ORIGINAL ARTICLE

Effect of pentoxifylline on diabetic distal polyneuropathy in type 2 diabetic patients: A randomized trial

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Background: Diabetes is one of the most common causes of peripheral neuropathy. There are no known cures for diabetic neuropathy. Pentoxifylline could theoretically be a beneficial treatment for diabetic sensory neuropathy, but there is not enough evidence to prove its effect. The aim of this study was to investigate the effect of pentoxifylline on distal diabetic neuropathy. **Materials and Methods:** In this randomized double-blinded placebo-controlled trial, 60 patients with diabetic peripheral neuropathy were randomized into two groups. The intervention group received Vitamin B1 (100 mg twice daily) and pentoxifylline (400 mg twice daily) and control group received Vitamin B1 (100 mg twice daily) and placebo (twice daily) for 2 months. Before and after the intervention, the symptoms of distal polyneuropathy were recorded by the Michigan Neuropathy Screening Instrument. ANCOVA, Paired *t*-test, unpaired *t*-test, Chi-square, and Fisher's exact test were used to compare changes in symptoms and sign of distal polyneuropathy. **Results:** The mean age of patients was 57.1 ± 8.02 years. There was no significant difference between the two groups in regard to the baseline variables. Blood pressure, body mass index, and blood glucose did not change significantly during the study. In the pentoxifylline group, the symptoms of peripheral neuropathy were significantly improved, in comparison with placebo group ($P = 0.042$). **Conclusion:** This study showed pentoxifylline could be effective in reducing the symptoms of distal diabetic neuropathy.

Key words: Diabetes, pentoxifylline, peripheral neuropathy

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INTRODUCTION

Diabetes is one of the most common causes of peripheral neuropathy in the world. More than half of the diabetic patients have neuropathy, and more than half of the patients with peripheral neuropathy have diabetes.[1,2] Diabetic neuropathy occurs in both type 1 and type 2 diabetes. This disorder may be manifested by polyneuropathy, mononeuropathy, or autonomic neuropathy.[3,4]

The symptoms of neuropathy depend on several factors; one of them is the type of nerves that are affected (sensory or motor). Damage to the motor nerve usually causes muscle involvement that is associated with weakness, cramp, and spasm.[5] Patients may have difficulty walking or running and feel that their legs are heavy, slipping, or getting tired. Damaging the nerves of the arm causes the patient to trouble doing daily tasks such as carrying, locking, and opening the locks. Sensory nerve damage can cause a variety of symptoms, such as itching, tingling, numbness, pain, unexplained burning sensations, and sharp stabbing pains.[6] The pain caused by diabetic peripheral neuropathy is worse during rest and at night and is classically symmetric and distal.[7] Damage to the autonomic nerves affects the internal organs and involuntary actions, causing abnormal blood pressure and heart rate, increasing

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or decreasing sweating, constipation, diarrhea, and incontinence.[6,8]

The most common type of diabetic neuropathy is polyneuropathy. Toes are usually involved initially. When the neuropathy progresses, the symptoms move from the toes toward the foot and gradually toward the knee.[5]

Diabetic autonomic neuropathy can involve multiple systems such as cardiovascular, digestive, and urogenital.[6] Autonomic neuropathy involving the cardiovascular system is one of the most important forms of autonomic dysfunction.[9] Vascular and neurological disorders are interrelated. The vascular system needs normal nervous system function and nervous system function dependents on adequate blood supply. In diabetic neuropathy, first pathological change in the small blood vessels is contraction of the muscular wall of the vessels.[1] As the disease progresses, neuropathy develops along with the progression of vascular abnormalities. Nervous system ischemia is one of the proven features of diabetic neuropathy. Vascular dilatation can lead to a significant improvement in the nerve tissue blood supply, which will coincide with the improvement in nerve conduction velocity.[10]

Diabetes mellitus is associated with hypercoagulation state and increased viscosity of blood, resulting in insufficient blood supply in the level of small blood vessels.[11] In addition, rheological abnormalities of erythrocytes (such as reduced ductility and decreased oxygen binding capacity and increased accumulation) can also be responsible for reducing oxygen supply to tissue.[12]

