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Original Article

Analgesic effect of duloxetine compared to nortryptiline in patients with painful neuropathy: A randomized, double-blind, placebo-controlled trial

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Abstract

Background: Diabetic neuropathic pain (DNP) is a common complication of diabetes and has a profound effect on patients' quality of life. Therefore. The purpose of the present study was to compare the analgesic effects of duloxetine and nortryptiline in the management of patients with diabetic neuropathy.

Methods: This was a randomized, double-blind, parallel-group, placebo-controlled trial in subjects with a proven diagnosis of DM and suffered from neuropathic pain**.** Patients were recruited in this study from 20 February 2016 (first patient, first visit) to 22 June 2017 (last patient, last visit), including 5 weeks follow-up. A diagnosis of DNP was based on history, clinical examination, Nerve conduction velocity and Diabetic neuropathy symptom score (more than one point).

Results: Both drugs reduced pain when compared with placebo. A significant VAS reduction from 6.4 at baseline to 3.75 at endpoint was observed in the duloxetine group. However, there was no significant difference in the efficacy between nortriptyline and duloxetine based on patient's visual analogue scale (VAS) ($p>0.05$). No clinically significant changes or serious adverse events were found among treatment groups including changes in vital signs, laboratory assessments, physical examination or electrocardiograms. The decrease in the mean pain intensity was significantly greater in the duloxetine and nortriptyline group compared to the placebo group both in the primary analysis and in the by-visit analysis ($p<0.003$).

Conclusion: The present study demonstrates the safety and effectiveness of both duloxetine and nortriptyline in the management of DNP.

Keywords: Diabetic peripheral neuropathy, Nortriptyline, Duloxetine, Diabetes, Pain

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Diabetes mellitus (DM) characterized by chronic hyperglycemic condition eventually results in resistance to insulin action (1). DM is commonly associated with number of long-term complications including neuropathy which affects approximately 70% of diabetic patients (2-6). According to the previous studies, the incidence of diabetes in Iranian population aged 25-64 is about 7% and its prevalence has risen rapidly in recent years (7). Approximately, half of patients who have lived with diabetes for more than 25 years, will eventually develop neuropathy during their course (8). Diabetic neuropathic pain (DNP) has a profound effect on the quality of life of patients (9). The precise pathogenesis of DNP is not yet fully understood.

However, several theories regarding the pain related to the diabetic neuropathy have been proposed including central and peripheral nervous system sensitization, changes in the blood vessels supplying the peripheral nerves, changes in sodium and calcium channel expressions and defect in endogenous analgesic mechanisms via descending spinal pathways that inhibit pain (10, 11).

For decades, tricyclic antidepressants (TCAs) such as imipramine, amitriptyline and nortriptyline have been used as a first-line therapy for controlling neuropathic pain in diabetic patients. The most common adverse effects of nortriptyline are including palpitations, dry mouth, constipation, urinary retention and blurred vision. Therefore, because of their broad side-effect profile, new drugs need to be developed and investigated. Recent clinical trial studies have suggested that serotonin–norepinephrine reuptake inhibitors (SNRIs), such as duloxetine have shown promise in patients with DPN (12-14). Management of DPN is mainly focused on palliative treatment and symptomatic pain relief. However, controlling symptoms using drug regimens are often limited by side effects and the development of tolerance (15). The treatment modalities recommended for first-line use in the management of DPN include the tricyclic antidepressants, duloxetine, venlafaxine, pregabalin, and gabapentin (16). Although the effect of nortryptilinein neuropathic pain has been demonstrated in numerous studies, its broader spectrum of activity and possible adverse effects may limit its use (17-19). On the other hand, duloxetine has been shown to be an effective and safe treatment option in patients with DNP (20). Therefore, the objective of the present study was to compare the effectiveness of duloxetine vs. nortryptiline among diabetic patients suffering from neuropathic pain.

Methods

Patients: The study population consisted of patients with 30 years of age and older with diabetes (type 2) for at least 1 year and referred to endocrinology outpatient department of our tertiary healthcare hospital (affiliated to Babol University of Medical Sciences, Babol, Iran). Patients were eligible to be recruited in the study if they met the following criteria: Patients with diabetes mellitus with stable glycemic control defined as a hemoglobin A_1C levels less than 9, symptoms suggestive of DNP such as dysesthesia, burning pain, hyperalgesia affecting both lower extremities for at least 1 month. A diagnosis of DNP was based on history, clinical examination, Nerve conduction velocity (NCV) and diabetic neuropathy symptom (DNS) score (more than one point) (21). Subjects were excluded if they had any unstable medical orpsychiatric condition, uncontrolled DM, renal or liver disease, previous history of epilepsy or taking anticonvulsants, uncontrolled hypertension, and pregnant women. Furthermore, patients with the use of concomitant medication including chronic use of antidepressants, antiemetics, analgesics (except aspirin up to 80 mg/day) were also excluded. Data regarding the possible adverse effects of drugs were obtained by calling each patient twice a week from the starting point of study.

