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Comparison of the Efficacy of Duloxetine Versus Pregabalin for Pain Relief of Neuropathy in Diabetics

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ABSTRACT

Background: Neuropathy is a common complication in diabetic patients with clinical manifestations of feet and hands paresthesia, pain in the lower legs, and a burning sensation in the soles. A wide variety of medications are used for diabetic neuropathy with varying degrees of pain relief reported. The study objective was to compare the efficacy of duloxetine versus pregabalin for pain relief of neuropathy in diabetics.

Methods: The study was a six-week, single-blind, Randomized Controlled Trial conducted at HBS Medical and Dental College and Hospital in Islamabad. Patients were randomly designated to either of the groups (A or B) with 50 participants in each group. Group A received 150mg of pregabalin twice a day while group B received 60mg of duloxetine once a day. Pain relief was the primary outcome which was considered as a ≥ 50% decrease in pain score on the Visual Analog Scale at 6 weeks from baseline.

Results: A total of 100 diabetic patients were registered in the study. The mean age in groups A&B was 48.36 and 50.56 (SD± 6.64) years respectively. The majority of the study population were males 39 (78%) and 42 (84%) in both groups. A total of 66% (n=33) in Group A and 74% (n=37) of the patients in Group B achieved pain relief. A comparison of the pain relief achieved between the two groups showed no statistical significance (p-value 0.383).

Conclusion: The study revealed that duloxetine and pregabalin are both efficacious in terms of pain relief for diabetic neuropathy in our population.

Keywords: Diabetes Mellitus, Diabetic Neuropathy, Duloxetine Hydrochloride, Pregabalin.

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INTRODUCTION

Diabetic neuropathy is the most common of the various complications of diabetes, affecting approximately 30% of people with diabetes[1]. Clinical manifestations include paresthesia and pain in the lower limbs (mostly feet) and rarely the hands. The pain is dull, achy, and worsens at night. Symptoms also include burning sensations in the soles of the feet and wide-based abnormal gait[2].

In diabetics, the pathogenesis of pain is multifactorial. It takes into account metabolic derangements such as hyperglycemia, impaired glucose tolerance, dyslipidemia, oxidative and nitrosative stress, growth factor deficiencies, microvascular insufficiency, and autoimmune damage to nerve fibers[3]. In routine practice, the diagnosis of neuropathy related to diabetes is established on history and examination[4]. The primary aim of the pharmacological intervention is to achieve pain relief [5]. Older agents like the tricyclic anti-depressant amitriptyline have been used for many years while recent times have seen the advent of innovative groups like SNRI (Serotonin and Norepinephrine reuptake inhibitors) (duloxetine) or anticonvulsants (pregabalin, gabapentin)[6]. Despite the options, one of the main deficiencies in the management of diabetic neuropathy is the relative dearth of comparative research.

Duloxetine belongs to the group serotonin and norepinephrine reuptake inhibitors (SNRI). It is permitted by the US Food and Drug Administration (FDA) for the management of painful neuropathy associated with diabetes at a dose of 60 mg once daily[7]. Effective pain relief was achieved in 59% of patients treated with duloxetine in one clinical trial[8]. Duloxetine is recommended by NICE (National Institute of Health and Care Excellence) guidelines as a first-line treatment for painful neuropathy associated with diabetes and pregabalin as a second-line agent[9]. Pregabalin is also FDA-approved for diabetic neuropathy[10]. It is an anticonvulsant that binds to the α_2-δ subunit of the Ca++ channel and relieves pain by reducing the discharge of norepinephrine and substance P. In one study comparing pregabalin in a dosage of 300 mg OD (Once daily) with placebo, pain relief was seen in 29.1% of patients[11]. American Academy of Neurology considers pregabalin as the first line and all other treatment options as a second line[12].