Pentoxifylline is a derivative of xanthine and is available with brand names of torental, pentox, pentoxine and artal (SPSS 18 (SPSS Software IBM, Inc., New York City, New York State, USA). It is in the group of nonselective phosphodiesterase inhibitors; it increases the intracellular cyclic adenosine monophosphate and activates protein kinase A.[13] Pentoxifylline is often prescribed as good tolerable medications for the improvement of peripheral blood flow defects. Pentoxifylline initially increases blood flow with a beneficial effect on the rheological properties of red blood cells and increases the oxygen content of the ischemic tissue. It also reduces the viscosity of plasma and blood. In addition, it prevents platelet aggregation, improves vascular dilatation by increasing prostacyclin, and has a special effect on immune responses through tumor necrosis factor (TNF)-α suppression.[14]

There are no known cures for diabetic neuropathy, and therefore, treatment is only symptomatic. Pentoxifylline could theoretically be a beneficial treatment for diabetic sensory neuropathy,[15] but there is not enough evidence to prove its effectiveness. The purpose of this study was to investigate the effect of pentoxifylline in improving diabetic distal polyneuropathy.

METHODS

We did a double-blind, randomized placebo-controlled trial (IRCT2016051827965N1) from July 2016 to June 2017. We design a parallel trial. The study population included type 2 diabetic patients with distal polyneuropathy based on the Michigan Neuropathy Screening Instrument (MNSI). Inclusion criteria included a history of type 2 diabetes for more than 1 year, aged 40–75 years, symptom of distal polyneuropathy according to the MNSI, and glycosylated hemoglobin (HbA1c) between 8% and 10%. Exclusion criteria included systolic blood pressure above 160 mmHg, advanced diabetic retinopathy, history of heart failure, renal failure, liver failure, pregnancy and lactation, history of amputation, and those who have recently used gabapentin or nortriptyline (4 weeks before trial initiation).

We calculated the sample size of 30 patients in each group. The sample size was calculated based on the comparing means formula and the mean difference of 4, the standard deviations of 4 and 7.5,[16] the power of 80%, and the Type 1 error of 0.05.

Participants were selected from patients who referred to private clinics and government clinics in Qom, Iran. For eligible patients, after a brief introduction about the study (how they are implemented, the purpose of the study, the time of study, the potential benefits and risks of study, and the expression of ethical points), patients who completed the informed consent form were included in the study.

Finally, 60 eligible patients were included in the study. Concealed random allocation was done using a randomized block design. Sixty patients allocated randomly based on the block randomization method in a 1:1 ratio. We used block size four (AABB, ABAB, ABBA, BBAA, BABA, and BAAB), and the third block was randomly selected. One of the researchers who was not care-provider did the random allocation sequence, enrolled participants, and assigned participants to interventions. Care provider who assessed outcomes and participants was blind about allocation.

For each participant, a questionnaire including age, sex, height, weight, HbA1c, fasting blood sugar (FBS), duration of diabetes, duration of distal polyneuropathy, and MNSI was completed.

The MNSI has two Parts A and B. Part A was used to record symptoms of neuropathy and was completed

by the patient, and Part B includes a clinical evaluation completed by a physician and only vibration test and ankle reflexes was used in this study. The questionnaire has high sensitivity (80%) and specificity (95%).[17]

After confirmation of neuropathy by a physician, patients were randomly assigned into two intervention and control groups. The intervention group received pentoxifylline (400 mg twice daily) and Vitamin B1 (100 mg twice daily) and control group received Vitamin B1 (100 mg twice daily) and placebo (twice daily) for 2 months. The shape and packing of placebo and pentoxifylline were similar. Before and after intervention, the symptoms of distal polyneuropathy were recorded by MNSI, and the vibration threshold was investigated by diapason (128 Hz). The standard treatment for diabetes, blood pressure medications, and lipid-lowering drugs remained unchanged during the study.

All patients completed the trial. Medications were delivered to patients monthly. Patients returned empty drug blister pack at the end of each month to confirm the use of medications.

The Ethics Committee of Qom University of Medical Sciences approved this study (IR.MUQ.REC.1395.12) and written informed consent was obtained from the all participants. Data were analyzed using SPSS 18 software (SPSS Software IBM, Inc., New York City, New York State, USA), and the statistical significance level of $P < 0.05$. Paired *t*-test, unpaired *t*-test, Chi-square, and Fisher's exact test were used to compare groups for outcomes. ANCOVA test was performed to compare the after-intervention outcomes with control of preintervention values. The assumptions needed for analyses tests, such as normality, homogeneity of variance, and random independent samples, were established.

