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Comparison of safety and efficacy of pregabalin, duloxetine and their combination with epalrestat in diabetic neuropathy: A prospective, double-blind, randomized, controlled Trial

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ABSTRACT

Neuropathic pain is a common disorder characterized by negative and positive subjective signs and symptoms ranging from numbness to crippling pain. Type 2 diabetes mellitus (T2DM) is the primary cause of neuropathy and neuropathic pain. Diabetic neuropathic pain (DPN) is one of the most common diabetes mellitus complications. The study was aimed to analyze the efficacy and safety of Pregabalin, Duloxetine, and their combination with Epalrestat in T2DM neuropathic patients. The study was conducted on 200 subjects. The patients were divided into 4 groups each comprising of 50 patients. Group I(P) was subjected to Pregabalin (150 mg O.D), Group II (D) to Duloxetine (60 mg O.D), Group III (P + E) to Pregabalin + Epalrestat (150 mg + 100 mg (O.D), and Group IV (D + E) to Duloxetine +Epalrestat (60 mg + 100 mg (O.D) and) for a period of 6 months. Various clinical parameters like vibration perception threshold, gycated haemoglobin level, visual analog scale, DPNdiabetic diagnostic questionnaire, advance glycated end products, thiobarbituric acid reactive substances, C-reactive proteins, SF12 score, and cost-effectiveness were assessed at baseline and 3 and 6 months. Results demonstrated that Pregabalin and Epalrestat therapy has a better effect on neuropathic pain reduction than Duloxetine and Epalrestat with strict glycemic control and favorably contributes to the health effective benefits by inhibiting disease progression and fulfills the alternate goals of management of DPN. It has been suggested that Pregabalin and Epalrestat therapy is more efficacious and armamentarium for patients with DPN. It has been suggested that Group III therapy is more efficacious, cost-effective, and armamentarium for patients with DPN.

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic syndrome which is marked by chronic hyperglycemia, glycosuria, hyperlipidemia, and balance of negative N_2 (nitrogen) and also sometimes ketonemia resulting from defects in the action of insulin and secretion of insulin, or both which may lead to an impaired mechanism of carbohydrate, lipid, and protein metabolism (Georgoulis *et al*., 2014; Hossain *et al*., 2013; Zychowska *et al*., 2013). The World Health Organization and the Diabetes Data Group classified diabetes as (A) insulin-dependent DM or Type 1 diabetes–idiopathic forms and immune-mediated forms of β cell destruction, which results in insulin deficiency. (B) non-insulin-dependent DM or Type 2 diabetes–disorder to adult-onset, which rises mainly from relative insulin deficiency and insulin resistance. By 2030, diabetics in India is expected to cross 101.2 million and in 20 years' time, expected to rise to 438 million, according to the International Diabetes Federation. About 7 million humans develop DM each year (Hossain *et al*., 2013). A burden to human health is represented by the increased prevalence of DM due of its long-lasting serious microvascular and nacrovascular complications

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(Zychowska *et al*., 2013). Hyperglycemia is the main cause of neuropathic pain and neuropathy. Neuropathyis caused due to both chronic type 1 (T1DM) and type 2 diabetes (T2DM) affecting upto 50% of those patients suffering from the disease (Zychowska *et al*., 2013). Neuropathic pain results from the central or peripheral nervous system damage or the disease and is led by a primary lesion or nervous system dysfunctioning. Ironically, about 25% and 62% of patients with idiopathic peripheral neuropathy have prediabetes, about 11% and 25% are considered to have peripheral neuropathy, and between 13% and 21% have neuropathic pain (Georgoulis *et al*., 2014).

Diabetic neuropathy has multiple symptoms: odd movement with large sensory fibers and frequent cold and/or hot feeling with limited sensory fibers and diagnostic criteria for small fiber neuropathy in clinical practice and research (Grazia *et al*., 2019). Chronic pain Includes increased perception of pain/response to painful stimuli (hyperalgesia), (allodynia) pain in reaction to stimulus usually not cause pain, (paresthesia) uncomfortable irregular sensation, and random pain. (Colloca *et al*., 2017; Grazia *et al*., 2019). Furthermore, the pathophysiology of diabetic neuropathy includes the protein kinase C (PKC) activity, polyol pathway, advanced glycation end products (AGEs), and oxidative stress. Long-term hyperglycemia enhances the polyol pathway and increases nonenzymatic glycation of various structural proteins, which further increases oxidative stress as well as the alteration in the PKC activity and poly-ADP-ribose polymerase activation that are all interrelated for the cause and development of neuropathy. These, in turn, activate or suppress the PKC activity or activate mitogen-activated protein kinase activity, resulting in functional and structural disturbance in the peripheral nervous system (Craige *et al*., 2016; Veves *et al*., 2008). Many reasons for neuropathy include lifestyle factors, contaminants to the environment, obesity, cigarette smoking, and nerve tumors. Different types of drugs are also used to treat diabetic neuropathy and neuropathic pain including anticonvulsants, opioids, antidepressants, and aldose reuptake inhibitors (Van Hecke *et al*., 2014). Antidepressants include tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRI). Tricyclic antidepressants are the first choice in the treatment of neuropathic pain, including painful diabetic neuropathy (Jain *et al*., 2014). Drugs include amitriptyline, imipramine, desipramine, nortriptyline, maprotiline, and clomipramine. Common side effects include visual blurring, dry mouth, cognitive impairment, tachycardia, orthostatic hypotension, sedation, and weight gain. SSRIs like fluoxetine, venlafaxine, paroxetine, and citalopram have been used for the relief of neuropathic pain. Anticonvulsants are used for the treatment of neuropathic pain. These include phenytoin, carbamazepine, oxcarbazepine, gabapentin, pregabalin, lamotrigine, clonazepam, valproic acid, topiramate, and tiagabine. These agents can be used for the first-line or add-on therapy. Pregabalin binds to the α2-based protein subunit of calcium voltage-gated channels and enhances the release of exciting neurotransmitters. Gabapentin is another drug in the treatment of neuropathic pain (Alles and Smith, 2017; Singh *et al*., 2016). The flux of glucose is reduced by aldose reductase inhibitors through polyol pathways, impedes the deposition of sorbitol and fructose, and inhibits the reduction of redox potential. It involves tolrestat, zopolrestat, alreastat, and epalrestat (Singh *et al*., 2016). Pregabalin is one of the generally used therapies currently for a number of neuropathic pain (NeP) conditions (Freynhagen *et al*., 2015).

