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A Comparison of Effectiveness of Amitriptyline and Topiramate in the Treatment of Painful Diabetic Neuropathy

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KEYWORDS

Neuropathy, Diabetes, Amitriptyline, Topiramate

A B S T R A C T

Painful diabetic neuropathy is defined as sensory pathways of central and peripheral nervous system dysfunction and may involve about 30% of people with diabetes mellitus. The aim of this study is to compare the effect of Amitriptyline and Topiramate in relieving symptoms of painful diabetic neuropathy. In this clinical trial that was performed between two 30-patient groups, in outpatient's clinics of diabetes and endocrinology of Tabriz University of Medical Sciences, the effect of Amitriptyline and Topiramate in relieving symptoms of painful diabetic neuropathy was evaluated. Mean age of patients in Amitriptyline group was 57.1 ± 0.80 and in Topiramate group was 58.87 ± 7.91 years. Mean primary pain severity based on VAS in Amitriptyline group patients was 77.66 ± 24.59, at two weeks , one month , two months and three months later were 62.17 ± 20.91 , 52.83 ± 20.91, 42.41 ± 21.98 and 37.76 ± 21.36, respectively. Mean primary pain severity based on VAS in Topiramate group patients was 81.66 ± 7.91, at two weeks , one month ,two months and three months later were 60.0 ± 8.16 , 57.5 ± 17.08 , 42.5 ± 33.04 and 45.33 ± 26.62, respectively. There was significant decrease in pain score of the patients at three months of treatment in both groups but the difference of changes was not significant between two groups. In this study, both applied therapies caused pain relief in painful diabetic neuropathy of patients and significant difference was not found in pain score of patients at the end of three months between two groups.
In the conditions that TCA can not be used, Topiramate can be prescribed as first line drug therapy for diabetic neuropathic pain.

Introduction

Diabetes is one of the most common chronic diseases, which mainly affect various organs, with the increasing prevalence (1-2). The prevalence of this disease was more than 382 million cases in 2013, which is expected to increase to 592 million in 2035 (1). The number of patients with diabetes type 2 is increasing in all

around the world; while 80% of diabetic patients live in low and middle-income countries, most of them are aged between 40 and 59 years (1).

Painful diabetic neuropathy, defined as a dysfunction in the sensory pathways of the Central and peripheral nervous system (CNS and PNS), has always been considered as a challenging complication of diabetes mellitus and affects approximately 30% of the patients(1-2).

16-26% of diabetic patients will experience chronic pain, which is called diabetic neuropathic pain (DNP) or diabetic peripheral neuropathic pain (DPNP) (3). The incidence of these side effects depends on the duration of the disease (1).

While numerous symptoms such as ocular and renal involvement are considered as the most harmful effects of the disease, the pain associated with diabetic peripheral neuropathy, significantly affects as a negative impact on patients' life quality and daily functions.

The classic pain of diabetic peripheral neuropathy is a burning pain in the lower extremities which could be accompanied by Numbness, sense disturbance or pain without stimuli.

Pathophysiology of neuropathic pain includes several reasons, such as unusual activity of peripheral neurons, a decrease in inhibitory of the central nervous system pathways, and increased response to the normal stimuli, which the multiplicity of factors, suggests different pathways of treatment (2).

Most of the time, management of acute painful neuropathy is difficult, and it would become more complex, because it is often associated with secondary sleep disorders and depression (4). Treatment of diabetic peripheral neuropathy involves the targeting and management of the disturbance's symptoms, which include blood sugar control, treatment of debilitating pain and treatment of sleep disorder that is caused by the pain (2).

