ORIGINAL ARTICLE

RANDOMIZED CONTROLLED CLINICAL TRIAL TO STUDY THE EFFECTS OF DULOXETINE ALONE AND IN COMBINATION WITH ALPHA-LIPOIC ACID ON SYMPTOMATIC IMPROVEMENT OF DIABETIC NEUROPATHY

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ABSTRACT

Objectives: To treat peripheral neuropathy in diabetic patients with minimum dose of duloxetine in combination with alpha lipoic acid avoiding the side effects associated with high dose of duloxetine

Methods: The study was conducted in the department of Medicine Lahore General Hospital, Lahore from November 2022 to April 2023. Sample size was calculated by using epi-info statistical package. Convenient sampling technique was used to enroll 240 patients, with distribution of 120 patients in each group. The patients included in the study with diabetes of more than 10 years of duration and HbA1C level < 8% having symptoms of numbness, paresthesia, tingling or burning sensation, pain and sensitivity to touch. The qualitative data was expressed as means and frequency distribution while the quantitative data was used to compare the means and standard deviations by using students T test.

Results: In group A, duloxetine alone was used in a dose of 30mg / day and the desired response compared between those who showed improvement in their symptoms and those who did not show any improvement. The calculated value of t came out to be t = 0.9161 and the p value = 0.3864 at 95% confidence level was not found statistically significant. In group B patients duloxetine 30mg / day along with lipoic acid 1200mg / day was used and the response between those who responded to treatment versus those who did not respond to treatment was compared and the calculated value of t = 2.6526 and the p value = 0.0291 at 95% confidence level was found statistically significant.

Conclusion: Duloxetine 30mg/day plus lipoic acid 1200mg/day can be used with significant improvement in numbness, paresthesia, tingling and burning sensation, hypersensitivity to touch and pain associated with peripheral neuropathy in diabetic patients. Combination therapy helps to avoid unpleasant side effects associated with high dose of duloxetine when used alone.

Key wards: Peripheral neuropathy, diabetes, duloxetine, lipoic acid

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INTRODUCTION

Diabetes mellitus is assuming the shape of monster as it is growing very fast in south east Asian countries especially in Pakistan. Diabetes is a chronic disease and the treatment continue lifelong. With increasing rates of essential drugs and cost of living, it is becoming increasingly difficult for the majority of the patients in developing countries to continue with standard of care for diabetes mellitus. Along with many other complications in diabetic patients, peripheral neuropathy (sensory, motor and autonomic neuropathy) is one of the most common problems. Around 10 – 14% patients face

peripheral neuropathy at the start of their illness while the vast majority, 50 – 60% develop the symptoms of peripheral neuropathy at around 10years from the start of their illness[1].

There are different ways to detect peripheral neuropathy. Most common and crude way of detecting peripheral neuropathy is monofilament test. The others are the use of DN4 Questionnaire, Visual analog score (VAS), vibrating tuning fork, neurothesiometer and NCS. The modern technique is cornel confocal microscopy (CCM).

There are different pharmacological and non-pharmacological treatment options are available to address peripheral neuropathy[2]. One of the first line treatment is SNRI (duloxetine) and tricyclic antidepressant (Amitriptyline). The second line treatment is the use of anti-epileptic drugs pregabalin and gabapentin. There are certain side effects associated with each of these drugs and these side effects become more pronounced with increasing dose of these drugs. Some of the most common side effects are headache, blurred vision, swelling of the hands and feet, xerostomia, seizures, sweating, allergy, effects on memory and weight gain. Intolerance / dropout of these drugs are due to the common side effects that intensifies as the required dose increases[3].

Some of the alternative medicines are increasingly being used along with the first line treatments including alpha lipoic acid (ALA), co enzyme Q, vitamin D3 supplement, capsaicin patch and Magnesium supplements with variable effects in improving the diabetic peripheral neuropathy. In this study we will add alpha lipoic acid in a dose of 1200 mg per day as an add on therapy to duloxetine which will be used in a dose of 30 mg per day[1,4].

METHODS

This randomized controlled clinical trial was conducted at Lahore General Hospital, Lahore in medical unit-III from November 2022 to April 2023. Sample size was calculated by using epi-info statistical package. Convenient sampling technique was used to enroll 240 patients, with distribution of 120 patients in each group. The patients included in the study with diabetes of more than 10 years of duration and HbA1C level < 8% along with the symptoms of numbness, paresthesia, tingling or burning sensation, pain and hypersensitivity to touch. DN4 questionnaire was used to assess the symptoms associated with neuropathy. 10mm nylon monofilament was used to assess the paresthesia, and to assess the vibration perception128–HZ tuning fork was used. Nerve conduction study (NCS) was used to quantify the severity and nature of sensory and motor neuropathy

RESULTS

In this study 240 patients were enrolled with 101 males (42%) and 139 female (58%) patients. The study group-A was given Duloxetine 30mg/day alone and in group-B, Duloxetine 30mg/day along with lipoic acid 1200mg/day were given. In group A, 50 patients were male and 70 were female patients. In group B, 51 were male and 69 were female patients. The patients enrolled in both groups were having the symptoms of numbness, pain, paresthesia, tingling and burning sensation and hypersensitivity to touch (Table-1).

