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ORIGINAL ARTICLE

A Study on the Effects of Pregabalin and Amitriptyline in Treatment of Patients with Painful Diabetic Neuropathy

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ABSTRACT

Objective: To compare the effect of Amitriptyline and Pregabalin in treatment of painful diabetic neuropathy**.**

Material and Methods: The design of this study was Randomized Controlled Trial study design. This study was conducted in the Department of Medicine in, Holy Family Hospital, Rawalpindi and the duration of this study was Six months after the approval of synopsis i.e from 1st November 2019 to 1st May 2020. Approval from ethical committee of the hospital was taken. Written informed consent was taken from patients. Consent form is attached with this. Patients were randomly allocated into two groups by lottery method. The dose of Pregabalin was used as 50mg thrice daily for a period of six weeks and label as group-A and group B received amitriptyline as 25mg once daily before bedtime for a period of six weeks as prescribed by a senior consultant who was blind to object of the study. At the start and end of treatment pain was marked by patients on Visual Analogue Scale (VAS) and numerical score. It was noted on the Performa.

Results: Total 100 patients were included according to the inclusion criteria of the study. The dose of Pregabalin was given in patients in group-A and group-B received amitriptyline. Mean age (years) in the study was 55.87+6.43 whereas there were 55 (55.0) male and 45 (45.0) female patients who were included in the study according to the inclusion criteria. In our study, frequency and percentage of effect (pain relief) among Pregabalin and Amitriptyline in treatment of painful diabetic neuropathy was 27 (54.0) and 11 (22.0) respectively which was statistically significant (p-value 0.001).

Practical Implication: In this study Pregabalin is more responsible for pain relief than Amitriptyline in treatment of painful diabetic neuropathy. Further studies at multiple studies must be conduct in future for determining the efficacy of amitriptyline and Pregabalin in diabetic neuropathy in order to formulate guidelines for management of diabetic peripheral neuropathy.

Conclusion: The study concluded that Pregabalin is more responsible for pain relief than Amitriptyline in treatment of painful diabetic neuropathy. Further studies at multiple studies must be conduct in future for determining the efficacy of Pregabalin and amitriptyline in diabetic neuropathy in order to formulate guidelines for management of diabetic peripheral neuropathy.

Keywords: Amitriptyline, Pregabalin, Neuropathy, Pain Relief, Diabetic Sensorimotor Polyneuropathy, Prevalence.

INTRODUCTION

The global statistics of diabetes mellitus in year 2013 indicated, about 382 million people had this disease worldwide, with type 2 diabetes making up about 90 % of the cases. This is equal to 8.3 % of the adult population with equal rates in both women and men [1,2] . In year 2015 diabetes resulted in mortality of 5.1 million people per year, making it the 4th leading cause of death in the world. Prevalence of diabetes in Pakistan is 28.3% in urban and 25.3% in rural areas (3). The commonest cause of peripheral neuropathy is diabetes, and 30-90% of patients with diabetes have peripheral neuropathy (4-5). Diabetic sensorimotor polyneuropathy (DSPN), the most common type of diabetic neuropathy, is associated with an impaired quality of life, significant morbidity and increased healthcare costs (7). Additionally, 06-34% of patients with diabetes report painful neuropathic symptoms and the prevalence are greater in type 2 diabetes (8). Achieving tight glycemic control is the corner stone in the management of painful diabetic peripheral neuropathy (PDPN). Pregabalin and Amitriptyline are usually recommended as first-line treatment for PDPN (9-10).