A study showed significant decreased pain intensity by both drugs in 66 patients from the Duloxetine group and 77 from the Pregabalin group (Joharchi *et al*., 2019). Despite the availability of several modalities for the prevention of diabetic neuropathy, mortality and morbidity rates are very high. The present clinical study examined the hypothesis that the combination of Pregabalin or Duloxetine with Epalrestat is efficient in slowing down the development of diabetic neuropathy. Therefore, our study aimed to compare the efficacy and safety of Pregabalin, Duloxetine, and their combination with Epalrestat in T2DM neuropathic patients. The primary outcome of the current clinical study is a decrease in pain score and hindering the progression of disease and secondary outcome measures included quality of life and cost-effectiveness.

MATERIAL AND METHODS

Permissions to perform the study were acquired from the Institutional Ethics committee (IEC No –PHMA /GSMCH-15/ IEC-38), Gian Sagar Medical College and Hospital, Rajpura, and the study was carried out by adopting the Helsinki agreement and the Effective Medical Practice Code. Patients with DPN having a disease duration of >10 years, who are willing to participate in the study and gave written informed consent, were enrolled in the study. Patients were diagnosed on the basis of inclusion and exclusion criteria.

Inclusion and exclusion criteria were designed for the study on the basis of disease duration, Pain Scales, and information from the clinicians.

Inclusion criteria

1. Patients of either sex with the age of above 18 years.
2. Have pain because of peripheral neuropathy affected by type II diabetes with the pain that starts in the feet and present from at least 6 months assessed by the diagnostic questionnaire (DN4).
3. Might not be pregnant and agree to the use of medically appropriate and effective means of birth control during study participation. Agree to randomize management assignment.
4. May give written informed consent
5. Able to comply with study procedures

Exclusion criteria

- Severe hepatic disease
- Substance abuse history or dependence within the past year, excluding nicotine and caffeine.
- Unstable cardiovascular or serious, hepatic (acute liver injury such as hepatitis or severe cirrhosis), kidney, respiratory diseases, blood disorder, seizure disorder, problems with peripheral vascular disease, or other medical conditions or psychiatric conditions that would hinder your participation or likely to lead to hospitalization during the course of the study.
- Uncontrolled or poorly controlled hypertension.

All the patients were evaluated for eligibility of inclusion/ exclusion criteria. Clinical evaluation of eligible patients was

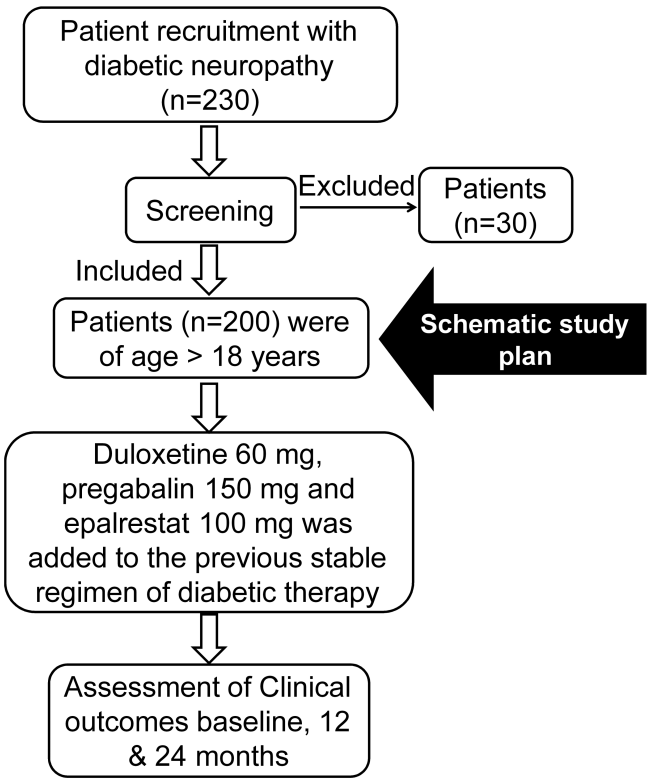
conducted out at baseline and scheduled clinical visits at 3 and 6 months after treatment. At each study visit, including the initial visit, all subjects underwent the same determination. All patients were continuing their previous regimen as such and duloxetine 60 mg, pregabalin 150 mg, and epalrestat 100 mg are added according to the groups to which the patient belongs.

STUDY DESIGN

The study was a double-blind, prospective, randomized, controlled parallel clinical study and conducted out in the Outpatient department, based at Gian Sagar Medical College and Hospital, Rajpura. The study lasted from November 2015 to January 2017. Clinical assessment of eligible patients was carried out at baseline and scheduled clinical visits including visual analog scale (VAS), Vibration Perception Threshold (VPT), DN4, gycated haemoglobin (HbA1c), thiobarbituric acid reactive substances (TBARS), AGEs, C-reactive proteins (CRP), and SF 12 at 3 and 6 months after the involvement of biochemistry parameters in the study using enzyme- linked immunosorbent assay analytical kits. At each study visit, including the initial visit, all subjects underwent the same determination.