The primary method of treatment is based on pharmacotherapy (2.) Consumption of narcotic drugs in the short term is an effective treatment for neuropathic pain. However, because of concerns about side effects and the risk of addiction, their use is limited. Neural modulators treatments include Tricyclic antidepressants and anticonvulsants, are the basis of treatment for neuropathic pain. Although these drugs cause incredible progress in pain control and improve the quality of life, but one of the primary factors that limit their widespread use, are uncontrollable side effects. For the treatment of painful diabetic peripheral neuropathy, first of all, a Tricyclic antidepressant (first choice: Amitriptyline), serotonin-noradrenalin specific reuptake inhibitor or alpha-2-delta agonist are recommended. In cases when the pain is not controlled, an opioid antagonist drug should be added (3-4). Due to the increasing prevalence of diabetes and the morbidities which are associated with the disease, the undesirable impacts of these side effects on quality of life and their pressure on the society, The lack of standard treatment for neuropathic symptoms and the lack of extensive studies to compare the Tricyclic and Topiramate as a first-line treatment at the same time. We decided to begin a study titled "compare the effects of Amitriptyline and Topiramate in the treatment of painful diabetic neuropathy" in the context of a clinical trial. We hope that this study provides the valuable information about the painful

diabetic neuropathy treatment to improve the quality of the patients' life and help to the planning organizations, involved in this field. The purpose of this study is to compare the effects of Amitriptyline and Topiramate in the treatment of painful diabetic neuropathy.

Material and methods

In a clinical trial, between the diabetic patients, referred to the endocrinology clinic of Tabriz medical sciences university, those who were eligible for this study were selected and Topiramate and Amitriptyline effects to control the pain, induced by painful diabetic neuropathy were compared and studied.

In this study sixth being treated diabetic patients, between 18 to 80 years old were chosen who felt the diabetic peripheral neuropathy symptoms (such as burning pains) during their rest for at least one month and the severity of the symptoms leads to disruption in their daily life and sleep. After history taking and physical examination, the severity of neuropathic symptoms was assessed by VAS and the first group was treated with Amitriptyline at a dose of 25 mg twice daily and the second group was treated with Topiramate at a dose of 25 mg three times a day. Also there was no change in diet therapy of the patients and the obtained results of these groups were compared.

At baseline and 3 months after treatment, the clinical and laboratory evaluation was routinely performed. According to age and sex, the patients were randomly divided into two equal groups. The sample consisted of patients, referred to specialty and subspecialty clinics of Tabriz Medical Sciences University.

Exclusion criteria

The people with any clinically significant disease, psychiatric disorders, patients with other causes of neuropathy, renal dysfunction, liver disease, seizures, uncontrolled hypertension, cancer, drug addiction, those who consume anticonvulsants, antidepressants, anti-localized pain (opioids) and pregnant or lactating women were excluded from study.

Ethical considerations

Informed consent was obtained from all patients who participate in this study. The cost of medical tests was provided by the patients to avoid from extra financial pressure and the cost of studied medication was provided by the researchers. Patient information is completely confidential, it means that their names would not be used anywhere.

Statistical analysis

The collected data were analyzed by SPSS-15 statistical software. The collected data were expressed as percentage and mean ± SD. Continuous (quantitative) variables were compared by Independent samples and Paired t test. Categorical (qualitative) variables were compared by contingency tables and Chi-square test or Fisher's exact test. P-value ≤ 0.05 was considered statistically significant.

Results and Discussion

In this study, we investigated the response of patients to both Amitriptyline and Topiramate in the treatment of painful diabetic neuropathy, 60 patients were analyzed in two separate groups and the following results were obtained:

The mean age of the patients, received Amitriptyline was 57.10 ± 0.8 years and the mean age of the patients, received Topiramate was 58.87 ± 7.91 years (Chart I) (P=0.473).

10 patients (3.33%) received Amitriptyline and 6 patients (20%) received Topiramate were male (P=0.243).

The mean height, weight, BMI and systolic and diastolic blood pressure of patients in both groups are shown in Table 1.

17 patients received Amitriptyline, and 24 patients received Topiramate had a positive family history in terms of diabetes (P=0.024).

Among patients received Amitriptyline, the mean baseline pain was 77.66 ± 24.59, at the end of the second week the pain was 62.17 ± 20.91 and at the end of the first, second, third month was respectively 52.83 ± 20.91, 42.41 ± 21.98, 37.76 ± 21.36. (Chart II)

There was a significant reduction in the pain levels of patients received Amitriptyline during the study (P<0.05).

