Original Article

Efficacy of Lacosamide in Patients with Diabetic Neuropathy

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ABSTRACT

Objective: To compare the efficacy of lacosamide versus placebo in patients with diabetic neuropathy in terms of reduction of the mean pain score.

Methodology: This randomized controlled trial (RCT) was conducted at the Department of Medicine, Nishtar Hospital, Multan from April to August 2025. After informed written consent, 60 patients with diabetic neuropathy were included and their baseline pain levels at recruitment were assessed using the visual analogue scale (VAS). The patients were enrolled using non-probability convenience sampling technique and subsequently randomized equally through a lottery method. Randomization was used to assign patients to either group A (lacosamide) or group B (placebo). Participants were administered either lacosamide (LCM; brand name atcomid) or a placebo that contained microcrystalline cellulose, which was commercially available and widely used in clinical trials involving diabetics. Both placebo & lacosamide were started at 100 mg daily and escalated to 400 mg/day over four weeks. Both were maintained at 400 mg for 12 weeks. The VAS was used to measure baseline and post-treatment pain scores. The variables of age, gender, duration of diabetes, obesity (body mass index ≥30 kg/m^2), and diabetes control were documented. Statistical Package for the Social Sciences (SPSS) version 26 was used for the analysis of the data.

Results: The age distribution of the study population was statistically similar in the two groups (46.67±9.66 years vs. 49.30±8.38 years; p=0.264). Majority of the participants were males in both groups (66.7% vs. 56.7%). The baseline VAS values were almost similar across the groups (group A: 7.40±1.96 vs. group B: 6.87±2.01; p=0.31). The lacosamide group showed a notable decrease in post-treatment pain scores as compared to placebo (3.90±1.92 vs. 6.73±1.72; p <0.001).

Conclusion: Lacosamide provided a statistically and clinically significant reduction in pain intensity among patients with diabetic neuropathy compared to placebo. The marked decrease in post-treatment VAS scores highlighted its potential as an effective adjunctive option for managing neuropathic pain in this population.

Keywords: *Diabetic neuropathy. Diabetes mellitus. Small fiber neuropathy. Visual analog scale. Lacosamide.*

INTRODUCTION

A significant public health challenge of this century is Diabetes mellitus. Its extended duration leads to a multitude of macro and microvascular complications that impact nearly all organ systems.[1] One in five individuals diagnosed with diabetes experiences chronic diabetic painful neuropathy (DPN). Distal symmetric polyneuropathy, which represents 80-90% of diabetic neuropathies, involves both small and large fiber damage. It is typically characterized by sensory disturbances that begin in the feet, progress upward to the calves, and, in advanced stages, extend to the upper limbs.[2] Damage to large nerve fibers leads to paresthesia, sensory loss, and muscle weakness, whereas small fiber damage is linked to pain, anesthesia, foot ulcers, and autonomic dysfunction.[3] Painful diabetic peripheral neuropathy significantly reduces quality of life in individuals with diabetes and, if left unrecognized and untreated, increases morbidity and mortality through non-traumatic amputations. Neuropathic symptoms, however, may be minimized with proper blood glucose control, lifestyle modifications, dietary management, and regular follow-up.[4]

Pharmacological approaches to managing DPN encompass a range of options, including antiepileptics like pregabalin & gabapentin, opioids, selective serotonin reuptake inhibitors, norepinephrine reuptake inhibitors, and tricyclic antidepressants (TCA). However, it is essential to note that these treatments may not yield optimal results for all individuals.[5] Furthermore, certain medications may exhibit significant negative consequences when used over prolonged periods.[3]

Lacosamide (LCM) is a newly recognized antiepileptic drug that demonstrated analgesic and neuroprotective properties across various studies. It works by blocking voltage-gated sodium channels in a slow inactivating manner and is linked to side effects like nausea and dizziness. Research conducted within Western populations has shown that LCM effectively alleviates neuropathic pain and is generally well tolerated in cases of DPN.[6]

Many foreign studies have examined lacosamide in diabetic neuropathy. Due to variations in glycemic

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management patterns, comorbidity burden, and medication metabolism, the effectiveness and tolerance of lacosamide may differ among local and international populations. There is a paucity of local evidence on the effect of lacosamide in painful diabetic neuropathy, where diabetes is among the most common diseases, and neuropathic consequences cause significant morbidity. Thus, this study fills a significant gap by comparing lacosamide to a placebo in Pakistani patients to enhance local guidelines and improve patient outcomes.

