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A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF AMITRIPTYLINE AND PREGABALIN IN DIABETIC NEUROPATHY

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ABSTRACT

Objective: To compare amitriptyline and pregabalin in terms of efficacy and safety in diabetic peripheral neuropathy patients.

Methods: This prospective, open-label, non-randomised, comparative study conducted in Department of Neurology, KIMS Hospital, Hubballi, Karnataka, India from January 2018 to December 2018. 110 patients were alternately allocated to receive amitriptyline 10 mg once daily or pregabalin 75 mg once daily for 12 weeks. Pain intensity after taking medication was assessed by Visual Analogue Scale (VAS), while sleep interference score was used as a secondary efficacy parameter. Patients were assessed at baseline and at 4 weeks, 8 weeks, and 12 weeks and adverse drug reactions were monitored. Chi-square test, independent t-test and paired t- test were used as appropriate.

Results: Amitriptyline and pregabalin treatment groups showed significant reduction in VAS scores from baseline to 12 weeks ($p < 0.001$), with no significant difference between the groups. Sleep interference scores also improved significantly in both groups at all visits, but statistically significant superiority of either treatment was not seen. Drowsiness was the common adverse effect observed in both groups at early follow-up. Dry mouth and constipation were frequently reported with amitriptyline, whereas dizziness was common with pregabalin group. In the pregabalin group three patients discontinued treatment because of adverse effects.

Conclusion: Both groups showed significant reduction in pain intensity and sleep disturbance over 12 weeks with no statistically significant difference observed between the groups in the measured efficacy outcomes.

KEYWORDS: Diabetic neuropathy; Amitriptyline; Pregabalin; Visual Analogue Scale; Sleep interference score; Neuropathic pain.

INTRODUCTION

Diabetes mellitus can lead to various vascular and non-vascular complications. Among them, neuropathy is the most common microvascular complication [1]. Diabetic neuropathy (DN) is a dysfunction of the nervous system and significant proportion of individuals with diabetes are affected by it. It causes significant morbidity in patients suffering with diabetes resulting in a huge economic burden on patients [2]. Even though diabetic neuropathy has significant impact on quality of life, it remains largely underdiagnosed and patients remain unaware of their condition [3].

Diabetes results in multiple forms of nerve damage, it can be either central or peripheral or both [4]. Frequently diabetic neuropathy presents as bilateral, symmetrical symptoms that primarily affects the feet and progresses from distal to proximal, it is often described as a "stocking–glove" distribution [5]. It is characterized by pain that may present as burning, pricking and electric shock-like sensation and has a negative impact on patients' daily lives, particularly sleep and quality of life [6].

At present the underlying pathophysiological mechanisms are incompletely understood and no therapeutic interventions have been shown to reverse or restore impaired nerve function. Current management strategies are directed more towards symptomatic pain relief rather than disease modification [7]. Management of diabetic peripheral neuropathy mainly depends upon glycemic control and pharmacological pain management. Glycemic control alone will not be sufficient in relieving neuropathic pain [8]. Pain in diabetic peripheral neuropathy is pharmacologically managed using multiple therapeutic groups drugs, each of them showing different levels of effectiveness, adverse effects, and patient acceptability. Previous studies have shown that both antidepressant medications and anticonvulsant agents can provide symptomatic relief in patients suffering from painful DPN. Antiepileptic medications such as gabapentin and pregabalin are now widely used in the management of DPN [9]. In addition, many randomized controlled trials have demonstrated the efficacy of tricyclic antidepressants such as amitriptyline in painful DPN [10]. Therefore, the study evaluated the comparative efficacy and safety of amitriptyline and pregabalin in alleviating pain associated with diabetic peripheral neuropathy.

MATERIALS AND METHODS

Study Design, Study Setting and Duration

This is a prospective, open label, non-randomised comparative study conducted in the Department of Neurology at KIMS Hospital, Hubballi, Karnataka, India from January 2018 to December 2018.

Study population and Sample size

Patients aged 18–60 years diagnosed with diabetic peripheral neuropathy attending KIMS Hospital, Hubballi were considered. The sample size was calculated using prevalence of diabetic peripheral neuropathy of 19.1% reported by Ashok et al, in patients with type 2 diabetes mellitus from south India [11]. With 95% confidence level and absolute precision of 8%, the minimum sample size was 93. Considering drop outs and loss to follow up the sample size was increased to 110 and 55 participants were enrolled in each treatment group.