Among patients received Topiramate, the mean baseline pain was 81.66 ± 7.91, at the end of the second week the mean pain was 60.00 ± 8.16 and at the end of the first, second, third month it was respectively 57.50 ± 17.08, 42.50 ± 33.04, 45.33 ± 26.62. (Chart III)

During the study, a significant reduction was shown in the pain levels of patients received Topiramate (P<0.05).

In Topiramate group, only 2 patients who had suffered from vertigo were excluded from study and two new patients were enrolled.

Table.I Demographic and laboratory findings of patients

	Group		P
	Amitriptyline	Topiramate	
Weight	78.47 ± 12.37	80.30 ± 14.39	0.599
Height	1.62 ± .08	1.64 ± .07	0.411
Primary BMI	29.90 ± 4.40	29.88 ± 4.56	0.992
Heart Rate	80.07 ± 8.54	78.57 ± 7.79	0.480
Primary Systolic Blood Pressure	128.33 ± 15.50	127.83 ± 16.90	0.905
Primary Diastolic Blood Pressure	76.33 ± 12.38	81.67 ± 5.31	0.034
Duration	11.60 ± 6.72	15.77 ± 8.99	0.047
Secondary BMI	29.30 ± 3.67	29.40 ± 3.95	0.919
Secondary Systolic Blood Pressure	126.17 ± 15.12	123.50 ± 9.02	0.410
Secondary Diastolic Blood Pressure	76.00 ± 11.85	81.00 ± 3.05	0.032
FBS Changes	-13.70 ± 45.62	-17.83 ± 67.72	0.783
HbA1c Changes	-.19 ± .91	-.74 ± 1.49	0.085
TG Changes	10.50 ± 50.98	-7.30 ± 50.87	0.181
Cholesterol Changes	3.07 ± 25.10	-4.07 ± 21.82	0.245
HDL Changes	-.27 ± 6.11	-2.93 ± 6.56	0.109
LDL Changes	2.20 ± 22.45	-3.83 ± 23.45	0.317
Creatinine Changes	-.03 ± .10	.00 ± .23	0.507

