ORIGINAL ARTICLE

Comparison of efficacy and safety of pregabalin and duloxetine in patients with diabetic neuropathic pain: A double-blind clinical study

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Abstract

Introduction: Neuropathic pain is defined as a hypersensitivity to pain and spontaneous pain in involvement with damage to or a lesion of nervous system. Various drugs are recommended for treatment of diabetic peripheral neuropathic pain which includes norepinephrine and serotonin and reuptake inhibitors, namely duloxetine, α-2δ ligands, namely pregabalin and gabapentin, tricyclic antidepressants, and opioid derivatives. The present study was designed to compare the safety and efficacy of duloxetine and pregabalin in the patients with diabetic neuropathic pain. **Materials and Methods:** The study was a prospective, randomized, and double-blind study. The 100 patients were selected and divided into two groups, each group was having 50 patients. Group I was receiving 60 mg of duloxetine once daily (O.D) and Group II was receiving 150 mg of pregabalin O.D. for 12 weeks. The efficacy of the drugs in diabetic neuropathic patients was assessed using following parameters: Diabetic neuropathic 4 (DN4) pain questionnaire, C-reactive protein (CRP), visual analog scale (VAS), and vibration perception threshold (VPT). **Results:** In the present study, the patients obtained a better pain reduction in the group which was treated with pregabalin compared with duloxetine using VAS and DN4. However, there is no significant difference in VPT and CRP scores in both groups. **Conclusion:** Hence, the present study concluded that pregabalin therapy has better efficacy for reducing neuropathic pain than duloxetine.

Key words: Diabetic neuropathic pain, diabetic neuropathic 4 questionnaire, duloxetine, pregabalin, vibration perception threshold, visual analog scale

INTRODUCTION

Diabetes mellitus (DM) is a multifactorial disease characterized by insulin resistance and/or abnormal insulin secretion. DM clinically classified as having Type 1 DM (formerly known as insulin-dependent DM) or Type 2 DM (formerly known as non-insulin dependent DM).[1,2] Diabetes persisting for long-duration over years is associated with a variety of life-threatening complications among which cardiovascular disease, retinopathy, distal peripheral neuropathy (DPN), and nephropathy are most frequent.[3] Diabetic neuropathy is a family of nerve disorder manifeed clinically as a long-term complication of DM[4,5] and is significant source of morbidity and mortality.[6] In DM neuropathy is a multifactorial disease.[7] The possible etiologic factors that play a role include hyperglycemia, nonenzymatic glycation, polyol pathway, free radical, and oxidative stress. These various pathogenic factors act synergistically.[8] Diabetic neuropathy comprises change in peripheral nerves, central nervous, autonomic nerves system with diffuse, or focal degeneration.[9] Neuropathic pain is defined as a hypersensitivity to pain and spontaneous pain in association with damage to or a lesion of nerve system.[10] In describing neuropathic pain, patient uses word for both negative and positive sensation, burning, numb, tingling, searing or scalding, cold, crushing, shooting, and stabbing.[11] Various drugs are recommended for treatment of diabetic peripheral neuropathic pain (DPNP) which includes

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serotonin–norepinephrine reuptake inhibitors (SNRIs) (norepinephrine and serotonin reuptake inhibitors), namely duloxetine and venlafaxine and α-2δ ligands (modulate voltage-gated calcium channels), namely pregabalin and gabapentin and tricyclic antidepressants (inhibit reuptake of norepinephrine and serotonin), namely desipramine and amitriptyline and opioids (which block μ-receptors), namely tramadol, oxycodone, morphine, methadone, levorphanol, and hydromorphone. Some topical agents such as capsaicin and lidocaine are also used for treatment of diabetic neuropathic pain. Duloxetine, a balanced SNRI, is indicated for the treatment of neuropathic pain.[12] Duloxetine is a potent and balanced reuptake inhibitor of both norepinephrine and serotonin, in contrast to most other dual-reuptake inhibitors. After the oral administration, duloxetine is well absorbed and takes 4–6 h to achieve maximum plasma concentrations.[13] The protein binding of duloxetine is very high (>95%).[14] The elimination of duloxetine is approximately 12 h.[12] Duloxetine should be administered at a total dose of 40 mg/day (given as 20 mg BID) to 60 mg/day (given either once a day or as 30 mg BID). In a recent study, it has been shown that duloxetine used for relief of pain in patients with DPNP and also approved by the Food and Drug Administration (FDA) for treatment of DPNP at total dosages of 60 mg/day and 120 mg/day.[14]

