetric neuropathy or diabetic neuropathy is the most common complication of diabetes and a significant cause of disability approximately 15 to 20 percent of patients have painful symptoms that can impair their function and quality of life and cause-related disabilities. This study's aim was to compare Venlafaxine with Gabapentin in reducing pain in patients with neuropathic diabetic pain and pain intensity reduction in both groups. The present study was a clinical trial. In this study, 60 patients were studied. Pain intensity in patients was estimated before treatment and eight weeks after treatment using VAS, which was given a score of one to ten, depending on the pain. The differences between the two groups in response to treatment were compared using statistical tests. Rate of pain reduction in both groups before and after treatment with Venlafaxine and Gabapentin was statistically significant (P <0.001).

The severity of initial and post-treatment pain in our study was significantly higher in the Gabapentin-treated group than in the Venlafaxine group (P <0.05). . Rate of pain reduction in both groups before and after treatment with Venlafaxine and Gabapentin was statistically significant (P <0.001) The results of our study, like many previous studies, showed that venlafaxine could be used as an effective drug for treating diabetic neuropathic pain. Results of this study also showed that the effect of Venlafaxine and Gabapentin in the reduction of pain intensity score is the same, and these two drugs are not superior to each other.

Keywords: Neuropathy, Venlafaxine, Gabapentin, Diabetes, Pain

Introduction

Neuropathic pain is defined as injury and disease in the somatosensory system. Nervous system enables the human being to perceive temperature, touch, pain, pressure, and vibration. Nerve fibers of this system originate in the fascia, muscles, joints, and skin and include heat, mechanical, chemical, itching, and pain receptors. Prevalence of neuropathic pain is estimated to be about 1 to 8% in the adult population [1]. Diabetic neuropathic pain (DNP) manifests as an electric shock with itching, burning, sharp pain, and tingling. Pain is usually moderate to severe, intensifying at night and interfering with sleep [2, 3]. These factors impair the patient's quality of life, daily activities, patient's mood and affect, all of which reduce the patient's social presence [2, 3]. Pathogenesis of DNP is unclear. Several theories support these neuropathic pains including changes in peripheral nerve blood vessels, metabolic and autoimmune disorders and their association with, changes in sodium and calcium channel expression, and recently central pain mechanisms, including increased thalamic blood flow and lack of Moderate suppressive / stimulus modalities are defined and glial cell activation [4].

Various classes of treatment have been approved, which include Antiepileptics such as Pregabalin, and Gabapentin, Carbamazepine, Serotonin-norepinephrine reuptake inhibitors(SNRI), e.g., Duloxetine, topical medication such as Capsaicin, and several off-label medications such as Antidepressants like Tricyclic antidepressants, Opioids, and Venlafaxine [5, 6]. Pregabalin has a higher addictive potential compared to Gabapentin. Unfortunately, several adverse effects, including antihistamine-mediated or anticholinergic adverse effects are reported in the patients, including sedation and dizziness [7] .Venlafaxine is a vital pain controller because the

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medication is a potent inhibitor of serotonin and also retaking of norepinephrine in the neuronal site as well as Venlafaxine has shown a weak inhibition of dopamine retaking [8]. Venlafaxine does not have antimuscarinic effects and is devoid of antihistamine-mediated adverse effects [7].

Simpson *et al*. [8] Reviewed the effects of Gabapentin and venlafaxine in treating of diabetic neuropathy in a double-blind clinical trial in 2001 in Michigan, USA, according to the results of this study, for patients who do not respond to monotherapy with Gabapentin, Venlafaxine can be prescribed among Gabapentin.

In a double-blind clinical trial in the United States in 2004, Rowbotham *et al*. [9] Examined the therapeutic effect of extended-release venlafaxine in treating painful diabetic neuropathy. This study showed that venlafaxine was safe and effective in diabetic neuropathy.

Razazian *et al*. [10] evaluated the efficacy and safety of Pregabalin, Venlafaxine, and Carbamazepine in patients with painful diabetic peripheral neuropathy over one year. According to the results of this study, it can be inferred that all three drugs are effective in reducing the pain of diabetic neuropathy.

Because of the high prevalence of neuropathic pain and the high number of patients with this disease in medical centers in this study, we decided to compare the effect of Venlafaxine with Gabapentin in patients with diabetic neuropathic pain referred to Urmia Endocrinology and Neurology Clinic.

Materials and Methods

The study was performed as a randomized clinical trial to compare the effect of Venlafaxine with Gabapentin in patients with diabetic neuropathic pain. In this study, 60 patients were studied who moved blindly from left to right according to the random number table, and patients were divided into two groups so that patients with even numbers in the Venlafaxine group and odd numbers in the Gabapentin group.