Inclusion criteria

i. All patients of age group 18-60 years, diagnosed with diabetic neuropathy
ii. Patients taking anti diabetic drugs or insulin for treatment of diabetes.
iii. Duration of pain for at least one month.
iv. Patients with pain score of at minimum 44 mm on the 100 mm visual analogue scale.
v. Patients agreeing to give consent for the study.

Exclusion criteria

i. Patients with neuropathies other than DPN.
ii. Patients with contraindications to study drugs.
iii. Patients with hepatic or renal dysfunction.
iv. Patients with recent cardiac or cerebral ischemic event.
v. Pregnant women.
vi. History of dependence on or abuse of alcohol/recreational drugs.
vii. Patients not willing to give consent.

Allocation and Intervention

Ethical clearance for the study was obtained from Institutional ethical committee, KIMS, Hubballi (IEC No KIMS/PGS/SYN/447/2017-18 dated 21/11/2017). 110 patients with physician-diagnosed diabetic neuropathy were enrolled in the study after considering inclusion and exclusion criteria and taking written informed consent. Participants were alternately assigned to amitriptyline or pregabalin group with 55 patients in each. Participants in amitriptyline group received amitriptyline 10 mg orally at night, once daily and patients in pregabalin group received pregabalin 75 mg orally at night, once daily. The investigators and participants knew the allocated treatment as this was an open-label study.

Data collection and follow-up

Data collection sheet which includes particulars of the patient, history, physical examination and relevant baseline investigations were filled for each patient. Patients were asked to follow up at 4, 8, and 12 weeks. At each follow up visit Visual Analogue Scale (VAS) was used to assess pain intensity and sleep interference was assessed using Sleep Interference Score and recorded in the data collection sheet. Adverse drug reactions, if any were documented at every visit.

Outcome measures

Assessment of pain: Visual analogue scale (VAS), a validated unidimensional scale, 10 cm (100 mm) in length, with two verbal descriptors “no pain” (score of 0) and “pain as bad as it could be” or “worst imaginable pain” (score of 100) describing extremes of pain was used. Patients marked the point on the scale that best represented their pain intensity. Score was interpreted as no pain (0-4 mm), mild pain (5-44 mm), moderate pain (45-74 mm), and severe pain (75-100 mm).

Assessment of sleep disturbance due to pain: sleep interference score was used to assess sleep disturbance due to pain. Patients were asked to rate the extent to which pain disturbed their sleep during the previous 24 h on an 11-point numerical rating scale ranging from 0 to 10 where 0 meant did not interfere with sleep and 10 meant completely interfered with sleep/unable to sleep due to pain.

Efficacy assessment

The efficacy of treatment was evaluated using the following outcome measures

- Primary measures of efficacy of treatment was decrease in pain as assessed by VAS.
- Secondary measure of efficacy was determined based on assessments of the Sleep interference score
- Safety assessment: By monitoring adverse effects reported by participants and those observed by the investigator during follow up visits safety was assessed throughout the study

Statistical analysis

Statistical analysis of the collected data was done using SPSS version 26. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test as appropriate. Continuous variables were shown as mean ± standard deviation. To compare mean of various baseline variables between the two study groups Independent sample t test was used. Intergroup comparisons of mean VAS scores and sleep interference scores at various time points were performed using Independent samples t-test and for comparison of VAS score and sleep interference score within groups paired t-test was used. A p-value below 0.05 was taken as statistically significant.

