

Original Research Article

Efficacy and safety of pregabalin versus amitriptyline in patients with painful diabetic neuropathy

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ABSTRACT

Background: Painful diabetic neuropathy is a common complication of long standing diabetes mellitus. Amitriptyline is commonly used to treat painful diabetic neuropathy. Pregabalin has been shown to be effective in the treatment of painful diabetic neuropathy with lesser adverse effects. Sustained release (SR) of pregabalin has the advantage of once daily dosing and a better patient compliance. Hence, this study was planned to compare the efficacy and safety of pregabalin-SR with amitriptyline in painful diabetic neuropathy.

Methods: It is a prospective, open labelled, randomized controlled study. A total of 80 patients diagnosed with painful diabetic neuropathy based on Diabetic neuropathy symptom score and Michigan neuropathy screening instrument, were randomized into two groups to receive amitriptyline and pregabalin SR. Amitriptyline was started at 25mg OD and pregabalin SR 75mg OD for 6 weeks with optional dose titration. Patients were assessed for pain relief by using visual analogue scale and an overall improvement in their general condition by patient's global impression of change scale. Adverse drug reactions were recorded on each follow up.

Results: All patients had significant improvement in pain relief in both the treatment groups. The median VAS (visual analogue scale) score was slightly higher in pregabalin SR group (25 vs 22) however it was not statistically significant. Intergroup comparison did not show any significant differences between the treatment groups. Good and moderate pain relief were noted in 37(92.5%) and 3(7.5%) patients on amitriptyline and 36 (90%) and 4 (10%) patients on pregabalin SR respectively. The common adverse effects reported in amitriptyline group were drowsiness (27.5%) and dry mouth (17.5%) and in pregabalin-SR group were drowsiness (15%) and dizziness (5%). No serious adverse event was reported in either of the groups.

Conclusions: In patients with painful diabetic neuropathy both amitriptyline and pregabalin-SR are equally effective in alleviating pain and improving the patient's general condition, but pregabalin-SR has the advantage of fewer adverse effects and convenient dosage timing.

Keywords: Amitriptyline, Painful diabetic neuropathy, Pregabalin

INTRODUCTION

Diabetic Neuropathy is one of the common micro vascular complications of diabetes affecting more than 50% of patients with long standing diabetes.¹ Among

patients with neuropathy, 11.6% with type-1 diabetes and 32.1% with type-2 diabetes mellitus have neuropathic pain. The rising prevalence of type-2 diabetes mellitus is more likely to increase the burden of this complication.² Diabetic neuropathy is defined as the presence of

symptoms and/or signs of peripheral nerve dysfunction in patients with diabetes, after exclusion of the other causes of neuropathy.³ Neuropathic pain frequently develops in some of these patients leading to Painful Diabetic Neuropathy (PDN).⁴ An acute (lasting < 12 months) and a chronic form of PDN have been recognised.⁵

The management of PDN includes adequate glycaemic control and drugs for pain relief.⁶ Several controlled studies have demonstrated that diabetic neuropathic pain can be relieved by antidepressants, anticonvulsants, tramadol, capsaicin, membrane stabilizers, analgesics and opioids.⁶ The use of these agents, however, is often limited by the occurrence of significant adverse effects, their dosing schedule and the delay in their onset of analgesic effect. Thus, a need is felt for safe, better tolerated and effective agents for the treatment of PDN.

The American diabetes association recommended amitriptyline, a tricyclic antidepressant (TCA), which acts by inhibiting the reuptake of norepinephrine (NE) and 5-hydroxytryptamine (5-HT) by their respective neurons, as the first choice; however, titration to higher doses is limited by its anticholinergic adverse effects.⁶ Amitriptyline does not have an approved labelling from the United States Food and Drug Administration (FDA) for its use in PDN. The American association of family physicians also recommends that unless contraindicated, TCA's can be used as the first line drugs for treating PDN.⁷