Study protocol: A randomized, double-blind, parallel-group, placebo-controlled trial in subjects with a proven diagnosis of DM and suffered from neuropathic pain was performed. Patients were enrolled in the study from 20 February 2016 (first patient, first visit) to 22 June 2017 (last patient, last visit), including 5 weeks follow-up. Written informed consent was obtained from all patients prior to the study. This study was registered in the Iranian Registry of Clinical Trial (www.irct.ir) with registration number ID: IRCT201512265692N8. The process of this study was performed in accordance with the Declaration of Helsinki and other applicable guidelines, laws, and regulations (22).

Study design: This study consisted of 1-week single-blind (patients) run-in phase to establish baseline scores and a 5-week, double-blind treatment phase. Patients were randomized in 1:1:1 ratio into one of the three treatment branches (Placebo, or nortryptiline, or duloxetine). The randomization was provided by an independent statistician using pre-programmed computer software (Microsoft Excel®) employing a random permuted block approach. Results of the randomization generation were concealed in sequentially numbered, sealed, opaque envelopes. The treatment assignment envelope was opened after all screening procedures were completed. Duloxetine and nortriptyline were administered at 20 mg daily and 25 mg once at bedtime, respectively. Drugs were randomly assigned to three groups of HB603N, UT862S and PS370M, using a computer matching list. After packing them in boxes containing 35 capsules, the medications were kept in sterile environment and were given to the patients over a period of 5 weeks by the endocrinologist and according to the list prepared by the statistical consultant. All participants were asked to stop taking their current pain medication before participating in the trial. For ethical reasons, opioids and nonsteroidal anti-inflammatory drugs (paracetamol up to 3

g⁄day) were allowed to continue to be taken only during the run-in period. Patients were given a daily pain diary to record their symptoms. The method of examining and interpreting pain severity was based on the visual analogue scale (VAS). The VAS prepared in this study had scores of 1 (minimum pain) to 10 (maximum pain). According to the previous clinical trials, reductions of ≥30 % were defined as clinically important reductions from baseline in the VAS (23, 24). During the period of 35 days, patients were contacted 1 to 2 times on average, and the questions were asked regarding how to use the drug, how to complete the VAS and the patient's pain changes. Patients were revisited at the end of 5 weeks.

Statistical analysis: The sample size calculation was based on the means and standard deviations (sd) observed from similar previous trials. The Kolmogorov-Smirnov test was used to evaluate data normality (normal distribution of quantitative variables). We used One Way ANOVA test to determine the continuous variables between the three study groups. Median pain scores between two groups based on patient VAS were compared using Wilcoxon's matched pair test. The repeated measure ANOVA was used to determine the effect of time and different groups on the pain. Moreover, Pearson's chi-square test and Fisher's exact test were carried out to determine the efficacy of the two treatments. A p- value lower than 0.05 was considered to be statistically significant. All data were analyzed using SPSS Version 18.0 Software (SPSS Inc. Chicago, IL, USA).

Results

Patients: A total of 90 patients were screened, and 66 patients were enrolled and randomized into three study group (22 placebo group; 22 nortryptiline group; 22 doluxetine group). Figure 1 summarizes the flow of patients through the study. As shown in table 1, demographic characteristics were generally similar across treatment groups. The evaluable population used for the main analysis included 19 of 22 patients in the placebo group, 18 of 19 patients in the nortryptiline group and 18 of 21 patients in the doluxetine group. Overall, 55 patients completed the study. The mean age of the subjects was 58.26±7.55 years and the mean duration of diabetes was 3.96±8.94 years. On average, mean HbA1c values were more than 8%. HbA1c levels were higher in the duloxetine group, which was significant among the three groups (P=0.024). The majority of our patients were females (88%). A total of 15 patients (24.2%) were treated with insulin and 47 patients (75.8%) were treated with oral anti-diabetic drugs.