There is inadequate data on the efficacy of duloxetine and pregabalin in residents. Moreover, to our knowledge, no study has compared the two agents directly in our settings. The purpose of this study was to compare the effectiveness of duloxetine with pregabalin for pain relief of neuropathy in diabetics so that the preferable treatment for this common disorder could be highlighted.

METHODS

Our study which was a six-month, single-blind, RCT was carried out at the Diabetic Clinic of HBS (Hazrat Bari Sarkar) Medical and Dental College and Hospital Islamabad from 15 January 2023 to 15 July 2023 after ethical approval from the hospital's ethical review committee with reference number EC18/169,15thOCT 2022. The study enrolled patients aged between 18-65 years of either gender, who had diabetes for at least five years and clinical manifestations of neuropathy for the last six months. Neuropathy was diagnosed based on history and examination. These included symptoms of pain, numbness, paresthesia, tingling, and burning in the feet and/or hands. Patients with co-morbid neurological conditions, critical medical conditions as well as pregnant and lactating females were excluded.

Randomization was done by lottery method and patients were allocated either to Group A or Group B (pregabalin or duloxetine respectively). Group A was prescribed 150mg of pregabalin twice daily and Group B was given 60mg of duloxetine once a day. Subjects were seen for a minimum of 3 visits: an initial enrollment visit (screening and randomization) and scheduled visits at the 3rd and 6th week of treatment. Visual Analog Scale (VAS) was utilized to track pain. It is a validated, subjective scale to measure pain where scores are documented by noting on a 10 cm line which denotes a scale starting from "0 as no pain" to "10 as worst pain". VAS scores were recorded at baseline and then after 6 weeks of treatment for both groups.

The demographic and clinical data were collected using a properly designed proforma. The data was then entered into version 25.0 of SPSS to be analyzed. Frequency and percentages were calculated for categorical variables while mean and standard deviation were calculated for continuous variables. The t-test was applied to assess the comparison of the dissimilarity in pain scores in the two groups with a p-value of ≤0.05 deemed significant. Effect modifiers were controlled by stratification.

RESULTS

A total of 100 patients participated in the study and they were randomized equally in either group consisting of 50 patients each. All the patients completed the six-week trial and there were no dropouts. A majority of the participants were males 81 (81%). The mean age was calculated to be 49.46 years (SD± 6.64). The mean duration of diabetes in these patients was 12.81 years with a Standard deviation (SD ± 1.45). The baseline demographics of the two groups are given in Table 1.

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Table 1: Baseline Demographics of the group A and B.

Variables		Group A	Group B
Gender n (%)	Female	39 (78.0%)	42 (84.0%)
	Male	11 (22.0%)	8 (16.0%)
Age Mean (±SD)		48.36 (±7.108)	50.56 (±6.172)
Duration Of Diabetes Mean (±SD)		11.16 (±.766)	14.46 (±1.313)
Medication Received		Pregabalin 150mg x BD	Duloxetine 60mg x OD

The mean pain score was calculated for the patients at baseline and then at the endpoint after 6 weeks of treatment. The mean score on the VAS at baseline for the sample was 6.83 (SD± .697) while the mean score for the participants after the clinical trial was 4.52 (SD± .588). The details of the mean scores on VAS for the two groups at baseline and 6 weeks are given in Table 2.

Table 2: Pain scores on the Visual Analog Scale (VAS) at baseline, week 3, and week 6 in both groups.

