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ORIGINAL ARTICLE

Comparison of Efficacy of Pregabalin Vs Duloxetine in Peripheral Neuropathy Pain in Type 2 Diabetic Patients at Low Doses

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ABSTRACT

Objective: This research is specifically designed to compare the efficacy, safety and dosage pattern of DLX and PGB in peripheral neuropathy pain in type 2 diabetic patients . In this clinical trial, we have used a low dosage of both drugs to measure the outcomes.

Place and Duration: Mayo Hospital Endocrine Out Patient Department . 01-01-2022 to 31-03-2022

Study type: Randomized controlled clinical trial

Methodology: All the patients were randomly divided into two equal groups of pregabalin and duloxetine. For this study, some empty capsules were prepared which were filled with either duloxetine, pregabalin, or starch as a placebo. Initially, patients of the duloxetine group received a placebo capsule once daily as a washout period for ten days. Later on, they received a fixed dose of 30 mg/d duloxetine in the first week of treatment and different doses of 30 mg/d to 60 mg/d were used for the next eleven weeks based on drug efficacy and tolerability. However, the group of pregabalin patients received a placebo capsule twice a day for ten days as a washout period. After that, they received 75 mg/Bd for the first week of treatment and 75 mg/Bd to 150 mg/Bd for eleven weeks of treatment.

Results: The current study reported 74% ADRs in the duloxetine group while pregabalin reported 37% adverse reactions to medication. The significant mean difference related to incidents was observed as ($p<0.05$, $=0.01$ and <0.001) between both groups. In some cases, mild and tolerable adverse reactions were reported however severe reactions led to discontinuation of the drug. In 19% of cases of the duloxetine group treatment discontinuation was reported while PGB only had a ratio of 7%.

Conclusion: In conclusion despite both drugs having equal efficacy still, the DPNP patients had a better tolerability ratio for pregabalin than duloxetine.

Keywords: Type 2 diabetes, Duloxetine, Pregabalin, Peripheral neuropathy pain

INTRODUCTION

Diabetes is an alarming epidemic in the Asian region. In Iran, nearly 4.5 million population is suffering from diabetes in 2011 and this ratio is expected to increase to 9.5 million by 2030.[1,2] However, the prevalence of diabetic peripheral neuropathic pain in diabetic patients in England, the United States, and the Middle Eastern region is reported as 20%, 10%, and 50% respectively.[3-5] In the Asian region especially in the Iran region prevalence of peripheral neuropathy in diabetic patients is observed as 30% to 50%. Meanwhile, no reports of DPNP have been produced in this region however it can be estimated that the largely diabetic population of Iran is suffering from DPNP.[6,7] Diabetic peripheral neuropathic pain has adverse effects on an individual's quality of life. The expensive treatment and high prevalence of disorder burdened the health care system of the country. The inconsistent and frustrating diabetic peripheral neuropathic pain (DPNP) also causes depression and limits the person's daily activities. DNPN involves three distinct types of pain including dysesthesia, paresthesia, and muscle electrical shock. Patients undergo severe colds along with hyperalgesia and allodynia. Symptoms occur in the lower extremities and disease progression leads toward the hands. At night the pain becomes severe and create disturbance in sleep along with a reduction of daily activities. The collapse in sleep and reduction in daily life activities worsen the blood glucose levels. Thus it progresses to diabetes.[8]

There are many pharmacological and non-pharmacological treatments present in the market. Some cases can be resolved by controlling blood glucose levels while acupuncture and electric nerve stimulation also relieve pain.[9,10] However, some drugs such as duloxetine, pregabalin, topical analgesics, and tricyclic antidepressants are also used in clinical settings.[11] Food and drug association of America has recommended duloxetine and pregabalin as first-line therapy however the results related to the effectiveness and safety of the drug vary from region to region due to genetic and environmental variations.[12,13] This research is specifically designed to compare the efficacy, safety, and dosage pattern of DLX and PGB. In this clinical trial, we have used a low dosage of both drugs to measure the outcomes.