METHODOLOGY

This randomized controlled trial was conducted at the Department of Medicine, Nishtar Hospital, Multan from April to August 2025. The study was approved by the institutional ethical board (Letter No. 3607/NMU, 10-03-2025) and registered with the Iranian Trial Registry (IRCT20250211064704N1; 21-05-2025). The sample size was calculated via OpenEpi software with 80% power, 95% confidence level, and based on mean post-treatment pain scores of 3.39±1.94 in the lacosamide group and 6.35±1.52 in the placebo group.[7] After informed written consent, 60 patients were included in the study and they were divided into two groups (30 in each). Male and female patients, aged between 20 to 60 years who had been diagnosed with diabetes mellitus for a minimum of five years and developed diabetic neuropathy were included. Patients were excluded if they had cardiovascular disease, renal impairment, elevated liver enzymes that were twice the normal range. Additionally, those receiving treatment with any painkiller like non-steroidal anti-inflammatory drugs, tramadol, TCA, mexiletine hydrochloride, lidocaine patch, or opioids were also excluded. Pregnant and breastfeeding mothers were also not included. The patients were enrolled using non-probability convenience sampling technique and subsequently randomized equally through a lottery method. A lottery employing sealed, opaque envelopes assigned patients to either group A (lacosamide) or group B (placebo).

Diabetic neuropathy was assessed clinically with history and physical examination for small and large fiber neuropathy. Age, gender, duration of diabetes, obesity (body mass index ≥30 kg/m^2), and diabetes control were documented. Diabetes control was evaluated by HbA1c results. HbA1c levels of all the patients were tested from the same laboratory. Patients exhibiting HbA1c values of 7% or lower had controlled diabetes, while those with values of more than 7% were classified as having uncontrolled diabetes. Participants were administered either lacosamide (LCM; brand name atcomid) or a placebo that contained microcrystalline cellulose, which was commercially available and widely used in clinical trials involving diabetics. Both placebo & lacosamide were given as oral tablets, starting from 100 mg/day during the first week and escalated to a maximum of 400 mg per day at the end of four weeks, with a weekly increase of 100 mg each week. After achieving the maximum dose of 400 mg/day as 200 mg BD (twice a day), the patients were maintained on this dosage for twelve weeks. Pain levels were assessed using the VAS at baseline and after a three-month treatment period with 400 mg/day dose. Pain scores ranged from 0 to 10 (0 as no pain, and 10 as extreme pain). In accordance with the established protocol, an evaluator, unaware of the treatment allocation, assessed the patients' pain levels at baseline and after the therapeutic intervention.

STATISTICAL ANALYSIS

The data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 26. The mean±standard deviations were presented for age, duration of diabetes, HbA1c level, and pain scores. The frequencies & percentages of gender, obesity, and both controlled & uncontrolled diabetes were documented. Categorical data were analyzed using the Chi-square test and an independent t-test was used to compare means of quantitative variables between two groups. Paired t-test was applied to compare mean pain scores at baseline and post-treatment (3 months) within the groups. A p-value of <0.05 was considered significant.

RESULTS

The mean age of patients was 46.67±9.66 years in group A and 49.30±8.38 years in group B, and most of the patients in both groups were more than 40 years old. The male demographic was more prevalent in both groups. The mean duration of diabetes mellitus in groups A and B was 22.90±13.08 years and 23.50±13.94 years, respectively. Less than half in both groups were obese (40% vs. 43.3%). However, both of the groups showed no statistically significant difference in terms of distributions of age, gender, obesity, and duration of diabetes mellitus. The two groups also showed no significant difference in terms of mean HbA1c levels (5.97±2.01% vs. 6.71±1.77%) (Table 1).

