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ORIGINAL ARTICLE

Role of Lacosamide in Diabetic Neuropathy: An Experience at Tertiary Care Hospital in Rural Sindh

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ABSTRACT

Background: Lacosamide is a relatively newer drug for treatment of chronic diabetic painful neuropathy (CDPN).
Objective: To analyse the effectiveness and safety of lacosamide in patients with diabetic neuropathy.
Study Design: Randomized controlled clinical trial.
Duration and Place of Study: This study was conducted at department of neurology, Khairpur Medical College, Khairpur Mir's, during from the period Oct 2021 to March 2022.
Methodology: Ninety-two patients of either gender, age 20-60 years, known case of diabetes mellitus for minimally 5 years having pain intensity in the range of 4-9 on 11-point (0–10) numerical rating scale & HbA1c value 6.1%-10% were included and assigned randomly (Lacosamide = 46 & Placebo = 46) after taking a valid informed/ written consent. Lacosamide 400 mg/ day was given upto 20 weeks which initially increased from baseline at rate of 100 mg per week. The primary outcome variable was changes from baseline in average pain scores.
Results: The mean age of lacosamide group was 40.26±11.33 while in placebo group was 41.30±10.46 years. The mean Pretrial Pain Score measured on NRS of lacosamide group was 6.59±1.95 which decreased to 3.39±1.94 and in placebo group was 6.71±1.89 which decreased to 6.35±1.52 by the end of maintenance phase (20 weeks; p<0.0001). Adverse events (59%) of the patients experience adverse events at least for 1 time. Common side-effects included headache (11% vs. 31%), dizziness (09% vs. 11%), nausea (15% vs. 8%), and diarrhea (8% vs. 19%) with lacosamide and placebo group respectively each (p<0.0001).
Conclusion: Lacosamide is a safe and effective drug and achieved in pain relief and may be prescribed as routine treatment of chronic diabetic painful neuropathy.
Keywords: Diabetes mellitus, Pain, Chronic diabetic painful neuropathy, Lacosamide, Numerical rating scale

INTRODUCTION

Diabetes mellitus is a chronic disease, and its long duration leads to a variety of complications encompassing almost all systems of human physiology. Every third diabetic patient develops chronic diabetic painful neuropathy (CDPN). [1] This pain can be severe and long-lasting and is associated with a lack of sleep, fatigue, depression, and a reduced quality of life. CDPN is associated with small fibre neuropathy (SFN), which often manifests with intense burning pain in the peripheral limbs. This is a common symptom of long-standing diabetes mellitus and increases with the progress of the disease. [1,2]

Pharmacological agents used for managing CDPN include selective serotonin, tricyclic antidepressants, opioids, norepinephrine reuptake inhibitors, and antiepileptic drugs, but these agents are not effective for all patients. Besides, these agents have major side effects with prolonged use. [3,4]

The search for a new, more effective, and safer CDPN treatment agent is ongoing.Lacosamide is a new ray of hope in this regard. Lacosamide (LCM), a recently developed novel antiepileptic drug, has shown analgesic and neuroprotective effects in different studies. [5,6] Lacosamide, [(r)-2-acetamido-N-benzyl-3-methoxypropionamide], is a functionalized amino acid that is fully absorbed via the oral route and has no or low potential to inhibit or induce cytochrome P-450 (CYP-450) isoforms. Thus, it does not cause any drug interactions. [7] LCM has very minimal known side effects like nausea, dizziness, etc. Therefore, it is gaining much focus for the treatment of CDPN now that it is an effective and safe drug. [8,9]

Evidence from western population studies suggests that LCM reduced neuropathic pain and was well tolerated in diabetic patients.[10,11] Despite a very rapid surge in the prevalence of DM in Pakistan, there is no data available in the local population regarding the effectiveness of LCM yet.

This study has been conducted with the aim of focusing a cohort of local patients with chronic diabetic painful neuropathy to investigate the usefulness of lacosamide and to compare it with a placebo. The evidence generated through this study will help determine and manage the neurological pain symptoms in local diabetic patients and minimise related morbidity and mortality in them.