Inclusion criteria

1) Neuropathic pain was over six months
2) No painkillers in the past month
3) Impairment in monofilament test or paresthesia in the form of gloves and socks
4) History of neuropathic pain for at least three months

Exclusion criteria included

1) Uncontrolled and poorly controlled blood pressure
2) History of seizures
3) Use of anticonvulsant drugs
4) Suffering from another type of pain unrelated to diabetic neuropathy pain.

Using the formula, according to the standard deviation and mean of pain based on VAS at the end of the second day (venlafaxine group: 2.70 9 9.12 and control group: 2.80 13 4.13) based on a study by Razazian *et al*. [10] Considering the 95% confidence interval and 80% test power, at least 29 people in each group were determined.

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \times (S_1^2 + S_2^2)}{\overline{X_1} - \overline{X_2}} \qquad (1)$$

Data collection tools were observation, interview, information forms, and use of laboratory findings.

Demographic and clinical information of patients, including age, sex, education, smoking, history, duration of diabetes, history of other systemic diseases, etc., extracted from patient's clinical records. Pain intensity in patients was estimated before and eight weeks after treatment using VAS, which was given a score of one to ten, depending on the pain. During eight weeks of treatment, the Venlafaxine group received 37.5 mg of this drug every 12 hours, and the Gabapentin group received 300 mg daily. Outcomes between the groups compared using statistical tests.

Permission obtained from the University Ethics Committee and the name, surname, and information of the individual will be confidential. Patients excluded from the study if they do not want to. Written consent is obtained from the patients, and no additional costs will be borne by the patients. This study was approved by the Ethics Committee of Urmia University under the code of ethics IR.UMSU.REC.1398.364

For statistical analysis, descriptive statistical method, including mean standard deviation, frequency index, and the percentage, was used. Chi-square test and Fisher's exact test used to compare qualitative data between the two groups of patients. Student t-test used to compare quantitative data between the two groups, and Paired t-test used to compare pain within each group if the data were normally distributed. Wilcoxon test used if the distribution was not expected. For Statistical analysis we used 20spss program. P value less than 0.05 was considered significant.

Results and Discussion

Sixty patients enrolled in the study that we divided them into two groups, 30 patients in the Venlafaxine-receiving group, and 30 patients in the Gabapentin-treated group. No patient excluded from the study group during the study process. Drug reaction, allergy, or severe complication not reported.

Evaluation of Age, Gender and Underlying Diseases among the Patients (Table 1-3)

The mean age of patients in this study was (54.55 ± 12.90) years. Mean age of patients in the Venlafaxine group was 51.83 ± 14.05 years, and in the Gabapentin group was (57.26± 11.21) years. According to the result of the Kolmogorov-Smirnov test, age distribution in the study population was normal (P = 0.2). To investigate the differences between the two groups in this study in terms of age, an independent t-test used which showed that the two groups did not have a statistically significant difference

in terms of age (P = 0.1) among the total study population, 27 patients (45%) were female and 33 patients (55%) were male. Among the patients in the Venlafaxine group, 14 patients (46.7%) were female, and 16 patients (53.3%) were male. This amount was equal to 13 patients (43.3%) female and 17 patients (56.7%) in the Gabapentin group. To compare the groups in terms of gender frequency, a Chi-square test used that there was no significant difference between the two groups in terms of gender. Among the 60 patients studied, the most common underlying disease was hypertension, which was present in 30% of patients (18 patients), 3 patients (5%) had hyperlipidemia, and 2 patients (3.3%) had a history of ischemic heart disease. Among patients treated with Venlafaxine, the prevalence of hypertension and hyperlipidemia was 16.7% (5 patients) and 3.3% (1 patient), respectively. In addition, ischemic heart disease was not reported in this group. Also, in group treated with Gabapentin, 43.3% of patients (13 patients) with hypertension, 6.7% (2 patients) of patients with hyperlipidemia, and 6.7% of patients (2 patients) with a history of coronary artery disease were found. Chi-square test used to evaluate the differences between the two groups regarding underlying condition. Results of this test showed that the two groups differed significantly only in the rate of hypertension (P = 0.024)

Table 1. Age distribution among the patients.

Variable / Group	AGE (MV±SD)	P-Value
Vanlafaxine	51.83±14.05	
Gabapentin	57.26±11.21	
Total	54.55±12.90	0.1

Table 2. Gender distribution among the patients.

Variable	Female	Male	P-Value
Venlafaxine	14(46.7%)	16(53.3%)	
Gabapentin	13(43.3%)	17(56.7%)	
Total	27(45%)	33(55%)	0.7

Table 3. Underlying disease.