The baseline VAS values for pain were similar across the groups, with group A scoring 7.40±1.96

and group B scoring 6.87±2.01 (p=0.31). Group A experienced a significant decrease in pain score to 3.90±1.92, whereas group B exhibited no significant difference after treatment (p=0.736). A statistically significant difference in post-treatment scores was found between the study groups (p <0.001) (Table 2).

Regarding age, gender, obesity, and diabetes control, mean VAS score was significantly lower in Lacosamide group (p <0.001). The duration of diabetes did not significantly influence treatment response in terms of VAS improvement (p >0.05) (Table 3).

Table 1: Demographic and Baseline Characteristics of the Study Groups

Characteristics		Group A (Lacosamide) Frequency & Percentage	Group B (Placebo) Frequency & Percentage	p-value
Age Groups (Years)	**20-40**	9(30%)	5(16.7%)	0.22
	41-60	21(70%)	25(83.3%)	
Gender	**Male**	20(66.7%)	17(56.7%)	0.43
	Female	10(33.3%)	13(43.3%)	
Duration of Diabetes Mellitus (Years)	**≤10**	8(26.7%)	9(30%)	0.77
	>10	22(73.3%)	21(70%)	
Obesity	**Yes**	12(40%)	13(43.3%)	0.79
	No	18(60%)	17(56.7%)	
Diabetes Control	**Controlled**	20(66.7%)	14(46.7%)	0.12
	Un-Controlled	10(33.3%)	16(53.3%)	

Table 2: Baseline and Post-Treatment Pain Score of the Study Groups

VAS score	Group A (Lacosamide)	Group B (Placebo)	p-value
Baseline Pain Score (Mean±SD)	7.40±1.96	6.87±2.01	0.31
Post-Treatment Pain Score (Mean±SD)	3.90±1.92	6.73±1.72	<0.001*
p-value	0.001*	0.736	

**Significant p-value*

Table 3: Post-Stratification Analysis of Post-Treatment VAS Scores in Groups A & B

Variables		Group A (Lacosamide) Mean±SD	Group B (Placebo) Mean±SD	p-value
Age Groups (Years)	**20-40**	4.44±2.06	7.00±2.12	<0.001*
	41-60	3.67±1.85	6.68±1.68	<0.001*
Gender	**Male**	3.90±1.84	6.47±1.88	<0.001*
	Female	3.90±2.18	7.08±1.49	<0.001*
Duration of Diabetes Mellitus (Years)	**≤10**	4.00±1.69	3.86±2.03	0.77
	>10	6.44±1.81	6.86±1.71	0.36
Obesity	**Yes**	3.25±1.54	7.23±1.42	<0.001*
	No	4.33±2.05	6.35±1.86	0.0002*
Diabetes Control	**Controlled**	3.95±1.72	7.29±1.68	<0.001*
	Un-controlled	3.80±2.25	6.25±1.65	<0.001*

**Significant p-value*

DISCUSSION

In Pakistan, diabetes stands as the leading cause of peripheral neuropathy. The occurrence of peripheral neuropathy in individuals with diabetes in Pakistan exhibits considerable variation, with rates spanning from 16.30% to 79.50%.[8]