Pregabalin, an analogue of the neuro-transmitter Gamma-Amino-Butyric Acid (GABA) is an alpha-2-delta (α 2- δ) ligand and has analgesic, anticonvulsant and anxiolytic activity.⁸ Pregabalin has demonstrated efficacy in treating neuropathic pain and sleep interference associated with PDN.¹ It is approved by the US FDA and considered as one of the first line drugs for the treatment of PDN.¹

There are very few studies that compare the efficacy between pregabalin and amitriptyline for the management of PDN.¹ These studies show that pregabalin is a safe alternative for amitriptyline in the management of PDN; however, some of these studies were not controlled or had a small sample size. The sustained release of pregabalin has fewer sedative adverse effects compared to the pregabalin capsules and has the advantage of once daily dosing. Hence, this study was designed to compare the efficacy and safety of pregabalin SR with amitriptyline for the management of PDN.

METHODS

The study was conducted in patients with type-2 diabetes mellitus visiting the endocrinology out-patient department, of a tertiary care hospital in North India. The study was approved by the institutional ethics committee. This study was a prospective, open labelled and randomized controlled study having enrolled 80 patients diagnosed with PDN as per the patient's history and

clinical findings. Diabetic neuropathy symptom (DNS) score and physical assessment by using Michigan neuropathy screening instrument (MNSI) were used for the diagnosis.^{9,10} All patients underwent a thorough clinical workup including a detailed history, general physical and systemic examination. Patients who fulfilled the inclusion criteria were enrolled into the study group after obtaining a written informed consent.

Patients having a neuropathic pain score of >30 as assessed by the visual analogue scale (VAS) were included in the study. All these patients with type-2 diabetes mellitus as diagnosed with PDN as per the patient's history and DNS-score of >1 point, MNSI-score of >2 points were in the age group of 18-65 years. Patients taking medication for PDN in the last two weeks prior to enrolment, patients with other causes of neuropathy (Alcoholism, HIV and AIDS, chemotherapy etc), taking anticonvulsants, antidepressants or opioids, patients with clinically significant medical or psychiatric illnesses, known cases of renal dysfunction, chronic liver diseases, known cases of epilepsy, malignancy, uncontrolled hypertension, substance abuse were excluded from the study. Pregnant and lactating women were also excluded.

All patients were randomized into two groups using computer generated random numbers. One group of patients received amitriptyline 25mg/day, orally for six weeks, with dose escalation based on pain relief at weekly intervals to a maximum of 125mg/day. The other group patients received pregabalin-SR 75mg/day, orally for six weeks, with dose escalation based on pain relief at weekly intervals to a maximum of 300mg/day. Other rescue medications taken by the patients were recorded. Follow up was done after one week of treatment for dose escalation if there is no pain relief and then at 2, 4 and 6 weeks.

The primary end point of the study was the reduction in the median pain score from baseline as assessed by the visual analogue scale (0-100 mm) at the end of six weeks. A VAS showing reduction in median pain score of more than 50%, between 25-50% and below 25% was considered as good, moderate and mild responses respectively.

Secondary outcome measures included patient's self-evaluation of overall change on a 7-point patient global impression of change (PGIC) scale and changes in blood sugar levels at the baseline and at the end of six weeks. (Fasting blood sugar, Post prandial blood sugar). Adverse drug reactions were monitored on each follow up visit at 2, 4 and 6 weeks by adverse drug reaction checklist and by voluntary reporting.

Statistical analysis

The primary and secondary efficacy analyses were performed on the per-protocol population, defined as a

subset of the Intension to Treat (ITT) population who completed the study without any major protocol violations. Values are expressed as mean±standard error (SE), median with interquartile range (IQR) and numbers and as percentages. The primary endpoint for pain relief i.e median pain score reduction and secondary end point PGIC between two groups were compared by using Mann-Whitney U test, student t-test, for inter and intra group comparison of blood sugar levels, and chi-square test for incidence of adverse events. A 'p' value of <0.05 was considered as statistically significant.