The purpose of this study is to estimate the change in pain intensity from baseline to the last week of locosamide treatment at a dose of 400 mg/day in patients with CDPN compared to a placebo.

MATERIALS AND METHODS

This randomized, single blind, placebo-controlled trial was conducted at the Neurology Department, KMC Khairpur Mir's. This study was performed after approval of ethical committee. The study was approved by the Ethical Review Committee. Total 92 participants [each group = (n1= 46 + n2= 46] was randomly included by enrolling chronic diabetics at the diabetes/ neurology OPD of KMC hospital. Patients of either gender, age 20-60 years, known case of DM for minimally 5 years were included. Patients had pain intensity in the range of 9-11 on 11-point (0–10) numerical rating scale. Patients were required to have had a fair glycemic control and HbA1c value 6.1%-10%

Cardiovascular disease, pregnant/ breastfeeding women were excluded from the trial. Any other underlying condition which could possibly lead to neuropathy including renal impairment, and liver functioning enzymes > twice of normal or those taking other medicine for pain (TCA, lidocaine patch, mexiletine hydrochloride, tramadol, opoids, AEDs and NSAIDS) were also excluded.

There were two groups; A & B. Group A received Lacosamide (LCM) while the group B received placebo. Allotment to groups however; was done randomly (through opaque envelope choosing). After completing one week run in period (in which no medicine was given), patients received Lacosamide 100 mg/ day which was increased upto 400 mg/ day (200 mg twice daily) gradually on 100 mg increase weekly basis. This dose was then maintained upto 20 weeks with a four weekly follow up for safety and efficacy assessment of patients. After completion of 20th week,

patient had the choice to terminate the treatment or enter the follow up week period. Controlled arm received placebo in place of LCM while the rest of treatment was same in the two groups. Safety variables included withdrawal due to adverse outcome, adverse events, vital sign measurements, clinical laboratory evaluation and neurological findings were also analysed.

Demographic data such as gender, age, residence were also collected. The primary outcome variable was changes from baseline in average pain scores. Numerical rating scale (11 point scale) was used for overall pain measurement. Global improvement was determined through Patient's Global Impression of Change scale which 7 point scale ranging from much better to worse.

Data were analyzed through SPSS version 25. Comparison of the two groups was made accordingly and tested through statistical tests. Effect modification was evaluated by Chi-square with P-value <0.05 as significant.

RESULTS

Twenty total patients were withdrawn from the study during first 3-4 weeks (16 from placebo group and 4 from lacosamide group). At the end of the maintenance period there were 42 and 30 participants in treatment (lacosamide) and placebo group respectively. In between some participants left the trial due to side effects or other reasons. The Extension Period of the trial was undertaken on 28 participants out of which 4 discontinued.

The mean age of lacosamide group was 40.26±11.33 while in placebo group was 41.30±10.46 years. The mean Pretrial Pain Score measured on Numerical Rating Scale of Lacosamide group was 6.59±1.95 while in placebo group was 6.71±1.89. Lacosamide 400 mg/d was administered to treatment group for up to 120 days. Both the groups were matching regarding gender distribution. Overall; there were more males and those from rural areas in both groups.

Reduction in pain scores with use of lacosamide was the primary outcome variable. It was noted that lacosamide had effect by the end of 1st week with 100mg/d dose. 2-point reduction in pain score was noted in lacosamide group as compared to placebo group.

Pin free days were also higher in lacosamide group (18.1%) in contrast to placebo group (7.5%). Thirty-two percent patients of lacosamide group used analgesics whereas 59% of placebo group used pain killers.

Participants also noted their improved general well-being, sleep, and daily life activity besides a >80% pain relief in lacosamide group in contrast to placebo group (20%). On global perspectives, ratings were more favourable for lacosamide.