RESULTS

All 60 patients received intended treatment, and all were analyzed for the outcomes. No participant was excluded during the, and there was no loss to follow-up.

The mean age of patients was 57.1 ± 8.02 years. There was no significant difference between the two groups in regard to the baseline variables [Table 1]. Seventy-five percent of patients taking any dose of statin (73.3% of intervention group and 76.7% of placebo group) ($P = 0.76$).

Blood pressure, body mass index, and blood glucose did not change significantly during the study [Tables 2 and 3]. In the pentoxifylline group, the symptoms of peripheral neuropathy were significantly improved ($P = 0.042$).

Table 1: Distribution of baseline variables of the subjects according to the group

Variable	Group	*n*	Mean±SD	*P**
Age (years)	Intervention	30	58.3±7.84	0.115
	Placebo	30	55.1±7.66	
Height (cm)	Intervention	30	162.7±1.83	0.295
	Placebo	30	159.63±10.63	
Weight (kg)	Intervention	30	84.73±19.46	0.937
	Placebo	30	84.4±12.43	
BMI	Intervention	30	32.02±6.37	0.4
	Placebo	30	33.28±5.06	

**P* value with two-tailed, unpaired *t*-test. BMI=Body mass index; SD=Standard deviation

Changes in neuropathy symptom [Table 4] and physical examination [Table 5] were also analyzed for each question. Changes were only significant for questions 6 (Does it hurt when the bed covers touch your skin?) and 12 (Do your legs hurt when you walk?).

DISCUSSION

The aim of this study was to evaluate the effects of pentoxifylline on distal diabetic neuropathy in patients with type 2 diabetes. In this study, MNSI questionnaire was used to evaluate the severity of polyneuropathy. There was no significant difference between the two groups in terms of initial variables. After the intervention, the mean score of the clinical symptoms decreased by 0.63 in the intervention group, whereas in the control group, the decrease was 0.13 and the difference was statistically significant ($P = 0.046$). However, there was no significant difference in the clinical examination between the two groups ($P = 0.471$).

Cohen and Harris first reported in 1987 that pentoxifylline was given to 8 patients for the treatment of neuropathy for 16 weeks; in 6 patients, neuropathy had improved; and in 2 patients, burning and numbness of the fingers improved perfectly, this effect was independent of the effect of the drug on blood glucose and renal function.[15] Afterward, Mr. Kalmansohn *et al*. reported in 1988 an 80-year-old patient with a 5-year history of diabetic distal neuropathy who had reduced the symptoms of neuropathy 1 month after the onset of pentoxifylline, and 4 months after, the drug has reached its maximum effect. Mr. Kalmansohn *et al.* said in his report that pentoxifylline is likely to increase blood flow to small vessels and improve neuropathy due to reduced blood viscosity and increased flexibility of red blood cells.[18]

In 1990, Cohen *et al*. studied 21 patients with diabetic neuropathy and treated 12 patients with 400 mg pentoxifylline, three times a day for 12 weeks and 9 patients with placebo. The severity of diabetic neuropathy was

Table 2: Change in outcome measures before and after the treatment with pentoxifylline in patients with diabetic neuropathy

Variable	Group	Baseline		After intervention	
		n	Mean±SD	*n*	Mean±SD
HbA1c	Intervention	30	8.43±1.52	30	8.45±1.479
	Placebo	30	8.63±1.347	30	8.51±1.237
FBS	Intervention	30	169.53±65.691	30	171.20±63.218
	Placebo	30	170.93±52.17	30	169.53±48.059
2HPP	Intervention	30	259.23±92.57	30	261.03±79.925
	Placebo	30	262.10±59.14	30	254.10±55.193
Systolic blood pressure	Intervention	30	126.50±12.33	30	129.50±11.916
	Placebo	30	136.53±24.95	30	135.80±12.901
Diastolic blood pressure	Intervention	30	82.17±14.58	29	83.28±11.823
	Placebo	29	80.00±9.54	30	81.43±9.644
Symptom score (MNSI)	Intervention	30	5.8±2.7	30	5.2±2.5
	Placebo	30	4.6±2.2	30	4.4±2.2
Physical examination score (MNSI)	Intervention	30	0.8±0.88	30	0.66±0.8
	Placebo	30	0.83±0.87	30	0.76±0.81