RESULTS

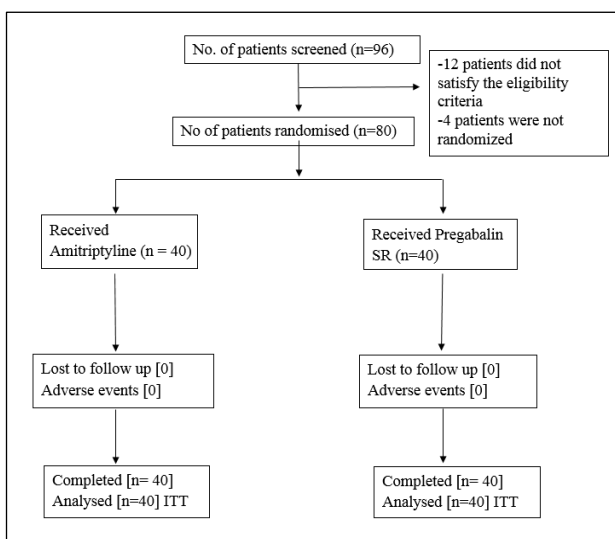
The demographic and baseline characteristics of study patients were similar between the two treatment groups as shown in Table 1.

Table 1: Baseline characteristics and demographic parameters (n=80).

Characteristics	Amitriptyline (40)	Pregabalin SR (40)
Age (years)	54.85±0.95	55.88±1.11
Sex (M:F)	16:24	17:23
VAS score	69(62-74)	65.5(60-72.75)
MNSI score	3.98±0.15	4.07±0.17
DNS score	1.5±0.095	1.4±0.093
FBS levels (mg/dl)	159.80±8.50	157.95±5.93
PPBS levels (mg/dl)	226.12±11.61	212.85±8.36
HbA1C (%)	7.78±0.24	7.42±0.18

VAS expressed as median with IQR (interquartile range) and all other values expressed as mean±SE (standard error); VAS - Visual Analogue Scale; MNSI - Michigan Neuropathy Screening Instrument; DNS - Diabetic Neuropathy Symptom; FBS - Fasting Blood Sugar; PPBS - Post Prandial Blood Sugar

Ninety six patients (96) were screened for the study and eighty were found to be eligible (Figure 1).



ITT – intention to treat analysis

Figure 1: CONSORT diagram.

These eighty patients were randomized to receive amitriptyline (n=40) and pregabalin SR (n=40).

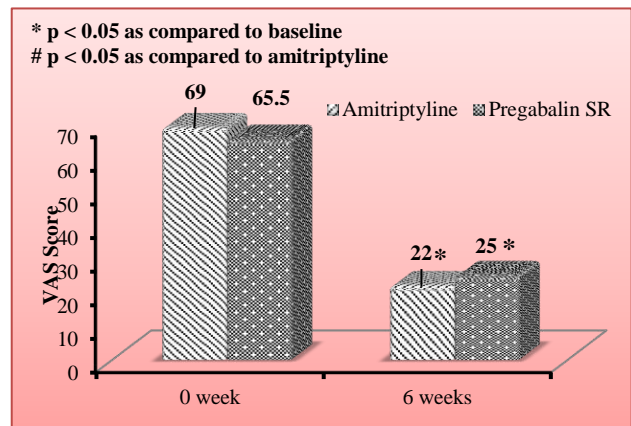


Figure 2: Pain scores at baseline and at the end of six weeks.

The two treatment groups, amitriptyline and pregabalin SR showed a significant reduction in median VAS for pain relief from baseline to six weeks (p<0.05) with no significant differences in between the two treatment groups (Figure 2).

The reduction in median pain score from baseline to 6 weeks was 68.12% with amitriptyline and 61.83% with pregabalin SR.

Out of 40 patients who received amitriptyline, 37 patients had a good pain relief of more than 50% and only 3 patients reported a moderate pain relief between 25- 50%. Similarly, out of 40 patients who received pregabalin SR, 36 patients had a good pain relief of more than 50% and 4 patients had a moderate pain relief of 25-50%. The analysis of secondary efficacy parameter with PGIC scale showed a good overall improvement in both the study groups (6 points in each group out of total 7) at the end of six weeks with no significant differences in between the two treatment groups.