Groups: The patients will be randomly divided into four groups and by appropriate sample size analysis of each group consisting of 200 patients, and coding of investigational product is accordingly done for double-blind study by following the Inclusion and Exclusion criteria:

Group I: Duloxetine; 60 mg/days (**D**), **Group II:** Pregabalin; 150 mg/days (**P**), **Group III:** Pregabalin 150 mg/days + Epalrestat 100 mg/days (**P + E**); **Group IV:** Duloxetine 60 mg/days + Epalrestat 100 mg/days (**D + E**).



Schematic study plan

All the data were collected and analyzed at scheduled clinical visits using the following parameters: Glycated hemoglobin: the 2009 International Expert Committee advised the usage of HbA1c to diagnose diabetes with a threshold of 6.5% (Edwards *et al*., 2008). C-reactive protein: high levels of serum CRP in a normal population is a sign of future development of diabetes. The levels of CRP in blood correlate with the severity of diabetes and the level of control (Farmer *et al*., 2012). AGE are developed from the overload of proteins, lipids, and nucleotides by the nonenzymatic reaction of glucose, which results in axon and nerve cell metabolism intervention and hence inhibits neuronal integrity and repair mechanisms (Yagihashi *et al*., 2007). VPT is a tool to detect diabetic neuropathy and dysfunction of nerves (Vinik, 2010).

Visual Analog scale (VAS): The VAS is a measure of pain intensity. VAS is a scale of 10 cm (100 mm) in length. For pain intensity, the scale is utmost generally anchored by "no pain" (score of 0) and "worst imaginable pain" (score of 10) (Koltezenburg and Scadding, 2001). DN4 Questionnaire (DN4 Q): Diabetic neuropathic pain (DPN) will be evaluated by administering the DN4 Q. This questionnaire consists of a set of four questions for the assessment of neuropathic pain (Khwaja and Chaudhry, 2007). TBARS: The excess production of free radicals in diabetes can trigger diabetic neuropathy via many mechanisms occurring in both the central and peripheral nervous systems. It is seen that this is the source of disorders of the nervous system (Bansal *et al*., 2006). Cost-effective analysis: Cost-Effectiveness Analysis contains the comparison of programs or management substitutes with different safety and efficacy profiles. Cost is calculated in rupees, and tests are also represented in units of effectiveness, a normal unit, or nonrupees (Syed, 2011).

Quality of Life: The U.S. Food and Drug Administration (FDA) has been boosting the use of Patient-Reported Outcomes in clinical studies to help offer materials regarding the status of the impact of the disease on patients' mental and physical health (Pradhan et al., 2001).

Statistical analysis

Continuous data are shown as mean±standard error of the mean. An evaluation between the groups was done using unpaired student t-tests. Statistical significance was assumed at $p < 0.05$. Statistical analysis was performed using Sigmastat 4.0 (Systat Software, San Jose, CA, USA).

RESULTS

Overall, 200 patients were involved in the study according to the exclusion and inclusion criteria. The study was followed, and the response was measured at baseline (0 days), 3 m,and 6 months.

Effect of treatments on glycated hemoglobin (%) (HbA1c)

Duloxetine + epalrestat management for a time span of 3 and 6 months created a difference from baseline of 11.586 ± 0.183 to 8.836 ± 0.187 in 3 months and 6.22 ± 0.162 in 6 months. With duloxetine, glycated hemoglobin was from 11.126 ± 0.258 to 10.06 ± 0.229 in 3 months and 9.092 ± 0.215 in 6 months. The decrease in HbA1c for the duloxetine + epalrestat group of patients was statistically significant relative to the respective

baseline value ($p < 0.05$). Pregabalin + Epalrestat treatment for a period of 3 and 6 months produced a difference from baseline of 12.116 ± 0.168 to 9.57 ± 0.155 in 3 months and 7.24 ± 0.118 in 6 months. With pregabalin, the change was from11.094 ± 0.239 to 9.69 ± 0.228 in 3 months and 8.394 ± 0.215 in 6 months. The lessening in HbA1c in the pregabalin + Epalrestat group equated to the relevant baseline values was statistically significant ($p < 0.05$). HbA1c for D + E and P + E for 3 and 6 months and Duloxetine + epalrestat treatment for a period of 3 and 6 months produced a difference from 8.836 ± 0.187 in 3 months and 6.22 ± 0.162 in 6 months, respectively (Fig. 1).

Effect of treatments on AGEs (µg/ml)

Pregabalin + Epalrestat and Pregabalin treatment for a time of 3 and 6 months formed a reduction in AGE from baseline of 4.28 ± 0.32 to 3.05 ± 0.29 in 3 months and 2.1 ± 0.15 in 6 months with Pregabalin + Epalrestat and the lessening in AGEs by pregabalin from baseline 4.33 ± 0.34 to 3.75 ± 0.23 in 3 months and 3.3 ± 0.21 in 6 months. The decrease in AGEs in the pregabalin + epalrestat group compared to the respective baseline values was statistically significant ($p < 0.05$). Duloxetine + epalrestat treatment for a period of 3 and 6 months produced a difference from baseline of 4.2 ± 0.34 to 3.3 ± 0.31 in 3 months and 2.9 ± 0.271 in 6 months, with duloxetine from 4.3 ± 0.387 to 3.9 ± 0.27 in 3 months and 3.6 ± 0.21 in 6 months. The decrease in AGEs in the duloxetine + epalrestat group compared to the respective baseline value was statistically significant ($p < 0.05$; Fig. 2).