2HPP=2-h postprandial blood sugar; FBS=Fasting blood sugar; MNSI=Michigan Neuropathy Screening Instrument; SD=Standard deviation; HbA1c=Glycosylated hemoglobin

Table 3: Comparison of outcomes in two groups after treatment with pentoxifylline adjusted for baseline measurement in patients with diabetic neuropathy

Variable	Source	Type III sum of squares	df	Mean square	*F*	*P**	η^2	Adjusted R^2
HbA1c	Pretest	103.49	1	103.49	1357.95	<0.001	0.96	0.958
	Group	0.253	1	0.253	3.326	0.073	0.055	
FBS	Pretest	170743.6	1	170,743.6	801.9	<0.001	0.934	0.912
	Group	667.265	1	667.265	2.462	0.122	0.041	
2HPP	Pretest	206,376.903	1	206,376.903	175.008	<0.001	0.754	0.755
	Group	1251.200	1	1251.200	1.061	0.307	0.018	
Systolic blood pressure	Pretest	2269.94	1	2269.94	19.386	<0.001	0.254	0.276
	Group	135.989	1	135.989	1.161	0.286	0.020	
Diastolic blood pressure	Pretest	1404.753	1	1404.753	14.877	<0.001	0.213	0.191
	Group	20.674	1	20.674	0.219	0.642	0.004	
Symptom score (MNSI)	Pretest	241.68	1	241.68	288.312	<0.001	0.835	0.832
	Group	3.646	1	3.646	4.349	0.042	0.071	
Physical examination score (MNSI)	Pretest	31.832	1	31.832	292.564	<0.001	0.837	0.832
	Group	0.078	1	0.078	0.714	0.402	0.012	

**P* value with ANCOVA test. 2HPP=2-h postprandial blood sugar; FBS=Fasting blood sugar; MNSI=Michigan Neuropathy Screening Instrument; df=Degrees of freedom; HbA1c=Glycosylated hemoglobin

measured by a questionnaire. This study showed that pentoxifylline had no advantage over placebo in reducing symptoms of the diabetic neuropathy.[19] In 1991, Cohen and Mathews treated 20 patients with diabetic neuropathy by pentoxifylline and 20 patients by placebo. After 6 months of treatment, the two groups did not have any significant difference in terms of visual analog scores, nerve conduction, and neuropathic examination.[16]

In 1992, Rendell and Bamisedun treated 24 patients with diabetic neuropathy with pentoxifylline for 6 months, of which 17 reported a decrease in symptoms. In this study, the skin blood flow was also examined by Doppler sonography, skin blood flow increased significantly after treatment, and the sensation threshold also improved after 6 months.[20]

In 1997, Lee *et al*. treated 25 patients with pentoxifylline and 25 patients with placebo; Lee reported there was no significant change in touch sense threshold, numbness and pain, after 6 weeks of treatment.[17]

In 2009, Laczy *et al*. also treated 77 patients with diabetic neuropathy with injections form of pentoxifylline and pentosan polysulfate and 12 patients with saline for 5 days. The threshold of vibrational sensation after the treatment was significantly improved in the intervention group compared with the placebo group.[10]

Despite the fact that for over 30 years, the treatment of neuropathy with pentoxifylline has passed, but so far, no good study has been done. Only five clinical trials for the use of this drug were found that a study was based on the

Table 4: Change in neuropathy symptom after the treatment with pentoxifylline based on question number of Michigan Neuropathy Screening Instrument

