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COMPARISON THE EFFECTS OF DULOXETINE AND NORTRIPTYLINE ON DIABETIC NEUROPATHY-RELATED PAIN CONTROL

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ABSTRACT

Introduction: Diabetic neuropathy is considered as one of the most common complications in both types of diabetes. The neuropathy associated with type 2 diabetes is estimated about 45% with pain, numbness, hypoesthesia, tingling and paraesthesia. The aim of this study was comparison of the analgesic effects of duloxetine and nortriptyline in patients with diabetic neuropathy.
Methods: In this clinical trial study, 54 diabetic patients with neuropathy manifestation were subjected to treat with 25-75 mg/d nortriptyline for 3 months. After one-month treatment disruption, 60 mg/dl duloxetine administered of additional 3 months. Investigation and interpretation of pain were performed based on Visual Analogue Scale.
Results: Analogue Scale score of patients after being treated with duloxetine and nortriptyline were 2.5 ± 1.35 and 3.2 ± 1.54, respectively ($p<0.05$). No sex-related significant differences were observed ($p=0.823$). The mean Visual Analogue Scale score was also 3.9 ± 1.2 ($p<0.05$) after one-month drug discontinuation.
Conclusion: Duloxetine is more effective with lower side effects for pain control in diabetic neuropathy compared to nortriptyline.

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Introduction

The increasing rate of incidence and prevalence of diabetes is the one of the medical problems in the developed and developing countries with an equal prevalence among men and women (1, 2).Diabetic neuropathy is one of the most complicated problems in both types of diabetes with about 45%(2, 3). Nerve damages can be developed throughout the body in diabetic patients, overtime. Nerve damage symptoms vary from no manifestations to symptoms such as pain, tingling, or numbness in the hands, arms, feet, and legs (4). Pain aggravation is usually happens at night and rest time and may cause sleeplessness and agitation or other problems. Less than 10% of patients suffer from neuropathy at the beginning of the disease. However, within a 25 year time period, its prevalence have increased to 50%(2, 3). It has been proven that, tight control of blood sugar is the best approach to prevent the progression of polyneuropathy (3, 4). The maximum dose of analgesic medication for diabetic neuropathy is rarely tolerated and the reduction of pain occurred in 60%(4). Visual Analogue Scale is an instrument that measures a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. It is often used in epidemiologic and clinical researches to measure the intensity or frequency of various symptoms (5). Duloxetine belongs to a group of drugs known as selective serotonin and norepinephrine reuptake inhibitors which are thought to work through increasing the activity of serotonin and norepinephrine in the brain (6).
The aim of this study was to investigate the analgesic effects of duloxetine in patients with diabetic neuropathy in comparison with nortriptyline in the treatment of neuropathic pain.

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Methods

Patients

54 diabetic patients (31 female and 23 male) referred to endocrine clinics of Imam Reza hospital were enrolled. This clinical study was also approved by the research (Code: 14862/4/5) and ethics (IRCT registration Code: IRCT2015111213612N7) committees of Tabriz university of medical sciences. Age more than 18, more than 5 years diagnosed diabetes record and at least 25 mg/d nortriptyline therapy for 3 months were considered as inclusion criteria. Patients with epilepsy, severe uncontrolled hypertension, chronic liver and kidney diseases and analgesics treatment record were excluded from study. 13 patients received insulin-only therapy, 23 patients were subjected for insulin and oral drug therapy and the remaining 18 patients received oral drug only medication.

Drug intervention

25-75 mg/d nortriptyline was prescribed according to tolerability doses for three months. 75, 50 and 25 mg/dl of nortriptyline were administered for 29, 18 and 7 patients, respectively. After this intervention, the medications were discontinued for 1 month and then they were treated for additional 3 months with 60 mg/dl duloxetine.

Visual Analogue Scale interpretation

Investigation and interpretation of pain were performed three times based on Visual Analogue Scale (from 1 to 9) after nortriptyline, discontinued drug administration and duloxetine therapy. Finally summed total score at the end of each period were calculated. Patients were also requested to refer immediately if they see any symptoms.

Data analysis

Data analysis was performed using SPSS 23 software. Visual Analogue Scale pain scores before and after treatments were analyzed using pier t test and p-value<0.05 was considered as significant level.

Results

General characteristics of individuals are shown in table 1. The average age of female and male patients was 64.5±4.2 and 60.4±3.42, respectively. Mean BMI of mentioned groups was also calculated as 28.45±5.41 and 25.32±3.8, respectively. All patients had a diabetic background more than 14 years. The average pain score in patient during nortriptyline therapy was 3.2 ± 1.54. The highest and the lowest visual analogue scale score during this treatment were also reported as 6 and 1, respectively. No significant differences were observed between sex groups during nortriptyline therapy (P-value = 0.823).

After nortriptyline discontinuation for one month, mean pain score reached to 3.9 ± 1.2 and the highest and the lowest score in this period was calculated as 6 and 2, respectively. No significant differences were observed between sex groups during drug discontinuation period (P-value = 0.260).