Effect of managements on CRP- (g/dl)

Duloxetine + epalrestat management for a time span of 3 and 6 months produced the difference from baseline of 8.544 ± 0.168 to 6.43 ± 0.14 in 3 months and 4.2 ± 0.069 in 6 months with duloxetine and the decrease in inflammation score by duloxetine from baseline 8.178 ± 0.202 to 7.164 ± 0.207 in 3 months and 6.182 ± 0.21 in 6 months (Fig. 5a and b). The decrease in CRP in the duloxetine + epalrestat group compared to their respective baseline value was statistically significant ($p < 0.05$). Pregabalin + Epalrestat and Pregabalin management for a time span of 3 and 6 months produced a decrease in CRP from baseline of 8.308 ± 0.29 to 6.23 ± 0.22 in 3 months and 3.9 ± 0.09 in 6 months with Pregabalin + Epalrestat and the lessening in CRP by pregabalin from baseline of 7.772 ± 0.331 to 6.342 ± 0.221 in 3 months and 5.11 ± 0.111 in 6 months. The decrease in CRP in the Pregabalin + Epalrestat treated patients compared to a particular baseline value was statistically significant ($p < 0.05$) (Fig. 3).

Effect of managements on VPT

Duloxetine + epalrestat treatment for a period of 3 and 6 months produced a difference from baseline of 30.4 ± 0.27 to 27.6 ± 0.22 in 3 months and 24.8 ± 0.12 in 6 months and with duloxetine from baseline of 29.2 ± 0.19 to 26.5 ± 0.16 on 3 months and 23.8 ± 0.13 in 6 months. Pregabalin + Epalrestat treatment for a period of 3 and 6 months produced the difference from baseline of 29.1 ± 0.481 to 26.6 ± 0.481 in 3 months and 24.8 ± 0.481 in 6 months and with pregabalin from baseline of 27.2 ± 0.21 to 25.1 ± 0.19 in 3 months and 24.6 ± 0.23 in 6 months. Comparative analysis of all groups on VPT has shown no statistically significant change (Fig. 4).

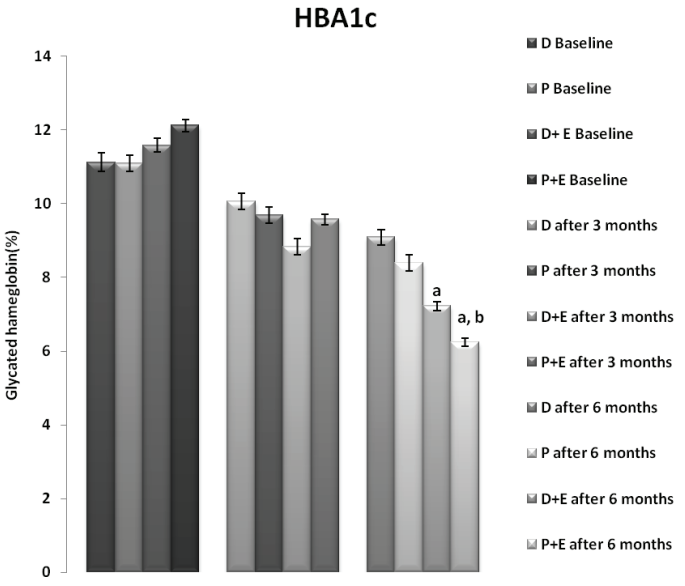


Figure 1. Effect of various treatments on HbA1c in Diabetic Neuropathic Patients.

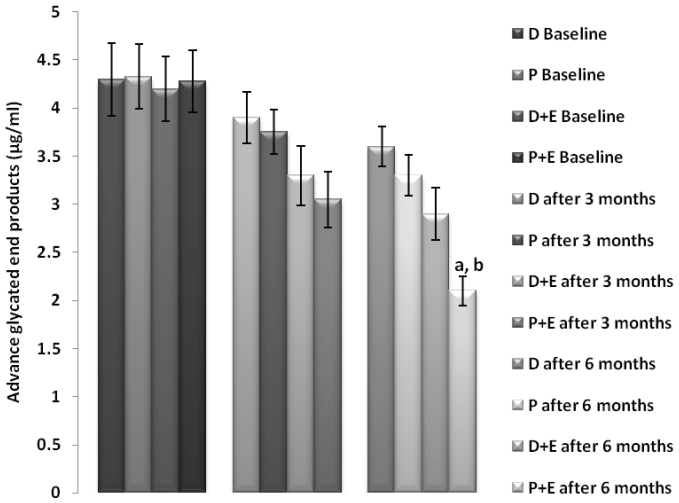


Figure 2. Effect of various treatments on AGEs in Diabetic Neuropathic Patients.

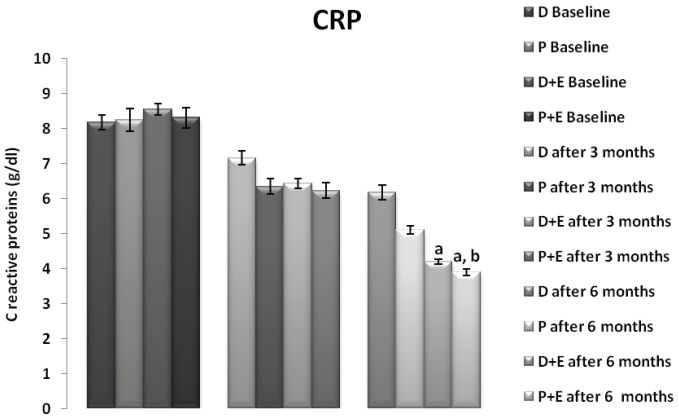


Figure 3. Effect of various treatments on CRP in Diabetic Neuropathic Patients.