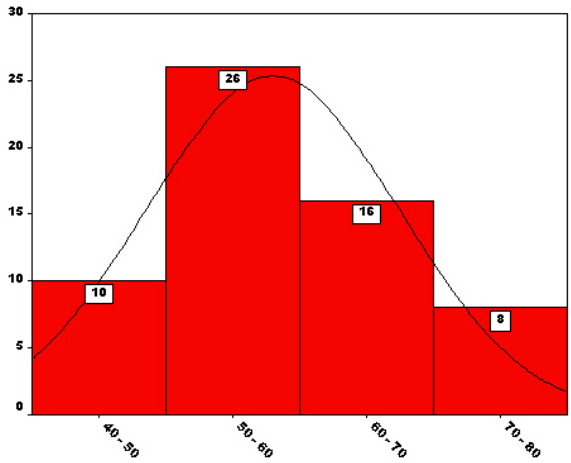

Chart.1 Age distribution of patients

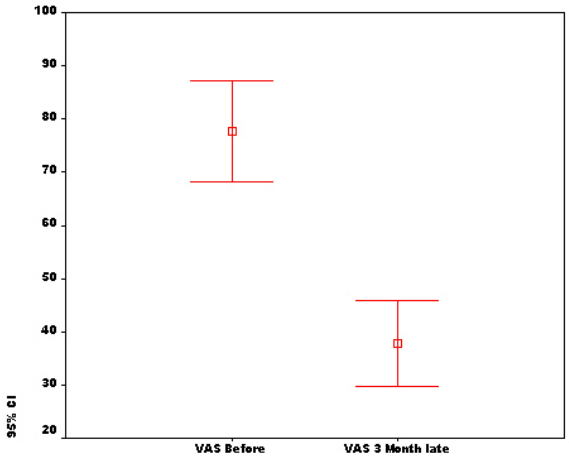

Chart.II Pain score (VAS) distribution of patients in Amitriptyline group

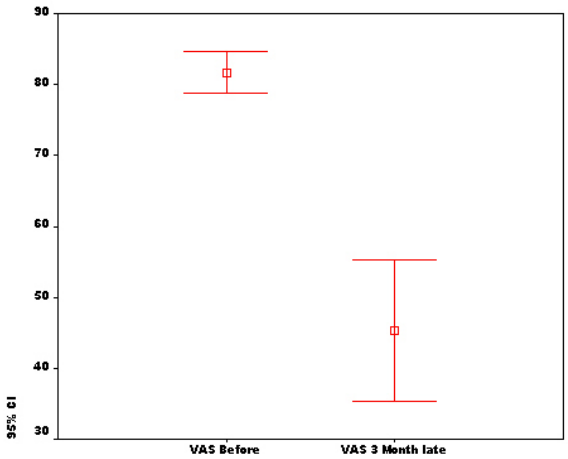

Chart.III Pain score (VAS) distribution of patients in Topiramate group

Distal symmetric polyneuropathy is the most common type of diabetic neuropathy that can cause significant disability. Severe pain, loss and lack of sensation and an increased risk of foot ulcers and amputation are the side effects caused by the diabetic neuropathy. We could reduce the risk of developing neuropathy with precise control of diabetes. In the study at Tehran University of Medical Sciences, diabetic foot ulcers were preventable in 15% of cases by the special care of patients and limiting the amputation. The risk of polyneuropathy in diabetic patients is 50-10 percent (5-8), observed in 10% of patients during diagnosis and it would be definitely observed in 50% of them after 25 years (9-10). Lifetime risk of amputation in patients with polyneuropathy is 15% (9).

Neuropathy through numbness and difficulty in proprioceptive perception, cause the inappropriate extra pressure, imposed on the feet and consequently it leads to feet ulceration. The ulcers would be exactly appeared where the extra pressure is entered (7).

The pain caused by diabetic neuropathy is usually resistant to conventional analgesics. Medicines such as narcotic analgesics, anticonvulsants, phenothiazines, anti-arrhythmias, Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and opioids, have no favorable effects in this regard. In addition their side effects are considered as a restrictive complication and a limiting problem (11).

In a study, conducted by Vrethem and colleagues, on the patients with painful diabetic neuropathy, in the neurology department of the Linkgtyom University in Sweden, it was indicated that Amitriptyline is an effective treatment to relieve symptoms of these patients (12).

In a study on the patients affected with painful diabetic neuropathy at the Auckland University in New Zealand, Bryson and his colleagues by researching on the Amitriptyline effects, found that over 75% of patients responded to this drug (13). Young and his colleagues stated that Amitriptyline and Imipramine are effective in the treatment of painful diabetic neuropathy (14).

In a study at the Mese University of Arizona in America, Biesbroeck and colleagues expressed that Amitriptyline could reduces the pains in 76% of patients who suffer from the painful diabetic neuropathy (15). In a study conducted by Joss and his colleagues at Lowa University in America, they displayed that Amitriptyline is the first choice for treatment of painful diabetic neuropathy (16).

In our study, as well as the above studies, Amitriptyline reduced pain levels in patients during the study and this reduction was significant. In a study, during the treatment of diabetic neuropathy, Kaur and colleagues (4) researched on the Amitriptyline therapeutic effects and its side effects and in comparison with the baseline sample they demonstrated that both drugs could cause a significant improvement in the pain but undesirable side effects such as dry mouth in patients treated with Amitriptyline are more than the patients treated with Duloxetine.

In a study by Boyd and colleagues in 2013, at the Internal Medicine department of Norfolk University in Virginia, on patients with diabetic neuropathy, the effects of Topiramate in improving symptoms and increasing the patients' life quality were reviewed and it was found that after receiving Topiramate the sensory

symptoms in these patients has improved, but there was no effect on motor symptoms (17).

In a study by Donofrio and colleagues in 2005, at the neurology department of Wake Forest University in Winston-Solen, the effects of Topiramate on patients with diabetic neuropathy were studied and they found that Topiramate could improve the patients' pain. The level of HbA1c before and after treatment was respectively 7.7% and 4.7% (18).

In our study, the mean of primary and secondary HbA1c in patients who received Topiramate was respectively 7.87 ± 1 and 7.13 ± 1.06 so ours were exactly the same as the above results. Also in both groups, the changes in laboratory findings were not significant. In a study conducted by Carrol and his colleagues at Tulsa in America, they researched about the effect of Topiramate on the treatment of painful diabetic neuropathy and stated that Topiramate is significantly decreased the pain severity in patients affected with painful diabetic neuropathy (19).