METHODOLOGY

This randomized double-blind control clinical trial was conducted in Mayo hospital for a time duration of 12 weeks. A total of 180 patients were recruited. The sample size was calculated by using the formula suggested for randomized clinical trials. For this study type, I error of 5% ($\alpha = 0.05$) and type II error ($\beta = 0.2$) of 20% with the power of 80% plus 20% dropout was used for sample size. Patients were voluntarily selected from diabetic clinics through inclusion and exclusion criteria.

All the patients with type 2 diabetes diagnosed according to the American Diabetes Association guideline 2017 were included.[14] The diabetic duration of patients was set as ≥5 years in the inclusion criteria. Only those patients whose DPNP was identified by Michigan Neuropathy Screening Instrument (MNSI) examination were selected.[15,16,17] Patients who reported DPNP severity≥40 mm of 11 points with pain duration ≥12 months on the visual analog scale were observed. We assured that all the selected patients were aged above 40 years. On the other hand, all the patients allergic to duloxetine and pregabalin were excluded. Cases of DPNP with a history of hepatic, renal, and heart failure, visual and intellectual disability, severe depression, and uncontrolled hyper expansion were excluded. Patients having pain attributable to different reasons were also not entertained. Those patients who consumed any other drug before 14 days of research and those with MNSI examination scores < 2 were also excluded. For this research diabetic control, drugs were unchanged.

All the patients were randomly divided into two equal groups of pregabalin and duloxetine. For this study, some empty capsules were prepared which were filled with either duloxetine, pregabalin, or starch as a placebo. Initially, patients of the duloxetine group received a placebo capsule once daily as a washout period for ten days. Later on, they received a fixed dose of 30 mg/d duloxetine in the first week of treatment and different doses of 30 mg/d to 60 mg/d were used for the next eleven weeks based on drug efficacy

and tolerability. However, the group of pregabalin patients received a placebo capsule twice a day for ten days as a washout period. After that, they received 75 mg/Bd for the first week of treatment and 75 mg/Bd to 150 mg/Bd for eleven weeks of treatment. After twelve weeks of treatment, drugs were continued or switched to other drugs based on efficacy, pain recovery, and tolerability. Efficacy and safety of drugs were observed on daily phone recordings and monthly physical examinations. Pain intensity was measured by the visual analog scale. Visual analog scale and adverse drug reactions were blinded to the drug type during the study. Discontinuation of treatment was based on the severity of ADRs.

Statistical Analysis: For this study, SPSS software version 19.0 was used and the significant statistical value was set as <0.05. To access the data normality Kolmogorov-Smirnov test was applied. Student t-test was used to compare the intensity, incidents of adverse drug effects, and demographic and biochemical markers. All the variables were reported in mean and standard deviations.

RESULTS

In the diabetic center of our institution total of 497 patients with peripheral pain were diagnosed. Out of these patients 180 who fulfilled inclusion were recruited for final analysis. Out of these patients majority of them were females 109 versus 71). In duloxetine, a group total of 66 (73%) patients was settled while 78 patients (87%) were placed in the pregabalin group. The demographic and clinical data of patients were represented in Table 1. According to the VAS score, the intensity of DPNP was reduced in comparison to the previous month however no significant difference was observed between both groups. In the current study, the time duration and drug interaction were significantly correlated (P < 0.001) (Table 2). Regarding adverse drug reactions, the current study reported 74% ADRs in the duloxetine group while pregabalin reported 37% adverse reactions to medication. The significant mean difference related to incidents was observed as (p<0.05, =0.01 and <0.001) between both groups. In some cases, mild and tolerable adverse reactions were reported however severe reactions led to discontinuation of the drug. In 19% of cases of the duloxetine group treatment discontinuation was reported while PGB only had a ratio of 7%.

