Amitriptyline, Pregabalin and Duloxetine for Treatment of Painful Diabetic Peripheral Neuropathy

Richa Nepal,[1] Manil Ratna Bajracharya,[1] Budda Bahadur Karki,[1] Dipak Mall,[1] Prajaya Shikhar Shrestha,[1] Kushal Prasad Wasti,[1] Anjal Bisht[1]

[1]Diabetes and Endocrine Unit, Department of Internal Medicine, National Academy of Medical Sciences, Bir Hospital, Kathmandu Nepal.

ABSTRACT

Background: Painful diabetic peripheral neuropathy is one of the frequent presenting complaints in diabetes and endocrine clinics. Our main objective was to compare effectiveness of three commonly prescribed drugs: amitriptyline, pregabalin and duloxetine for treatment of painful diabetic peripheral neuropathy.

Methods: This was a comparative, prospective, observational study conducted among 99 diabetic patients with painful diabetic peripheral neuropathy having numeric rating pain scale ≥ 4. Thirty-three patients in each group were consecutively prescribed amitriptyline, pregabalin and duloxetine in lower dose (10mg/75mg/20mg) for first two weeks to gradually up titrate to higher dose (25mg/150mg/30mg) as per pain response for total duration of eight weeks.

Results: At the end of eight weeks, 84.9% in amitriptyline, 78.7% in pregabalin and 60.6% in duloxetine group had adequate pain reduction in form of mild or no pain. Among total patients, 42.5% patients had severe pain at baseline that decreased to 5% by the end of our study. Out of three drugs, 45.5% patients in amitriptyline group had complete resolution of pain as compared to 24.2% in pregabalin and 18.2% in duloxetine group (p value 0.05). Drowsiness (42.4%), dizziness (21.2%) and dry mouth (21.2%) were the commonest side effects among total participants in our study.

Conclusions: Amitriptyline, pregabalin and duloxetine were all associated with adequate pain reduction among patients of painful diabetic peripheral neuropathy in our study, however, amitriptyline had more favorable findings with tolerable side effects.

Keywords: Amitriptyline; duloxetine; Nepal; painful diabetic peripheral neuropathy; pregabalin.

INTRODUCTION

Prevalence of painful diabetic peripheral neuropathy (PDPN) ranges from 10 to 70% across various studies globally.[1-3] The overall prevalence of diabetic peripheral neuropathy in studies done from Nepal ranges from 45% to 59%.[4-5] Persistent neuropathic pain has been associated with sleep loss, anxiety, depression and has a major negative impact on quality of life among patients with diabetes.[6] Pregabalin (PGB) and duloxetine (DLX) are two agents approved by American Diabetes Association for management of this painful condition.[7] Apart from them, amitriptyline (AMT) has been classically used for management of PDPN. AMT is cheaper than PGB or DLX, thus can be utilized as a forerunner for PDPN in low resource settings, provided the effectiveness is equivalent, if not superior to other two drugs and adverse effects are well tolerated.[8] This study aims to compare the effectiveness of above three drugs for reduction of pain scale of painful peripheral neuropathy among patients with diabetes.

METHODS

This was a comparative, prospective, observational study conducted in Diabetes and Endocrine unit of National Academy of Medical Sciences (NAMS), Bir Hospital. Data collection was done over the span of six months from

Correspondence: Dr Richa Nepal, Diabetes and Endocrine Unit, Department of Internal Medicine, National Academy of Medical Sciences, Bir Hospital, Kathmandu Nepal.
Email: nepaldeepika123@gmail.com, Phone: +9779860236283.

June, 2023 till November, 2023 after the study protocol was approved by Institutional Review Board of NAMS (IRB no. 846/2079/80). All patients of 30 years and above who presented to endocrine OPD during the study duration were screened for symptomatology of PDPN. If patients reported painful neuropathic symptoms for at least 4 weeks typical for PDPN, they were subjected to bilateral feet assessment and underwent four basic clinical tests of diabetic peripheral neuropathy (pin prick sensation, vibration test, 10-gram Semmes-Weinstein monofilament sensation and ankle reflex test).[9]

