https://doi.org/10.29309/TPMJ/2023.30.05.6721

The Professional Medical Journal
www.theprofesional.com
2023, Volume, 30 Issue, 05

ORIGINAL ARTICLE

Comparison of efficacy of pregabalin with duloxetine in the management of patients with painful diabetic neuropathy.

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Article Citation: Nagra MA, Hanif M, Shafaq Un Nisa, Hafeez A, Ahmed M, Bashir B. Comparison of efficacy of pregabalin with duloxetine in the management of patients with painful diabetic neuropathy. Professional Med J 2023; 30(05):630-636. https://doi.org/10.29309/TPMJ/2023.30.05.6721

ABSTRACT… Objectives: To compare pregabalin with duloxetine in terms of mean reduction in pain score, in the management of patients with painful diabetic neuropathy. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Medicine, FMU & Affiliated Hospitals, Faisalabad. **Period:** 1st March, 2020 to 3rd March 2021. **Material & Methods:** A total of 180 patients with known diabetics of at least 5 years duration, 18 to 75 years of age were included. Patients with ischemic pain or other types of pain not related to diabetes such as arthritic pain or phantom pain secondary to amputations, CRF & CLD were excluded. Group A received 150mg of Pregabalin at night before sleeping and was increased to 150mg twice daily after 02 week if VAS pain score reduction was found to be less than 50% from baseline. Group B received 60mg Duloxetine at bed time and it was increased to 120mg after 04 weeks if the VAS pain score was less than 50% after 04 weeks. The patients were again assessed after another 04 weeks to assess VAS Pain Score reduction. The primary outcome is pain as assessed by the Visual Analogue Score (VAS) at the end of 04 weeks from start of medications. **Results:** Age range in this study was from18 to75 years with mean age of 40.87±13.67 years. The mean age of patients in pregabalin group was 38.80 ± 13.01 years and in duloxetine group was 41.07 ± 13.85 years. Majority of the patients 34 (56.67%) were between 20 to 40 years of age. Mean reduction in pain in pregabalin group was 1.63 ± 1.07 while in duloxetine group was 3.23 ± 1.38 (p-value =0.0001). **Conclusion:** This study concluded that duloxetine had significantly greater pain reduction than pregabalin in the management of patients with painful diabetic neuropathy.

Key words: Diabetes, Duloxetine, Painful Diabetic Neuropathy.

INTRODUCTION

Diabetes mellitus (DM) has now become a major cause of morbidity and even mortality in both the developed as well as under-developed countries. With an estimated prevalence of about 10% globally, about one and half million deaths in the world annually are due to complications of diabetes. Similarly, in our country, Pakistan prevalence of DM is about 17% among males and 20% among females.[1] Diabetic peripheral neuropathic pain (DPNP) a chronic complication of DM, resulting from neuronal damage due to prolonged periods of hyperglycemic states, can also lead to significant morbidity in affected patients (6% to 34%). Among the major risk factors leading to DPNP, poor glycemic control with episodes of significant variation of blood sugar level affects the occurrence and severity of this condition.[2]

The disturbance of pain inhibitory pathway due to abnormally high blood glucose in the body leads to sensitization of the pain-transmitting neurons ending up in the DPNP. Symptoms range from tingling sensation to severe burning sensation in the feet becoming worse at night disturbing the routine activities. Some patients complaint of numbness in hands and feet progressing in a proximal pattern.[3]

Among the common complications encountered by most of the physicians and endocrinologists,

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Article received on: 28/07/2021
Accepted for publication: 21/03/2023

diabetic neuropathy can occur both with DM1 and DM2 and more than two third of the patients are affected. Common complaint is pain but its exact mechanism is still not understood completely. Most of the pathologist believes that the toxicity of abnormally raised blood glucose is the main culprit. While managing the DPNP, step one is the exclusion of all other causes of neuropathic pain then comes the control of blood sugar along with drugs controlling and relieving pain. These include anti-convulsants, like pregabalin, gabapentin and anti- depressants, especially SSRIs.[4] Duloxetine, gabapentine, Pregabalin and some anti depressants have been commonly used in the management of DPNP. Many controlled trials have been done to determine the outcome of duloxetine in the pain management of DPNP. Tanenberg et al. reported an equal outcome of duloxetine and pregabalin in DPNP pain management.[5] Jaeger MD, et al reported that with use of pregabalin, neuro- metabolites concentration in the brain was almost the same as that seen in placebo group, some difference was observed in the left thalamus.

