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EFFICACY OF EPALRESTAT, DULOXETINE AND EPALRESTAT IN COMBINATION WITH METHYLCOBALAMINE IN DIABETIC PERIPHERAL NEUROPATHY

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Abstract

Diabetic neuropathy is a major long term problem allied with diabetes that can cause serious disability and also death. Fifty to seventy five percent of all ulcerations and non trauma amputations are a consequence of diabetic neuropathy. Epalrestat, duloxetine and epalrestat with methylcobalamine are widely used to overcome neuronal damage. This study was designed to evaluate the efficacy of these three drug regimens. ***Material and methods:*** *Patients included in this study were experiencing pain because of diabetic neuropathy for more than 6 months but not more than 5 years.* ***Results:*** *From 236 subjects with diabetic neuropathy included in the study, 181 patients concluded final analysis. 55 patients dropped from the study (14, 23 and 18 patients from duloxetine, epalrestat+methylcobalamine combination and epalrestat respectively). Mean pain score was reduced from 5.01±1.99 (severe pain) at first visit to 2.86±2.10 (moderate pain) in the epalrestat group, from 6.41±1.73 (severe pain) at first visit to 2.38±1.58 (mild pain) in the duloxetine group and from 5.86±1.76 (severe pain) to 2.88±1.91 (mild pain) in the epalrestat with methylcobalamine group.* ***Conclusion:*** *We conclude that duloxetine was significantly more effective than epalrestat and epalrestat in combination with methylcobalamine in relieving diabetic neuropathic pain.*

key words: *Diabetes, Peripheral Neuropathy, Epalrestat, Duloxetine, Methylcobalamine*

Background and Aims

Diabetic neuropathy (DN) encompasses a wide, heterogeneous group of clinical and subclinical syndromes [1]. It is a major long term problem allied with diabetes that can cause serious disability and also death [2]. Fifty to 75% of all ulceration and non-traumatic amputations are a consequence of diabetic neuropathy, and cause more hospitalizations than all other diabetic complications [3]. DN affects the nervous system and causes extensive damage. Neurologic complications are not reserved for specific type of diabetes but occur equally in type 1 and type 2 [4]. Diabetic peripheral neuropathy (DPN) is often painful and debilitating condition that is caused by damage to any nerve in the peripheral nervous system. It

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is a family of nerve disorders that are directly caused by diabetic complications [5]. Poor diabetic control, obesity, high blood pressure, high cholesterol and triglycerides are risk factors for developing neuropathy [6]. It affects somatic and autonomous nervous systems and is different from peripheral arterial disease which affects the blood vessels rather than the nerves and vasa nervorum [7]. Many physicians misinterpret symptoms related to neuropathy in diabetic patients. Treatment is directed towards preventing neuropathy progression, reducing symptoms and implementing measures to prevent complications of insensate extremities [8].

The aim of this study was to analyze the effect on neuropathic pain of three widely used drugs: epalrestat, duloxetine and epalrestat + methylcobalamine.

Material and methods

This was a prospective observational study carried out in Sri Bhadrakali Diabetic Clinic, Naimnagar, Hanamkonda. Institutional Human Ethics committee endorsement was seek and obtained before conduct of the trial (VCOP/PHARMD/V/2015/15/7). Selection of subjects was done according to the following inclusion-exclusion criteria:

