Evaluation of Topiramate Efficacy on Neuropathic Pain in Patients With Diabetic Polyneuropathy

Sedigheh Shamsinejad[1], Ali Davati[2], Mehrdad Roughani[3], Amir Ghasemlouie[1], Siamak Afshinmajd[4]

[1] *School of Medicine, Shahed University, Tehran, Iran*

[2] *Department of Social Medicine, Shahed University, Tehran, Iran*

[3] *Department of Medical Physiology, Neurophysiology Research Center, Shahed University, Tehran, Iran*

[4] *Department of Neurology, Neurophysiology Research Center, Shahed University, Tehran, Iran*

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Abstract- Polyneuropathy is one of the most common and disabling complications of diabetes. Severe pain is one of the complications of diabetic polyneuropathy .Over the years, many drugs for the treatment of the pain in diabetic neuropathy have been tried. However, no one is completely effective. In a single-blind clinical trial, 200 patients with painful diabetic neuropathy were studied over 12 weeks. In the intervention group, 100 patients were treated with 100 milligrams of Topiramate per day and 100 patients in the control group treated with 90 milligrams of Gabapentin per day. Pain intensity recorded with Visual analogue scale between 0 to 100 millimeter over twelve weeks. Reduction in pain intensity of ≥30 mm was considered as effective response. The purpose of this study was to investigate the effect of Topiramate in the treatment of pain in diabetic polyneuropathy. The mean reduction in pain intensity over twelve weeks in Topiramate groups were 33.83±12.17 and in Gabapentin group were 30.25±15.66. The relative improvement in the Topiramate group was 89.17%, and in the Gabapentin group was 71.25%, respectively. There was a reduction in the mean pain score in both groups, although no statistically significant difference between the two groups was observed. Both of Topiramate and gabapentin were effective on reduction of pain in diabetic polyneuropathy. We can use both of them separately or in combination with each other or other drugs.
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Introduction

The World Health Organization estimates that the global prevalence of diabetes is currently approaching 5%; thus, this disease can be called an epidemic of the 21st century. Diabetes is considered a major cause of mortality and morbidity, and statistically, diabetic polyneuropathy is the second most common cause of nerve damage (1-3). Therefore, and clinical reality suggests the need for the effective treatment of polyneuropathy pain accompanying diabetes. There are three main types of diabetes: insulin-dependent diabetes mellitus (type 1), non-insulin-dependent diabetes mellitus (type 2), and gestational diabetes. Diabetes mellitus is a group of metabolic diseases characterized by high blood glucose concentration, frequent urination, and increased thirst and hunger. Diabetes is one of the leading causes of neuropathy worldwide. Diabetic polyneuropathy is not always painful; however, 12% of all diabetic patients are affected with symptomatic painful diabetic polyneuropathy, the most common chronic and earliest occurring complication (4-6). Diabetic polyneuropathy affects all peripheral nerves including pain fibers, motor neurons, and the autonomic nervous system. The pathogenesis of diabetic polyneuropathy is complicated, and the mechanism of this disease remains poorly understood. It has been suggested that hyperglycemia is responsible for changes in the nerve tissue. There are two main suppositions of this proposed mechanism: vascular and metabolic (4,7). The current hypothesis suggests that neuroimmune interactions actively contribute to the onset and persistence of pain in diabetes (8-10). The drugs currently used for the treatment of diabetic neuropathic pain include antidepressants, such as tricyclic antidepressants or duloxetine; and typical analgesics,

Corresponding Author: S. Afshinmajd
Department of Neurology, Neurophysiology Research Center, Shahed University, Tehran, Iran
Tel: +98 21 88926340, Fax: +98 21 88966132, E-mail address: safshinmajd@yahoo.com

such as tapentadol; anticonvulsants, such as pregabalin, and topiramate (8,11-14).

Topiramate

Topiramate is a successor sulfate monosaccharides. It is an anticonvulsant that approved by Food and Drug Administration (FDA) in 1996 for use in partial seizures. Because none of the available drugs such as carbamazepine and gabapentin are completely effective for pain reduction in patients with diabetic polyneuropathy drugs such as Topiramate (Topamax), have come in focus (13).

Furthermore, the use of current drugs in neuropathic pain does not have adequate effect, and further trials are required for other drugs.

This drug has little sleepiness effect and tolerance of it is much better than other drugs, and it hasn't the complication of obesity and also results in weight loss.

Therefore, this study designed to investigate the effect of Topiramate on neuropathic pain in patients with diabetic polyneuropathy and comparison of its effects with Gabapentin.