In a local study in Pakistan, pregabalin was compared with amitriptyline in terms of pain score reduction. Mean pain score at baseline and after 6-weeks was3.43 ± 0.87 and 2.18 ± 0.67. Significant reduction in pain was seen in 46.36% after 6 weeks of treatment with pregabalin and 57.88% with amitriptyline use after 6 weeks.[7] In another study, change in the pain VAS Score (Mean ± SD) after 4 weeks were more in Duloxetine users compared to Pregabalin users.[8] In another study, it was reported that the pain VAS scores at baseline and after 4 weeks were: DLX group 6.72±1.93 and 3.24 ± 0.85(reduction of 3.48 ± 1.08) and in PGA group 6.17 ± 1.63 and 2.97 ± 0.78 with reductionofs3.2±0.8.

Despite the debate regarding the high morbidity of diabetes, management of complications of diabetes still need a lot of research.[9,10]

The rationale of our study was that no local study have been conducted comparing the outcome/ efficacy of pregabalin and duloxitine. Although pregabalin is used more frequently as compared to amitriptyline and duloxetine, the one with low cost and incidence of adverse effects should be recommended. Aim of our study is to find a better and suitable regimen for the management of diabetic patients of our country.

OBJECTIVES

"To compare pregabalin with duloxetine in terms of mean reduction in pain score, in the management of patients with painful diabetic neuropathy."

OPERATIONAL DEFINITIONS

Painful Diabetic Neuropathy

Cases of diabetes meeting the LANSS criteria: The diagnosis of diabetic painful peripheral neuropathy will be made according to LANSS Criteria (Leads Assessment of Neuropathic Signs and Symptoms). (ANNEXURE I) EFFICACY in terms of reduction in pain score:

Reduction in pain score was calculated after 4 weeks of therapy with pregabalin / duloxetine and efficacy was measure in terms of reduction of VAS pain score.

Percentage of patients achieving 50% reduction in VAS pain Score were also calculated.

Pain Score

Pain was accessed using pain score on Visual Analog Scale (VAS) from 0 to 10 with no pain at 0 and extreme pain on score 10.

Hypothesis

There is a significant difference in the efficacy of pregabalin versus duloxetine in the management of patients with painful diabetic neuropathy in terms of reduction in pain score.

MATERIAL & METHODS

This Randomized Control trial was conducted at Medicine Department of FMU & Affiliated Hospitals, Faisalabad for six month after approval of Synopsis.

The Sample size was calculated using WHO sample size calculator by non-probability consecutive sampling.

Expected reduction in DLX group of 3.48 ± 1.08 and that in PGA group of 3.2 ± 0.85[9] Power of study = 80% Level of significance = 5%

Sample size = 90 in each group (total 180)

Inclusion Criteria

Patients with known diabetics of at least 5 years duration with HbA1c of 10% or less, diagnosed with Peripheral Neuropathy according to LANSS Criteria (Annexure)

Age 18 years to 75 years.

History of Neuropathic pain for at least 03 months.

Patients with a visual analogue score of pain of 4 or more on visual analogue scale from 0-10 where 0 denoted no pain and 10 denoted the most severepains.

Exclusion Criteria

Patients suffering from ischemic pain or other types of pain not related to diabetes such as arthritic pain or phantom pain secondary to amputations;

Patients suffering from C.K.D; Patients using anti depressants, sedatives for anti psychotic drugs for any reason in the last 04 weeks.

Patients having alcohol or other drug dependence; Pregnant patients or females' patients planning pregnancy in the coming sixmonths;

Patients with Chronic Liver Disease; Patients who were suffering from chronic medical ailments like SLE, RA, epilepsy, psychiatric illness, malignancy and substance abuse (all these conditions can cause neuropathic pains thus acting as confounders).

Data Collection Procedure

After the approval of the ethical review committee (48-ERC/2020-21/PHRC/FMU/40) and informed written consent, diabetic patients included in the study were divided into two groups. Group pregabalin or group A was given pregabalin and group duloxetine or group B was given Duloxetine for 4 weeks. Pain will be accessed using pain score on Visual analog scale (VAS). The diagnosis of diabetic Painful Peripheral Neuropathy was made according to LANSS Criteria (Leads Assessment of Neuropathic Signs and Symptoms). Written informed consent was obtained from all the patients five patients were selected according to the following inclusion and exclusion criteria. The patients were randomized through a computer-generated randomization / schedule into groups A & B; Group A received 150mg of pregabalin at night before sleeping and was increased to 150mg twice daily after 02 weeks if VAS pain score reducation was found to be less than 50% from base line. Group B received 60mg Duloxetine at bed time and it was increased to 120mg after 04 weeks if the VAS pain score was less than 50% after 04 weeks. The patients were again assessed after another 04 weeks to assess VAS Pain Score reduction. The primary outcome is pain as assessed by the Visual Analogue Score (VAS) at the end of 04 weeks from start of medications.