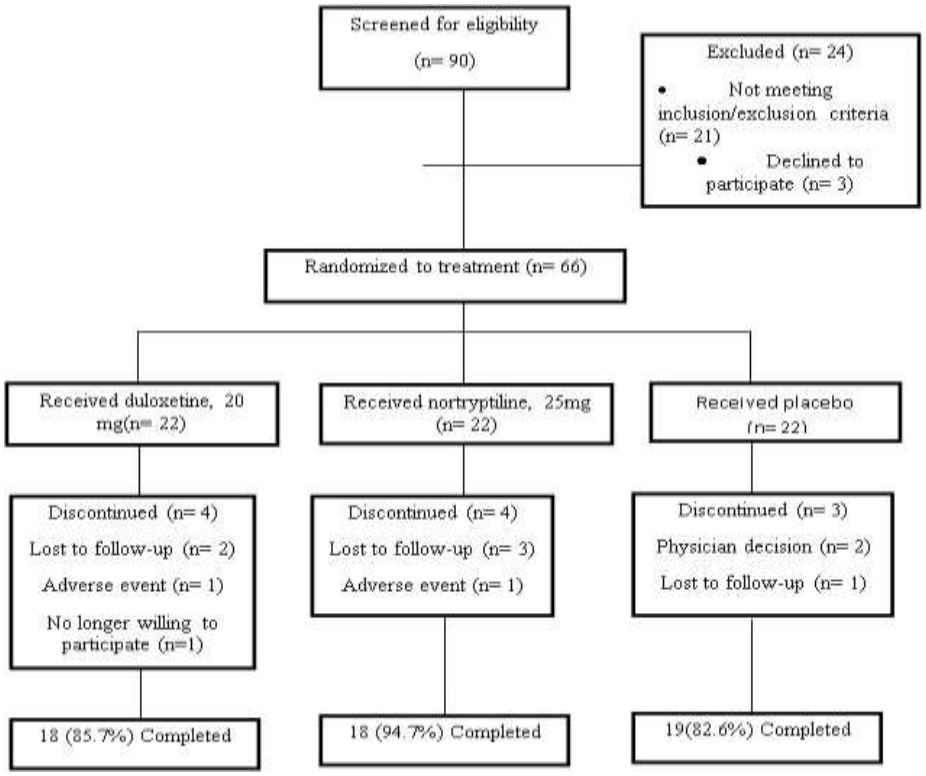

Figure 1. CONSORT flow diagram of patient disposition.

Table 1. Demographic and clinical characteristics of patients.

Variable	Group 1 Duloxetin (n=18)	Group 2 Nortriptyline (n=18)	Group 3 Placebo(n=19)	p-value
Gender (%)				
Female	17 (94.4)	16 (88.9)	19 (95.0)	0.72
Male	1 (5.6)	2 (11.1)	1 (5.0)	
Medication (%)				
Insulin	4 (22.2)	2 (11.1)	3 (16.7)	0.67
Oral antidiabetic drugs	14 (77.8)	16 (88.9)	15 (83.3)	
Age (years)	57±6.45	57.63±7.08	60 ± 8.81	0.396
FBS (dL/mg)	169.86±50.42	162.37±40.8	158.32±51.89	0.732
TG (dL/mg)	181.24±64.51	158.68±67.69	176.91±57.12	0.495
Chol (dL/mg)	175.57±30.1	165.68±20.33	166.05±26.12	0.387
LDL (dL/mg)	100.33±30.23	97.67±25.81	96.82±24.94	0.908
HDL (dL/mg)	42.29 ±6.71	43.47±8.55	41.86±7.14	0.78
HbA1C (mmol/mol)	8.41±1.03	8±0.68	7.71 ± 0.67	0.024
Duration of diabetes development (year)	9.48±4.7	9.53±3.87	7.91± 3.16	0.341
BMI (kg/m^2) (%)				
25>	6(33.3)	5(27.8)	7(36.8)	0.91
25-29.99	8(44.4)	7(38.9)	8(42.1)	
<30	4(22.2)	6(33.3)	4(21.1)	

Values expressed as percentage for categorical data and mean ± SD for continuous data. P values are from the Fisher exact test.
BMI, body mass index; HbA1c, glycatedhaemoglobin; FBS, fasting blood glucose; TG, triglyceride;
LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Efficacy: All patients were evaluated for pain intensity based on VAS scale. As shown in Table 2-4, the severity of pain was recorded per week for each group, and the mean pain intensity was also compared between the three arms of treatment in each week.

There was no significant difference in the efficacy between nortriptyline and duloxetine based on patient's VAS (p>0.05). However, improvement in pain reduction was noticed from the first week through the fifth week when comparing both baseline and post-treatments values (P=0.004). Overall, approximately two-thirds of the study population considered their pain intensity changes declined. A significant VAS reduction from 6.4 at baseline to 3.75 at endpoint was observed in the duloxetine group. Furthermore, the decrease in the mean pain intensity was significantly greater in the duloxetine and nortriptyline group compared to the placebo group both in the primary analysis and in the by-visit analysis (p<0.003) (figure 2).