Variable	Group	Improved, *n* (%)	Not change, *n* (%)	*P**
Q1	Intervention	3 (10.0)	27 (90.0)	0.306
	Placebo	1 (3.3)	29 (96.7)	
Q2	Intervention	0	30 (100.0)	-
	Placebo	0	30 (100.0)	
Q3	Intervention	8 (26.7)	22 (73.3)	0.347
	Placebo	5 (16.7)	25 (83.3)	
Q4	Intervention	0	30 (100.0)	-
	Placebo	0	30 (100.0)	
Q5	Intervention	2 (6.7)	28 (93.3)	0.500
	Placebo	1 (3.3)	29 (96.7)	
Q6	Intervention	5 (16.7)	25 (83.3)	0.026
	Placebo	0 (0.0)	30 (100.0)	
Q7	Intervention	2 (6.7)	28 (93.3)	0.246
	Placebo	0 (0.0)	30 (100.0)	
Q8	Intervention	0	30 (100.0)	-
	Placebo	0	30 (100.0)	
Q9	Intervention	2 (6.7)	28 (93.3)	0.246
	Placebo	0 (0.0)	30 (100.0)	
Q10	Intervention	1 (3.3)	29 (96.7)	0.5
	Placebo	0 (0.0)	30 (100.0)	
Q11	Intervention	1 (3.3)	29 (96.7)	0.5
	Placebo	0 (0.0)	30 (100.0)	
Q12	Intervention	4 (13.3)	26 (86.7)	0.056
	Placebo	0 (0.0)	30 (100.0)	
Q13	Intervention	2 (6.7)	28 (93.3)	0.246
	Placebo	0 (0.0)	30 (100.0)	
Q14	Intervention	1 (3.3)	29 (96.7)	0.754
	Placebo	1 (3.3)	29 (96.7)	
Q15	Intervention	0	30 (100.0)	-
	Placebo	0	30 (100.0)	

**P* value with Chi-square and Fisher's exact test. Q1=Are you legs and/or feet numb? Q2=Do you ever have any burning pain in your legs and/or feet? Q3=Are your feet too sensitive to touch? Q4=Do you get muscle cramps in your legs and/or feet? Q5=Do you ever have any prickling feelings in your legs or feet? Q6=Does it hurt when the bed covers touch your skin? Q7=When you get into the tub or shower, are you able to tell the. hot water from the cold water? Q8=Have you ever had an open sore on your foot? Q9=Has your doctor ever told you that you have diabetic neuropathy? Q10=Do you feel weak all over most of the time? Q11=Are your symptoms worse at night? Q12=Do your legs hurt when you walk? Q13=Are you able to sense your feet when you walk? Q14=Is the skin on your feet so dry that it cracks open? Q15=Have you ever had an amputation?

Table 5: Change in physical examination after the intervention the treatment with pentoxifylline in patients with diabetic neuropathy

Variable	Group	Improved, *n* (%)	Not change, *n* (%)	*P**
Right vibration perception	Intervention	2 (6.7)	28 (93.3)	0.5
	Placebo	1 (3.3)	29 (96.7)	
Left vibration perception	Intervention	2 (6.7)	28 (93.3)	0.5
	Placebo	1 (3.3)	29 (96.7)	
Right ankle reflexes	Intervention	0	30 (100.0)	-
	Placebo	0	30 (100.0)	
Left ankle reflexes	Intervention	0	30 (100.0)	-
	Placebo	0	30 (100.0)	

**P* value with Chi-square test

injectable formulation with pentosan, and another study did not have a control group, and three other studies had a small sample size (12 patients, 20 patients, and 25 patients, in each study).

In animal studies, Flint *et al*. also looked at the effect of pentoxifylline on diabetic neuropathy in mice, which the results of the study showed that pentoxifylline could improve neuropathy by the improvement of nerves tissue blood flow.[21]

Most studies have suggested that the effect of pentoxifylline is by reducing the viscosity of the blood and increasing the resiliency of red blood cells and thereby increasing the blood flow of the nerves.[18] Satoh *et al*. suggested that pentoxifylline can improve diabetic neuropathy by reducing TNF-α and reducing free radicals.[22] In another study, Garcia *et al*. showed that pentoxifylline reduces inflammatory factors such as TNF-α, interleukin-6, and inducible nitric oxide synthase, which can improve diabetic neuropathy by reducing inflammation.[13] The lack of changes in blood glucose control (FBS, HbA1c, 2-h postprandial blood sugar) after study and the lack of changes in patient's blood pressure in the present study can show that the mechanism of pentoxifylline effect is independent of the effect on these factors.

The main limitation of the study was low number of patients in the intervention and placebo groups.

CONCLUSION

The results of this study and its comparison with previous studies showed that pentoxifylline could be effective in reducing the symptoms of diabetic distal neuropathy. However, further evidence is needed to prove this effect. Long-term clinical trials are recommended to investigate the long-term effects of this drug.

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Conflicts of interest

There are no conflicts of interest.

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