Structured proforma was filled and relevant clinical examination was done by the investigator. PDPN was diagnosed on basis of clinical history of diabetes with typical painful neuropathic pain suggestive of PDPN with or without signs of peripheral neuropathy.[10] Patients were asked to scale their pain in the 11-point Likert like numeric rating scale (NRS) from 0 to 10 with 0 being "no pain" and 10 being "worst pain possible'. Pain was categorized as mild for scores 1-3, moderate for scores 4-7 and severe for scores 8 to 10.[11] All consecutive diabetic patients of 30 years and above who were diagnosed to have PDPN of at least four weeks duration with NRS of ≥ 4 were included in our study. However, patients with recent glycated hemoglobin level ≥10%, pregnant and lactating females, patients with chronic kidney or chronic liver disease, patients under treatment with drugs that impair nerve function like antiepileptic, cytotoxic, anti-tubercular drugs and patients who had history of diabetic foot ulcers or amputations were excluded.

Using the following formula, sample size for each group of patients in our study was calculated as 33.

$$n = \frac{2(z_\alpha + z_\beta)^2 S^2}{d^2}$$ where

$z_\alpha = 1.96\ at\ 95\%\ confidence\ level$ and

$z_{\beta=1.28\ at\ 90\%\ power}$

Based on a study by Shahid et al[12], d = mean difference in numeric rating scale at 12 weeks between two groups = 4.91 - 4.01 = 0.9 and S =1.12 (larger standard deviation of NRS among two groups). Assuming similar for third group, equal sample was taken for each group. Thus, the sample size for each group of patients of painful diabetic peripheral neuropathy was calculated as 33 with the total sample being 99 for our study.

After obtaining informed written consent, study participants were allocated to receive one out of three drugs for treatment of PDPN consecutively. 1st study participant received amitriptyline, 2nd received pregabalin, 3rd study participant received duloxetine and the order continued till required sample size was met. AMT, PGB and DLX were started at the lower dose of 10mg, 75mg and 20mg per day. First follow up was done in the OPD at the end of 2 weeks and dose was titrated to 25mg, 150mg and 30mg per day for AMT, PGB and DLX for those who persisted to have moderate to severe pain. Lower dose was continued for those who reported mild pain or had complete resolution of pain at the end of two weeks. Second and final follow up was done at the end of 4 and 8 weeks respectively, either through OPD visit or telephone conversations by the investigator as per feasibility of the patient. NRS scores for PDPN and adverse effects were duly recorded during each follow up. Those patients who could not complete stipulated follow up were excluded from this study. Details regarding dose titration and follow up has been demonstrated in Figure 1. Response was considered to be adequate if pain severity decreased to the level of mild or no pain.

Data was collected in a structured proforma, transferred and analyzed in SPSS version 20. Descriptive statistics were calculated using frequency and percentage for qualitative variables, whereas mean and standard deviations (SD) were used for quantitative variables. Chi square and Fischer exact test were used to compare parametric qualitative variables. ANOVA was used to compare means of parametric quantitative variables whereas Kruskal Wallis test was used to compare medians of non-parametric quantitative variables. P value ≤ 0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics of the study population has been tabulated in Table 1. Mean age of patients in AMT group was slightly lower (52.6±10.5 years) as compared to PGB and DLX group (57.1±11.2 years, 60.8±11.5 years). Mean duration of diabetes and prevalence of proteinuria was also lower among AMT group (1.42±1.2, 42.4%) as compared to PGB (2±1.9, 63.6%) and DLX group (2.2±0.9, 60.6%). However, number of smokers were higher among AMT group (24.2%) as compared to PGB (15.2%) and DLX (18.1%). Number of patients who had past treatment for PDPN at least six months back were also higher in DLX group (21.2%) as compared to PGB (9%) and AMT group (6%).

Comparison of responses of reduction of pain severity by AMT, PGB and DLX has been tabulated in Table 2 and 3. Baseline pain scores were comparable in all three treatment groups with 57.6% patients reporting

moderate pain and 42.4% patients reporting severe pain in each treatment group. At the end of eight weeks, 84.9% in AMT, 78.7% in PGB and 60.6% in DLX group had adequate symptomatic benefit in terms of pain relief to mild or no pain. Out of total patients, 42.5% patients had severe pain at baseline that decreased to 5% by the end of our study.