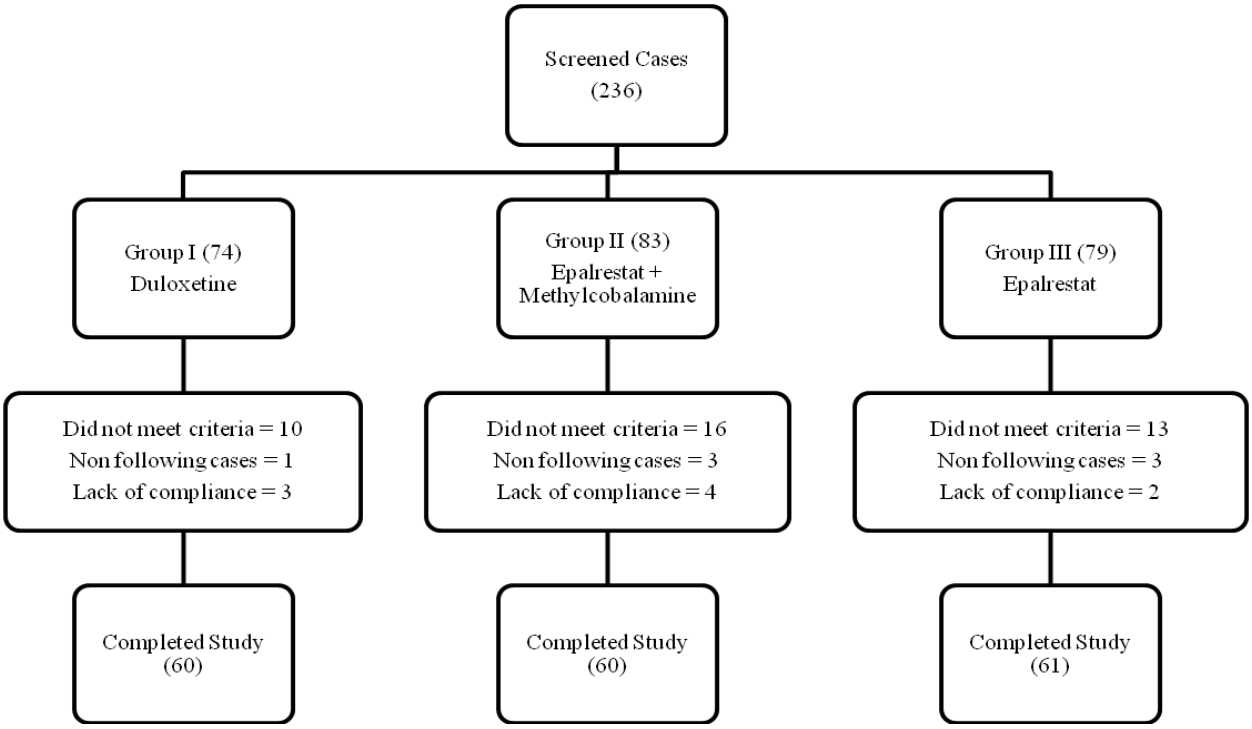

Figure 1. *Distribution of Patients according to DPN guidelines.*

Inclusion criteria: Males and females 18-75 years age; Diabetes mellitus (Type1 or Type2); Experiencing pain due to diabetic neuropathy for at least 6 months but not more than 5 years; Neuropathic pain must begin in the feet with relatively symmetrical onset; Patients who had Douler neuropathic pain questionnaire [DN4] Score 4 or more and patients who had a Vibration Perception Threshold (VPT) score of above 15; Keeping all appointments for clinic visits, tests and procedures.

Exclusion criteria: Suffering from ischemic pain and other types of pain unrelated to diabetic neuropathy such as phantom pain due to amputation or arthritis; Pregnancy or breast-feeding; previous renal transplant or current renal, respiratory, or haematological illness; Symptomatic peripheral vascular disease, or other medical conditions or psychological

conditions that might compromise participation in the study; Any clinically significant neurological disorders, significant unstable medical or psychiatric conditions that would interfere with the patient's ability to participate in the study.

Written and oral informed consent forms were obtained and evaluated before any study procedures.

The patient disposition is given in Figure 1. Thus, a total of 236 subjects with diabetic neuropathy (DPN) were included in the study. They were randomized in three study groups, to receive duloxetine (Group 1), epalrestat + methylcobalamine (Group 2) and epalrestat (Group 3). Of these, 55 patients dropped from the study (14, 23 and 18 patients from the duloxetine, epalrestat+methylcobalamine combination and epalrestat groups respectively). The treatment was carried out with any one choice of the three options, administered once daily.

Patient's medical history and demographic details were documented at screening visit. Before starting the therapy, first parameters were evaluated from patient's records. Pain scores were confirmed by pain rating scale and VPT was evaluated with a biothesiometer. Patients received the drugs for 6 months period and returned for final evaluation at the last day. During the course of the trial, progress of patients was tracked using the Douler's neuropathic pain questionnaire (DN4) by assessing burning, itching, numbness, loss of heat and cold sensations, electric shocks, tingling and brushing symptoms. Clinic and laboratory collected data included weight, systolic and diastolic blood pressure (BP), glycated hemoglobin (HbA1C), Fasting Blood Glucose (FBG), Post Prandial blood Glucose (PPG), serum creatinine, serum electrolytes, microalbuminuria, hemoglobin and lipid profiles. Vibration Perception Threshold (VPT) and intensity of pain were witnessed at start and end of the study. Comparison of pain score was done with Numeric Pain Rating Scale [NPRS] [9].