Duloxetine therapy caused a decrease in the mean visual analogue scale score (2.5 ± 1.35). The highest and the lowest scores were 5 and 1, respectively and no significant differences were observed between sex groups during duloxetine therapy (P-value=0.874).

Significant differences of visual analogue scale score was observed between nortriptyline and duloxetine therapy period (P-value <0.01). A significant increase in pain score was also observed in drug discontinuation period (P-value <0.01) (Table 2). Additionally, a significant difference was observed after nortriptyline intervention between different treatment groups (p=0.044). No significant differences were observed after drug discontinuation and duloxetine therapy between groups (Table 3).

Discussion

Pain control is a critical part of the health problems in patients with diabetic neuropathy and significantly affects patient's quality of life(7, 8). So far, 21 million diabetic patients are diagnosed in United States, whereas, about 8.1 million are remained undiagnosed (1, 4). It has been also estimated that 26-47% of diabetic patients suffer from peripheral neuropathy causing loss of sensation or pain (2, 3, 5). Larijani et al (9) reported that the only controllable risk factors for diabetic neuropathy is hyperglycemia. Blood glucose control reduces the incidence and the rate of progression of diabetic neuropathy and improves diabetic's quality of life. Yavari et al (10) also have shown that close monitoring, tight blood glucose control and regular exercise in older patients with a prolonged high blood sugar history are considered as effective approaches for neuropathy pain control. Furthermore, it has been reported that tight blood glucose control causes a clear reduction in diabetic neuropathy progression in type 1 diabetic patients with no significant effects in type 2 diabetes (3, 11).

Other studies have focused on the effects of different drugs on diabetic-related neuropathy pain control. In Hanna et al (12) study, amitriptyline and carbamazepine were effective in pain control with no significant difference. Talayi et al (13) also reported that vitamin B_{12} treated patients exhibit significant changes in clinical symptoms compared to nortriptyline treated group.

In our study, significant lower pain scores was reached during both nortriptyline and duloxetine therapy compared to discontinued drug period, indicating the positive impact of both drugs in diabetic neuropathy pain reduction. Tajti et al (14) also have shown that duloxetine is a more effective drug in diabetic neuropathy-related pain control compared to gabapentin. Furthermore, recent studies have reported that duloxetine is more effective in diabetic neuropathy pain control compared to placebo,

pregabalin and amitryptiline(15). Duloxetine and N-methyl-duloxetine have been also suggested as effective drugs in pain control(16).

Different studies have suggested duloxetine as the first choice for pain control because of cost effectiveness and lower side effects compared to tricyclic antidepressants(17, 18). Roy et al(19) also showed that both duloxetine and pregabalin has the similar efficacy but patients are more comfortable with duloxetine. In our study, no side effects of duloxetine were also observed during patient's treatment and follow-up.

Additionally, recent studies have suggested duloxetine combination therapy protocols for more effective treatment approaches. Tesfaye et al(20) demonstrated that combination therapy of duloxetine and pregabalin has a high effectivness in diabetic neuropathy treatment. Furthermore, Backonja et al(21) showed that multiple drug therapy will provide better results in patients with pain score more than 7.

According to our finding, duloxetine seems to be a more effective choice for treatment because of better pain control compared to nortriptyline, lower specific complications during therapy and patients compatibility with this drug. However, further studies with a larger number of patients are needed to better understanding the different aspects of duloxetine physiology. Double blind clinical trial accompanied with nerve conduction velocity is also recommended for future investigations.

Acknowledgment

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Conflict of Interest

No potential conflict of interest was reported by the authors.

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Table 1. General characteristics of patients.

Parameters	Male(45%)	Female(55%)
Age (year)	60.4±3.42	64.5±4.2
BMI (kg/m^2)	25.32±3.8	28.45±5.41
Duration of diabetes (year)	14.18±7.89	16±9.86
Insulin (%)	33	45
Insulin& oral hypoglycemic agent (%)	55	37
Oral hypoglycemic agent (%)	12	18

Data are presented as Mean ± SD.

Table 2. Mean pain scores patients after different drug intervention.

Drugs	**Nortriptyline**	**Drug discontinuation period**	**Duloxetine**	**p-value**
Score pain (Mean±SD)	3.2±1.54	3.9±1.20	2.5±1.35	>0.05*

* P-value between Nortriptylin and Duloxetine

Table 3. Correlation of treatment types with pain scores after different drug intervention.

Drugs	**Insulin**	**Insulin + oral drugs**	**Oral drug**	**p-value**
nortriptyline	4.0±1.73	2.6±1.42	3.71±1.49	0.044
Drug discontinuation period	4.33±1.52	3.60±1.07	4.11±1.33	0.552
duloxetine	3.66±1.52	1.8±1.03	3.0±1.29	0.220

Data are presented as mean±SD.