Pregabalin is a higher potency gabapentinoid with a similar mechanism of action to gabapentin and reported an improvement in pain scores following Pregabalin therapy. A dose-dependent response in reduction of sleep interference and speed of onset of relief has been reported (11). Diabetes mellitus is one of the non-communicable diseases with the highest causes of death of about 1.6 million people per year. According to the data stated by Indonesia's Basic Health Research in 2018, there were approximately 16 million of Indonesians who suffered from diabetes, and it is estimated to increase up to about 21.3 million people by the year 2030. Diabetes is a group of chronic metabolic disorders characterized by high blood sugar levels (hyperglycemia) caused by defects in insulin secretion, insulin action, or both due to the damage of pancreatic β-cells. Mistreatment or late treatment of diabetes may lead to further complications. Microvascular complications such as neuropathy, nephropathy, and retinopathy are the complications that often occur in diabetic patients (10). Unfortunately, about 75% of patients may be asymptomatic and therefore fail to recognize the early symptoms of this disease, resulting in further serious complications or even death. Painful diabetic neuropathy is one of the complications that often occur in patients with diabetes mellitus and is caused by disruptions in the metabolic and vascular systems. Symptoms of diabetic neuropathy are prickling and tingling sensation, numbness, pain with burning sensation, and stabbing pain in certain body parts. It is necessary to provide the appropriate treatment for patients who suffer from painful diabetic neuropathy as it limits their daily activities (5). The treatment available for these patients is still in the form of symptomatic treatment such as pregabalin, gabapentin, and amitriptyline, thus requiring additional treatment. Therefore, healthcare professional, specifically neurologists and other general practitioners that often handle neuropathy patients with the history of diabetes need to provide the proper treatments and strict glycemic control for diabetic patients with painful diabetic neuropathy to alleviate the pain and prevent further progression of painful diabetic neuropathy to help patients enhance their quality of life and well-being.Amitriptyline has multimodal actions. It includes blocking of serotonin and noradrenaline reuptake from synaptic clefts and varying degrees of anticholinergic receptor inhibition (12). Bansal et al has also demonstrated in a trial comparing amitriptyline and Pregabalin that there were few differences between the two treatments in efficacy, though Pregabalin might be the alternative as it is associated with fewer adverse effects in our population (13). Another study reported lower efficacy of Amitriptyline (25.0%) as compared to Pregabalin (50.0%) in alleviating pain associated with DPN (14).

After the literature review, it is established that there is gap to have more evidence on comparative study on efficacy of amitriptyline and Pregabalin in diabetic neuropathy. Our randomized control trail will provide high level evidence of research (15). Results of this study will not only help to establish guideline for management of diabetic peripheral neuropathy but to alleviate patient's ailment.

MATERIAL AND METHODS

The design of this study was Randomized Controlled Trial study design. This study was conducted in the Department of Medicine in, Holy Family Hospital, Rawalpindi and the duration of this study was Six months after the approval of synopsis i.e from 1st November 2019 to 1st May 2020.

Sample size: 100 (50 in each group) Sample size calculated by WHO sample size calculator through following formula used for hypothesis testing population proportion (taken from study in reference 9).

n= (Z1− 2PQ Z(+P P_1 −1− $_2$)PQ $PQ_2$1 1 + 2 2)2

P P^{1+2},Q= −1 P

where P=

2

Q1 = −1 P1 and Q2 = −1 P2

P1=25.0%=0.25 P2=50%=0.50

Power of test=80% Level of significance=5% n=sample size=46

To be consistent with most clinical trial studies. 50 in each group was taken as study.

Sample Technique: Non-probability consecutive sampling

Inclusion criteria:

- Type II diabetic patients with painful diabetic neuropathy as per operational definition
- Both genders male and female were included
- Age 45 to 65 years

Exclusion Criteria:

- Patients already taking medications for any psychiatric illness or epilepsy.
- Patients suffering from chronic medical ailments like chronic kidney disease, chronic liver disease, rheumatoid arthritis, osteoporosis, and malignancy. It was known through their medical record.
- All pregnant women or those intending to conceive and lactating mothers.
- Chronic infections
- Burn patients.

Data Collection Procedure: Approval from ethical committee of the hospital was taken. Eighty patients coming in medicine department outdoor with symptoms of painful diabetic neuropathy fulfilling the inclusion criteria was included in the study. Written informed consent was taken from patients. Consent form is attached with this. Patients was randomly allocated into two groups by lottery method. The dose of Pregabalin was used as 50mg thrice daily for a period of six weeks and label as group-A and group B received amitriptyline as 25mg once daily before bedtime for a period of six weeks as prescribed by a senior consultant who was blind to object of the study. At the start and end of treatment pain was marked by patients on Visual Analogue Scale (VAS) and numerical score. It was recorded in both groups of intervention. The outcome variable of this study was pain relief which was measured on scale score as per operational definition and it was noted on the Performa (copy attached).

Data Analysis Techniques and Tools: All data was entered using software SPSS version 23.0. Mean and standard deviation was calculated for age, duration of diabetes and BMI. Frequencies and percentages were calculated for gender, residential status, pain relief and hypertension in both groups. Chi-square was applied to compare the outcome (pain relief) in both groups. Stratification of age, gender, duration of diabetes, BMI, residential status, and hypertension was done to control the effect modifiers. P-value < 0.05 was considered as significant. Poststratification chi-square test was applied.