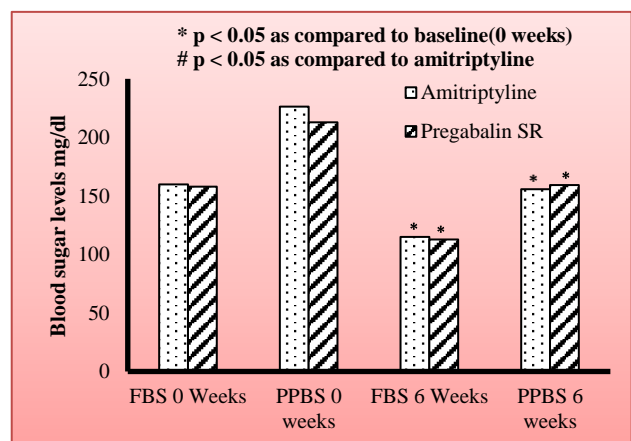


Figure 3: Fasting and post prandial blood sugar levels at baseline and at the end of six weeks.

The two study groups showed a significant reduction in the fasting and post prandial blood sugars from baseline to six weeks with no significant differences between the two groups as shown in Figure 3.

There were no serious adverse effects reported in either of the treatment groups (Table 2).

Table 2: Reported adverse events in the study.

Adverse events	Amitriptyline (40)	Pregabalin SR (40)	P value
Drowsiness	11 (27.5%)	6 (15%)	0.17
Dry mouth	7 (17.5%)	0	0.01*
Dizziness	0	2 (5%)	0.49
Constipation	2 (5%)	0	0.49
Headache	0	1 (2.5%)	>0.9

*p value significant (<0.05) Comparison made by Chi square test

In patients who received amitriptyline, 11 (27.5%) had complaints of drowsiness, 7 patients (17.5%) complained of dryness of mouth which was statistically significant and 2 patients (5%) complained of constipation. However, none of the patients were withdrawn from the study drug. Similarly, in pregabalin SR group, out of total 40 patients, 6 patients (15%) had complaints of drowsiness, 2 patients (5%) complained of dizziness and 1 patient (2.5%) complained of headache after taking pregabalin-SR. All adverse events were self-limiting and did not require withdrawal of treatment.

DISCUSSION

The results of present study indicate a female preponderance in both the treatment groups which is different from other studies which have reported a male predominance.^{1,10-12} This could be probably due to geographical variations or less pain threshold and emotional liability of females.

The evaluation of efficacy of the study drugs was based on pain relief at the end of 6 weeks. Patients, who received amitriptyline, had an expected pain score reduction and the pain relief was noted within 5-6 days after starting the treatment. Those patients who received pregabalin SR also showed a good pain score reduction which is comparable to that of the other studies and pain relief was reported even as early as 4 days from the day of starting treatment. Another recent study from India also reported that pregabalin has a much faster and better pain relief compared to gabapentin.¹² Few other placebo controlled studies conducted with pregabalin for a period of five and eight weeks have documented a significant reduction in pain compared to placebo (P<0.001).^{13,14}

The studies that evaluated amitriptyline for PDN have used amitriptyline in a dose of 10mg to 100mg per day.^{1,15-17} Certain guidelines suggest that amitriptyline can be started at 10mg and can be titrated up to 150mg at

bed time to treat PDN.¹⁸ We started amitriptyline 25mg HS (*hosa somni*: at bed time) and dose escalation was done according to patient's verbally reported pain relief. Only five patients needed a dose escalation and the dose was increased to 50mg HS. The maximum dose of amitriptyline used was 50mg. This is comparable and coincides with the similar studies conducted in India earlier and this also signifies that in Indian patients the dose needed for amitriptyline to treat PDN is 10-50 mg.^{1,15}

