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Comparing the Efficacy of Duloxetine with High Tone Power Therapy in Diabetic Peripheral Neuropathic Pain: A Double-Blind Randomized Phase III Clinical Trial

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ABSTRACT

Background & Objective: Diabetic neuropathy pain is a common pain condition that has a major negative impact on health-related quality of life. However, despite many studies, it remains difficult to treat neuropathic pain. This study aimed to compare the efficacy of duloxetine with high tone power therapy (HTPT) in diabetic peripheral neuropathic pain.

Materials & Methods: The study is a single-centre, phase III clinical trial comparing the effect of HTPT versus treatment with duloxetine in diagnosed diabetic neuropathy patients between October 2019 to December 2020. In the case group, the HTPT was used with a four-second duration for 30 minutes daily. This treatment was continued twice a week for 10 sessions. The control group received duloxetine (30 mg/m2 once a day). The treatment response was assessed based on the VAS score.

Results: The results showed that in both groups, there was a significant reduction in pain severity. In HTPT group, the average pain decreased from 7.36 to 4.6 and in duloxetine group from 7.7 to 4.8. During 8 measurements after the intervention; decrease in VAS score was higher in HTPT group (5.6) than in duloxetine group (6.5) in the first and fourth times after the intervention (P-Value=0.01). Further analysis demonstrated a positive correlation between pain severity and age so that, the pain also increases with advancing age.

Conclusion: The results of the present study showed that both duloxetine and high tone therapies are safe and effective methods for neuropathic pain relief.

Keywords: Diabetic Neuropathy, Duloxetine, TENS

Introduction

Neuropathy is a nerve injury that can lead to sensory disturbances, including a decreased sense of protection, making patients more prone to foot injuries (1). This disorder starts in the feet and progresses up the legs. In neuropathy, initially the feet are affected, followed by the legs and fingers (2). Common neuropathy symptoms include numbness, tingling, pain, or weakness that starts in the lower extremities (3). Approximately 20 to 30 million people suffer from symptomatic neuropathy, which will double by 2030 (4). Diabetic neuropathy (DN) is a multifunctional disorder whose primary pathophysiology and treatment methods have not yet been determined. Risk factors for neuropathy include poor glucose control, advanced age, duration of diabetes, impaired lipid levels, and high blood pressure. Diabetes has been identified as the most important risk factor for neuropathy (5). It has been reported that approximately 66 and 59% of patients with type 1 and type 2 diabetes tend to develop neuropathy, respectively (6). Therefore, diabetic neuropathy is a relatively common disorder. Because it is painful and progressive, treatment and control of the patient's condition are important.

Therapy based on the mechanism of painful diabetic neuropathy is challenging, but symptom-based classification may be a way to develop therapeutic implications. Because the cause of DN in humans is not well understood, symptomatic treatment with analgesics, tricyclic antidepressants, and external muscle stimulation can often reduce neuropathic symptoms and pain (7). Recently- published studies have shown that transcutaneous electrical nerve stimulation (TENS) (8), percutaneous electrical nerve stimulation (9), spinal cord stimulation (10), electrical stimulation therapy (11), and

other physical therapies (12) were successfully performed as non-pharmacological treatments. In addition to non-pharmacological therapies, pharmacological treatments are also used to suppress DN. For example, duloxetine (DLX) as a neuronal reuptake inhibitor of serotonin and norepinephrine, enhances serotonergic and noradrenergic activities in the descending pathways of central nervous system pain inhibitors (13, 14). DLX reduces persistent pain mechanisms, including central tenderness and high irritability in the spinal and supraspinal pain transmission pathways (15). Extensive studies have evaluated the role of DLX pain relief in DN management (15–19). Comparison and evaluation ofthe effect of pharmacological and non-pharmacological therapies on the pain and clinical condition of DN patients and achieving a reliable result can make treatment easier for the physician and reduce the additional cost for the patient.

Materials and Methods

Study design

The current study is a single-centre, phase III clinical trial that compares the effect of high tone versus treatment with duloxetine in diagnosed DN patients recruited to the diabetes clinic at Ahvaz Golestan Hospital, Ahvaz, Iran, between October 2019 to December 2020. The study was based on the approval of the Medical Ethics Committee of Jundishapur Ahvaz University (Reference Number: IR.AJUMS.REC.1398.776) and performed as a phase III clinical trial (code IRCT20200827048547N1).