Table 1: Flow of the study

Phase	Intervention/ Rx specification	End result	Group		Remarks
			Lacosamide	Placebo	
Enrolment [N = 92; n_1= 46 (Lacosamide) + n_2 = 46 (Placebo)]			46	46	
Run in Period(46+46)	One week; no medicine	Started with	46	46	
		Discontinued	-	-	
		Completed	46	46	
Titration Period (46+46)	(Lacosamide 100mg/ day increasing 100mg/ every week till 4th week (400mg)	Started with	46	46	Adverse events (n = 01) Pain (n = 06)
		Discontinued	02	05	
		Completed	44	41	
Maintenance Period (44+41)	Lacosamide 400mg maintained upto 20 weeks	Started with	44	41	Other reasons (n = 03) Pain; Loss to Follow up (n = 10)
		Discontinued	02	11	
		Completed	42	30	
Extension Period of the trial (25 + NA)	Lacosamide 400mg maintained upto one year	Started with	28		Discontinued (n 4)
		Discontinued	04		
		Completed	24		

With continuation as Extension Period; twenty four participant patients received lacosamide for at next six months (totalling one year) by trial termination time in March 2022. The mean exposure to lacosamide was 370.1±125.5 days. It was noted that, when optimal dose once started to use, patient remains on that dose which is 400mg/d. If not tolerated, then they left the study in maintenance phase.

Fifty-nine percent of the patient experienced atleast 1-treatment emergent adverse effect and its incidence rate was also higher in placebo group. The most common adverse events included headache (11% vs. 31%), dizziness (9% vs. 11%), nausea (15% vs. 8%), and diarrhea (8% vs. 19%) with lacosamide and placebo group respectively each. Adverse events associated to nervous system, GI tract and general disorders were not related to lacosamide group and frequency of adverse events was higher during titration period.

The effectiveness of lacosamide in neuropathic pain reduction was with all tested doses. Pain score from baseline to end maintenance phase was significantly reduced. CGIC also confirms that considerable reduction in pain score marked as "much better" from baseline to the end of the treatment.

Table 2: Baseline demographic characteristics (n= 92)

Characteristics	Lacosamide Group	Placebo Group
Age of patient	40.26±11.33	41.30±10.46
Diabetes mellitus duration (years)	10.80±3.84	9.70±3.63
BMI (Kg/$m^{2)}$	25.31±3.61	25.72±3.84
HbA1c (%)	9.10±1.435	9.23±1.433
Pretrial Pain Score (NRS)	6.59±1.95	6.71±1.89

Table 3: Other characteristics at time of inclusion (n= 92)

Variable	Lacosamide		Placebo	
	No.	%	No.	%
Gender				
Male	24	57.14	23	54.76
Female	18	42.86	19	45.24
Residence				
Urban	17	40.48	16	38.10
Rural	25	59.52	26	61.90
Comorbidity				
Hypertension	2	4.76	3	7.14
CVD	1	2.38	2	4.76
Asthma	4	9.52	2	4.76
Renal Disease	2	4.76	1	2.38
Liver Disease	1	2.38	1	2.38
Medicine History*				
Amitriptyline	4	9.52	5	11.90
AEDs	2	4.76	1	2.38
Dextromethorphan	4	9.52	4	9.52
Gabapentin	9	21.43	6	14.29
Opioids	4	9.52	6	14.29
Paracetamol	6	14.29	4	9.52
Tramadol	6	14.29	5	11.90

Table 4: Effect of other variables on IDA in Restless Leg Syndrome Patient

Phase of study	NRS pain score	Lacosamide			Placebo
		Nil	100 mg	400 mg	
Pre-trial	Mean ± SD	6.59±1.95	-	-	6.71±1.89
	No.	46	-	-	46
	P-value	<0.001	-	-	<0.001
Run in Period	Mean ± SD	6.65±1.91	-	-	6.67±1.80
	NO.	46	-	-	46
	P-value	<0.001	-	-	<0.001
Titration	Mean ± SD	-	5.77±1.37	-	6.70±1.82
	No.	-	44	-	41
	P-value	-	<0.001	-	<0.001
Maintenance	Mean ± SD	-	-	3.39±1.94	6.35±1.52
	No.	-	-	42	30
	P-value	-	-	<0.001	<0.001
Extension	Mean ± SD	-	-	3.14±1.88	-
	No.	-	-	24	-
	P-value	-	-	<0.001	