Variable / Group	HFEMALE		P-Value
Gabapentin	13(43.30 %)	2(6.70 %)	2(6.70 %)
Venlafaxine	5(16.70 %)	0	1(3.30 %)
P-Value	0.024*		0.55

Evaluation and comparison of post-treatment complications in the study population (Table 4)

Out of 60 patients, 43 (71.7%) had not experienced any complications. Ten patients (16.6%) reported headache as a complication, of which 8 (13.3%) had a mild headache, and 2 (3.3%) had a severe headache. In addition, dizziness observed in 6 patients (10%), of which 2 patients (3.3%) experienced extreme dizziness, and 4 patients (6.7%) experienced mild dizziness. One patient (1.7%) had sleep disorders. Patient was a 40-year-old man with no history of underlying disease treated with Venlafaxine. Among patients treated with Venlafaxine, 63.3% (19 patients) did not experience any side effects. Also, no cases of dizziness were observed in these patients. All 10 patients who underwent headaches were in this group. Among the Gabapentin group, 80% of patients (24 patients) had no side effects. Also, all 6 patients with dizziness were in this group. A chi-square test used, the results of which showed a significant difference between the two groups in terms of complications (P = 0.004). Dizziness in Gabapentin group and headache in the Venlafaxine group was significantly higher.

Table 4. Comparison of pain before and after treatment.

Group / Pain	Mean ± Standard deviation			P value
	Venlafaxine	Gabapentin	Total	
Pain before treatment	5.35.33 ± 1.373 ± 1.37	6.80 ± 2.15	6.06 ± 1.93	0.003 *
Pain after treatment	2.30 ± 1.34	4.21 ± 2.17	3.25 ± 2.03	* <0.001
Pain reduction	3.03 ± 1.29	2.58 ± 1.37	2.80 ± 1.34	0.19

Evaluation of the study population in terms of pain relief after treatment (Table 5)

Patient's pain assessed before and after treatment with VAS criteria. Mean pain intensity before treatment among 60 patients was, (6.06 ± 1.93). Amount and severity of pain after treatment was, (3.25 ± 2.03). Also, rate of pain reduction in all patients was evaluated with a mean reduction of (2.80 ± 1.34) and a range of changes of 5 to 0. There was no increase in pain after starting treatment. In group treated with Venlafaxine, mean pain intensity before, and after treatment and mean reduction were, (5.33 ± 1.37), (2.30 ± 1.34), and (3.03 ± 1.29), respectively. These values in group treated with Gabapentin were, (6.80 ± 2.15), (4.21 ± 2.17), and (2.58 ± 1.37), respectively.

An independent T-test used to compare the two groups regarding pain intensity. Results showed that there was a significant difference in fear between the two groups in terms of mean pain intensity before, and after treatment between the two groups (P = 0.003 and P <0.001, respectively). Rate of pain reduction in the group treated with Venlafaxine was higher than in the Gabapentin group, this difference was not statistically significant (P = 0.19).

Table 5. Comparison of pain intensity before and after treatment.

Pain intensity / Group	Mean ± Standard deviation		Percentage compared to before treatment	P value
	Before treatment	After treatment		

Venlafaxine	5.33 ± 1.37	2.30 ± 1.34	43	* <0.001
Gabapentin	6.80 ± 2.15	4.21 ± 2.17	61	

Comparison of pain reduction in each treatment group

To evaluate the changes in pain score in each group before and after treatment, paired t-test used, and results showed that in both groups treated with Venlafaxine, and Gabapentin the rate of pain score reduction was statistically significant (P<0.001). Post-treatment pain was 43% in the Venlafaxine group, and 61% in the Gabapentin group.

Evaluation and comparison of pain before and after treatment and its reduction in both sexes

Mean pain score before and after treatment, was evaluated among males, and females. In males, these values are (5.81 ± 2.18), (3.18 ± 1.99), and pain reduction score was (-2.63 ± 1.16), and in females was (6.37 ± 1.57), (3.35 ± 2.12), and pain reduction score was (-3.01 ± 1.53). To evaluate and compare the two sexes, results of the independent T-test showed that there was no significant difference between the two sexes in terms of any of the above (P = 0.27, P = 0.75, and P= 0.29, respectively) **(Table 6).**

Table 6. Comparison of pain before and after treatment in males and females.

