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Original Article

Efficacy of Pregabalin Versus Duloxetine in Patients with Diabetic Painful Neuropathy

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Abstract

Background: Diabetic neuropathy occurs in 30% of patients and presents with paraesthesia in the feet, cutaneous hyperaesthesia and abnormal gait. There is a difference in opinion regarding the first line agents for painful diabetic neuropathy.

Objective: The objective of the study was to compare the efficacy of pregabalin and duloxetine in terms of good pain relief in patients with diabetic neuropathy.

Methods: This randomized controlled trial was conducted in 116 patients after an informed consent. VAS was used to assess the baseline pain level and the patients were allocated to either group A (Pregabalin group; 150mg twice a day) or group B (Duloxetine group; 60mg once a day) for up to 6 weeks using single blind technique and lottery method. Patients were assessed at weeks 3 and 6 to assess the relief in pain.

Results: Mean age in both the groups was 48.36+7.10 and 50.56+6.17 respectively. Mean pain (VAS) at baseline in both the groups were 6.44+0.92 and 7.22+0.46 respectively whereas mean pain (VAS) at 06 weeks were 4.0+0.60 and 5.04+0.57 respectively. Frequency and percentage of good pain relief was 33(66%) and 37(74%) respectively (p = 0.383). Among the patients who reported good pain relief, 70 were male while 4 were female patients and out of those 26 patients that did not meet the criteria for good pain relief, 11 were male and 15 patients were female.

Conclusion: The study concluded that both duloxetine and pregabalin were equally effective in diabetic painful neuropathy with variable results in male and female patients.

Keywords: Diabetic Neuropathy, Pregabalin, Duloxetine.

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Introduction

Diabetic neuropathy occurs in 30% of patients with diabetes Mellitus but it is asymptomatic in majority of these patients.[1] Symptoms include paraesthesia in the feet, pain in the lower limbs (dull, aching, worse at night and mainly felt on anterior aspect of the legs), cutaneous hyperaesthesia and abnormal gait (commonly wide-based).[2,3]

Clinical guidelines recommend the use of antidepressants such as amitriptyline and duloxetine, the γ-aminobutyric acid analogues gabapentin and pregabalin, opioids and topical agents such as capsaicin for the relief of pain in DPN.[4,5] However, there is a difference in opinion regarding first line agents for painful diabetic neuropathy. In 2014, it was statistically proved that the low doses of pregablin and gabapentin are less effective in the treatment of patients with DPN as compared to duloxetine.[6]

The objective of this study was to compare the efficacy of pregabalin and duloxetine to rationalize the treatment of DPN in terms of good pain relief.

Methods

After an informed consent, 116 patients aged between 18 and 70 years from either gender (male and female) were enrolled. Patients with ≥ 5 years history of diabetes and symptoms of diabetic neuropathy for at least 6 months with a pain score >5 on visual analog

scale (VAS) were included in the study. However, patients who had been already taking duloxetine or pregabalin during the previous three months were excluded. All the patients who had a history of alcoholism, autoimmune diseases or malignancy (with or without the use of chemotherapeutic agents), pregnant or lactating women were also excluded.

Baseline pain was recorded on the VAS at the start of the study. Single blind method was used and patients were allocated to either group A (Pregabalin group) or group B (Duloxetine group) for up to 6 weeks. Group A was given 150mg Pregabalin twice a day and Group B was given 60mg Duloxetine once a day. Patients were instructed to record the severity of the symptoms every morning with a follow-up assessment at 3 and 6 weeks interval. Good pain relief was the outcome of the study which was accessed as a decrease in VAS pain score of more than 50% at 06 weeks from the baseline. Follow-up assessment at 6 weeks interval was the primary end-point of the study however any drug or dose-limiting adverse events were considered as secondary end-points. Chi-square test was used to compare good pain relief in both the groups.

During the study, 16 patients discontinued the prescribed drug from both the groups on account of adverse events. Out of these 16 patients, 7 patients belonged to group A (Pregabalin group) and 9 to group B (Duloxetine group).

Results

Mean ages in both the groups that were Pregablin and Duloxetine, were 48.36+7.10 and 50.56+6.17 respectively (Table 1). Gender distribution showed majority were male patients in both the groups, 39 (78%) and 42 (84%) respectively while female patients were 11 (22%) and 8(16%) respectively (Table 2). Mean pain (VAS) at baseline in both the groups were 6.44+0.92 and 7.22 + 0.46 respectively, whereas mean pain (VAS) at 06 weeks in both the groups were 4.0+0.60 and 5.04+0.57 respectively (Table 3). Frequency and percentages of good pain relief, defined as decrease in VAS pain score of more than 50% at 06 weeks from the baseline, in both the groups was 33 (66%) and 37 (74%) respectively. Chi-square test was used to compare good pain relief in both the groups which was statistically not significant (p = 0.383), which meant there was no difference in pain relief between Pregabalin and Duloxetine, as shown in Table 1. Effect modifier like gender of patient was controlled by stratification. 74 out of 100 patients reported good pain relief where as 26 patients did not meet the criteria for good pain relief, as shown in Table 2. Of these 74 patients, 70 were male while 4 were female patients. Likewise, out of those 26 patients that did not meet the criteria for good pain relief, 11 were male and 15 patients were female.