At the onset of the Trial, general physical examination and neurological examination was carried out of the patients in two groups along with recording of BMI, complete blood count, Renal Function tests, Lipid profile, Liver function tests, hemoglobin A1c (HbA1c) and blood sugar profile (Fasting and 2 hours post-prandial) was recorded at each visit. The patients were excluded from the study if the liver enzymes increased more than twice the upper limit of normal.

Data Analysis Procedure

The results were analyzed using statistical technique for Social Sciences SPSS Version 20. Mean and standard deviation were calculated for numerical variables in both groups like age, duration of diabetes, BMI, HbA1c, VAS score at baseline, after 4 weeks, mean change in the VAS score from baseline to 4 weeks. Frequency and percentage were calculated for qualitative variable like gender, significant reduction (>50%) in the VAS score from baseline to 4 weeks of treatment. Mean of VAS score at baseline and mean reduction in VAS were compared with VAS at 4 weeks using independent sample

t-test between both groups. P-value ≤0.05 was considered significant.

Effect modifiers like age, gender, duration of disease and control of diabetes (access using HbA1c with HbA1c of < 9 taken as good/fair control) were controlled by stratification. Post-stratification independent sample t-test was applied. Frequency of patients who achieved significant reduction in VAS score was compared between two groups and chi square was applied, taking p value <0.05 as statistically significant.

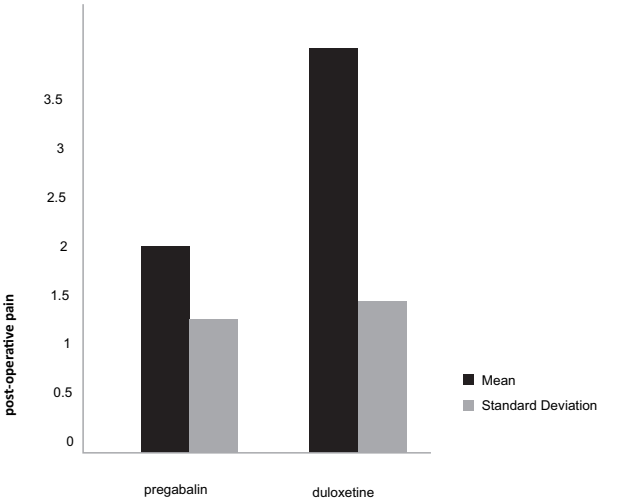
RESULTS

Age range in this study was from 18 to 75 years with mean age of 40.87 ±13.67 years. The mean age of patients in pregabalin group was 38.80 ± 13.01 years and in duloxetine group was 41.07 ± 13.85 years. Majority of the patients 34 (56.67%) were between 20 to 40 years of age as shown in Table-I.

Mean duration of disease was 8.31 ± 2.35 years (Table-II). Distribution of patients according to control of DM & gender is shown in Table-III & IV respectively.

Mean reduction in pain in pregabalin group was 1.63 ± 1.07 while in duloxetine group was 3.23 ± 1.38 (p-value = 0.0001) as shown in Figure-1.

Stratification of post-operative pain with respect to age, gender, duration of disease and control of diabetes is shown in Table-V.



	Pregabalin	Duloxetine
Mean	1.63	3.23
Standard Deviation	1.07	1.38

➢ P-value = 0.0001 which is statistically significant.

Figure-1. Mean reduction in pain in both groups.

Age (years)	Pregabalin (n=90)	Duloxetine (n=90)	Total (n=180)
	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)
18-45	54 (60.0%)	48 (53.33%)	102 (56.67%)
46-75	36 (40.0%)	42 (46.67%)	78 (43.33%)
Mean ± SD	38.80 ± 13.01	41.07 ± 13.85	40.87 ± 13.67

Table-I. Age distribution for both groups (n=180).

Duration of Disease (in years)	Pregabalin (n=90)	Duloxetine (n=90)	Total (n=180)
	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)
≤6 years	21 (23.33%)	15 (16.67%)	36 (20.0%)
>6 years	69 (76.67%)	75 (83.33%)	144 (80.0%)
Mean ± SD	8.27 ± 2.33	8.43 ± 2.34	8.31 ± 2.35

Table-II. Distribution of patients according to duration of disease.

Control	Pregabalin (n=90)	Duloxetine (n=90)	Total (n=180)
	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)
No	33 (36.67%)	36 (40.0%)	69 (38.33%)
Yes	57 (63.33%)	54 (60.0%)	111 (61.67%)

Table-III. Distribution of patients according to control of DM.