Measurements of treatment efficacy:

The primary efficacy measure for this study was the reduction of pain scores. Subjective pain was assessed by numeric pain rating scale [NPRS] and rated by patients. Patients ratings were tabulated for calculation of mean scores at baseline and endpoint. The NPRS severity sub-scores included, No Pain- 0; Mild-1 to 3; Moderate-4 to 6; Severe-7 to 10.

The secondary efficacy measures collected were vibration perception threshold (VPT) by using a biothesiometer. The VPT by using biothesiometer has been used to identify peripheral sensory neuropathy and subjects at risk of foot ulcerations. The biothesiometer is a rapid, portable, and sensitive method of assessing VPT and has been used to identify subclinical neuropathy and to monitor the progress of the disease. It allows increasing the vibrating strength and measuring the threshold of vibration perception by gradually increasing the vibrations. Interpretation of the results is made using a biothesiometric score as detailed in Table 1. Patients with a VPT greater than 25 were considered to have a significant neuropathy.

Table 1. Biothesiometer score interpretation.

Severity	VPT
Normal	Up to15 volts
Grade 1	16-25 volts
Grade-2	>25 volts

Testing vibration sensation with the biothesiometer: A probe is applied on the foot, usually on the big toe. The probe can be made to vibrate at increasing intensity by tuning a dial. The person being tested indicates as soon as

he/she can feel the vibration and the reading on the dial at that point are recorded. The biothesiometer has a reading from 0-50 volts. Data from the literature show that the risk of developing a neuropathic ulcer is much higher if a person has a biothesiometer reading greater than 30-40 volts [9].

Statistical Analysis: Data analysis was done using Graph Pad Prism software (version 5). Mean and Standard deviation (SD) were calculated for the normal distributed variables - efficacy measures, laboratory measures and vital signs. Difference between quantitative variables was evaluated by using the analysis of variance [one way ANOVA]. Statistical significance was recognized at $p < 0.05$.

Results

Demographic characteristics of the study population are given in Table 2.

Table 2. Patient demographic characteristics of the study population (n=181).

Characteristics	Values (Mean±SD)
Age (years)	54±10
Male n (%)	79 (43.6)
Female n (%)	102 (56.3)
Rural n (%)	130 (71.8)
Urban n (%)	51 (28.1)
Height (cm)	157.3±9.12
Weight (kg)	65.84±10.15
BMI (kg/m²)	26.64±3.82
With family history of diabetes n (%)	93 (51.3)
Without family history of diabetes n (%)	88 (48.6)
Smoking n (%)	39 (21.5)
Non-smoking n (%)	142 (78.4)
Alcohol n (%)	71 (39.2)
Duration of diabetes (years)	8.11±5.45
Duration of diabetic peripheral neuropathy (months)	29.2±23.6

VPT assessed with the biothesiometer in the right leg

At Visit 1 the mean VPT score of duloxetine [D] was 27.7±5.34 and decreased at Visit 2 to 21.6±5.38. In epalrestat plus methylcobalamine, [E+M] group, the mean VPT score decreased from Visit 1 (27.32±6.98) to Visit 2 (22.0±7.49). Finally, in the epalrestat group [E], the mean VPT score also decreased from Visit 1 (25.0 ± 7.45) to Visit 2 (20.46 ± 7.07) as detailed in Figure 2.

Comparing the improvement of the VPT score in the 3 study groups we observed that the reduction of the VPT score was significantly higher with duloxetine (6.05±0.04) when compared with epalrestat+methyl-cobalamine (5.32±0.57) and epalrestat (4.61±0.38), with a p value of 0.0093. However, there was no statistically significant difference between the epalrestat and epalrestat+ methylcobalamine groups.

VPT assessed with the biothesiometer in the left leg

At Visit 1, the mean VPT score of duloxetine was 27.9±5.76 and decreased at Visit 2 to 20.9±6.88. In the second group [E+M], the mean VPT score decreased from Visit 1 (27.3±5.92) to Visit 2 (22.0±7.6). Finally, in the epalrestat group [E], the mean VPT score also decreased from Visit 1 (22.7±5.92) to Visit 2 (18.7±5.83) as detailed in Figure 3.

Comparing the improvement of the VPT score in the 3 study groups we observed that the reduction of the VPT score was highest in group

1 [D] (25.06%) compared with the other two groups (19.57% for group 2 [E+M] and 17.38% for group 3 [E]), the difference being statistically significant ($p < 0.0001$).