Sex / Pain	Mean ± Standard deviation		P value
	Females	Males	
Pain before treatment	6.37 ± 1.57	5.81 ± 1.57	0.27
Pain after treatment	3.25 ± 2.12	3.18 ± 1.99	0.75
Pain reduction	3.01 ± 1.53	2.63 ± 1.16	0.29

Symmetrical distal neuropathy or diabetic neuropathy is the most common complication of diabetes and a significant cause of disability. According to statistics published by the World Health Organization, 382 million people worldwide are affected by diabetes, as one of the most important causes of neuropathy [11]. Distal symmetrical polyneuropathy (DSPN) is the most common form of diabetic neuropathy, affecting more than 90% of these patients. DSPN typically affects the toes and extremities of the foot, but can slowly involve the proximal areas of the foot. It also clearly destroys nerve cells of both somatic and autonomic types [12]. Neuropathic ulcers and pain are the most critical clinical complications of DSPN, which are associated with high mortality and morbidity [13]. Patients often need medical attention when the clinical manifestations of pain appear [14], while only 10 to 26% of this population has pain [15]. Disease causes gradual loss of nerve fibers, and the resulting symptoms begin distally and symmetrically in the fingers, toes, and feet. In addition to the neurological disabilities associated with loss of sensation and risk of leg ulcers and amputations, approximately 15 to 20% of patients have painful symptoms that can impair their function and quality of life. Pain is usually in the form of burning or neuralgia as a sign of involvement of tiny nerve fibers containing myelin. In some patients the pain may be self-limiting and resolve spontaneously within one year of onset, in other patients these symptoms may persist and cause-related disabilities. Symptomatic treatment of neuropathic pain is an essential part of the care and treatment of diabetic patients. First line of pharmacological treatment for diabetic neuropathic pain includes several antidepressants, such as Duloxetine, Venlafaxine, Amitriptyline, and anticonvulsant drugs, such as Pregabalin and Gabapentin. This study aimed to compare the effect of venlafaxine with Gabapentin in reducing pain in patients with diabetic neuropathic pain.

In this study, the mean age of patients was (54.55 ± 12.90) years, and there was no significant difference between the two groups in terms of age. 45% of patients were female, and 55% were male, so there was no significant difference between the two groups.

In the study of Razazian *et al*. [10] in 2014 in Kermanshah, IRAN, to evaluate the efficacy and safety of Carbamazepine, Pregabalin, and Venlafaxine on painful diabetic neuropathy, the mean age was close to our study and was 56.3 years. Also, like our study, there was no significant difference between the two groups in terms of age and sex. In addition, in the 2004 study by Rowbotham *et al.*, Which evaluated the efficacy and safety of a 6-week treatment with extended-release Venlafaxine in patients with diabetic neuropathic pain, the mean age of the patients was close to ours.

In the study population, in terms of the prevalence of the underlying disease, hypertension was significantly higher in the gabapentin-treated group than in the venlafaxine group. Fact that in previous studies, one of the most crucial side effects of this drug is high blood pressure. This difference may be due to the preference of physicians to maintain caution in prescribing Venlafaxine to patients with a history of hypertension.

The results of our study showed that the administration of Venlafaxine or Gabapentin could either significantly reduce the severity of pain.

A 2001 study by Simpson *et al*. [8] Comparing the effects of Gabapentin and venlafaxine in treating diabetic neuropathy in the United States found that, like us, Gabapentin and Venlafaxine could be effective in reducing neuropathic pain. This study also showed that Venlafaxine could be used in patients who did not respond well to Gabapentin treatment.

Sindrup *et al*. [16] also compared the effects of Venlafaxine and Imipramine in treating of painful polyneuropathy in 2003. Study

showed that Venlafaxine could effectively reduce the pain of neuropathy. After 4 weeks of treatment, the pain was 80% of the baseline. Results are consistent with our study.

In the study of Razazian *et al*. [10] results showed the effect of venlafaxine in reducing neuropathic pain, which is in line with the results of our research.

In addition, results of our study showed that there was no significant difference between the numerical rates of pain reduction based on VAS criteria in the two treated groups. It can be concluded that Venlafaxine alone can be as effective as Gabapentin in the treatment of neuropathic pain.

As the results of our study in the study of Sindrup *et al*. [16], was found that the administration of Venlafaxine alone can be effective on pain caused by neuropathy, wich is similar to the effect of Imipramine.

In addition, Razazian *et al*. [10], Contrary to the present study, Pregabalin shown more significant effect on neuropathic pain than Venlafaxine. Our analysis of Gabapentin, another member of the antiepileptic drug class, did not show a significant difference in the effect of venlafaxine. Difference may be due to the different methods of drug administration and sample size in these two studies.

Conclusion:

The results of our study, like many previous studies, showed that venlafaxine could be used as an effective drug treating diabetic neuropathic pain. Results of this study also showed that the effect of Venlafaxine and Gabapentin in reduction of pain intensity score is the same, and these two drugs are not superior to each other. In addition, the other new trials with a higher sample size, placebo-controlled groups and double-blinded randomization could be more helpful in investigating the efficacy and safety of venlafaxine in pain reduction in patients with diabetic neuropathy.

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