RESULTS

Data was entered and analyzed in SPSS version 23.0. Total 100 patients were included according to the inclusion criteria of the study. The dose of pregabalin was used as 50mg thrice daily for a period of six weeks and label as group-A, and group-B was receiving amitriptyline as 25mg once daily. Descriptive statistics of age (years) of patient was also calculated in terms of mean and standard deviation. Mean age (years) in the study was 55.87+6.43, as shown in Table.1, Distribution of gender of patient was also calculated in terms of frequency and percentage of male and female patients. There were 55 (55.0) male and 45 (45.0) female patients who were included in the study according to the inclusion criteria, as shown in Table. 2. Similarly, descriptive statistics of duration of diabetes was calculated in terms of mean and standard deviation. Mean duration of diabetes of patients among both the groups was 6.28+2.15 and 6.24+2.02 respectively, as shown in Table. 3. Descriptive statistics of body mass index (BMI) was calculated in terms of mean and standard deviation. Mean body mass index in patients presenting with diabetic neuropathy among both the groups was 30.36+3.38 and 31.04+3.68 respectively, as shown in Table. 4.

Table 1: Descriptive Statistics of Age (years) of patients

	Mean	Std. Deviation
Age (years)	55.87	6.43
Pregabalin Group	55.84	6.46
Amitriptyline Group	55.90	6.46

Table 2: Distribution of Gender

		Two Groups		Total
		Pregabalin	Amitriptyline	
Gender	Male	34	21	55
		68.0%	42.0%	55.0%
	Female	16	29	45
		32.0%	58.0%	45.0%
Total		50	50	100

Table 3: Mean Duration of Diabetes of Patients Among Both the Groups

	Two Groups	n	Mean	Std. Deviation
Duration Of Diabetes	Pregabalin	50	6.28	2.15
	Amitriptyline	50	6.24	2.02

Table 4: Mean Body Mass Index (BMI) of Patients Among Both the Groups

	Two Groups	n	Mean	Std. Deviation
Body Mass Index (BMI)	Pregabalin	50	30.36	3.38
	Amitriptyline	50	31.04	3.68

Table 5: Frequency & Percentage of Residential Status of Patients Among Both the Groups

		Two Groups		Total
		Pregabalin	Amitriptyline	
Residential Status	Urban	34	32	66
	Rural	68.0%	64.0%	66.0%
		16	18	34
		32.0%	36.0%	34.0%
Total		50	50	100

Frequency and percentage of residential status (urban / rural) of patients was assessed in the study. There were 66 (66.0) who have urban residential status whereas 34 (34.) patients were belong from rural area, as shown in Table. 5. Frequency and

percentage of hypertension of diabetic neuropathy patients was assessed in the study. Majority of the patients 75 (75.0) were observed hypertensive in our study, as shown in Table.6. The objective of the study is to compare the effect of Amitriptyline and Pregabalin in treatment of painful diabetic neuropathy. In our study, frequency and percentage of effect (pain relief) among Amitriptyline and Pregabalin in treatment of painful diabetic neuropathy was 27 (54.0) and 11 (22.0) respectively which was statistically significant (p-value 0.001), it showed that Pregabalin is more responsible for pain relief than Amitriptyline in treatment of painful diabetic neuropathy, as shown in Table.7.

Table 6: Frequency & Percentage of Hypertension of Patients Among Both the Groups

	Two Groups		Total
	Pregabalin	Amitriptyline	
Yes Hypertension	38	37	75
	76.0%	74.0%	75.0%
No	12	13	25
	24.0%	26.0%	25.0%
Total	50	50	100

Table 7: Comparison of Effect (Pain Relief) Of Pregabalin and Amitriptyline in Treatment of Painful Diabetic Neuropathy

		Two Groups		Total	p-value
		Pregabalin	Amitriptyline		
Effect (Pain relief)	Yes	27	11	38	
	No	54.0%	22.0%	38.0%	
		23	39	62	0.001
		46.0%	78.0%	62.0%	
Total		50	50	100	