Materials and Methods

The main objective of the paper examined the effect of Topiramate on neuropathic pain in patients with diabetic polyneuropathy. The study was a single-blind clinical trial performed on diabetic's patients. This study settled on diabetics' patients between 35 to 75-year-old. The samples were assigned alternatively to two groups of patients. One hundred patients treated with Topiramate 100 milligram at night in the intervention group and 100 patients took Gabapentin 300 milligrams three times daily in the control group.

Selection of patients was on the basis of clinical symptoms. All patients followed for three months, and the increase of drug dose was gradually over three weeks. Pain assessment at baseline and follow-up of the changes were made by VAS. This scale has a 100-millimeter horizontal line drawn on paper, as it is oriented to the left of zero indicates absence pain to 100 mm on the right axis that represents the worst possible pain. Patients mark the line according to their pain severity.

Patients were examined for pain at baseline and then every two weeks for three months. All patients were between 35 to 75-year-old, and they had diabetes at least for eight years. Physical examination and electrophysiologic tests were done, and distal symmetrical polyneuropathy was proven by either clinical or electrodiagnostic tests with rule out of radiculopathy and entrapment syndromes. If the patient had clinical symptoms but did not perform electrophysiological tests, these tests were done to confirm the diagnosis.

Patients who did not fulfill criteria and all the patients who used analgesics, anticonvulsants, antidepressants, antipsychotics or any history of allergy to drugs were excluded. Study aims' was explained to all patients and informed consent according to the ethical committee of Shahed University was completed by all patients. The emergence or worsening of symptoms and drug side effects were explained for the patient, and non-tolerant patients were excluded from the study. In the end, all collected samples were booked, and statistical analysis was performed on it. The mean change in pain intensity scale of more than 30 millimeters in VAS scale was considered significant.

After the collection of sufficient sample size to conduct the project and access to information, the available data were analyzed by statistical software SPSS 11.5. This study is registered in Iranian registry of the clinical trial site by number IRCT 2016110330680N1.

The most important limitation of this study was the probability of failure for patients to follow-up. Bad drug tolerance of some patients was also a limitation. Another limitation of our study was the possibility of drug shortage.

Results

Age frequency

Age Frequency was similar in both groups and was not followed by a significant difference.

Table 1. Prevalence of patients' age in both groups at baseline

Treatment group	average+/-SD	Test	*P*
Topiramate	61.28+/-9.72	T-test	
Gabapentine	61.15+/-9.75	T-test	0.994

SD: Standard Deviation

Sex frequency

Sex frequency was similar in both groups with no significant difference.

Table 2. Prevalence of sex in both groups at baseline

Treatment group	Male	Female	Test	*P*
Topiramate	57(47.50%)	63(52.50%)		
Gabapentin	37(46.25%)	43(53.75%)	X^2	0.862

Weight frequency

The weight distribution of patients was similar in both groups with no significant difference.

Table 3. Prevalence of weight in both groups at baseline

Treatment group	SD+/average	Test	*P*
Topiramate	69.90+/-8.40		
Gabapentine	69.30+/-8.08	T-test	0.737

SD: Standard Deviation

Changes in mean pain intensity

According to the data obtained in this study, the average pain intensity according to VAS scale in the 1, 4, 6, 8, 10, 12 weeks during the treatment process are calculated, and the results are given in table 4. (Repeated measurements' test has been used).

In the case of repeated measurements between the two groups of Topiramate and Gabapentin *P*>0.357 was obtained.

Given the trend decline in mean pain intensity on a VAS, patients in both groups indicated that both drugs were effective in reducing pain (*P*<0/001). But between the two groups, there were no statistically significant differences in terms of pain reduction. Gabapentin group had reduced pain intensity from week 1-10, It was somewhat greater than the effect of topiramate, but between the 10th to the 12th-week effect of topiramate in reducing pain intensity was greater (Figure 1).

Table 4. Average pain intensity in both groups during the study period

Treatment process	Treatment group	SD +/-average	Number
First week	Topiramate	68.08+/-16.91	100
	Gabapentin	65.87+/-19.46	100
Fourth week	Topiramate	66.41+/-16.23	100
	Gabapentin	63.87+/-19.19	100
Sixth week	Topiramate	56.41+/-15.97	100
	Gabapentin	54.12+/-18.12	100
Eight week	Topiramate	45.33+/-15.87	100
	Gabapentin	42.50+/-17.17	100
Tenth week	Topiramate	35.83+/-14.05	100
	Gabapentin	37.00+/-16.41	100
Twelfth week	Topiramate	34.25+/-12/94	100
	Gabapentin	35.62+/-16.67	100