Study population

In this clinical trial, patients with DN were randomly divided into intervention and control groups. The inclusion criteria for selecting the patients were as follows: patients aged ≥18 with diabetes diagnosis regardless of diabetes type, patients with 24 visual analog scale (VAS) mean, at least 2 points of Michigan neuropathy screening instrument (MNSI) scoring, with symptoms of neuropathy (including axonal in electrophysiological findings), without any restriction for gender. Exclusion criteria were considered as the history of heart dysfunction, liver dysfunction, epilepsy, peripheral vascular disease, uncontrolled acute angle-closure glaucoma, mood disorder, diffuse anxiety disorder, glomerular filtration rate (GFR) less than 30 mol/min, pregnancy, breastfeeding, metastatic disease, HbA1C>12 g/dl, the existence of neuropathy due to other reasons, receiving treatment for DN control 2 weeks before, and diabetes history shorter than one year or over 15 years. Eligible patients were randomly divided into two groups based on the quadruple random blocks method. All patients' informed written consent was provided before entering the study .Also, regarding the stage of the diabetic patients and whether there were kidney or liver problems along with diabetic neuropathy and how well the three-month glucose (HbA1c) was controlled, HbA1c, Cr, FBS and BUN tests were performed once , when the subject entered the examination.

Treatment

In the case group, the high tone treatment was performed twice a week, placing therapeutic electrodes in the femoral muscles area using 230V muscle stimulation with a stimulation duration of 4 seconds. This treatment method was performed daily for 30 minutes for 10 sessions. The control group received duloxetine (30 mg/m^2 once a day); in cases with no-response to treatment, the dosage was increased twice daily.

Clinical Assessment

The treatment response was assessed based on the VAS score. VAS score was based on self-reported measures of pain intensity ranging from 0: no pain to 10: worst pain. A higher score indicates greater pain intensity. Also, VAS score intervals of 0-3, 4-6, and 7-10 were identified as mild, moderate, and severe pain, respectively (20). In both treatment groups, all patients were examined through weekly visits during the treatment period. Adverse events (AEs) and the VAS score were recorded weekly.

Statistical analysis

The chi-squared test was used for comparing categorical data between the two groups. Independent sample t-test was used to compare quantitative variables between the two groups. Pearson test and linear regression were used to investigate the relationship between variables. The significant P-value was considered <0.05. All data were analyzed by SPSS software (V24).

Results

Thirty-six participants were included for the current clinical trial and randomly divided into the case (n =18) and control (n =18) groups. Of these, 58.3% (21) were female, and 41.7% (15) were male (Table 1). Among all patients, 91.7% (33) had type II, and 8.3% (3) had type I diabetes.

Table 1. The demographic information of patients

Variables	HTPT group (n =18)	Duloxetine group (n=18)	p-value
Gender			
Male, n (%)	12 (66.7)	9 (5)	0.31
Female, n (%)	6 (33.3)	9 (5)	
Mean age ± SD	52.3 ± 9.3	56.3 ± 11.3	0.25

Variables	HTPT group (n =18)	Duloxetine group (n=18)	p-value
Diabetes type			
Type I	1 (5.67)	2 (11.2)	0.54
Type II	17 (94.4)	16 (88.9)	

*** p-value< 0.05**

Clinical Outcome

The results showed that there was a significant reduction in pain severity in both groups,. In group one, the average pain decreased from 7.36 to 4.6, and in group two from 7.7 to 4.8. During 8 measurements after the intervention, the results showed a statistically significant difference between the two groups in the first and fourth times after the intervention (Table 2). Further analysis demonstrated a positive correlation between pain severity and age so that with advancing age, the pain also increases. On the other hand, in the present study, there was no statistically significant relationship between pain and laboratory parameters including HbA1c, Cr, FBS and BUN (p>0.05, Table 3).

Because current DN therapies have limited effect, we examined the patients' treatment and pain control methods with pharmacological (duloxetine) and non-pharmacological (electrical stimulation) interventions in this study.