Pregabalin is a selective, high-affinity ligand for the α-2δ subunit of voltage-gated calcium channels[15] and for modulating neuropathic pain pregabalin plays an important role,[16] by binding to the α-2δ subunit, thereby inhibiting calcium influx and decreases neurotransmitter release.[17] Pregabalin is reported to be effective in patients with painful DPN and animal models of neuropathic pain.[18] Pregabalin is well absorbed after oral administration, with bioavailability >90%. Pregabalin does not bind to plasma protein and is eliminated primarily through renal excretion and it does not undergo significant metabolism.[19] The most common adverse effect includes dizziness, weight gain, sleepiness, blurry vision, and dry mouth. Pregabalin has been studied in many randomized, double-blind, and placebo-controlled trials for the treatment of DPNP which have been found to be effective.[20,21] Pregabalin has been approved by the USFDA for treatment of DPNP.[22] However, there is no study which directly compares the effect of pregabalin and duloxetine in term of diabetic neuropathic pain. Therefore, in this study, we compare and evaluate the safety and efficacy of duloxetine and pregabalin in patients with diabetic neuropathic pain.

MATERIALS AND METHODS

Study Design

In this prospective randomized, double-blind study, 120 diabetic neuropathy patients (aged >18 years) were enrolled from an outpatient patient department at the Department of Medicine, Gian Sagar Medical College and Hospital. Eligible patients after screening were randomized into two groups in equal numbers to receive 12 weeks of treatment with duloxetine (D) (60 mg/day, $n = 50$) and pregabalin (P) (150 mg/ day, $n = 50$), as an adjunct to existing drugs, respectively. Patients who are suffering from pain due to bilateral peripheral neuropathy caused by Type 2 diabetes with the pain beginning in the feet and present for at least 6 months were included in the study and patients with uncontrolled hypertension, serious or unstable cardiovascular, hepatic (acute liver injury such as hepatitis or severe cirrhosis), kidney, respiratory, blood disorder, seizure disorder, problems with peripheral vascular disease, or other medical conditions or psychiatric conditions were excluded from the study. The study protocol was approved by the Regional Ethical Research Committee and was performed in accordance with the declaration of Helsinki and the code of Good Clinical Practice. All patients provided written informed consent to participate after a full explanation of the study. All groups advised to maintain a hypocaloric diet and increase their physical activity by walking briskly for 25–60 min daily for 12 weeks throughout the study and the patients were instructed often through personal contacts or phone calls to take their doses on proper time and do physical activity regularly. An initial evaluation of the vibration perception threshold (VPT), diabetic neuropathic pain questionnaire, visual analog scale (VAS), and C-reactive protein (CRP) parameters were done at baseline and after 12 weeks of therapy. All the data were collected and analyzed at scheduled clinical visits.

Safety and Tolerability

Safety assessment was monitored by physical examination, including vital signs (blood pressure (BP), body weight, and pulse rate) on each clinical scheduled visit hospital. Various hematological tests, namely hemoglobin, erythrocyte sedimentation rate (ESR), total leukocyte count (TLC), differential leukocyte count (DLC), and biochemical tests, namely serum creatinine, blood glucose, serum uric acid, serum alanine aminotransferase (ALT), and serum aspartate aminotransferase (AST) were carried out using standard methods to assess safety profile of the test results of drugs. Data from the laboratory tests, physical examination, and interview of the subjects for adverse effects were done for the analysis of drug tolerability and safety.

Statistical Analysis

In the study, the result obtained was subjected to statistical analysis for appropriate outcome. The data are expressed as mean ± standard error of the mean. The comparison of result data obtained for differences within the groups was performed using student's intergroup comparisons which were carried out using unpaired *t*-test and paired *t*-test for VPT and VAS. Chi-square test was applied to diabetic neuropathic 4 (DN4) score for assessing statistical significant difference. $P \leq 0.05$ was considered as statistically significant.

RESULTS

Effect of Treatments on Visual Analog Pain Scale (VAS)

Pregabalin treatment for a period of 12 weeks produced a reduction in pain score from baseline of 8.74 ± 0.23 to 5.20 ± 0.20 in 12 weeks, respectively. With duloxetine, the reduction in pain score observed was from 8.86 ± 0.20 to 6.80 ± 0.20 in 12 weeks [Figure 1]. The decrease in pain score in the pregabalin group compared to their respective baseline value was statistically significant ($P < 0.05$). The change in pain score in pregabalin treated group was more as compared to duloxetine and the difference was statistically significant between the pregabalin groups, respectively, to the treatment period [Figure 2].