Table-1 Symptoms Frequency

Symptoms	Male (101)	Female (139)
Numbness	71	119
Pain	87	127
Paresthesia	92	89
Tingling and burning sensation	78	102
Hypersensitivity to touch	32	41

Table -2 Diagnostic Tool used for the detection of Peripheral Neuropathy with their critical cut off values

Tolls	Scores indicating neuropathy	Scores indicating no significant neuropathy
Monofilament (Total score 10)	Perceived sensations < 8 points	Perceived sensations ≥ 8 points
128-HZ vibrating tuning fork	Perceived vibrations for ≤ 4 sec	Perceived vibrations for ≥ 5 sec
DN4 Questionnaire	4/10 score	>4/10 score
NCS	-Abnormality in nerve conduction velocity -Abnormality in action potential	-No abnormality in nerve conduction velocity -No abnormality in action potential

We have used the different tools to assess the peripheral neuropathy. The tolls that were used included monofilament test, 128-HZ tuning fork, DN4 questionnaire and nerve conduction study. The parameters and scoring system used are given in table 2. The grade of neuropathy was labeled as none (≥18 sec), mild (12-17 sec), moderate (5-11 sec) and severe (0-4 sec), based on the duration of vibrations perceived by the patient in seconds. Monofilament testing results stratified by mean vibration duration in 240 patients with diabetes and symptoms of peripheral neuropathy before and after the treatment applied in both groups were evaluated (Table-3) and the results showed (Table-4) that the patients in group B responded to treatment and the difference was statistically significant at 95% confidence level. It was observed that the patient who were given duloxetine and lipoic acid show more symptomatic improvement as evident by DN4 questionnaire responses done pre and post treatment along with improvement in the results of monofilament and mean vibration duration perceived by the patients.

Table-3 Monofilament testing results stratified by mean vibration perception duration and verified by NCS

Mean	Patients	Monofilament test +ve	NCS <30 m / sec	NCS 30-50 m / sec	NCS > 50 m /sec
0 - 4	154	74	26	93	0
5 - 11	28	61	13	37	21
12 - 17	31	28	1	23	9
≥ 18	27	24	0	7	10
	240	187	40	160	40

Table-4 Treatment Response in both groups after six months of therapy (based on DN4 Questionnaire score)

	Duloxetine 30mg/day		Duloxetine 30mg/day + Alpha lipoic acid 1200mg/day	
	Responded Patients	Non-Responded Patients	Responded patients	Non-Responded Patients
Numbness	79	41	87	21
Paresthesia	62	58	71	9
Pain	39	48	51	12
Tingling & burning	55	22	44	33
Hypersensitive to Touch	12	14	11	6

Table: 5 Treatment Response Statistical Analysis Based on Chi-Square Test

Symptoms	Responses	Duloxetine 30mg/day	Duloxetine 30mg/day + alpha lipoic acid 1200mg/day	p-value
Numbness	Responded to treatment	79 (87.37) [0.80]	87 (78.63) [0.89]	The chi-square statistic is 6.2228. The *p*-value is .012611. The result is significant at $p < .05$.
	Not responded to treatment	41 (32.63) [2.15]	21 (29.37) [2.38]	
Paresthesia	Responded to treatment	62 (79.80) [3.97]	71 (53.20) [5.96]	The chi-square statistic is 29.63. The *p*-value is < .00001. The result is significant at $p < .05$
	Not responded to treatment	58 (40.20) [7.88]	9 (26.80) [11.82]	
Pain	Responded to treatment	39 (52.20) [3.34]	51 (37.80) [4.61]	The chi-square statistic is 19.8686. The *p*-value is < .00001. The result is significant at $p < .05$.
	Not responded to treatment	48 (34.80) [5.01]	12 (25.20) [6.91]	
Tingling & Burning sensation	Responded to treatment	55 (49.50) [0.61]	44 (49.50) [0.61]	The chi-square statistic is 3.4222. The *p*-value is .064324. The result is *not* significant at $p < .05$.
	Not responded to treatment	22 (27.50) [1.10]	33 (27.50) [1.10]	
Hypersensitivity to touch	Responded to treatment	12 (13.91) [0.26]	11 (9.09) [0.40]	The chi-square statistic is 1.4221. The *p*-value is .233066. The result is *not* significant at $p < .05$.
	Not responded to treatment	14 (12.09) [0.30]	6 (7.91) [0.46]	