By the end of eight weeks, 45.5% patients in AMT group had complete resolution of pain as compared to 24.2% in PGB and 18.2% in DLX group (p value 0.050). Though a smaller number of patients had complete pain resolution in PGB group, a greater number of patients had mild pain by end of study (54.5%) as compared to AMT (39.4%) and DLX (42.4%). More number of patients in DLX group had moderate pain (33.3%) at end of eight weeks in comparison to AMT (15.2%) and PGB (12.1%). Likewise, 6% patients in DLX group and 9% patients in PGB group had persistent severe pain by end of study as compared to no patients in AMT group (Table 2).

Among 84.8% patients in AMT group who had adequate pain reduction at the end of eight weeks, 54.5% received lower dose in comparison to 30.3% who received higher dose of AMT (p value 0.019). For those having adequate pain reduction at end of eight weeks in PGB group, 63.6% patients were on low dose PGB as compared to 15.1% who were on high dose PGB (p value 0.304). However, with respect to DLX, a greater number of such patients had received higher dose as compared to low dose (42.4% versus 18.2%) (p value 0.053).

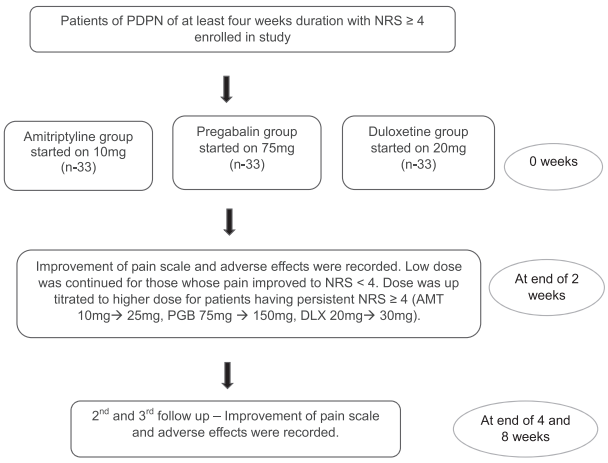

Figure 1. Flow chart demonstrating dose titration and follow up in each treatment group in our study.

Commonest adverse effects among total study participants in our study were drowsiness (42.4%), dizziness (21.2%), dry mouth (21.2%) and constipation (4%) (Table 4). A greater number of patients taking PGB (42.4%) had experienced at least one adverse effect as compared to 36.4% taking AMT or 27.3% taking DLX. Most of the side effects in our study were self-limiting and did not lead to drug discontinuation.

Table 1. Baseline characteristics of the study population.

Baseline characteristics	Amitriptyline (33)	Pregabalin (33)	Duloxetine (33)
Age (years)	52.6±10.5	57.1±11.2	60.8±11.5
Male:Female	16/17	11/22	20/13
Active Smoker	8 (24.2%)	5 (15.2%)	6 (18.1%)
Illiterate	18 (54.5%)	11 (33.3%)	12 (36.3%)
Hypertension	15 (45.5%)	22 (66.6%)	24 (72.7%)
Ischemic heart disease	0 (0%)	2 (6%)	3 (1%)
Current statin use	13 (39.4%)	18 (54.5%)	23 (69.7%)
Duration of symptoms (months)*	7 (2,24)	5 (2,12)	10 (2.5,21)
Duration of Diabetes (years)	1.42±1.2	2±1.9	2.2±0.9
Glycated hemoglobin (%)	7.5±1.3	7.7%±1.1	7.4%±1.4
Presence of diabetic retinopathy	7 (21.2%)	8 (24.2%)	7 (21.2%)
Presence of proteinuria	14 (42.4%)	21 (63.6%)	20 (60.6%)
Past treatment for neuropathy	2 (6%)	3 (9%)	7 (21.2%)

*Expressed as median value with value of 1st and 3rd quartile expressed within parenthesis.

Table 2. Treatment response to PDPN during each follow up visit.