Table 2. Comparison of both groups for VAS scoring during treatment

Variables	Mean (SD)		Median		P-Value
	HTPT	Duloxetine	HTPT	Duloxetine	
VAS0	7.36(0.68)	7.7(1)	7	8	0.14
VAS1	6.9(0.80)	7.7(1.01)	6.75	8	0.01
VAS2	6.6 (0.68)	7.1(0.85)	6.5	7	0.08
VAS3	6.4(0.77)	6.7(1)	6	7	0.18
VAS4	5.8(0.71)	6.5(0.85)	6	6.5	0.01
VAS5	5.6(0.81)	5.9(0.80)	5.5	6	0.19
VAS6	5.1(0.47)	5.5(1.04)	5	5.5	0.17
VAS7	4.6(0.69)	4.9(0.72)	4.5	5	0.15
VAS8	4.6(0.69)	4.8(0.78)	4.5	5	0.39

VAS: Visual Analog Scale

Table 3. The correlation between pain and other factors

VAS score		Age	Pain duration	FBS	HbA1C	BUN	Cr
VAS1	r	0.494	0.194	-0.214	-0.208	0.101	0.329
	P-Value	0.002	0.256	0.211	0.223	0.558	0.05
VAS2	r	0.565	0.142	-0.319	-0.271	0.049	0.287
	P-Value	<0.001	0.41	0.058	0.110	0.778	0.90
VAS3	r	0.474	0.071	-0.033	-0.320	-0.035	0.193
	P-Value	<0.004	0.682	0.047	0.057	0.838	0.258
VAS4	r	0.531	-0.049	-0.259	-0.284	-0.035	0.177
	P-Value	<0.001	0.777	0.127	0.093	0.838	0.302
VAS5	r	0.456	0.065	-0.271	-0.331	-0.078	0.197
	P-Value	0.005	0.705	0.110	0.049	0.651	0.242
VAS6	r	0.589	0.092	-0.084	-0.025	0.089	0.384
	P-Value	<0.001	0.592	0.628	0.887	0.607	0.021

VAS score		Age	Pain duration	FBS	HbA1C	BUN	Cr
VAS7	r	0.5	-0.016	-0.204	-0.273	-0.07	0.267
	P-Value	0.002	0.928	0.232	0.107	0.684	0.115
VAS8	r	0.426	-0.060	-0.150	-0.236	-0.096	0.254
	P-Value	0.01	0.726	0.383	0.166	0.576	0.314

VAS: Visual Analog Scale; FBS: Fasting Blood Sugar; HbA1C: Hemoglobin A1C; BUN: Blood Urea Nitrogen; Cr: Creatinine.

Discussion

Diabetes mellitus is one of the major health problems of the international community, with a prevalence rate of 5-22% in Iran (21, 22). DN is the most common microvascular complication of diabetes, characterized by severe pain, loss of sensation, increased risk of foot ulcers, and amputation (1). Distal symmetrical neuropathy and polyneuropathy are the most prevalent types of diabetic neuropathy that cause significant disability (23). Nevertheless, finding an effective therapeutic strategy to manage and reduce disease complications remaina challenging issue and although there are different types of chemical drugs, efforts to replace a more efficient treatment will continue (24).

It was understood that hyperglycemia and hypoxia cause downregulation of nerve growth factor (NGF), which play a crucial role in DN development. In this regard, it was demonstrated that duloxetine by intervention in neuronal pathways and especially through sciatic NGF overexpression has an influential role in neuropathic pain treatment (13, 25). Despite showing the positive effect of duloxetine in DN treatment, recently, Shukla et al., reported a DN case that showed an increase in blood pressure one week after duloxetine use (26). Hence, there is a need for more surveys to address these controversial results.

Several defects account for DN development including spared nerve injury, chronic constriction injury, and spinal nerve ligation (23). Bioelectronic medicines have recently shown a therapeutic effect on diabetic neuropathy. In this method, the damaged nervous system is stimulated to treat the damaged tissue (27, 28). Numerous researchers have investigated the various types of bioelectronic medicine in the treatment of DN (29). Despite the proliferation of studies in this field, there is no comprehensive data about the side effect of bioelectronic medicines and the best type of intervention. Since there is scant data on high tone efficacy in DN, we compared the efficacy of high tone and nortriptyline in the current survey. High tone therapy involving the nerve and muscle stimulation has a great effect on cellular metabolism with remedial effects on renal disease and uremic peripheral neuropathy.

Nevertheless, there is scant data ont the exact mechanism of DN injury. Hence it is necessary to investigate various possible treatments to achieve the best therapeutic pathway. In this regard, the current study aims to compare the effect of high tone therapy and duloxetine in DN patients. Our previous investigation revealed that using duloxetine and nortriptyline was safe and beneficial; however, duloxetine had better outcomes (30).