RESULTS

Participant flow and baseline characteristics

120 participants aged between 18–60 years were screened, inclusion and exclusion criteria were considered for eligibility. Of the 120 patients, 110 patients were eligible and gave consent to participate in the study. Study participants were alternately assigned to amitriptyline group (n=55) and pregabalin group (n=55). In the amitriptyline group, 3 patients were lost to follow-up but no patient discontinued treatment due to adverse effects, leaving 52 patients for final analysis. In the pregabalin group, 3 out of 55 patients discontinued the treatment because of adverse effects and 2 were lost to follow-up, resulting in 50 patients being included in the final analysis. (Fig.1)

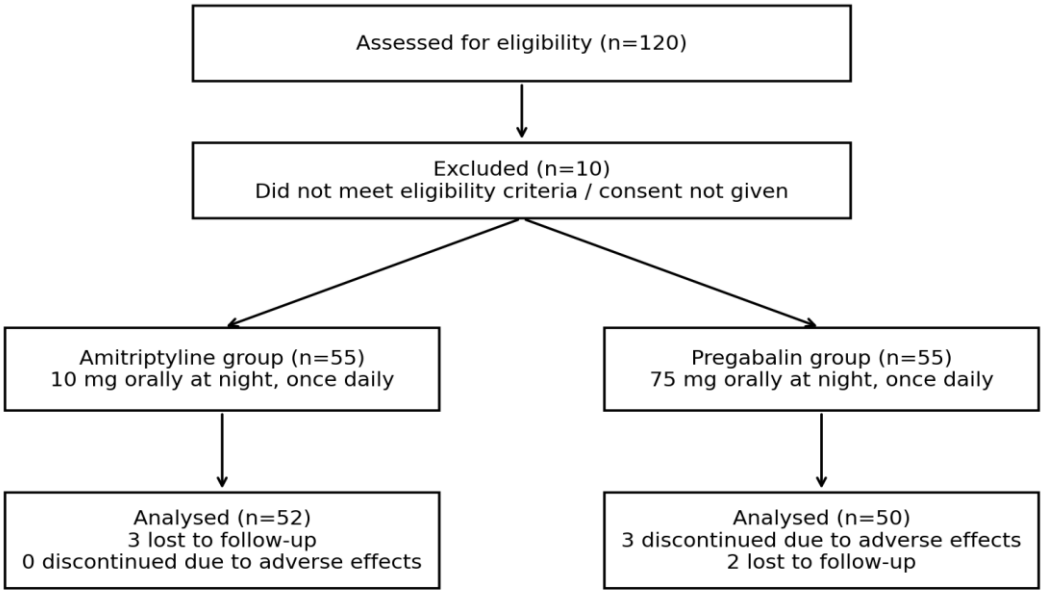


Fig. 1: Flow diagram of participant screening, alternate allocation, follow up and analysis

All baseline demographic characteristics and clinical characteristics between the two groups were generally comparable although the duration of diabetes tended to be higher in amitriptyline group showing borderline between-group difference ($p = 0.050$). Considering both groups together, the mean age of participants was 49.6 years, and 49 (44.5%) participants were female. In the study patients mean of duration of diabetes was 9.29 years and mean of duration of neuropathic symptoms was 7.95 months. The values are expressed as Mean ± SD or n, as appropriate (Table 1).

Table 1: Baseline characteristics of study participants

Variable	Amitriptyline (n=55)	Pregabalin (n=55)	p-value
Age (in years)	49.2 ± 7.38	49.93 ± 7.86	0.627
Gender (Male/Female)	34/21	27/28	—
Duration of diabetes (years)	10.09 ± 4.75	8.49 ± 3.66	0.050
Duration of symptoms (months)	8.76 ± 6.93	7.15 ± 4.10	0.139
RBS (mg/dL)	157.45 ± 17.25	160.62 ± 18.38	0.354
HbA1c (%)	5.79 ± 0.90	6.09 ± 1.07	0.105
Baseline VAS score	63.7 ± 11.6	63.9 ± 11.8	0.935
Baseline Sleep interference score	6.25 ± 1.28	6.00 ± 1.26	0.296

Values are mean±standard deviation or n. VAS: Visual analogue scale; HbA1c: Glycated haemoglobin

Efficacy outcomes

Pain assessment (VAS score)

The baseline VAS scores were comparable between the amitriptyline and pregabalin groups ($p = 0.94$). Over the follow up visits (4, 8, and 12 weeks) mean VAS scores progressively decreased in both groups. However, no statistically significant difference was observed in mean VAS scores between the two groups at baseline or at any of the follow-up visits ($p > 0.05$). (Table 2)