Duration	NRS	Drug			P value
		AMT	PGB	DLX	
At baseline	Moderate	19 (57.6%)	19 (57.6%)	19 (57.6%)	1
	Severe	14 (42.4%)	14 (42.4%)	14 (42.4%)	
At 2 weeks	No pain	5 (15.2%)	2 (6%)	1 (3%)	0.016*
	Mild	15 (45.5%)	17 (51.5%)	6 (18.2%)	
	Moderate	9 (27.3%)	8 (24.2%)	19 (57.6%)	
	Severe	4 (12.1%)	6 (18.2%)	7 (21.2%)	
At 4 weeks	No pain	12 (36.4%)	8 (24.2%)	5 (15.2%)	0.065
	Mild	15 (45.5%)	16 (48.5%)	15 (45.5%)	
	Moderate	6 (18.2%)	4 (12.1%)	11 (33.3%)	
	Severe	0 (0%)	5 (15.2%)	2 (6%)	
At 8 weeks	No pain	15 (45.5%)	8 (24.2%)	6 (18.2%)	0.050*
	Mild	13 (39.4%)	18 (54.5%)	14 (42.4%)	
	Moderate	5 (15.2%)	4 (12.1%)	11 (33.3%)	
	Severe	0 (0%)	3 (9%)	2 (6%)	
N		33 (100%)	33 (100%)	33 (100%)	

*P value ≤ 0.05 was considered to be statistically significant.

Table 3. Treatment response to PDPN at 8 weeks stratified as per the dose and duration of follow up.

NRS	Drug								
	AMT			PGB			DLX		
	Low	High	P	Low	High	P	Low	High	P
No pain	11 (33.3%)	4 (12.1%)	0.019*	7 (21.3%)	1 (3%)	0.30	4 (12.1%)	2 (6.1%)	0.053
Mild	7 (21.2%)	6 (18.2%)		14 (42.5%)	4 (12.1%)		2 (6.1%)	12 (36.3%)	
Moderate	0 (0)	5 (15.2%)		0 (0)	4 (12.1%)		0 (0)	11 (33.3%)	
Severe	0 (0)	0 (0)		0 (0)	3 (9%)		0 (0)	2 (6.1%)	
N - 33 (100%)	18 (54.5%)	15 (45.5%)		21 (63.8%)	12 (36.2%)		6 (18.2%)	27 (81.8%)	

*P value ≤ 0.05 was considered to be statistically significant.

Table 4. Adverse events profile in each treatment.

Adverse events**	AMT	PGB	DLX	P value
Dysgeusia	2 (6%)	0% (0%)	1 (3%)	0.771
Dry mouth	12 (36.4%)	3 (9%)	6 (18.1%)	0.022*
Constipation	4 (12.1%)	0 (0%)	0 (0%)	0.033*
Urinary hesitancy	0 (0%)	1 (3%)	0 (0%)	1
Headache	0 (0%)	2 (6%)	1 (3%)	0.771
Peripheral edema	0 (0%)	2 (6%)	0 (0%)	0.327
Dizziness	2 (6%)	10 (30.3%)	9 (27.3%)	0.032*
Drowsiness	16 (48.5%)	17 (51.5%)	9 (27.3%)	0.095
Tremors	1 (3%)	1 (3%)	0 (0%)	1
Insomnia	0 (0%)	0 (0%)	2 (6%)	0.327
No adverse events	9 (27.3%)	10 (30.3%)	16 (48.5%)	-
1 adverse event	12 (36.36%)	14 (42.4%)	9 (27.3%)	-
2 adverse events	9 (27.3%)	5 (15.2%)	4 (12.1%)	-
3 or more adverse events	3 (9.1%)	4 (12.1%)	4 (12.1%)	-

*P value ≤ 0.05 was considered to be statistically significant. **Adverse events were recorded as a multiple response variable.