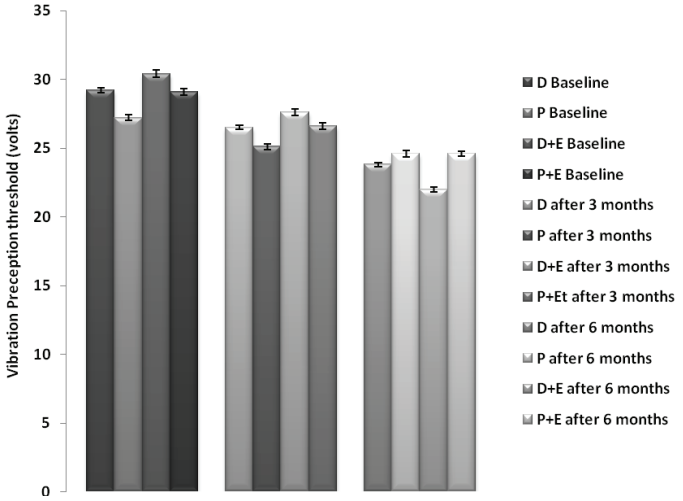


Figure 4. Effect of various treatments on VPT in Diabetic Neuropathic Patients.

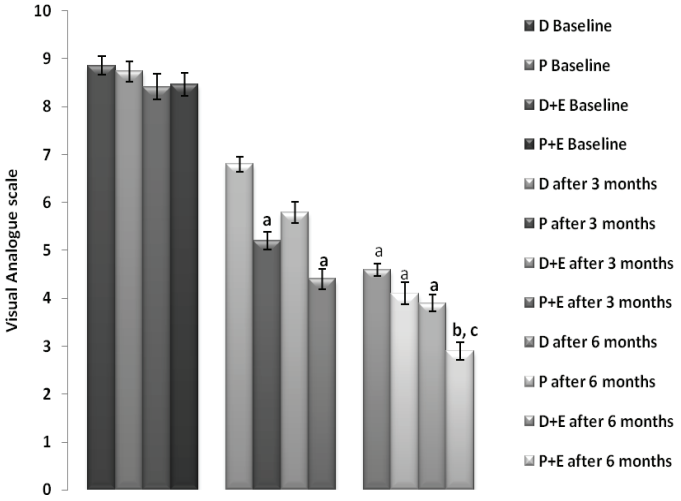


Figure 5. Effect of various treatments on VAS in Diabetic Neuropathic Patients.

Effect of managements on the VAS

Duloxetine + epalrestat management for a time span of 3 and 6 months produced the difference from baseline of 8.42 ± 0.27 to 5.08 ± 0.22 in 3 months and 3.9 ± 0.17 in 6 months and with Duloxetine from baseline of 8.86 ± 0.12 to 6.8 ± 0.16 in 3 months and 4.6 ± 0.13 in 6 months. The decrease in VAS score in the Duloxetine + epalrestat and duloxetine group compared to respective baseline values was statistically significant ($p < 0.5$). Pregabalin + Epalrestat treatment for a period of 3 and 6 months produced a difference from baseline of 8.46 ± 0.24 to 4.4 ± 0.21 in 3 months and 2.96 ± 0.18 in 6 months and with Pregabalin from baseline of 8.74 ± 0.21 to 5.2 ± 0.019 in 3 months and 4.1 ± 0.023 in 6 months. The lessening in VAS pain parameter in the pregabalin + epalrestat and pregabalin treated group compared to the relevant baseline value was statistically significant ($p < 0.05$; Fig. 5).

Effect on DN4 Q

Duloxetine + epalrestat management for a time span of 3 and 6 months produced the difference from baseline of 8.42 ± 0.27 to 4.1 ± 0.22 in 3 months and 2.9 ± 0.17 in 6 months and with Duloxetine from baseline of 7.8 ± 0.19 to 5.7 ± 0.016 in 3 months and 4.2 ± 0.13 in 6 months. The reduction in the DN4 score in the duloxetine + epalrestat group compared to the specific baseline values was statistically significant, i.e., $p < 0.05$. Pregabalin + Epalrestat treatment for a period of 3 and 6 months produced a difference from baseline of 8.32 ± 0.24 to 4.9 ± 0.21 in 3 months and 3.5 ± 0.018 in 6 months and with Pregabalin from baseline of 8.2 ± 0.021 to 4.66 ± 0.19 in 3 months and 3.4 ± 0.23 in 6 months. The reduction in the DN4 score in the pregabalin + epalrestat and pregabalin group equated to the respective baseline value was statistically significant ($p < 0.05$; Fig. 6).

Effect of treatments on TBARS

Duloxetine + epalrestat management for a period of 3 and 6 months produced the difference from baseline of 6.42 ± 0.172 to 4.2 ± 0.152 in 3 months and 3.6 ± 0.109 in 6 months and with Duloxetine from baseline of 6.54 ± 0.31 to 5.2 ± 0.25 on 3 months and 4.22 ± 0.23 in 6 months respectively. Pregabalin + Epalrestat treatment for a period of 3 and 6 months produced the

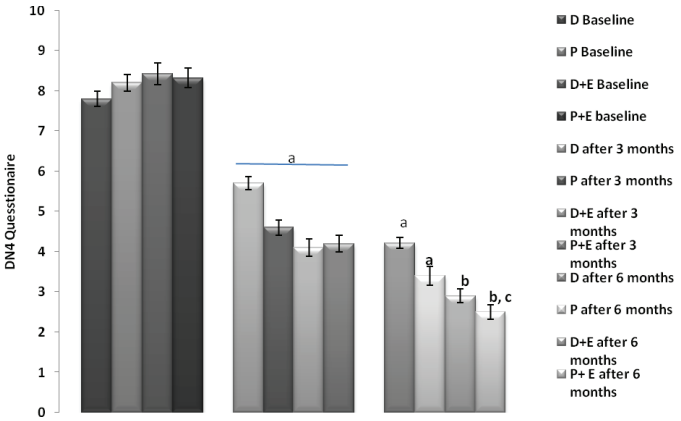


Figure 6. Effect of various treatments on DN4 Q in Diabetic Neuropathic Patients.