The studies that have evaluated the efficacy and safety of pregabalin for the treatment of PDN have used the plain pregabalin capsules and all these studies have concluded that the recommended dose of pregabalin for PDN is 300mg to 600mg per day in two or three divided doses.^{1,11-14,19} Authors used pregabalin sustained release preparation and started pregabalin SR at 75mg HS and according to the patients need the dose was titrated upwards. Only 11 patients needed a dose escalation up to 150mg. This is one of the main advantages of sustained release preparation that it has a once daily dosing schedule which may decrease the adverse effects and increase the patient compliance. Two other Indian studies have also used plain pregabalin capsules at a dose of 75-150mg per day to treat PDN and found to be efficacious.^{12,20} Another recent multicentre study conducted in India, with the sustained release of Pregabalin and methylcobalamin has also demonstrated that Pregabalin-SR (75-150 mg) has significantly reduced the neuropathic pain at a lower than recommended doses (150-600), in Indian patients, with an advantage of lesser adverse effects.²¹ This difference in dose is difficult to explain and may need further studies in larger number of patients. It is being reported from few recent studies that Indian patients, probably Asian's too need lower doses of Pregabalin, particularly when used as a sustained release formulation to achieve the therapeutic goal with lesser adverse effects.^{12,20,21}

Authors also evaluated the patient's self-evaluation of overall change after treatment by using PGIC scale. This scale assessed the patient's improvement in quality of life in different aspects like activity limitations, symptoms, emotions etc. Both the groups showed a higher response in patient's global impression of change which is reflected by the values in PGIC score indicating a better improvement from the patient's point of view following treatment. This is probably related to similar quantum of improvement in the pain parameter following treatment. Some of the earlier studies had also used clinician's global impression of change scale to assess the overall improvement of the patients. However, as pain is a subjective sensation and quality of life in such patients correlates well with the pain control, we considered using the PGIC scale for determining the overall treatment effect.

The proper management of PDN includes adequate glycaemic control and drugs to relieve the neuropathic

pain.¹⁵ So as a safety and as a secondary outcome measure we have evaluated the fasting and post prandial blood sugar levels to know the glycaemic control in these patients. The significant reductions of blood sugars in both the treatment groups must have definitely contributed to the good pain relief and an improvement in the quality of life. Without adequate control of blood sugars PDN cannot be treated properly over a long term period.

The safety and tolerability studies did not show any unusual or severe adverse events in our research study. The dose limiting adverse effects remain a major problem for patients' with neuropathic pain. The tolerability profile in this study was generally consistent with the previous studies.^{1,11-15,19,20} Patients who took amitriptyline reported mainly dry mouth and drowsiness and was more with patients who took 50mg HS. Very few patients who took pregabalin complained of drowsiness and only 2 patients out of 40 had complaints of dizziness. The reported number of adverse events was less with pregabalin SR in this study.

Regarding cost effectiveness, pregabalin SR 75/150mg once daily is much costlier than amitriptyline. So, for similar results amitriptyline is definitely more cost effective than the sustained release preparation of pregabalin or even the plain pregabalin capsules.

Several strengths and limitations of this study need to be highlighted. Authors have used the standard validated scales and scores for the diagnosis of PDN and for assessing the primary outcome measure pain relief. Authors have applied percentage reduction in the primary efficacy parameter to analyse the difference between the two groups. To the best of our knowledge, not many studies have used percentage reduction, which is more sensitive to less number of patients than the simple absolute values. There have been a few limitations in this study. This was an open label study without any blinding. The follow-up of patients was only for 6 weeks and therefore, the long term efficacy and safety of the study drugs could not be assessed.

Thus, in conclusion both amitriptyline and pregabalin SR are equally efficacious in relieving pain in PDN. Pregabalin SR has the advantage of once daily dosing over the pregabalin capsules and has fewer reported adverse effects and hence a better patient compliance on long term use. Amitriptyline is more cost effective than pregabalin SR which is an important factor to keep in mind while treating patients.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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