Table 1: *Descriptive Statistics of Age (yrs)*

	Groups	N	Mean	Std. Deviation
Age 18-70yrs	Pregablin 150mg BD	50	48.36	7.108
	Duloxetine 60mg OD	50	50.56	6.172

Table 2: *Comparison of Pain (VAS) at Baseline and 06 wks*

	Groups	N	Mean	Std. Deviation
Pain (VAS) at baseline	Pregabalin 150 mg BD	50	6.44	.929
	Duloxetine 60 mg OD	50	7.22	.465
Pain (VAS) at 06 wks	Pregabalin 150 mg BD	50	4.00	.606
	Duloxetine 60 mg OD	50	5.04	.570

Table 3: *Comparison of Good Pain Relief in Both the Groups*

		Groups		*p*-value
		Pregablin 150mg BD	**Duloxetine 60mg OD**	
Good Pain Relief	Yes	36 (66%)	38(74%)	0.383
	No	14(34%)	12(26%)	
	Total	50(100%)	50(100%)	

Discussion

Among the micro-vascular complications, diabetic polyneuropathy (DPN), involving autonomic and peripheral nervous system, is one of the most common complications of diabetes.[1] According to the estimates, 10% to 30% of diabetic patients suffer from clinical and subclinical neuropathy.[7] Diabetic neuropathy is clinically categorized into distinct syndromes depending upon the neurologic distribution. DPN is a predominantly sensory neuropathic condition that progresses in a distal to proximal direction (in a glove-and-stocking distribution). DPN is characterized by an unrelenting pain that negatively affects the patient's sleep, mood and functional capacity which results in a poor quality life.[8,9]

Diabetic polyneuropathy has no known cure and the management plans are focused on slowing down the progression of the disease, management of complications, pain relief and restoration of functional status. Gabapentin, Pregablin, Carbamazepine, tricyclic antidepressants, SSRIs, SNRIs and duloxetine are currently used for pain relief.[4] American Diabetes Association, however, recommends the use of duloxetine, a selective serotonin and norepinephrine reup-

take inhibitor, as the first treatment.[7]

The efficacy of duloxetine is well established through multiple studies for the treatment of DPN and fibromyalgia which is based on at least 50% pain relief over 12 weeks. In 2015, Carlos F et al studied direct medical costs that included acquisition of drug and additional medical care regarding the treatment of adverse events and poor pain relief. The study showed that duloxetine was superior in terms of direct cost, adverse events profile and pain relief.[10] Similar findings were reported by Shahid et al. after establishing efficicacy of Duloxetine at a daily fixed dose of 60 mg in the relief of neuropathic pain.[11] Hossain SM, however, questioned the effectiveness of duloxetine when his study found no conclusive evidence of superiority for duloxetine over pregablin or amitriptyline. Hossain suggested that the hypothesis for superiority of duloxetine against pregabalin or amitriptyline should be further investigated.[12] This was further supported by the results of a non-blinded, randomized control trial conducted by Arshad et al. which enrolled 320 patients. 160 patients each were assigned to Pregabalin group & Amitriptyline group. 104(65%) achieved good pain relief in Pregablin group as compared to just 76 (47.5%) patients assigned to Amitriptyline group (p-value= 0.002).[13]

This current study was conducted as a direct comparison of efficacy of duloxetine and pregablin and it was found out that mean pain (VAS) at baseline in both the groups was 6.44+0.92 and 7.22+0.46 respectively, whereas mean pain (VAS) at 06 weeks in both the groups was 4.0+0.60 and 5.04+0.57 respectively. Frequency and percentages of good pain relief in both the groups was 33 (66%) and 37 (74%) respectively. Chi-square test was statistically not significant ($p = 0.383$), which meant there was no difference in pain relief between pregabalin and duloxetine. These results were synonymous with the study conducted by Devi et al in India where it was shown that the use of pregablin, duloxetine and gabapentin significantly reduced pain score (VAS) in all the treatment groups across time ($p<0.05$) with no significant statistical difference. They, however, observed that the improvement in pain scores (VAS) and sleep interference score was higher with pregablin as compared to duloxetine and gabapentin.[14,15]

Effect modifier like gender of patient showed that 70 patients who reported good pain relief were male however only 4 female patients noticed good pain relief. Among those 26 patients who did not meet the criteria for good pain relief, there were 11 males and 15 females. This is noteworthy that only 4 female patients reported good pain relief however a significant population of male patients had a positive outcome.

The current study proves that among the available treatment options duloxetine and pregablin are equally effective. While superiority of duloxetine is established through some of the studies, there is data that proves that pregablin is more effective in certain populations especially in second tier economic population. Both duloxetine and pregablin exert a variable degree of control over pain in patients of DPN albeit with a drug or dose limiting adverse events profile. An interesting observation is a negligible effect on female population in terms of good pain relief as compared to the male population. This observation is, however, based on a small cohort and must be investigated further for conclusive evidence which is statistically significant.

Despite the statistical significance, the study was limited in recording adverse events associated with the use of duloxetine or pregablin (nausea, hypersomnia, drowsiness, dizziness, tremors, xerostomia) and did not consider the duration of diabetes while enrolling the patients which can be a significant variable for extent or severity of DPN and may affect the outcome. However, the study was able to prove that both duloxetine and pregablin are equally effective in achieving good pain relief in DPN. A large multicentre trial centered on female patients with DPN, from different age groups and ethnicities, that includes adverse events and duration of diabetes along with good pain relief must be initiated to further investigate the observation made in the current study.

Conclusion

The study concluded that both pregablin and duloxetine achieved good pain relief in male cohort and were equally effective however the same was not observed in the female population. A large multicentre study on female population that includes severity and extent of DPN and adverse events caused by the drugs should be initiated to further investigate this effect.

Conflict of Interest

None

Funding Source

None

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