difference from baseline of 6.32 ± 0.172 to 3.9 ± 0.154 in 3 months and 2.7 ± 0.0993 in 6 months and with Pregabalin from baseline of 6.8 ± 0.28 to 5.66 ± 0.272 in 3 months and 4.12 ± 0.263 in 6 months. The decrease in TBARS in treatment groups equated to their individual baseline assessment was statistically significant ($p < 0.05$; Fig. 7).

Effect of treatments on SF 12 physical health score (PCS)

Duloxetine + epalrestat management for a phase of 6 months produced the difference from baseline of 37.54 ± 1.82 and 56.12 ± 2.2 in 6 months and with Duloxetine from baseline of 37.33 ± 1.9 to 53.22 ± 2.38 in 6 months. Pregabalin + Epalrestat treatment for a period of 6 months produced the difference from baseline of 38.23 ± 2.09 and 65.33 ± 2.46 in 6 months and with Pregabalin from baseline of 39.23 ± 1.33 to 58.57 ± 2.01 in 6 months. The reduction in PCS in the studied groups compared to the respective baseline value was statistically significant ($p < 0.05$; Fig. 8).

Effect of treatments on SF 12 mental health score (MCS)

Duloxetine + epalrestat management for a phase of 6 months showed the difference from baseline of 42.23 ± 1.92 and 61.12 ± 2.62 in 6 months and with Duloxetine from baseline of

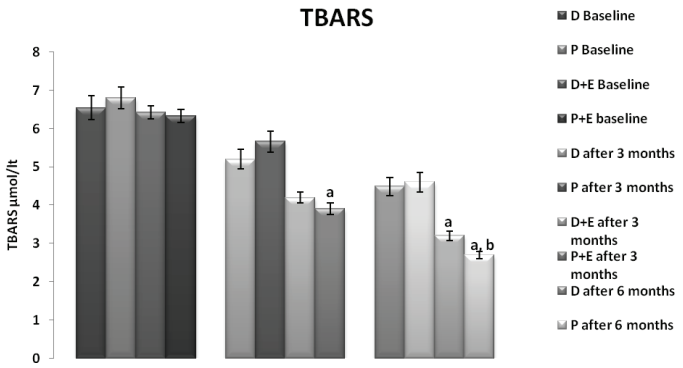


Figure 7. Effect of various treatments on TBARS in Diabetic Neuropathic Patients.

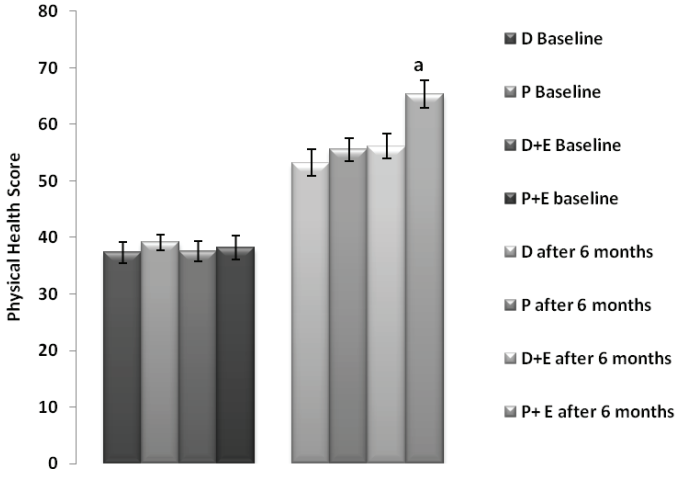


Figure 8. Effect of various treatments on PHS in in Diabetic Neuropathic Patients.

42.33 ± 1.55 to 63.32 ± 2.8 in 6 months. Pregabalin + Epalrestat treatment for a period of 6 months produced the difference from baseline of 44.13 ± 2.15 and 58.31 ± 2.59 in 6 months and with Pregabalin from baseline of 43.13 ± 1.56 to 58.57 ± 2.3 in 6 months. The decrease in MCS in both groups compared to their particular baseline assessment was statistically significant ($p < 0.05$; Fig. 9).

Cost-effectiveness

From the present study, the pharmacoeconomics evaluation shows that P + E treatment is cost-effective in comparison to the D + E treatment concerning for direct cost and incremental cost effective ratio (ICER). The ICER for P + E treatment works out to be 145.16 rupees (Tables 1 and 2), which means that it costs 145.16 rupees to generate each additional unit of health benefit gained in adding P + E to the existing medical regimen (percentage change in effect with P + E is 53.90% and 47.70% with D + E concerning for cost of treatment; Fig. 10).