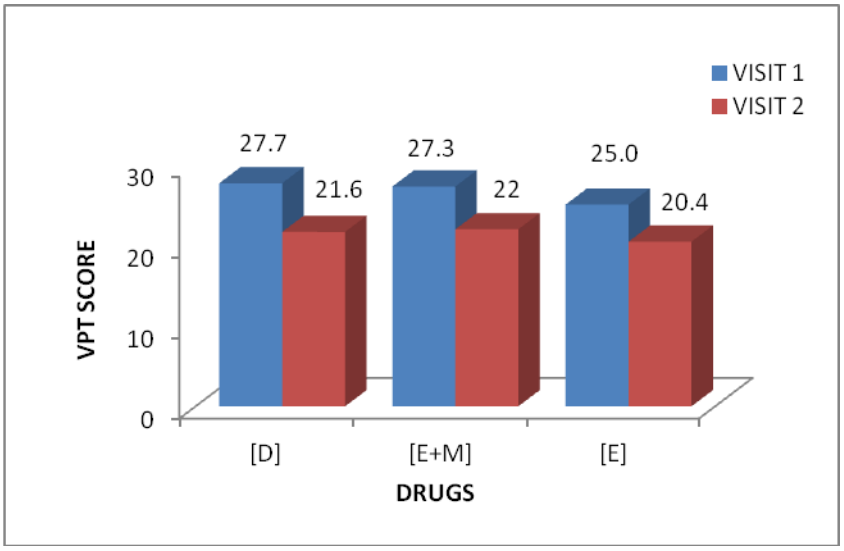

Figure 2. *Right leg mean VPT score of the 3 drugs, at Visit 1 and Visit 2.*

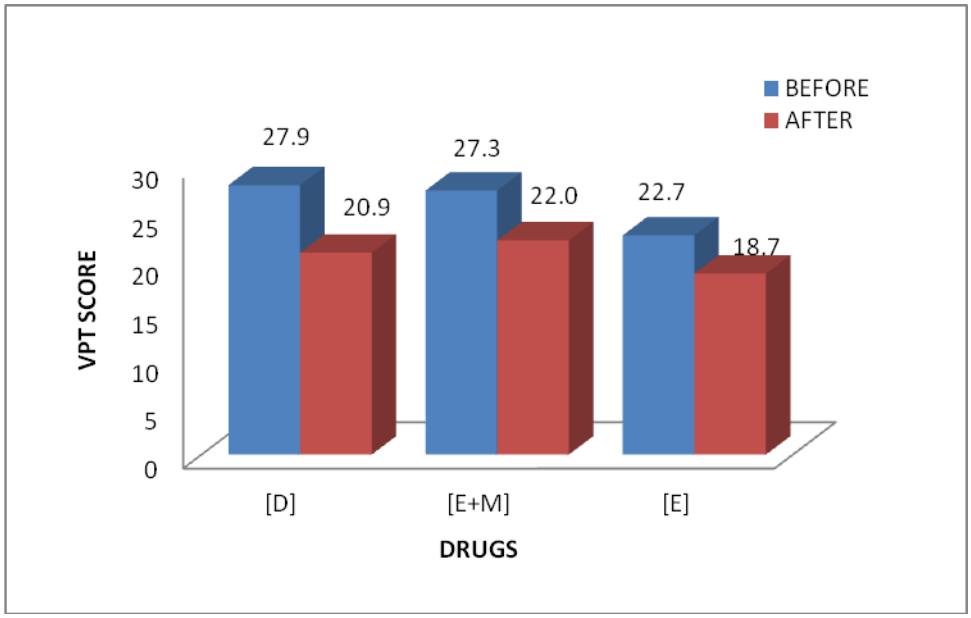

Figure 3. *Left leg VPT Score of the three study groups, at Visit 1 and Visit 2.*

Effect of treatment on the pain intensity score

In the first group [D], pain intensity score decreased from 6.4±1.73 (severe pain) at Visit1 to 2.3±1.58 (mild pain) at Visit 2. For the second group [E+M] it decreased from 5.8±1.76 (severe pain) at baseline to 2.8±1.91 (mild pain) at the end of the treatment, and from 5.0±1.99 (severe pain) at baseline to 2.8±2.10 (moderate pain) at the end of the treatment for the third group [E], respectively, as detailed in Figure 4.