Mean ± SD	GROUP A	GROUP B	OVERALL
VAS Pain score (at baseline)	6.44 ± .929	7.22 ± .465	6.83 ± .697
VAS Pain score (at 3 weeks)	5.38+-.428	6.50+_.576	5.94+-.502
VAS Pain score (at 6 weeks)	4.00 ± .606	5.04 ± .570	4.52 ± .588

*t-test applied to compare the pain scores of two groups

Pain relief was the primary outcome of the study. The primary outcome was defined as a drop in the VAS score of >50% at six weeks from that at the baseline. A total of 66% (n=33) in Group A and 74% (n=37) of the patients in Group B achieved pain relief. A comparison of the percentage of pain relief achieved between the two groups showed no statistical significance (p-value 0.383). Figure 1

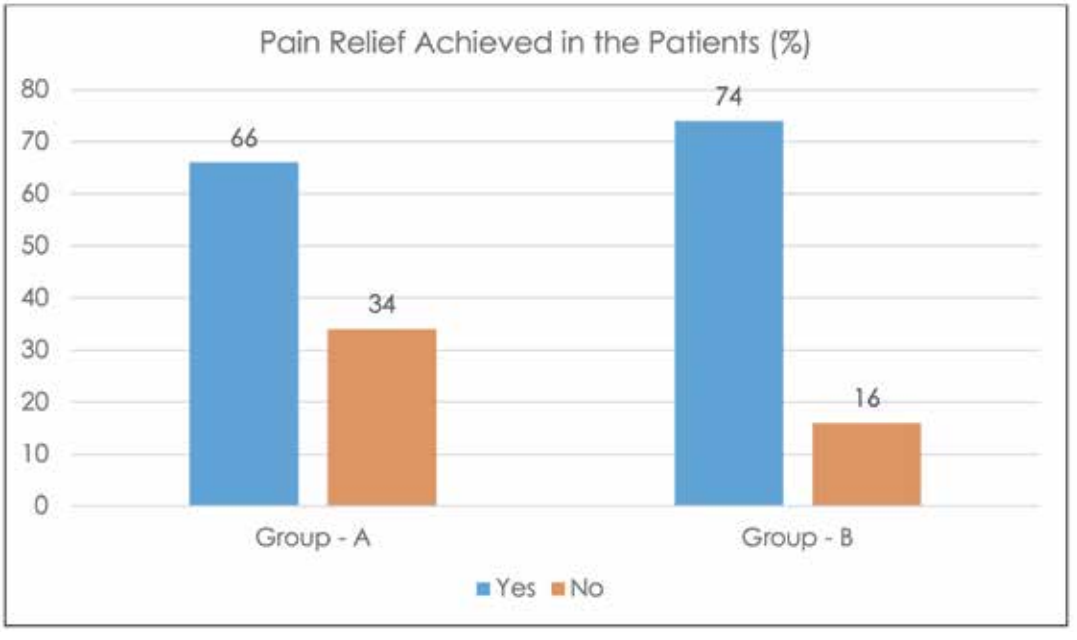

Figure 1: Comparison of the percentage of pain relief in the two groups.

Few adverse effects were noted in the study though not statistically significant as shown in table 3. Some important to note was increased somnolence in the pregabalin group in 4 (8%) patients as compared to the duloxetine group, only 1 (2%) patient. 4 (8%) patients reported GI disturbances like vomiting and constipation in the Duloxetine group as compared to only 2 (4%) in the pregabalin group.

Table 3: Frequency of side effects experienced in both the study groups (n = 100).

Adverse Event	Duloxetine n (%)	Pregabalin n (%)
Sedation	1 (2%)	4 (8%)
Loss of appetite	1 (2%)	1 (2%)
Pedal Edema	NA	2 (4%)
Postural Hypotension	3 (6%)	NA
Sexual dysfunction	NA	1 (2%)
GI Disturbances	4 (8%)	2 (4%)

DISCUSSION

One of the troubling and common complications of diabetes mellitus is the development of neuropathy[13]. It disrupts the quality of life of many diabetic patients and also burdens the health system. Newer medications are constantly undergoing trials for the relief of neuropathic pain in diabetics and many are now FDA-approved. Duloxetine which is an SSNRI. is one of these novel medications that is quite effective with a good safety profile[14].