DISCUSSION

Painful diabetic polyneuropathy (PDP) is a common longterm complication of diabetes (15). Despite its typical clinical picture (burning pain, electrical shocks associated with paresthesia, dysthesia, and/or allodynia), the diagnosis of PDP is still missed in many patients (16-17). In a community-based study, 13% of the patients with PDP had never reported their pain to the treating physician and 39% of the patients with PDP were never treated for their complaints (18). Neuropathic pain has major consequences for the patient's functioning and quality of life (QoL), with restriction in daily and social activities, depression, sleep disturbances, and anxiety (19). A significant proportion (10–20%) of type 2 diabetic patients with PDP requires medical treatment for their pain, however, in daily practice often insufficient time is spent to address patient's pain history and patients often have multiple comorbidities hindering medical treatment. Moreover, it seems likely that both the patient and the treating physician do not always associate painful symptoms in the legs with PDP (20). A detailed medical history is necessary in all patients to rule out other diagnoses that can contribute to or cause the pain; in addition, several patients have neuropathy due to other causes than diabetes. Patient's pain history should preferably be assessed and quantified using a questionnaire. Furthermore, the 0–10 pain numeric rating scale (NRS) is widely used to assess pain.

Pain grades of "no/mild" (0–3), "moderate" (4–6), and "severe" (7–10) were established for diabetic polyneuropathy (DPN)- specific NRS measures in the United States (21). A 50% reduction in the NRS has historically been used to classify treatment response, although a 30% reduction is clinically important. Treatment of PDP requires a systematic approach that should include psychosocial factors, education, glucose control (3). Recently, in a Dutch survey, medical treatment was not prescribed in half of the patients and only a minority of the patients was treated with potentially effective drugs, such as antiepileptics or opioids (22). Treatment of neuropathic pain can be a clinical challenge given the limited efficacy of current pharmacotherapy and although knowledge of the treatment of PDP is growing, still there is no consensus on the most effective treatment (18).

To our knowledge, OPTION-DM is the longest blinded neuropathic pain trial to date,

with each patient undergoing all three treatment pathways over 50 weeks. Unlike previous combination-treatment crossover trials, the durations of monotherapy and combination treatments were sufficiently long to assess the full treatment effects, even though this resulted in higher-than-expected dropout mainly for personal and other non-treatment-related reasons (73%). Moreover, previous combination trials used fixed-dose titration regimens regardless of treatment response, which does not reflect clinical practice, and resulted in higher relative dropout rates. Our trial used a flexible dosing regimen to achieve maximum tolerated doses, based on individual responses. Although other tricyclic antidepressants are available, we used amitriptyline as it is the most widely prescribed tricyclic worldwide and a first-line agent in most guidelines. We did not use gabapentin as there was little rationale for studying two α-2-δ ligands, and because it is a thrice-daily drug, does not have linear pharmacokinetics (unlike pregabalin), and requires a long titration period of up to 2 months to avoid toxicity. We did not examine the pathway of pregabalin supplemented with duloxetine (P-D) because of the COMBO-DN findings, in which no difference in pain reduction was found if pregabalin was added to duloxetine or vice versa. However, duloxetine was better than pregabalin as an initial treatment at moderate doses and is a once-daily preparation, and thus we opted to examine the D-P pathway. Moreover, adding the P-D pathway would have prolonged the trial by 4 months. Finally, as both amitriptyline and duloxetine are antidepressants, there was little rationale for combining both

In study of Greets et al mean age (years) of patients was 67+10 whereas mean age (years) in our study was 55.87+6.43. Distribution of gender of patient was calculated in terms of frequency and percentage of male and female patients. There were 55 (55.0) male and 45 (45.0) female patients who were included in the study according to the inclusion criteria, similarly study conducted in 2012; majority 55% of the case were male patients (9). Mean duration of diabetes of patients in our study was noted as approximately 6.28+2.15 years whereas Greets et al almost all the patients (98%) had type 2 diabetes with duration of diabetes of 13+9 years (9). Comparison of efficacy of Amitriptyline and Pregabalin in treatment of painful diabetic neuropathy. In our study, frequency and percentage of effect (pain relief) among Amitriptyline and Pregabalin in treatment of painful diabetic neuropathy was 27 (54.0) and 11 (22.0) respectively which was statistically significant (p-value 0.001) (23,24), it showed that Pregabalin is more responsible for pain relief than Amitriptyline in treatment of painful diabetic neuropathy whereas Greets et al reported lower of efficacy of Amitriptyline (25.0%) as compared to Pregabalin (50.0%) in alleviating pain.

CONCLUSION

The study concluded that Pregabalin is more responsible for pain relief than Amitriptyline in treatment of painful diabetic neuropathy. Further studies at multiple studies must be conduct in future for determining the efficacy of amitriptyline and Pregabalin in diabetic neuropathy in order to formulate guidelines for management of diabetic peripheral neuropathy.

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