DISCUSSION

On comparing baseline characteristics of our study with previous study done by Chakraborty et al, mean age and glycated hemoglobin levels were similar across all three treatment groups.[8] However, mean duration of diabetes mellitus in our study was lesser (1.42±1.2 years for AMT, 2±1.9 years for PGB and 2.2±0.9 years for DLX) as compared to Chakraborty et al (8.31±3.2 years for AMT, 8.12±3.8 years for PGB and 7.93±3.4 years for DLX). Lower mean duration of diabetes in our study was due to the fact that there was wide variation in duration of diabetes, ranging from few months to more than 10 years, among study participants in each treatment group. In our study, median duration of symptoms of PDPN was 7,5,10 months for AMT, PGB and DLX with first quartile value around 2 months for each group and third quartile value being 24,12,21 months for AMT, PGB and DLX. This finding was different from Chakraborty et al where mean duration of PDPN symptoms was 7.7±2.0 months for AMT, 7.59±1.3 months for PGB and 8.41±1.6 months for DLX. This finding signified that there was wide variation of duration of symptomatology in each treatment group in our study. Years of untreated pain in a subgroup of our study participants may be due to relapsing and remitting nature of neuropathic pain, delay in seeking care for this painful condition in diabetic clinics and lack of active case finding approach among treating physicians. All three drugs were found to be efficacious for treatment of PDPN in the study by Chakraborty et al, similar to findings in our study where more than 50% patients in each treatment group had adequate pain reduction at the end of eight weeks.[8]

In our study, 84.9% patients in AMT group had adequate pain reduction as compared to 78.7% in PGB group. This finding contrasted a study by Shabbir et al where a greater number of patients taking PGB (91.2%) had significant pain reduction by end of six weeks as compared to those taking AMT (78.5%).[13] In both these studies, AMT was associated with adequate pain reduction in more than 75% patients. This is a significant finding as AMT is a cheaper drug as compared to PGB and DLX. The fact that AMT has adequate clinical response to pain with tolerable side effects and cheaper market price could affect choice of drug prescription among clinicians working in lower middle-income countries like Nepal.

In our study, 60.7% patients in DLX group had adequate pain reduction at the end of eight weeks as compared to 78.7% patients in PGB group. This finding contrasted a study by Shah et al where DLX effectively controlled neuropathic pain in greater number of PDPN patients (81.4%) than PGB (74.4%) at the end of four weeks.[14] Similarly, in another study by Kaur et al, around 80% patients in each group of AMT and DLX had good (> 50%) to moderate (25 to 50%) pain reduction at end of six weeks suggesting both AMT and DLX were equally efficacious for pain reduction among PDPN patients.[15]

DLX had comparatively less favorable outcomes in our study. While interpreting results of DLX in our study, it is necessary to consider the fact that 21.2% patients in DLX group had received past treatment for PDPN as compared to 9% in PGB and 6% in AMT group. Previous treatment in patients might be a predictor of relatively resistant type of pain that usually requires higher dose of individual drugs or combination therapy.[16] Also, mean age of patients and median duration of PDPN symptoms were higher for DLX group which might have contributed to comparatively inadequate response to DLX in our study.

In our study, dry mouth occurred significantly more in patients taking AMT (36.4%) as compared to PGB (9%) and DLX (18%) (p value 0.022). Similar findings were reported by Kaur et al where dry mouth was reported by 55% patients on AMT as compared to 24% patients on DLX (p value < 0.01).[15] Drowsiness was least common among patients taking DLX (27.3%) in comparison to AMT (48.5%) and PGB (51.5%) (p value 0.095). This finding was also comparable to the study by Chakraborty et al, where somnolence was only reported by 3% patients on DLX, as compared to 27% on PGB and 40% on AMT.[8] Similar to our study, DLX was a better tolerated drug in this study by Chakraborty et al where out of total adverse effects, 23% occurred with DLX, 29% occurred with PGB and 49% occurred with AMT.

One of the major limitations of our study was assessment of pain scale being a qualitative measurement. Reduction of pain severity could have subjective variation among study participants. This variation might have impacted study results. Consecutive sampling technique used in this study also could have led to sampling bias. Small sample size was another limitation. The results need to be tested in larger diabetic population to validate both positive and negative findings of our study. We have used low to intermediate dose of individual drugs in our study. Nearly one fourth of total participants had suboptimal pain reduction at end of our study, who might have responded to higher dose titration of these individual drugs which was beyond the scope of this study.

CONCLUSIONS

This treatment based comparative study concluded that amitriptyline, pregabalin and duloxetine were all associated with adequate pain reduction in patients of painful diabetic peripheral neuropathy with slightly more favorable response to amitriptyline. Despite the sample size being small, preliminary findings regarding effectiveness of this cheaper drug with tolerable side effects can act as a basis to design future larger studies suitable for lower middle-income countries like Nepal.

CONFLICTS OF INTEREST

None

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