Our results have shown that both treatments have a therapeutic effect on DN improvement. Further analysis demonstrated that duloxetine administration is not superior to high tone therapy in reducing DN pain. However, only some slight side effects were observed following the use of duloxetine. The adverse events may be associated with the patient's condition, such as drug intolerance, sensitivity, or ethnicity. Furthermore, some evidence demonstrated that the serotonin transporter gene and the specific cytochrome 2 D6 (CYP2D6) affect hepatic metabolism and drug adverse effects (31); being a primary reason for reported complications.

The dosage of 30 mg for the present survey was prescribed based on the previous literature (13). In accordance with our findings, Wajeeha Shahid et al., and Sameer Khasbage et al., elucidated that DLX has an acceptable safety and efficacy in relieving neuropathic pain and improving patient outcomes but with a daily dose of 60 mg (14, 32). It could be concluded that the effective DLX dosage can be adjusted depending on patients' condition, such as drug tolerance and side effect manifestations during early days after prescription. Similarly, Naderi Nabi et al., investigated a pharmacological and non-pharmacological method to reduce neuropathic pain in a randomized clinical trial and found that DLX and TENS had beneficial effect on painful DN healing (31). Thus, it is noteworthy that before each prescription, factors such as BMI, patient's condition, and genetic polymorphisms should be considered.

Similarly, Ahmed Magdy Alshimy et al., also indicated that high tone therapy was beneficial and improved neurophysiological indicators and functional outcomes in DN patients (33). Moreover, Dagmar Schaffler-Schaden et al., compared high-tone external muscle stimulation with TENS in chemotherapy-induced polyneuropathy and revealed that HTEMS improves neuropathy symptoms (34). In a similar study, Reichstein et al., compared the efficacy of TENS with high-frequency external muscle stimulation in patients with symptomatic DN. They reported that both methods have a therapeutic effect on DN treatment,

although the efficacy of high-frequency was higher in reducing pain (11). In another pilot study, Klassen A et al., evaluated the high-tone external muscle stimulation effect on diabetic peripheral polyneuropathy; they found that high tone stimulation causes improvement of diabetic peripheral polyneuropathy and significantly reduces pain severity (35). These findings are in agreement with our study that high tone can be helpful in DN treatment. In contrast, Weintraub et al., reported that high tone therapy did not affect the DN pain, which is proposed to be related to the different time exposures and target population or disease severity of participants (36). Sample size and follow-up timespan of studied method, and pain relief indicators can also justify discrepancies in this field.

Although both studied methods in our research were satisfactory in recovery time, the shorter duration of positive results in the high tone method (5 weeks) compared to duloxetine (8 weeks) was noticeable. Whereas, due to the need for multiple regular visits and financial burden of the high tone method, the acceptance of the drug treatment to follow up and continue treatment was higher than high tone therapy. In our past investigation, the efficacy of TENS with nortriptyline was compared, the findings show that both therapies have the same efficacy. This is in line with our present survey. Also, in a previous study, we found that TENS was accompanied by less frequent complications, which is followed by the present finding that high tone therapy has fewer adverse events (37).

Since the present study was the first clinical comparison of duloxetine with the high tone as a rehabilitation method in DN treatment, some limitations, including small sample size, and patient's follow-up timespan, limited our results. Multi-dimensional studies with a more extensive follow-up time and more comprehensive examination of patients in the case of DN parameters and polymorphisms involved in drug side effects are needed for further studies to definitive generalizations about the prescription of therapeutic strategy.

Conclusion

The present study results confirmed that both duloxetine and high tone therapies reduce neuropathic pain. However, our finding revealed that increasing the dose of duloxetine might be more helpful in DN management. It seems that due to the need for multiple regular visits and the financial burden of the high tone method, the acceptance of the drug treatment is higher. Nevertheless, regarding the low-level adverse effects in duloxetine usage, for patients who suffer from difficulties in drug tolerance or its complications and depending on pain severity, the high tone therapy only or in combination with duloxetine may be more appropriate.

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Authors' contributions

M.Z conceived the manuscript and revised it. Z.Gh, M.Sy, Sh.R, Z.K, and M.H performed the experimental procedures, performed the statistical analysis, and prepared tables and figures.

Conflict of Interest

The authors declare no conflict of interest. All procedure performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or compare ethical strand.

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