Effect of Treatments on DN4 Pain Questionnaire

Duloxetine and pregabalin treatment for a period of 12 weeks produced a reduction in pain score from baseline 7.8 ± 0.21 to 5.7 ± 0.23 in 12 weeks with duloxetine and the reduction in pain score by pregabalin from baseline 8.20 ± 0.28 to 4.60 ± 0.26 in 12 weeks [Figure 3]. The decrease in pain score in the pregabalin group is statistically significant as compared to duloxetine group ($P < 0.05$).

Effect of Treatments on Creatinine Reactive Protein

Pregabalin and duloxetine treatment for a period of 12 weeks produced a reduction in pain by pregabalin from baseline of 8.24 ± 0.33 to 6.34 ± 0.11 in 12 weeks and by duloxetine from baseline 8.17 ± 0.20 to 7.16 ± 0.21 in 12 weeks. Results in both groups found statistically nonsignificant [Figure 4].

Effect of Treatments on VPT

Pregabalin and duloxetine treatment for a period of 12 weeks produced a reduction in pain by pregabalin from baseline of 27.2 ± 0.21 to 25.1 ± 0.23 in 12 weeks, respectively, and by duloxetine from baseline of 29.2 ± 0.19 to 26.5 ± 0.13 in 12 weeks, respectively, [Figure 3]. Results in both groups found statistically nonsignificant.

DISCUSSION

Neuropathy is often associated with significant burning, tingling pain or stabbing, numbness, and can result in sleep depression, interference, severe disability, and anxiety.[14] In comprehensive care, pain management is a crucial component for patients. Numerous studies have been conducted on painful diabetic peripheral neuropathy using various types of drugs such as antidepressants, opioids, topical agents, anticonvulsants, and α-2δ ligands. No agent has been found to attenuate the pain in patients. This undoubtedly, reflects that different mechanisms are involved in the propagation and development of neuropathic pain. However, two agents, pregabalin and duloxetine, have received specific FDA approval for the treatment of DPNP.[22]

However, there is no study which directly compares the effect of pregabalin and duloxetine in term of diabetic neuropathic

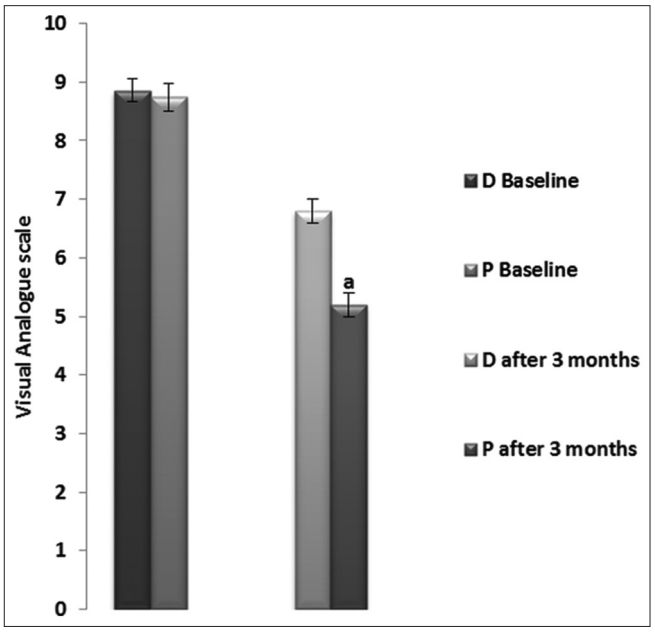

Figure 1: Effect of treatments on visual analog pain scale in diabetic neuropathic patients. Values are expressed as mean ± standard error of the mean. [a]$P < 0.05$ versus pregabalin baseline and duloxetine baseline