DISCUSSION

Diabetic peripheral neuropathy directly affects the physical functioning of patients and become disabled. It is highly prevalent. Painful diabetic peripheral neuropathy is a challenging

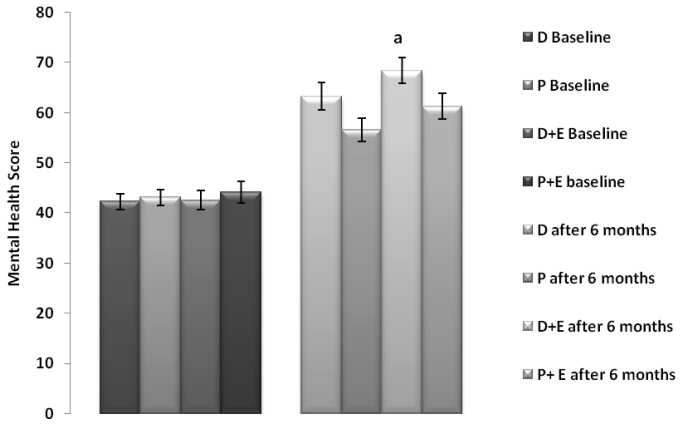


Figure 9. Effect of various treatments on MHS in Diabetic Neuropathic Patients.

Table 1. Incremental cost effective analysis in diabetic neuropathy patients.

Treatment	24 weeks cost per patient	ICER*/month
Pregabalin + Epalristat GpIII	5,670 Rs	145.16 Rs.
Duloxitene + Epalristat Gp IV	4,770 Rs	–

The average total cost of P + E versus D + E treated group for 24 weeks was found to be Indian Rs. 5,670 and 4,770, respectively.

neuropathic pain syndrome (Syed, 2011). Pain management is an essential component in the comprehensive care of diabetic patients. Neuropathy is frequently linked with important burning, stabbing, or tingling pain and numbness, and may show sleep interference, depression, anxiety, and severe disability as a consequence. In the present time, only glucose control and pain management like treatments are effective, but they do not prevent nerve degeneration (Pradhan *et al*., 2001). High levels of proof help the usage of evident anticonvulsants and antidepressants for the management of pain in diabetic peripheral neuropathy, opioid, topical agents, and α-2δ ligands. However, two drugs, Duloxetine and Pregabalin, have received specific FDA approval for the treatment of diabetic peripheral neuropathic pain (DPNP) (Ryle and Donaghy, 1995). In addition to epalrestat, the AGE inhibitor is a widely used drug in diabetic complications. Overall, it is assessed that diabetic peripheral neuropathy (DNP) progresses in 10%–20% of the diabetic population and may be found in 40%–60% with documented (Ferraz *et al*., 1990; Garrow and Boulton, 2006). One research revealed that approximately 12% of patients with DNP had not ever stated this disorder to their clinicians (Bouhassira *et al*., 2005). Glucose control decreases the progression of the disease. In 1993, the DCCT study group tracked over 1,400 subjects for 5 years and discovered a 60% lessening in the development of neuropathy in maintaining strict glycemic control. In a study for 3 months, the randomized, double-blind multicenter research evaluated the efficacy of Pregabalin in the management of painful diabetic neuropathy. A total of 246 men and women having painful diabetic neuropathy received Pregabalin (150 or 600 mg/day) or placebo. The results of the efficacy of drugs reported that Pregabalin 600 mg/days significantly decreased the mean pain score to 4.3 versus 5.6 for placebo. More patients receiving Pregabalin 600 mg/days showed an improvement, as rated on the

Table 2. Contribution of various parameters in direct medical cost in DPN.

S. No	Direct cost	Description	Average cost (duloxitene + epalristat) per patient	Description	Average cost in Rupee per patient (Pregabalin + Epalristat)
1	Cost of medicine	Duloxetine	525[a] Rs.	Pregabalin	675 Rs
		Epalristat	270[b] Rs.	Epalristat	270 Rs
		Oral Hypoglycemics	180.00[c] Rs.	Oral Hypoglycemics	180 Rs
		Other drugs	155.44[d.] Rs.	Other drugs	155.44 Rs
2	Monitoring cost	Lab	83.33[e] Rs.	Monitoring cost	83.33Rs
3	Consultation Charges	Doctor consultation	5[f] Rs.	Doctor consultation	5 Rs
Total cost			1,135.44		1,280.44

Average cost of treatment for 1 month has been shown in Indian Rs.
[a]Average cost of duloxitene per patient.
[b]Average cost of epalristat per patient.
[c]Average cost of oral hypoglycemic agents.
[d]Average cost other adjuvant drugs like PPIs & multivitamins.
[e]Average lab parameters cost during 3 phases of study per patient.

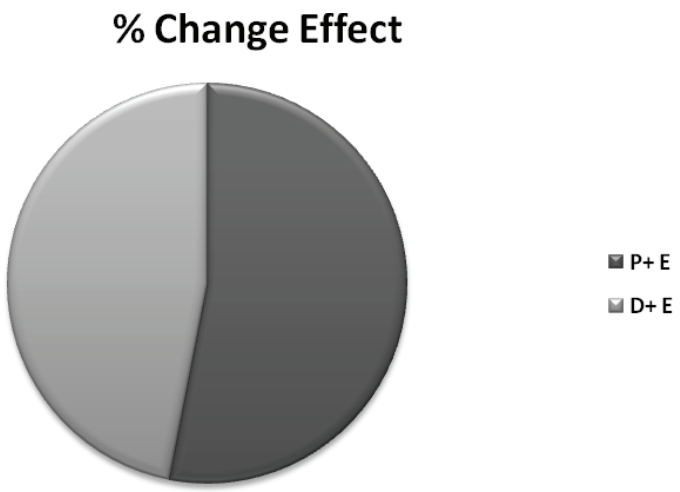


Figure 10. Percentage change in effect with P+E and D+E with respect to cost of treatment in Diabetic Neuropathic Patients.