Table 1: Demographic and clinical representation of participants[18]

Variables	Interventional groups		P-value
	Pregabalin (n= 78) Mean ± SD	Duloxetine (n= 66) Mean ± SD	
Age in years	54.03 ± 4.46	54.93 ± 3.70	0.388
Gender			
Female	49	39	
Male	29	27	
Body Mass Index (kg/m2)	26.55 ± 0.99	26.12 ± 1.02	0.595
Duration of Diabetes	9.05 ± 2.85	9.57 ± 3.20	0.145
HA1c (mg%)	8.7 ± 1.72	8.9 ± 1.20	0.655
Duration of DPNP	4.09 ± 2.02	3.55 ± 1.66	0.067
Fasting Blood Glucose (mg/dl)	144.74 ± 19.44	146.34 ± 13.39	0.699
Serum Creatinine (mg/dl)	1.02 ± 0.09	0.95 ± 0.11	0.088
Michigan Neuropathy Scale Instrument questionnaire	6.71 ± 2.03	6.65 ± 1.80	0.810
Visual analogue scale	61.74 ± 16.34	67.23 ± 19.29	0.052
Michigan Neuropathy Scale Instrument examination	2.82 ± 0.43	2.69 ± 0.55	0.076

Table 2: Comparison of DPNP Intensity in both groups[18]

Variables	Visual Analogue score of DPNP (mm)		P- Value
	Pregabalin Mean ± SD	Duloxetine Mean ± SD	
Before treatment	61.7 ± 16.3	67.2 ± 19.3	< 0.001
1st month	29.7 ± 7.8	32.4 ± 8.5	< 0.001
2nd month	22.3 ± 6.4	22.3 ± 6.4	< 0.001
3rd month	16.0 ± 5.5	16.2 ± 4.2	< 0.001

Table 3: Adverse drug reaction in both groups[18]

Adverse drug reaction (ADRs)	Pregabalin N (%)	Duloxetine N (%)	P- value
Edema	11(12%)	0 (0%)	< 0.001
Anorexia	2 (2%)	22 (25%)	< 0.001
Somnolence	18 (20%)	8 (9%)	0.06
Nausea	2 (2%)	20 (23%)	< 0.001
Dizziness	14 (15%)	4 (5%)	0.06
Vomiting	0 (0%)	10 (11%)	< 0.001
Weight gain	16 (18%)	0 (0%)	< 0.001
Shivering	0 (0%)	16 (18%)	< 0.001
Increased micturition	1(1%)	8 (9%)	0.01
Agitation	0 (0%)	14 (16%)	< 0.001
Arrhythmia	0 (0%)	4 (5%)	0.06
Tremor	0 (0%)	14 (16%)	< 0.001
Tachycardia	2 (2%)	10 (11%)	0.01
Muscle rigidity	0 (0%)	14 (16%)	< 0.001
Hypertension	2 (2%)	10 (11%)	0.01
Diaphoresis	0 (0%)	11(12%)	< 0.001
Headache	6 (7%)	4 (5%)	0.75
Abdominal cramp	2 (2%)	14 (16%)	0.02
Hyperthermia	0 (0%)	8 (9%)	< 0.001
Diarrhea	3 (3%)	10 (11%)	0.02