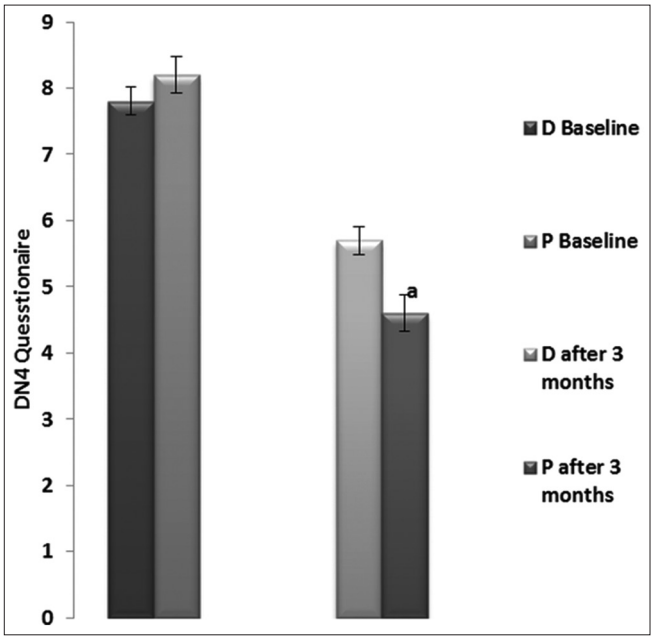

Figure 2: Effect of treatments on diabetic neuropathic four pain questionnaire in diabetic neuropathic patients. Values are expressed as mean ± standard error of the mean. [a]$P < 0.05$ versus P baseline and D baseline

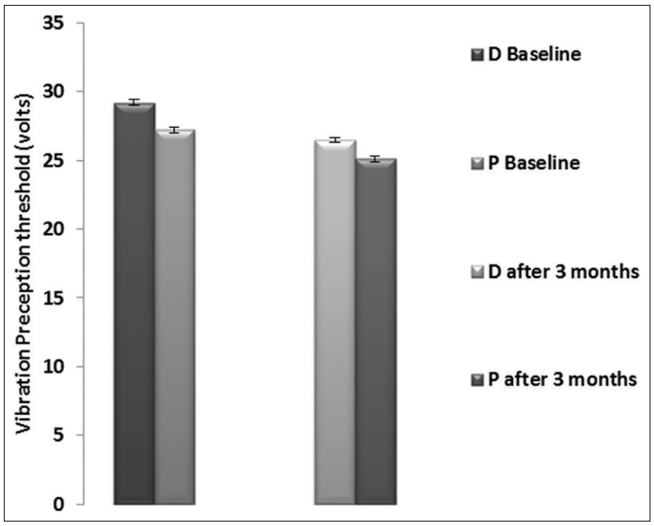

Figure 3: Effect of treatments on vibration perception threshold in diabetic neuropathic patients. Values are expressed as mean ± standard error of the mean

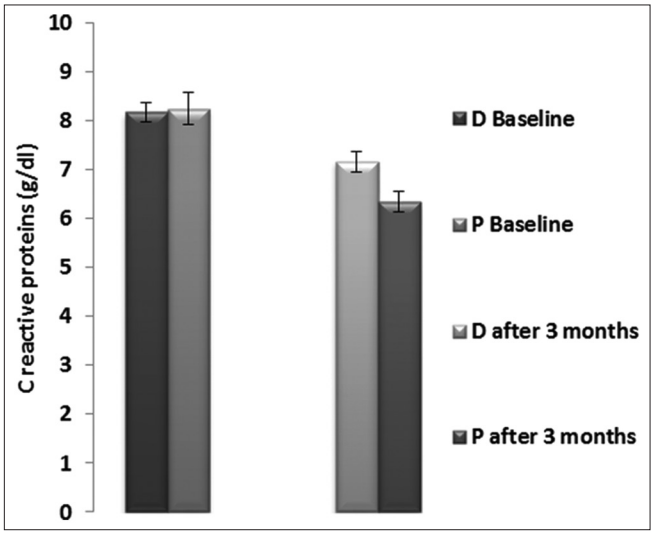

Figure 4: Effect of treatments on creatinine reactive protein in diabetic neuropathic patients. Values are expressed as mean ± standard error of the mean