In group A, the patients with variable symptoms responded to treatment versus those not responded to treatment were compared by using the t-test and it was found that the two tailed p value equals to 0.3864 and by conventional criteria, this difference was considered to be not statistically significant at 95% confidence level p>0.05. (95% confidence interval from -19.42 to 45.02). Intermediate values used in calculations t = 0.9161, df = 238 and standard error of the difference =13.972. The statistical values calculated for group B patients, the parameters responded to treatment and not responded to treatment were compared by using the t-test and the two

tailed p value equals to 0.0291 and by conventional criteria this difference was considered statistically significant at 95% confidence level $p<0.05$. The calculated value of $t = 2.6526$ with degree freedom $df = 238$ at 95% confidence level. The man value compared between the responder and non-responder was 52.80 vs 18.20 with Sd 28.85 vs 10.94 and SEM 12.90 vs 4.89. Nineteen (19) patients in both the groups had diabetic foot with tuning fork vibration perception ≤ 4 seconds while the 2 patients in both the groups had diabetic foot with vibration perception ≥ 5 seconds. Chi-square test was used to compare the treatment response in both groups in all categories of symptoms by calculating the chi-square statistics keeping the p value < 0.05 as significant as shown in table 5. The difference between group A and Group B was found significant for Numbness, paresthesia and pain at 95% confidence interval with significance level of < 0.01 while no difference was found for tingling and burning sensation and hypersensitivity to touch between the groups.

DISCUSSION

In our study we compared the response of duloxetine in a dose of 30mg/day versus the duloxetine (30mg/day) along with lipoic acid to treat peripheral neuropathy in diabetic patients. Our aim was the use of lower therapeutic dose of duloxetine as compared to the other studies in which high dose of duloxetine 60mg once or twice a day was used with certain associated undesired able effects. We compared our study results with the results of other studies and found that the duloxetine and alpha lipoic acid have comparable effects as in our study but these agents are used separately in majority of the studies. We used them in combination with low dose of duloxetine to avoid adverse effects associated with high dose of duloxetine.

In a study conducted by Juan Jose Valenzuela-Fuenzalida "Effectiveness of Duloxetine versus other therapeutic modalities in patient with diabetic neuropathy pain: a systemic review and meta-analysis in 2024 pointed out that the duloxetine appears to be effective in relief of pain, peripheral neuropathy and other symptoms associated with peripheral neuropathy[5]. However, the difference in pain management on VAS was not found much difference between gabapentin and duloxetine. In this study duloxetine was used alone in a dose of 60mg/day and compared it with gabapentin.

In another study conducted by Gulzar HR in 2024 pointed out that there is no difference between the effects of duloxetine and pregabalin for the relief of pain in patients with peripheral neuropathy in patients with diabetic peripheral neuropathy. This study conducted in Islamabad and majority of the patients in this group was male patient[6].

In a study conducted by Ruey-Yu Hseih et all, in 2023, to study the effects of oral alpha lipoic acid treatment on diabetic polyneuropathy: meta-analysis and systematic review and found alpha lipoic acid as an effective treatment measure to control the symptoms of diabetic polyneuropathy. However, no improvement was appreciated when vibration perception threshold and nerve conduction study was checked[7].

In a study conducted by Han Na Jang in 2023 to study the effects of pharmacological and non-pharmacological treatments for painful diabetic peripheral neuropathy pointed out that when duloxetine combined with some non-pharmacological agents produced more favorable results compared to its usage as single agent[8].

CONCLUSION

Duloxetine 30mg/day plus lipoic acid 1200mg/day can be used with significant improvement in numbness, paresthesia, tingling and burning sensation, hypersensitivity to touch and pain associated with peripheral neuropathy in diabetic patients. Combination therapy helps to avoid unpleasant side effects associated with high dose of duloxetine when used alone.

ETHICAL APPROVAL

Ethical approval was granted by the Institutional Review Board of Postgraduate Medical Institute, Ameer-ud-Din Medical College, Lahore General Hospital, Lahore.

CONFLICT OF INTEREST:

Authors declare no conflict of interest.

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AUTHOR'S CONTRIBUTIONS

TS: Research and manuscript writing
SF, MM: Data analysis and critical intellectual input
MK, RA, UE: Data collection and drafting of the work
ALL AUTHORS: Approval of the final version of the manuscript to be published.

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