DISCUSSION

In this clinical trial comparison of efficacy, safety and dosage pattern of duloxetine and pregabalin was drawn on a sample in context of diabetic peripheral neuropathic pain. In both groups intensity of DPNP was reduced in comparison to the previous month. However, no significant difference related to VAS score was reported between groups. Many studies had similar results and examined the same issue.[18-25] A study by Boyle et al[18], Tannenberg et al[19], and Devi et al[20] conducted a direct comparison of two drugs while Quilici et al[21] performed a meta-analysis on nine seperate researches. All these studies found relief effects of both drugs on DPNP patients without any significant difference. Furthermore, in the current study, the dose of treatment was flexible and dependable on patients' responsiveness. The average dose of duloxetine in current study was parallel to the previous studies.[18-21,23,26,27] Two non-interventional post-hoc studies conducted on the German and American populations used average doses of 53.9 and 55.2 mg/d for DPNP patients.[26,27] This average dosage was comparatively higher than our study. Meanwhile study by Boyle et al[18] reported a higher dosage of duloxetine in DPNP patients in the United Kingdom. They used 60 and 120 mg/d doses for their participants however both doses were efficient without any significant difference. Tannenberg et al[19] conducted their study on the worldwide white population and suggested 60 mg/d dosages of duloxetine for DPNP patients. Literature of Asian countries had similar findings. A study conducted on the Indian population prescribed 20 to 80mg of duloxetine for DPNP patients via dose responses.[20] However, they did not report the average dose of duloxetine and pregabalin for their participants. However, another clinical trial by Zakerkish et al.[28] suggested a 30 to 60 mg/d dose of duloxetine in comparison to Nortriptyline for DPNP cases in Southern Iran. The average dose of the current study is nearer to the Japanese study by Yasuda et al[22] which gave a fixed dose of 40 mg/d however, the fixed dose of the current study was 30mg/d. The average weight of the current study was 60kg parallel to the mentioned Japanese study. However, a study by Raskin et al used a fixed dose of 120 mg/d of duloxetine on patients with an average weight of 80kg and observed effective outcomes. However, in the current study, no correlation analysis was performed related to weight and dose of DLX.

Comparing the data of the pregabalin drug study Happich et al[26] reported an average dose of 173.5 mg/d. However, in the current study, the average dose was comparatively lower than in

three other studies.[18,19,25] Devi et al[20] observed average consumption of 150 to 600 mg/d ideal whereas a study by Boyle et al[18] and Tannenberg et al[19] suggested an average dosage of 600/d and 300 mg/d of pregabalin respectively. However, all these suggestions are above the average doses of pregabalin consumed in the current study. On contrary, the adverse drug reaction of pregabalin was similar to many previous studies. These reactions included dizziness, drowsiness, edema, and weight gain similar to previous studies.[18-20] The reaction was more adverse in the pregabalin group than duloxetine. Interestingly the reactions reported in the duloxetine group were not reported earlier. Previous studies reported nausea, anorexia, vomiting, and diaphoresis in the duloxetine group.[18-23,28] However in the current study duloxetine causes hypertension, muscle rigidity, shivering, and tremor. According to Sternbach and Hunter's criteria[29] diaphoresis, nausea and hyperthermia are the symptoms of Serotonin syndrome (SS). Due to moderate to severe cases of serotonin syndrome reported in the current study duloxetine was discontinued. However the cases of arrhythmia incidence were statistically lesser in the DLX group than in the PGB group but due to ADR, the other incidence rate was reported as 5% in DLX.

In the current study due to adverse drug reactions, the discontinuation of duloxetine was observed in 19% cases and pregabalin discontinuation was reported in 7% cases. These results are comparatively higher than the study of Devi et al., in which he reported a 9% discontinuation ratio of pregabalin without the reason of adverse drug reaction. Meanwhile, a study by Zakerkish et al[28] had no reason for discontinuation while Yasuda et al[22] reported 96% ADRs and 22% discontinuation. Gene polymorphism is the major explanation for the effective dose and safety of duloxetine.[30] Genotypic differences can be the reason for diverse efficacy and drug safety in different populations. Some studies reported that patients with CYP1A2 gene polymorphism suffered from severe adverse drug reactions to anti-rheumatic drugs.[31,32] Other factors like the social and natural environment and mental conditions can cause variation in dose-response and ADRs in different regions.[33,34]

CONCLUSION

In conclusion despite both drugs having equal efficacy still, the DPNP patients had a better tolerability ratio for pregabalin than duloxetine. Thus this research supports the pregabalin drug for the treatment of diabetic patients however if duloxetine is required very minimum dose should be prescribed to avoid the incidents of serotonin syndrome.

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