SD: Standard Deviation

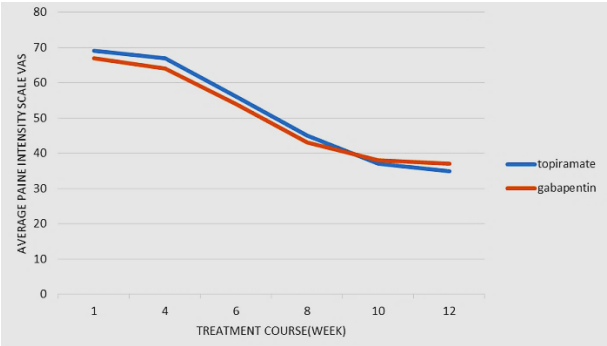

Figure 1. Changes in pain scores during the treatment period

For efficacy in reducing pain

A comparative test between the first week and final weeks in Topiramate group respectively showed significant and positive impact in reducing pain in patients that took topiramate (*P*<0.001).

In a similar experiment to compare the severity of pain between the first and end of the study, the group taking gabapentin had a positive impact in reducing pain in patients (*P*<0.001).

Starting time of drug effects

To study the starting time of drug effects in each treatment group, the mean pain intensity was measured in weeks 4, 6, 8, 10, and 12. Greater than or equal to the 10-millimeter change in VAS scale was measured as the criterion for the onset of the drug efficacy. The results are given in table 5.

According to the findings listed in the table, drug's effects in both groups started in the sixth week.

Table 5. Mean changes in pain reduction during the treatment period compared to the first week

Changes in pain reduction/period	Treatment group	Number	SD+/-average
During the 4 weeks	Topiramate	100	1.66+/-3.74
	Gabapentin	100	2.00+/-4.02
During the 6 week	Topiramate	100	11.66+/-8.02
	Gabapentin	100	11.75+/-8.53
During the 8 week	Topiramate	100	22.75+/-11.51
	Gabapentin	100	23.37+/-12.21
During the 10 week	Topiramate	100	32.25+/-12.39
	Gabapentin	100	28.87+/-14.58
During the 12 week	Topiramate	100	33.83+/-12.17
	Gabapentin	100	30.25+/-15.66

SD: Standard Deviation

Maximum effect of the drugs

In order to evaluate the maximum effect of the drug in each of the first four weeks, the second four weeks and third four weeks, based on changes in pain intensity scale was calculated VAS per month. The mean reduction in pain intensity changes are shown in table 6.

According to the table 5, the highest effects of drug were during the second month.

Table 6. The mean reduction in pain intensity at the various time the separation of drug

	Treatment group	number	SD+/-average
First to fourth	Topiramate	100	1.66+/-3.74
	Gabapentin	100	2.00+/-4.02
Fourth to eighth	Topiramate	100	21.08+/-10.67
	Gabapentin	100	21.37+/-11.33
Eighth to twelfth	Topiramate	100	11.08+/-8.28
	Gabapentin	100	6.87+/-9.22

SD: Standard Deviation

Percent recovery

In this study, the relative recovery based on changes in pain intensity greater than or equal to 30 millimeter according to VAS scale at the beginning and end of study (week 1 and week 12) were determined. Finally, 89.17 percent of patients taking topiramate and 71.2 percent of gabapentin group had good recovery from pain. The 6.66 percent of topiramate group and 20 percent of gabapentin group had mild improvement. 4.17 percent of patients taking topiramate and 8.75 percent of patients taking gabapentin showed no difference in pain intensity. The pain did not get worse in both groups.

Complications

During the study, 5 patients due to unknown causes and 4 patients due to drowsiness and drug intolerance were excluded from the study. Also, 4 patients in the gabapentin group due to unknown reason and 3 patients due to drowsiness and dizziness were excluded from the study.

Discussion

According to the data obtained in this study, the average pain intensity on VAS scale in weeks 1, 4, 6, 8, 10, and 12 during the treatment process were calculated. Results showed decline in mean pain intensity according to VAS scale and in patients of both groups both drugs were effective in reducing pain.

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in gabapentin group had mild improvement.

Also, 4.17 percent of patients taking Topiramate and 8.75 percent of patients taking gabapentin showed no difference in pain intensity. The pain did not get worse in both groups.

In study conducted by Edwards results issued that Topiramate efficacy is very low in relief of neuropathic pain. Number of patients in this study seems to be higher than in our study, and because of the sample size, the results is more accurate (15).

In summary, this study indicated that Topiramate and Gabapentin are effective in decreasing the severity of neuropathic pain in patients with diabetic polyneuropathy. Both drugs can be used separately, or in combination with each other, however, both of these drugs are not completely curative, and further investigation is recommended for confirmation.

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