Table 2: Comparison of mean vas scores between the two treatment groups

Time	Amitriptyline	Pregabalin	p-value
Baseline	63.7 ± 11.6	63.9 ± 11.8	0.94
4 Weeks	46.9 ± 15.4	45.2 ± 14.2	0.54

8 Weeks	37.9 ± 14.0	34.8 ± 15.2	0.27
12 Weeks	30.8 ± 11.8	27.8 ± 13.4	0.21

Values are mean±standard deviation. VAS: Visual analogue scale

Within each treatment group, VAS scores showed a significant reduction from baseline at 4, 8, and 12 weeks ($p < 0.001$), indicating that both the drugs amitriptyline and pregabalin were effective in reducing pain in diabetic neuropathic patients with pain. (Table 3)

Table 3: Within group comparison of vas scores from baseline

Time from Baseline	Amitriptyline	Pregabalin
4 weeks	$t = 9.015$, $p < 0.001$*	$t = 11.145$, $p < 0.001$*
8 weeks	$t = 15.989$, $p < 0.001$*	$t = 13.368$, $p < 0.001$*
12 weeks	$t = 20.733$, $p < 0.001$*	$t = 18.842$, $p < 0.001$*

*P < 0.05. VAS: Visual analogue scale

Sleep interference score

The baseline sleep interference scores were comparable between the amitriptyline and pregabalin groups ($p = 0.30$). Progressively decreased mean sleep interference scores were observed in both groups during all follow up visits (4, 8, and 12 weeks). However, no statistically significant difference was observed in mean sleep interference scores between the two groups at baseline or at any follow-up visit ($p > 0.05$). (Table 4)

Table 4: Comparison of mean sleep interference scores between the two treatment groups

Time of sleep interference scoring	Amitriptyline	Pregabalin	p-value
Baseline	6.25 ± 1.28	6.00 ± 1.26	0.30
4 weeks	4.63 ± 1.88	4.64 ± 1.70	0.98
8 weeks	3.54 ± 1.67	3.32 ± 1.39	0.48
12 weeks	2.63 ± 1.53	2.20 ± 1.16	0.11

Values are mean±standard deviation

Within each treatment group, sleep interference scores showed a significant reduction ($p < 0.001$) from baseline at all the follow up visits 4, 8, and 12 weeks, indicating reduction in sleep interference due to pain with both amitriptyline and pregabalin. (Table 5)

Table 5: Within group comparison of changes in sleep interference scores from baseline

Time from Baseline	Amitriptyline	Pregabalin
4 weeks	$t = 7.882$; $p < 0.001$*	$t = 7.108$; $p < 0.001$*
8 weeks	$t = 16.322$; $p < 0.001$*	$t = 21.581$; $p < 0.001$*
12 weeks	$t = 19.300$; $p < 0.001$*	$t = 21.380$; $p < 0.001$*

*P<0.05

Adverse effects

Adverse effects were reported comparatively more during the initial follow-up period and decreased over subsequent visits in both treatment groups. Drowsiness was the common adverse effect reported during the initial treatment period in both the amitriptyline and pregabalin groups. In the amitriptyline group dry mouth and constipation were reported across all follow-up visits but their frequencies changed over time.

In the pregabalin group, dizziness was the commonly reported adverse effect at the later follow -up visits. Three patients in the pregabalin group discontinued treatment because of adverse effects before the 4-week follow-up, these adverse effects were included in the adverse-effect data for the initial treatment period. No treatment discontinuations due to adverse effects were observed in the amitriptyline group. There were no adverse effects reported as serious during the study period. (Table 6)

Table 6: Adverse effects observed at 4, 8, and 12 weeks in the amitriptyline and pregabalin groups