In our study, Topiramate causes a significant reduction in the pain severity compared to the baseline in the third months after the study too. In a study by Raskin and colleagues in 2004, at Texas University in Dallas, the effects of Topiramate on improving the painful diabetic neuropathy were studied and they presented that Topiramate is decreased the pain severity and can resulted in improving the painful diabetic neuropathy compared to the placebo sample and This effect was significantly higher than placebo and Leads to the pain reduction from 68% to 46.2% (20). In our study, the mean baseline pain in the patient belonging to the Topiramate group was 81.66 ± 7.91 and at the end of the third months, the pain mean in that group was 45.33 ± 26.62 which significantly decreased during the three months after treatment.

In a study by Thicnel and colleagues on patients with diabetic neuropathy, they studied about the effects of Topiramate and reported that the effects of Topiramate on improving the symptoms and pain in patients with the painful diabetic neuropathy is more than placebo sample (21).

Kline and his colleagues expressed that Topiramate is one of the most effective treatments to improve the symptoms of painful diabetic neuropathy in patients with this disease (22). Vinkle and his colleagues stated that Topiramate besides reducing blood pressure, cholesterol and hemoglobin A1C, would improve the symptoms of diabetic peripheral neuropathy and it could increase the conductivity fluctuations and intra-epidermal nerve fibers.

In a study by MAX and colleagues on the therapeutic effects of Desipramine, Amitriptyline and Fluoxetine on pain caused by the diabetic neuropathy, they expressed that Desipramine reduces the pain associated with painful diabetic neuropathy such as Amitriptyline, So it can be used as a substitute for this drug and Fluoxetine that inhibits the serotonin reuptake (serotonin reuptake inhibitor) is not more effective that placebo (23).

Both drugs (Amitriptyline and Topiramate) used in our study, leads to pain relief and improving the painful neurology in diabetic patients and there was no significant difference between the pain mean among the patients in both groups at the end of the third month (P=0.234).

In a study by Freeman and colleagues, the effects of Topiramate on improving the neurological function in patients suffered from the painful diabetic neuropathy was researched and they reported that Topiramate has no significant effect to improve the neurological function in these patients (24).

In a study by Wiffin and colleagues in 2013, at Oxford University in London, the effects of Topiramate on improving the diabetic neuropathy were studied and they presented that this medication has no effect on improving the symptoms of the patients (25). Considering that there is no study in which Topiramate is used as a first line medication for diabetic neuropathy treatment so our study is the first research used Topiramate as a first line of treatment for diabetic neuropathy.

Our results showed that Topiramate, as a first line of treatment, is effective in controlling the patients' pain like Tricyclic drugs and it has no difference compared with Tricyclic drugs in pain management. Therefore we might be able to suggest this drug as a first line medication. Due to favorable metabolic effects of Topiramate on weight loss, we might be able to use this drug better for obese diabetic patients requiring pain management. Because of the short duration of our study this conclusion is not possible. During our study, side effects such as dizziness was observed in only 2 patients treated with Topiramate so these two patients were excluded, and two other patients were assigned.

Conclusion

Among patients received Amitriptyline, the mean baseline pain was 77.66 ± 24.59 which significantly reduced during the study and at the end of the third month it reached to 37.76 ± 21.36 among these patients. The mean baseline pain of the patients received Topiramate was 81.66 ± 7.91 which significantly reduced during the study like Amitriptyline group and at the end of the third month it reached to 37.76 ± 21.36 among these patients. There was a significant decrease in pain severity of the patients at the end of the third months compared to baseline in both groups. Both drugs (Amitriptyline and Topiramate) lead to the pain reduction in the patients suffered from painful diabetic neuropathy and the pain mean has no significant difference between two groups at the end of the third month. According to favorable effect of Topiramate on pain control in the patients with painful diabetic neuropathy, prescription of this drug for pain control is suggested indeed. Also, new studies on larger sample size and Long-term prevention of patients are recommended.

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