In our study, the mean age of the patients was 46.67±9.66 years in group A and 49.30±8.38 years in group B with a majority of males. A study reported that most of the patients with diabetic neuropathy were males (61.8%) and above 60 years old (85.6%).[9] Hussain et al. observed that age above 50 years was significantly associated with DNP.[8] A study conducted at Sheikh Zayed Hospital, Lahore, reported a 20% prevalence of DNP in patients aged ≥60 years, compared to 8.9% in those aged ≤35 years.[10] The majority of patients presenting with diabetic neuropathy had more than 10 years of duration since diagnosis, and the mean duration of diabetes mellitus in groups A and B was 22.90±13.08 and 23.50±13.94 years, respectively. Consistent with our findings, a nationwide study depicted that over 10 years after the diagnosis of diabetes was associated with painful DNP. Moreover, the presence of other co-morbid conditions like hypertension and ischemic heart disease was also related to the early development of diabetic neuropathy.[11] Bondar et al. also stated that DNP was the most prevalent microvascular complication in individuals with diabetes, affecting more than half of patients after 20 years of disease progression.[12]

Despite being on hypoglycemic medications, 43.3% of patients in the current study had uncontrolled diabetes, indicated by HbA1C levels above 7%. Previous literature emphasized that chronic hyperglycemia increased the risk of peripheral diabetic neuropathy.[13] Nozawa et al. also reported that higher 3-year mean HbA1c levels showed a significant association with the occurrence of DPN (adjusted odds ratio: 1.23; 95% CI: 1.06-1.42).[9] Another study observed that increasing HbA1c levels were significantly associated with the occurrence of DNP ($p < 0.05$).[11] Hepsen et al. found that even HbA1c levels of prediabetics showed a significant positive correlation ($r=0.188$, $p=0.014$) with VAS score.[14]

Despite the effectiveness of traditional treatments like pregabalin, duloxetine, or tricyclic antidepressants, neuropathic pain continued to be a considerable contributor to morbidity and disability.[13,15] When the mean post-treatment pain scores were evaluated, the lacosamide group exhibited a significant reduction in pain scores from 7.40±1.96 to 3.90±1.92 ($p < 0.001$), compared to the placebo group in our study. A study from Sindh, Pakistan reported that patients in the lacosamide group had a mean pre-trial pain score of 6.59±1.95, which declined to 3.39±1.94. In comparison, the placebo group showed a baseline score of 6.71±1.89, decreasing only to 6.35±1.52 after the 20-week maintenance phase ($p < 0.0001$).[7]

In a recent multicenter trial to study the effect of lacosamide on peripheral neuropathic pain, lacosamide reduced the pain intensity by up to 50% in patients with peripheral neuropathic pain.[16] In a meta-analysis, LCM was reported to be more effective than placebo in reducing the pain of DPN, but showed inferior efficacy when compared to 1st line drugs like duloxetine and pregabalin. However, it was more tolerable and had fewer side effects.[17] In a study conducted in Swat, Riaz et al. combined LCM with pregabalin and reported that the pregabalin group demonstrated a mean post-treatment score of 3.07±1.32, whereas the combination of pregabalin and lacosamide achieved a lower mean score of 2.30±1.16 ($p < 0.05$). Treatment effectiveness was observed in 58.2% of the pregabalin group compared to 80.6% in the combination group ($p < 0.05$).[18] In a recent study on the Indian population, Lacosamide significantly reduced pain (numeric rating score: 7.7 to 2.50) compared to pregabalin (7.6 to 4.27) ($p < 0.001$), indicating greater effectiveness. [19]

CONCLUSION

Lacosamide showed significantly higher efficacy in reducing pain intensity indicated by lower VAS scores among patients with diabetic neuropathy compared to placebo. When compared with placebo, lacosamide significantly lowered pain scores across age, gender, diabetes control, and obesity groups. The marked decrease in post-treatment VAS scores highlighted its potential as an effective adjunctive option for managing neuropathic pain in diabetic patients.

LIMITATIONS & RECOMMENDATIONS

Our study had a few limitations, including a single-centered study and a small sample size. Moreover, a fixed dose of lacosamide was studied. Further studies are recommended on lacosamide at various doses, with a special emphasis on its side effects and tolerability. Studies on combination treatments are also recommended for the future.

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Authors Contributions:
A.A: Conception of the idea and data collection
S.A.K: Data collection and analysis
U.A: Manuscript writing and proofreading

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