Gender	Pregabalin (n=90)	Duloxetine (n=90)	Total (n=180)
	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)
Male	51 (56.67%)	42 (46.67%)	93 (51.67%)
Female	39 (43.33%)	48 (53.33%)	87 (48.33%)

Table-IV. Distribution of patients according to gender.

Co-morbid Conditions		Pregabalin (n=90)		Duloxetine (n=90)		P-Value
		Reduction in Pain		Reduction in pain		
		Mean	SD	Mean	SD	
Age (years)	18-45	1.67	1.19	3.44	1.50	0.0001
	46-75	1.58	0.90	3.0	1.24	0.0001
Duration (years)	≤6	1.71	1.38	2.20	0.45	0.0001
	>6	1.61	0.99	3.44	1.42	0.0001
Gender	Male	1.41	0.87	3.50	1.70	0.0001
	Female	1.92	1.26	3.0	1.03	0.0001
Control of DM	No	1.55	0.93	3.25	1.60	0.0001
	Yes	1.68	1.16	3.22	1.26	0.0001

Table-V. Stratification of post-operative pain with respect to age, gender, duration of disease and control of diabetes.

DISCUSSION

Diabetic peripheral neuropathy is defined as, "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes".[11] The diagnosis relies on both clinical signs as well as quantitative testing, and may be present despite a lack of reported symptoms.[11] The estimated prevalence of peripheral neuropathy among adults with diabetes in the US is 28%.[11,12] The consequences of diabetic peripheral neuropathy can be devastating. Approximately 50% of people with diabetes will develop a foot ulcer during their lifetime[13-15], and diabetes is a leading cause of lower limb amputation.[16] In addition, neuropathic pain and decreased sensation can contribute to an array of poor outcomes including falls, impaired quality of life, restrictions in activities of daily living, and depressive symptoms.[17]

We conducted this study to compare pregabalin with duloxetine in terms of mean reduction in pain score, in the management of patients with painful diabetic neuropathy. In our study, Mean reduction in pain in duloxetine group was 1.63 ± 1.07 while in pregabalin group was 3.23 ± 1.38 (p-value = 0.0001). In a local study in Pakistan, pregabalin was compared with amitriptyline in terms of pain score reduction. Mean pain score at base line and after 6-weeks was 3.43 ± 0.87 and 2.18 ± 0.6. Significant reduction in pain was seen in 46.36 % after 6 weeks of treatment with pregabalin and 57.88% with amitriptyline use after 6 weeks.[7] In another study, change in the pain VAS Score (Mean ± SD) after 4 weeks were more in Duloxetine users compared to Pregabalin users.[8] In another study, it was reported that the pain VAS scores at baseline and after 4 weeks were: DLX group 6.72±1.93 and 3.24± 0.85(reduction of 3.48 ± 1.08) and in PGA group 6.17 ± 1.63 and 2.97± 0.78 with reduction of 3.2 ± 0.85.[9]

A large placebo controlled study has reported that GBP is effective in alleviating DPNP and the calculated Number Needed to Treat (NNT) for 50% pain relief for GBP was 3.7.[18]A similar placebo controlled study conducted with PGB for a period of five weeks has documented a significant reduction in pain compared to placebo (P<0.001).[19] Both GBP and PGB bind to the α2δ site of L type voltage gated calcium channel and modulate the influx of calcium during neuronal depolarization in the central nervous system. Further, a recent placebo controlled, multi-centric, randomized study demonstrated that DLX was superior to placebo with 50% reduction in the 24-h average pain score.[20] DLX is considered balanced and potent dual reuptake inhibitor of serotonin and norepinephrine which is thought to inhibit pain via descending pain pathways.

Our result was comparable to where patients treated with duloxetine had significantly greater pain reduction than pregabalin at week 4 and at each successive week up to the 12-week endpoint.

CONCLUSION

This study concluded that duloxetine had significantly greater pain reduction than

pregabalinin the management of patients with pain ful diabetic neuropathy. So, we recommend that duloxetine should be used routinely in these particular patients in order toreduce the morbidity.

REFERENCES

1. Shera AS, Basit A, Fawwad A, Hakeem R, Ahmedani MA, Hydrie MZI. **Pakistan National Diabetes Survey: prevalence of glucose into lerance and associated factors in the Punjab Province of Pakistan.** Prim Care Diabetes 2010; 4(2):79-83.

2. Alleman CJM, Westerhout KY, Hensen M, Chambers C, Stoker M, Long S, etal. **P0Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: A review of the literature.** Diabetes Research and Clinical Practice 2015; 109(2):215-25.