Clinical and Patient Global Impression of Change Scales, 73% vsversus 45%, 85% vsversus 47%, than placebo respectively. The study results showed that Pregabalin 600 mg/days was safe and effective in reducing the pain and other associated symptoms of painful diabetic neuropathy (Kitto *et al*., 1992). Duloxetine 60 mg/days proved statistically significantly larger progress compared with placebo on the pain score, through the 12-weeks trial. Duloxetine at 60 mg/days and 120 mg/days was safe and efficient in the treatment of diabetic peripheral neuropathic pain (Callaghan *et al*., 2012; Detsky and Naglie, 1990; Sundaram *et al*., 2007). Data collected from six clinical trials were assessed, and it was observed that Epalrestat 50 mg 3 times/days may enhance subjective neuropathy symptoms and motor and sensory nerve conduction velocity (Charles et al., 2006) Some studies have shown that Pregabalin, Epalrestat, and Duloxetine as individual drugs were used to show the clinically significant decrease in pain earlier (Daousi *et al*., 2004; Richter *et al*., 2005). However, uptil now, there has been no research which directly compares the effect of Duloxetine, Pregabalin, and Epalrestat in the case of DPN. The present study was conducted to compare the efficacy and safety of two drugs, i.e., Duloxetine and Pregabalin with the combination of Epalrestat on neuropathic pain in diabetic patients which was the double-blind clinical study to prevent biased results. The Double-Blind Clinical Study is a clinical trial in which the subjects and the researchers were not knowing which active medication, treatment, etc., they are receiving and which subjects were not receiving: it is one of the methods for excluding subjective bias from the test results. The finest and most dependable form of research is double-blind. The purpose of this type of study is to eradicate the power of suggestion (Goldstein *et al*., 2005; Raskin *et al*., 2005; Ramirez and Borja, 2008). The double-blind study retains both doctors and participants in the dark as to who is receiving which treatment. The double-blind procedure is a method of enhancing internal validity in an experiment. The outcome of the present study revealed a significant decrease in pain score, HbA1c, CRP, AGE, TBARS, and SF 12 score with the combination of Pregabalin + Epalrestat and Duloxetine + Epalrestat in comparison to duloxetine and pregabalin alone. This reflects that when epalrestat was given in combination with pregabalin and duloxetine, there is a greater reduction in pain, HbA1c, inflammation, AGEs, and SF12 score with glycemic control in patients with DPNP. The combination of pregabalin + epalrestat is cost-effective in comparison to duloxetine + epalrestat and showed better therapeutic results. Epalrestat, in hyperglycemia, reduces intracellular sorbitol accumulation by an uncompetitive aldose reductase inhibition, reducing the progression of symptoms, which shows that Epalrestat is more efficacious when used in combination with oral hypoglycemic agents. Pregabalin interacts with α-2δ subunit of voltage-gated calcium channels in the presynaptic neurons and reduces the entry of calcium causing a drop in the release of many excitatory neurotransmitters, i.e., Glutamate, Substance P, CGRP, and Noradrenaline, leads to the reduction of the pain intensity and Duloxetine works by inhibiting serotonin and norepinephrine reuptake which works as inhibitors for pain impulses transmission (Lesser *et al*., 2004; Rosenstock *et al*., 2004). The probable intention for better efficacy of Epalrestat is because of its lowering of intracellular sorbitol accumulation. The adverse effects were observed in 6% (3/50) of patients in the group treated with Pregabalin and 8% (4/50) of patients in the groups treated with Duloxetine. Patients taking Pregabalin therapy faced dizziness with 10 % (n = 5), dry mouth with 5 % (n= 1), weight gain was combated in two patient 4 % (n = 2). In the Duloxetine treated

group, two patients experienced somnolence 6 % (n = 3), dry mouth 5 % (n = 1), constipation was encountered in one patient (5%), and nausea observed in two patients (4%). In the epalrestat treated group, two patients experienced g.i.t discomfort 5% (n = 1), nausea, and vomiting 10 % (n = 5). In the present study, to assess the safety of Pregabalin, Duloxetine, and Epalrestat, evaluation of biochemical parameters disclosed no significant changes in the patients. However, in the duloxetine-treated group, a minor decrease in blood pressure and heart rate was detected, but it was of no significance. All other safety parameters, namely, serum creatinine, total leucocyte count, hemoglobin, differential leucocytes count, erythrocyte sedimentation rate, aspartate aminotransferase, and alanine aminotransferase, did not indicate any significant change.

The drug therapies were discovered to be well tolerated. Any major adverse effects were not observed throughout the course of the research in the treated groups, i.e., during the 6-month duration. Pregabalin showed minor side effects like dry mouth, dizziness, and weight gain, whereas Duloxetine reported dry mouth, nausea, constipation, and gastrointestinal tract discomfort with Epalrestat. Based on the results obtained in the present study, it has been determined that duloxetine and pregabalin are efficient in the decrease of DPN but pregabalin is more potent and efficacious in decreasing neuropathic pain probably by restraining the release of neurotransmitters concerned in transmission of the pain signal. Pregabalin + Epalrestat showed a major reduction in the VAS and DN4 Q as compared to Duloxetine + Epalrestat. Epalrestat was able to hinder the progression of neuropathy and stops further nerve degeneration with strict glycemic control. Pharmacoeconomic evaluation revealed that the combination of Pregabalin + Epalrestat is cost-effective in comparison to Duloxetine + epalrestat and showed better therapeutic results. Hence, we can conclude from this current study that Pregabalin + Epalrestat treatment has enhanced effectiveness intended for decreasing neuropathic pain than Duloxetine + epalrestat with strict glycemic control.

CONCLUSION

From the present study, it is concluded that the treatment with Pregabalin + Epalrestat favorably contributes to the effective health benefits by inhibiting disease progression and fulfills the alternate goals of management of DPN. The results of the present study conclude that Pregabalin + Epalrestat treatment is more efficacious, cost-effective, and armamentarium for patients with DPN.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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