Comparing the NPRS improvement for the three study groups, the mean difference of pain intensity was higher in the [D] group (4.03±0.15) when compared with the [E+M] group (2.98±0.15) and [E] group (2.15±0.11), the difference being statistically significant ($p<0.0001$).

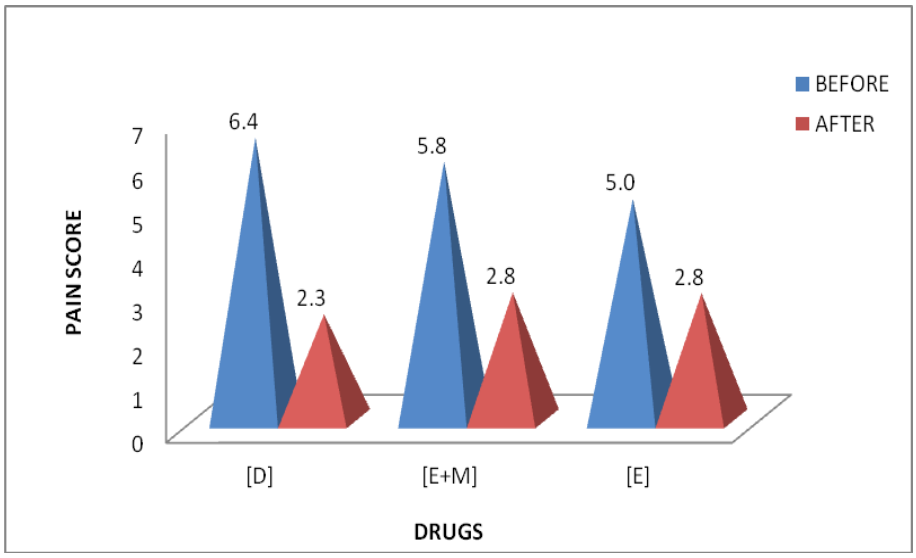

Figure 4. *Pain intensity score in the three study groups at Visit 1 and Visit 2.*

Discussion

Poor glycemic control is a key factor for the development of diabetic neuropathy. Specific treatment of neuropathic pain leads to an improvement in the quality of life of these patients. This research was carried out to assess the efficacy and safety of three available treatment regimens in patients with diabetic neuropathy. Loss of sensation, numbness, weakness, pain, loss of thermal sensitivity, burning sensation and muscle cramps have been evaluated in this study, all these being the most common diabetic neuropathy complaints.

A great deal of evidence suggests that Selective Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) are efficient in relieving DPN symptoms [10]. Duloxetine is a second line treatment FDA approved for the treatment of neuropathic pain. It seems to be safe, with no clinical relevant changes in heart rate or weight that were experienced by patients taking duloxetine [11]. Methylcobalamine and vitamin B_{12} are also effective in alleviating symptoms of neuropathy [12]. Finally, epalrestat interferes potentially by preventing or ameliorating long term diabetic complications and is a new drug in this category as an effective treatment option for diabetic neuropathy [13]. Epalrestat+methyl-cobalamine combination could have the advantage of both mechanisms of neuroprotective activity. Epalrestat helps in preventing degeneration of neurons by decreasing the sorbitol accumulation and reducing the oxidative stress while methylcobalamine heals the injury.

This research revealed that all the three drugs had a positive effect on pain intensity scores of patients with diabetic neuropathy. No statistically significant difference in laboratory parameters was observed. For all patients' good glycemic control, lipid management, maintaining healthy life style and monitoring of all parameters of diabetes management as advised by the physicians are of paramount importance. The fact that the three drugs tested in this study did not change the laboratory parameters during the study period may indicate that these drugs are safe in using DPN patients.

Conclusion

The results of the present study reveal that all the three groups showed an improvement in diabetic neuropathy symptoms after 6 months of follow-up. All evaluated neuropathy efficacy parameters showed statistically significant

improvements. In patients treated with duloxetine pain relief was stronger and greater reductions of VPT scores were recorded when compared with patients receiving epalrestat alone or epalrestat in combination with methylcobalamine.

In conclusion, duloxetine was significantly more effective in relieving diabetic neuropathic pain than epalrestat, and epalrestat in combination with methylcobalamine in short term admnistration.

Conflict of Interest: No Conflict of Interest.

Disclosure: Penchala Abhilash and Macharla Manasa equally contributed in this study and may be considered as first authors.

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