3. Snyder MJ, Gibbs LM, Lindsay TJ. **Treating painful diabetic peripheral neuropathy: An Update.** Am Fam Physician 2016; 94(3): 227-34.

4. FinnerupNB, Att al N, Haroutounian S, McNicol E, Baron R,D workin R Hetal. **Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis.** Lancet Neurol 2015; 14(2): 162-73.

5. Tanenberg RJ, Irving GA, Risser RC, et al. **Duloxetine, pregabalin,anddulox etineplusgabapentinfordiabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: An open-label, randomized, noninferiority comparison.** Mayo ClinProc 2011; 86:615–26.

6. Jaeger MD, Goudman L, Schuerbeek PV, Mey JD, Keymeulen B, Brouns R, etal. **Cerebral biochemical effect of pregabalin in patients with painful diabetic neuropathy: A randomized controlled Trial Diabetes** Ther 2018; 9: 1591-604.

7. Soomro IA, Ahmad F, Ahmed N. **Comparison between the efficacy of pregabalin and amitriptyline in alleviating pain associated with painful diabetic peripheral neuropathy.** Pak Armed Forces Med J 2018; 68(2):198-201.

8. Shahid W, Kumar R, Shaikh A, Kumar S, Jameel R, Fareed S. **Comparison of the efficacy of duloxetine and pregabalin in pain relief associated with diabetic neuropathy.** Cureus. 2019; 11(7):e5293.

9. Shera AS, Basit A, Fawwad A, Hakeem R, Ahmedani MA, Hydrie MZI. **Pakistan National Diabetes Survey: prevalence of glucose into lerance and associated factors in the Punjab Province of Pakistan.** Prim Care Diabetes 2010; 4(2):79-83.

10. Alleman CJM, Westerhout KY, Hensen M, Chambers C, Stoker M, Long S, etal. **P0Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: A review of the literature.** Diabetes Research and Clinical Practice 2015; 109(2):215-25.

11. Snyder MJ, Gibbs LM, Lindsay TJ. **Treating painful diabetic peripheral neuropathy: An Update.** Am Fam Physician 2016; 94(3): 227-34.

12. Finnerup NB, Att al N, Haroutounian S, McNicol E, Baron R,D workin R Hetal. **Pharmacotherapy for neuropathic pain in adults: A systematic review and meta- analysis.** Lancet Neurol 2015; 14(2): 162-73.

13. Tanenberg RJ, Irving GA, Risser RC, et al. **Duloxetine, pregabalin,anddulox etineplusgabapentinfordiabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: An open-label, randomized, noninferiority comparison.** Mayo ClinProc 2011; 86:615-26.

14. Jaeger MD, Goudman L, Schuerbeek PV, Mey JD, Keymeulen B, Brouns R, etal. **Cerebral biochemical effect of pregabalin in patients with painful diabetic neuropathy: A randomized controlled Trial Diabetes.** Ther 2018; 9:1591-604.

15. Soomro IA, Ahmad F, Ahmed N **Comparison between the efficacy of pregabalin and amitriptyline in alleviating pain associated with painful diabetic peripheral neuropathy.** Pak Armed Forces Med J 2018; 68(2):198-201.

16. Shahid W, Kumar R, Shaikh A, Kumar S, Jameel R, Fareed S. **Comparison of the efficacy of duloxetine and pregabalin in pain relief associated with diabetic neuropathy.** Cureus. 2019; 11(7):e5293.

17. Joharchi K, Memari M, Azargashb E. **Efficacy and safety of duloxetine and Pregabalin in Iranian patients with diabetic peripheral neuropathic pain: A double- blind, randomized clinical trial.** J Diabetes Metab Disord 2019; 18,575-582.

18. Feldman EL, Bennett DL, Nave K, Jensen TS. **New Horizons in Diabetic Neuropathy: Mechanisms, Bioenergetics, and Painneuropathic pain in China: A double-blind randomized trial of duloxetine vs.** placebo Neuron. 2017; 93(6):1296-313.

19. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, etal. Diabetic neuropathy: A position statement by the american diabetes association. Diabetes Care. 2017; 40 (1):136-154.

20. Gregg EW, Gu Q, Williams D, de Rekeneire N, Cheng YJ, Geiss L, etal. **Prevalence of lower extremity diseases associated with normal glucoselevels, impaired fasting glucose, and diabetes among U.S. adults aged 40 or older.** Diabetes Res ClinPract. 2007; 77 (3):485-488.

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2	Muhammad Hanif	Proof reading.	
3	Shafaq Un Nisa	Author.	
4	Arsalan Hafeez	Data collection.	
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6	Badar Bashir	Proof reading.	