pain. The present study was conducted to compare the safety and efficacy of two drugs, i.e., duloxetine and pregabalin, on neuropathic pain in diabetic patients. Duloxetine and pregabalin therapies individually have been reported to cause a statistically and clinically significant decrease in pain in diabetic neuropathic patients previously.[14] Duloxetine 60 mg/days demonstrated statistically significant that better improvement compared with placebo on the pain score, through the 12-week trial. Duloxetine at the dose of 60 and 120 mg/days was effective and safe in the management of DPNP.[14] A randomized controlled trial demonstrates that pregabalin, a new drug which interacts with the α-2δ protein subunit of the voltage-gated calcium channel, is a safe and efficacious treatment for the pain of this condition.[21] VAS used in the present study is a reliable measurement scale which is used commonly in health care research. It has been reported that an approximately 30% decrease in pain score is measured as clinically meaningful for an agent to be considered as effective in DPNP. This change in pain score is considered as good sign of a patient-determined, clinically essential response. On the other, more conservative, investigators have suggested that a 50% reduction in pain score corresponds to a clinically significant improvement. By either criterion, both pregabalin and duloxetine were found to be associated with significantly greater percentages of patients achieving a clinically meaningful response.[23] In the present study, the patients obtained a pain reduction in pregabalin treated group is statistically significant and nonsignificant duloxetine treated group using VAS. The diabetic neuropathic pain questionnaire method was used for assessing the change in pain score which is a validated instrument for assessment of the DPNP.[23] A reduction in the pain score assessed using DN4 pain questionnaire was also observed statistically significant in the pregabalin treated group, respectively, at the end of the study. These findings are consistent with earlier reports in which statistically and clinically significant decrease in pain score, i.e., >50% has been observed with these treatments.[14]

On the other hand, it also has been reported that diabetic neuropathy may also influence peripheral nerve leading to impairment of nerve sensation. To assess the effect of duloxetine and pregabalin on nerve function, vibration sensitivity in DPNP patients was evaluated. VPT was systematically assessed using sensitometer and it is the oldest,[24] most frequently and widely used cited device for quantitative assessment of vibration sensitivity in diabetic neuropathy.[25] In the present study, results observed from the VPT reflect that both of the drugs did not produce improvement of the sensation in the patients indicating both of the drugs could not generate any neuroprotection. This suggests that these two drugs are efficacious in decreasing the pain sensation with pregabalin being more efficacious. However, as far as nerve sensation is concerned, these two drugs were unable to improve nerve sensation. Thereby indicating that there is need to include agents which are able to prevent nerve degeneration and promote nerve regeneration which is ultimately improve nerve sensation. The agents that can be combined are vitamin B12, aldose reductase inhibitors, alpha-lipoic acid, and gamma linoleic acid, whereas there are no significant changes shown in the CRP. The results thus obtained in the present study reflect that pregabalin is more effective than duloxetine in lowering diabetic neuropathic pain and the reason for this may be that pregabalin interacts with α-2δ subunit of voltage-gated calcium channels in the presynaptic neurons and decreases the influx of calcium resulting in reduction of release of various excitatory neurotransmitters, i.e., glutamate, substance P, calcitonin gene-related peptide, and noradrenaline, thereby reducing the pain intensity whereas duloxetine acts by inhibiting the reuptake of serotonin and norepinephrine which act as inhibitors for transmission of pain impulses. The possible reason for better efficacy of pregabalin can be due to its property to inhibit the release of neurotransmitters responsible for pain signal transmission in synapse.

The adverse effects were observed in the 25% (12.50/50) of patients in the pregabalin treated group and in 30% (15/50) of patients in the duloxetine treated groups. Patients receiving pregabalin therapy experienced dizziness with 15% (n = 7.50), dry mouth with 5% (n = 2.50), and weight gain was encountered in two patients 5% (n = 2.50). In the duloxetine treated group, two patients experienced somnolence 10% (n = 5), dry mouth 5% (n = 2.5), constipation was encountered in 5% patients, and nausea observed in 10% patients. In the present study, to assess the safety of pregabalin and duloxetine, analyses of various biochemical parameters were done which revealed no significant changes in the patients. However, there was a significant reduction in uric acid levels in the duloxetine treatment group. However, in duloxitene treated group a slight decrease in BP and heart rate was observed, but it was not significant. All other safety parameters, namely TLC, serum creatinine, DLC, ESR, AST, ALT, and hemoglobin did not show any significant change. The present study confirms that both drugs are well tolerated as there was no withdrawal from the study.

CONCLUSION

Both duloxetine and pregabalin therapies were found to be well tolerated. There were no major adverse effects observed during the time of the study in both treated groups. From the results, it can be concluded that pregabalin and duloxetine are effective in reduction of diabetic neuropathic pain, but pregabalin is more potent and efficacious in reducing diabetic neuropathic pain possibly by inhibiting the release of neurotransmitters involved in pain signal transmission. Hence, from the results of the present study, it can be concluded that pregabalin therapy has better efficacy for reducing neuropathic pain than duloxetine.

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AUTHORS' CONTRIBUTIONS

Conceived and designed the experiments: RSJ and TGS. Performed the experiments: RSJ. Analyzed the data: RSJ, HKR, and TGS. Wrote the manuscript: RSJ and HKR. Critically reviewed the article: HKR and TGS.

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