*IDA=Iron deficiency anemia

DISCUSSION

There is a rapid surge in prevalence of diabetes mellitus worldwide such that it is estimated that by the year 2030, about 366 million people will be living with the chronic disease. Prevalence of DM is

increasing very rapidly in our nation similarly - so are its complications. The chronic diabetic painful neuropathy (CDPN) is the most common and debilitating complication. Patients live in constant painful situation which worsen their daily life. Of many pharmacological options (TCAs, SSRIs, SNRIs Anti-arrhythmic, opioids and AEDs), the recent includes lacosamide with better results in controlling CDPN pain more than others.[2-5,12,13]

The current study was conducted to evaluate the effectiveness of lacosamide in reducing the neuropathic pain and its clinical comparison with placebo in local settings. The study found that lacosamide 400 mg/ day was effective for this purpose. A relatively early and significant reductions in pain scores began during the titration period and which further increased during maintenance and continuation phase till one year period.

The current study also noted that a higher proportion of patients experienced about 50% reductions in pain score and this effect was comparatively significantly much higher than the placebo group (<18%; p<0.001). Shaibani and coworkers[11] in their study found that over the treatment period (Titration + Maintenance), pain relief was significantly higher with lacosamide 400 mg than placebo (p value = 0.02). Similarly; other studies reported as much as 30-50% relief in neuropathic pain with Lacosamide.[1,14] Further; we did not find any significant pain relief with placebo effect which Shaibani and coworkers[11] claimed. Other studies also evaluated 200 and 600 mg/ day doses but found 400 mg more effective and safe. Rauck et al[15] found that lacosamide had significantly (i-e; 60% vs. 50% pain relief by 2-point decrease in pain score). The most common side effects were headache, dizziness and nausea. The mean pain reduction with lacosamide was 4.5±2.6 compared to 3.7±2.6 with placebo.

In a larger study conducted at more than fifty locations in Europe taking patients of Type 1 or Type 2 diabetes mellitus; Ziegler et al[16] found that lacosamide in dose of 400mg per day is the optimum in maximum reduction of pain however; the overall score in pain reduction was not statistically significant and was only −0.66 and −0.79 Numeric Pain Rating Scale points between placebo and the lacosamide 400 mg and 600 mg doses. Wymer et al[17] found at least 2 point pain relief in 58% of patients in the lacosamide 400 mg/d group compared with 46% of placebo group. Other doses of lacosamide 200 mg/d and 600 mg/d were found less effective or had higher side effects leading to withdrawal (40%). Some of the patients discontinued trial which was due to minor side effects or other reason however; the lacosamide was well tolerated. Minor side effects were like headaches, dizziness, nausea and diarrhea. Like previous trials from other populations, we did not find any serious adverse effect. Shaibani and coworkers[11] found higher withdrawal with 600 mg/day.

Shaibani et al[11] commented that in some of their patients who received concomitant tricyclic antidepressants, it is difficult to draw any conclusions regarding the changes in pain scale scores as they adjuvant received TCAs which might have their effect on pain reduction. They also found that difference of pain reduction score among those receiving lacosamide with TCAs and without TCAs resembled. We had stopped other medicine for pain during or before the run-in period. This might have been the reason of larger loss to follow-up in placebo group; though paracetamol was the option for them if they needed for pain. The lacosamide was not compared to any other competitor like anticonvulsants and TCAs. This may effect in underrating or overestimation of effect of the drug under study.

The current study also assessed the patients' satisfaction through Patient's Global Impression of Change (PGIC) and found that in parallel to NRS pain score; there was a relatively more feeling of better condition from pain among lacosamide group in the maintenance phase.

Overall this study is a local evidence of utility of lacosamide a newer pain reliving pharmacological agent among patients living with the chronic diabetic painful neuropathy. Current study however; had certain limitations. The loss to follow-up/ withdrawal and the overall length of trial should be taken into account cautiously before comparing this study results. Further; as the study was a single center study where majority of participants were from rural areas therefore; the results of this study may be referred carefully as might not be generalizable to other populations.

CONCLUSION

Lacosamide is a safe and effective drug that achieved better pain relief compared to a placebo among patients with chronic diabetic neuropathy. Lacosamide may be administered or suggested as a routine treatment option for patients suffering from diabetic neuropathic pain.

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