Diabetes mellitus is prevalent in adults aged 20 years or above in the US at around 12.9%. Moreover, the prevalence of impaired BSF (blood sugar fasting) is 25.7%, and impaired glucose tolerance is 13.8%. This predicts that more than 40% of adults aged >20 years have either diabetes mellitus or pre-diabetes, and this prevalence is on the rise[15]. Around 25% of diabetic patients suffer from symmetrical peripheral neuropathy and 7.5% to 24% of diabetics suffer from neuropathic pain[16]. On average 56% of type 1 diabetics and 41% of type 2 diabetics develop neuropathy in their lifetime, with diabetics having an incidence of 2% to develop symmetrical neuropathy annually[17]. The global epidemic of type 2 diabetes mellitus will eventually lead to a greater number of people being affected by peripheral neuropathic pain due to diabetes[18].

Tricyclic anti-depressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have long been used primarily for painful peripheral neuropathy linked with diabetes[19]. They have been effective in some patients with milder pain according to many clinical trials[20]. The side effects of TCAs and SSRIs are troubling. They include gastrointestinal disturbances namely nausea, constipation, and diarrhea. They also include problems with sleep and sexual function making these medications difficult to take for longer duration[21].

In contrast to TCAs and SSRIs, duloxetine hydrochloride and pregabalin are found to be more effective in pain relief in diabetic neuropathy with a better safety profile, making them more feasible to take for longer periods. Both drugs are approved by the FDA (Food & Drug Administration). Duloxetine is also effective in certain other disorders like depression, anxiety, and fibromyalgia[22,23]. In our study, the mean $\pm$ standard deviation of the age of patients in the Pregabalin and Duloxetine groups were 48.36$\pm$7.10 and 50.56$\pm$6.17 respectively. In a similar study, the age of patients in the Pregabalin group was 55.44$\pm$9.7 and for Duloxetine was 58.48$\pm$8.8 respectively[24].

In a study, it was found that the frequency and percentages of male and female patients in the Pregabalin group were 32(61%) and 20(38.4%) respectively. Whereas the frequency and percentages of male and female patients in the Duloxetine group were 27(54%) and 23(46%) respectively[25]. In our study, the frequency and percentages of male patients in both groups were 39 (78.0%) and 42 (84.0%), and the frequency and percentages of female patients were 11 (22.0%) and 08(16.0%) respectively[25]. Devi et al in their study explained the mean and standard deviation (SD) that was estimated for pain (VAS) at baseline. In their study, Pregabalin was found as 64.9$\pm$18.9 in terms of VAS score at baseline. For the Duloxetine group, the mean and standard deviation for the VAS score was 57.1$\pm$ 16.1[25]. Similarly, in our study, the mean pain (VAS) in the Pregabalin and duloxetine groups at baseline was 6.44$\pm$0.92 and 7.22$\pm$0.46 respectively.

Some limitations of our study were a smaller sample size or group and a localized study area. Involving more people belonging to different geographical locations and social circles would make the study more superior.

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CONCLUSION

In conclusion, data from our study reveals that both duloxetine and pregabalin are effective therapies for pain relief in painful diabetic neuropathy as evidenced by the VAS pain score in both groups A and B after 3 and 6 weeks of treatment duration. Treatment with duloxetine gave slightly better pain relief than pregabalin for this disabling complication of diabetes according to our study, though not statistically significant as also seen in previous studies. The adverse effects of both therapies were minimal.

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CONFLICT OF INTEREST

All the authors at this moment declare that there is no conflict of interest.

ETHICAL APPROVAL

Ethical Approval was obtained from HBS General Hospital with reference number EC18/169,15thOCT 2022.

PATIENT CONSENT

Informed consent was obtained from the patient before enrolling in the study.

AUTHORS CONTRIBUTION

HR: Major contribution in writing the manuscript, NZ: Major contribution in writing the manuscript, AZ: Major contribution in writing the manuscript, HS: Major contribution in writing the manuscript, MT: Data Collection and Analysis, AB: Formal Analysis and Editing.

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