Table 2. The mean pain intensity changes based on VAS scale from the first to fifth weeks

	Duloxetine (Mean ± SD)	Nortiptyline (Mean ± SD)	Placebo (Mean ± SD)	p-value
Week 1	6.43^a ± 1.74	6.15^a ± 1.99	7.52^b ± 1.35	0.035
Week 2	4.88^a ± 2.38	4.8^a ± 2.67	7.1^b ± 1.81	0.001
Week 3	4.3^a ± 2.52	4.62^a ± 2.84	6.69^b ± 2.15	0.003
Week 4	4.05^a ± 2.74	4.22^a ± 2.92	6.72^b ± 2.21	0.005
Week 5	3.75^a ± 2.99	4.19^a ± 3.05	6.87^b ± 2.1	0.002
Difference between first and fifth week	-2.68^a ± 2.01	-1.96^a ± 1.77	-0.64^b ± 1.28	0.006

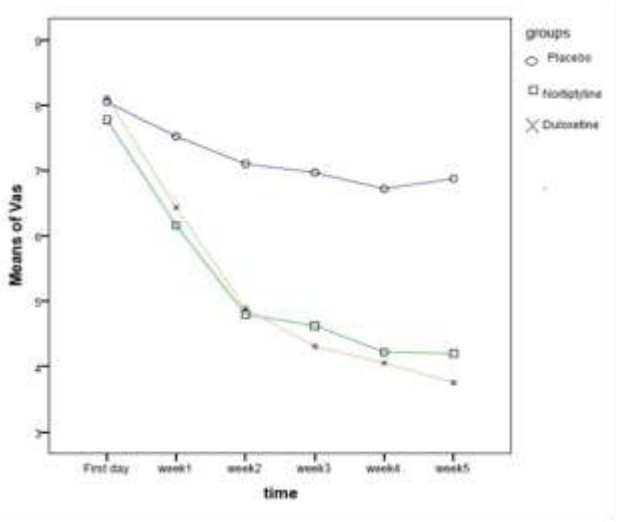

Figure 2. Mean changes in the daily pain severity according to visual analogue scale (VAS) of patients during the study period.

Safety: No clinically significant changes or serious adverse events were found among treatment groups including changes in vital signs, laboratory assessments, physical examination or electrocardiograms. Seven patients withdrew prematurely due to an adverse event (one from nortriptyline group, three from the duloxetine group, and three from the placebo group). No deaths occurred during the study period.

Discussion

The results of the current study suggest that both drugs were safe and effective for the management of DNP. In this study, no superiority of either drugs was observed. According to VAS scoring system, improvement in pain score was observed in 59% of patients treated with duloxetine compared to 55% of patients with nortriptyline. These findings are in concordance with past studies that reported a similar range of pain-evaluation scores (25, 26).

The pain severity reduction observed in the present study was significantly maintained and persistent from week 1 through the end of week 5. A treatment regimen consisted of starting dose of 20 mg duloxetine and 25 mg nortriptyline. Previous trials had shown an effective dose range of 60– 120 mg and 25–150 mg for duloxetine and nortriptyline, respectively (19, 26). Goldstein et al. (26). Compared the effect of duloxetine (administered at dosages of 20 mg, 60 mg, or 120 mg) and placebo in reduction of pain severity among patients with DPN. Duloxetine 60 mg and 120 mg per day showed significantly greater reduction in pain severity compared to placebo, but the same effect was not observed in duloxetine 20 mg/day. However, in the current trial pain relief was attained with relatively low doses of both drugs (duloxetine 20mg, nortriptyline 25mg). This fact could be explained by the possible effect of lower body size and weight of the Iranian population and also variability in individual differences in drug metabolism. Overall, both duloxetine and nortriptyline were found to be well tolerated and safely administered. There was no significant adverse event experienced in this trial. Our data are in agreement with previous trials suggesting that there were no significant differences in various other outcomes before and after the treatment (25, 27, 28).

The strengths of the present study include the randomized, double-blind, placebo-control trial design to investigate the therapeutic effects of both duloxetine and nortriptyline in the management of DNP. In addition, the presence of placebo arm enhanced the sensitivity for identifying the pain relief changes with each drug in DNP. However, this study was limited by number of reasons including shorter duration of follow-up and exclusion of patients whose medical conditions or concomitant medications might have interfered with the efficacy of the examined drugs.

In conclusions in summary, the result of the present study demonstrates the safety and effectiveness of both duloxetine and nortriptyline in the management of DNP. Duloxetine 20 mg once daily, was non-superior to nortriptyline 25 mg and both drugs had a similar magnitude in pain reduction in patients with DNP. Although, duloxetine is relatively more expensive, it offers an effective and safe alternative to those who cannot tolerate nortriptyline. However, these findings require confirmation by larger studies with longer duration of follow up.

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Conflict of Interest: The authors have no conflict of interest to declare.

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