Adverse Effects	Amitriptyline 4 Weeks (%) (n=52)	Pregabalin upto 4 Weeks (%) (n=55)	Amitriptyline 8 Weeks (%) (n=52)	Pregabalin 8 Weeks (%)(n=50)	Amitriptyline 12 Weeks (%) (n=52)	Pregabalin 12 Weeks (%) (n=50)
Drowsiness	13 (25.0)	6 (10.9)	2 (3.8)	3 (6.0)	1 (1.9)	1 (2.0)
Dizziness	2 (3.8)	4 (7.3)	0 (0.0)	5 (10.0)	0 (0.0)	4 (8.0)
Somnolence	1 (1.9)	0 (0.0)	1 (1.9)	0 (0.0)	1 (1.9)	0 (0.0)
Weight gain	2 (3.8)	1 (1.8)	2 (3.8)	1 (2.0)	2 (3.8)	1 (2.0)
Dry mouth	6 (11.5)	0 (0.0)	5 (9.6)	0 (0.0)	4 (7.7)	0 (0.0)
Constipation	1 (1.9)	0 (0.0)	3 (5.8)	0 (0.0)	2 (3.8)	0 (0.0)
Edema	1 (1.9)	0 (0.0)	1 (1.9)	0 (0.0)	1 (1.9)	0 (0.0)
Lethargy	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea and vomiting	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages for the 4-week period were calculated using the number of patients who received treatment from baseline upto 4 weeks (n=55), including patients who discontinued before 4-week assessment due to adverse effects. Percentages at 8 and 12 weeks were calculated using the number of patients assessed at each respective follow-up visit.

DISCUSSION

The present comparative study was done on painful diabetic peripheral neuropathy patients to evaluate the efficacy and safety of Amitriptyline and pregabalin. Treatment response was assessed based on improvement in pain and sleep interference, as symptom relief is the primary therapeutic goal in these patients.

The demographic characteristics and clinical characteristics were comparable between the two study groups, except for a slightly longer duration of diabetes in the amitriptyline group. Most patients were between 51 and 60 years of age, supporting the well-established association between advancing age, longer duration of diabetes, and increased risk of diabetic neuropathy.

Both amitriptyline and pregabalin produced significant improvement in pain scores over the follow up period. However, there was no significant difference noted between the two treatment groups, suggesting that both drugs provide comparable efficacy in reduction of diabetic peripheral neuropathy pain.

These findings of improvement in pain are in concordance with Sankar V et al. [12] and Daniel S R et al. [13], who also reported that pain evaluation score of both Amitriptyline and Pregabalin showed equal responses in the patients receiving them. In contrast to this study, Soomro I A et al. [14] showed results wherein amitriptyline group had more effective alleviation of pain when compared with pregabalin group.

Both treatment groups demonstrated improvement in sleep interference during follow-up, with no evidence of superiority of either drug. Improvement in sleep is likely secondary to better control of neuropathic pain, although the sedative properties of both medications might have contributed. In contrast Boyle J et al.[15] reported that pregabalin significantly improved sleep efficiency and total sleep time while reducing waking up after sleep compared to Amitriptyline.

Adverse effects were reported in both the treatment groups all through the study. In pregabalin group three patients discontinued treatment due to of adverse effects, whereas no patients discontinued treatment in amitriptyline group due to adverse effects. Overall both drugs were generally well tolerated during the study period. The adverse effects observed in the present study were comparable to that of Bansal et al. [16] and Daniel S R et al. [13] where drowsiness was the predominant adverse effect with both amitriptyline and pregabalin. Amitriptyline was associated with a higher number of reported adverse effects, particularly drowsiness and dry mouth, whereas fewer adverse effects were reported with pregabalin.

Limitations of the study

- The study was an open label design. non-randomised, no titration protocol of drugs was used.
- Objective measures of assessment of pain and Nerve Conduction Studies were not employed.
- Safety was assessed by the incidence of adverse effects without considering the severity of the adverse effects.

CONCLUSION

In conclusion, the present study demonstrated that amitriptyline 10 mg once daily and pregabalin 75 mg, once daily showed significant reduction in pain intensity and sleep interference score over the study period in patients with painful diabetic peripheral neuropathy. No statistically significant difference was observed between the groups. Although adverse effects were more frequent with amitriptyline, both medications were generally well tolerated.

Authors' Contributions

All the authors equally contributed to designing, collecting the data and analysis of results and writing the study.

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Conflict Of Interest: None declared

Ethical Approval: The study was approved by the Institutional Ethics Committee, KIMS, Hubballi (IEC No KIMS/PGS/SYN/447/2017-18 dated 21/11/2017). Written informed consent was obtained from all participants.

AI Use Statement
The authors used ChatGPT and Paperpal for language editing, sentence clarity and grammar. The authors reviewed and take full responsibility for the final content.

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