

Evaluation of efficacy of Amitriptyline vs. Gabapentin in diabetic peripheral neuropathy

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Abstract: *Background:* The management of patients with Diabetic peripheral neuropathy (DPN) is challenging and often difficult to treat with current drug regime. *Objective:* To compare efficacy of Amitriptyline and Gabapentin in DPN. *Methods:* Patient screening and recruitment were carried out with diagnosis of DPN based on clinical history, complete physical examination and Michigan Neuropathy Scoring Instrument (MNSI) in this unicentric, prospective, open labeled, study with two parallel treatment arms. Following selection and recruitment, 100 adults aged 18 years and more, having MNSI score above 4 and Physical assessment part score above 2, were randomly assigned into two groups viz. Group A received oral Amitriptyline and Group B received oral Gabapentin for a duration of 12 weeks. The patients were examined four times during the study period. After the baseline visit, patients were asked to report at subsequent visits at 4 weeks interval up to 12 weeks. Efficacy was measured by using 11-point numeric pain rating scale and MNSI score. *Results:* On comparing both the treatment groups, the mean pain score reduction as per 11-point numeric pain rating scale was statistically significant at 4 weeks ($p=0.0025$), 8 weeks ($p=0.0109$) and 12 weeks ($p=0.0412$) in between the two groups. This study shows statistically significant difference in reduction in mean pain score between the two groups. It was seen that Gabapentin reduces pain more significantly than amitriptyline at 4, 8 and 12 weeks ($p<0.05$) as per NPRS scale assessed on NPRS scale and PPR (4-point scale) across the time while Amitriptyline was associated with more adverse effects. *Conclusions:* Our study shows that Gabapentin relieves pain faster than amitriptyline with lesser adverse drug reaction.

Keywords: Diabetic Peripheral Neuropathy, Amitriptyline, Gabapentin.

Introduction

Diabetic Peripheral Neuropathy (DPN) is one of the most prevalent and troublesome long term micro vascular complication during the course of both type 1 and 2 diabetes mellitus with ill understood etiology. Most common type of neuropathy is somatic or sensorimotor neuropathy with peripheral symptoms of burning, shooting, tingling and allodynia [1-2]. DPN reduces quality of life of up to half of diabetics by increasing susceptibility to foot or ankle fractures and ischemic ulceration leading to lower-limb amputations, depression and early death [3]. There are no approved treatments that restore nerve function. Interventions are primarily aimed at intensive glycemic control, pharmacotherapy of pain, depression and convulsion [4].

Amitriptyline is effective in upto one-third of DPN by blocking the reuptake of either norepinephrine or serotonin, neurotransmitters that are released by pain modulating systems that descend from the brain stem to the spinal cord [5-9]. Gabapentin is a novel anticonvulsant since last two decades for adult patients with partial epilepsy in United States open-label case series to be effective in the treatment of pain syndromes, including painful diabetic neuropathy [10-11]. The proposed analgesic mechanism of action involves binding to the $\alpha 2\text{-}\delta$ subunit of calcium channels in hyper-excited afferent neurons, which reduces the release of glutamate, norepinephrine, and substance P, thereby reducing pain signals transmitted from the periphery to the brain [12-13].

An extensive search of literature has revealed that there are very few studies involving direct comparisons between Gabapentin and Amitriptyline in India for making evidence-based decision in the treatment of diabetic peripheral neuropathy. In the above scenario, the study was planned to find the comparative efficacy of amitriptyline versus gabapentin in patients of Diabetic peripheral neuropathy.

Material and Methods

The present study was conducted at the department of Medicine at a tertiary care teaching institute of Punjab. Patient screening and recruitment were carried out with diagnosis of Diabetic Peripheral neuropathy based on clinical history, complete physical examination and Michigan Neuropathy Scoring Instrument (MNSI).

Inclusion Criteria: A total of 100 consenting adults aged 18 years and more were recruited in the study with the diagnosis of Diabetic Peripheral Neuropathy having MNSI score above 4 and Physical assessment part score above 2.

Exclusion Criteria:

- a. Persons suffering from epilepsy, psychiatric illness, and other causes of neuropathy like post herpetic neuralgia, peripheral vascular disease, lumbosacral polyradiculopathy etc.
- b. Persons with significant cardiovascular defects with uncontrolled hypertension
- c. Persons with hypersensitivity to the study drugs
- d. Persons with renal dysfunction (serum creatinine >1.5mg/dl)
- e. Persons with liver disease (ALT and AST>3 times normal level) were also excluded
- f. Pregnant and lactating females were excluded from the trial
- g. Persons already on any investigational drug within past one month
- h. Persons with malignancy
- i. Persons on non-steroidal anti-inflammatory drugs, vitamin B₁₂, antidepressants, sedative-hypnotic or psychotropic drugs, local anesthetics,
- j. Persons with alcohol, opioids and illicit substance use
- k. Severely debilitated and non-consenting patients

Study design: Necessary ethical clearance was obtained from the Institutional Ethics Committee. In this unicentric, prospective, open labeled, randomized study with two parallel treatment arms, a simple randomization was done on the basis of a computer generated random number list. The selected 100 patients were randomly assigned into two groups. Group A received oral amitriptyline and group B received gabapentin. For the individual patient, the treatment duration was for 12 weeks following selection and recruitment. The patients were examined four times during the trial. After the baseline visit, patients were asked to report at subsequent visits at 4 weeks interval up to 12 weeks. The participants enrolled for the study were individually counselled not to concomitantly consume non-steroidal anti-inflammatory drugs, vitamin B₁₂, antidepressants, sedative-hypnotic or psychotropic drugs, local anesthetics, opioids and alcohol during the study period and to report immediately if there was any dire emergency to use so.

Study drugs: Patients of group A were given oral amitriptyline 50mg/day in daily divided doses. Those of group B received Gabapentin 1800mg/day in daily divided doses [14]. In the first visit, all participants were screened which also served as their baseline visit if they were not receiving any interacting drugs. At screening a thorough medical history and clinical examination of the participants was done to assess their suitability for participation in the study. Body weight, height, resting pulse rate, respiratory rate, and blood pressure were recorded. Blood investigations such as fasting and post prandial blood glucose level, HbA1c, fundus examination, complete blood count, blood urea, serum creatinine, SGOT, SGPT, urine routine were done prior to enrollment. Patients who fulfilled the inclusion and exclusion criteria were enrolled into the study followed by obtaining of informed written consent in vernacular individually. The primary end point of the study was the reduction in mean pain score from baseline as assessed by the numeric pain rating scale (11- point scale from 0-10) at the end of 4, 8 and 12 weeks. NPRS is a standard instrument in chronic pain

studies. It is an 11-point Numerical pain rating scale (NPRS), where 0 = no pain and 10 = worse pain [15]. Percentage of pain relief (PPR) [16] and neuropathy scoring as per Michigan Neuropathy Screening Instrument (MNSI), [17] fasting blood glucose levels were the secondary efficacy parameters.

The study drugs were prescribed to the subjects after randomization. Improvement in pain was assessed according to the PPR (Percentage of Pain Relief) criteria at the end of 12 weeks by comparing with the baseline scoring on a five point improvement scale which is as follows: No pain (100%), Mild (80% - <100), Moderate (50% - < 80%), Severe (30% - < 50%), Worse (< 30%) [16]. The MNSI score consists of two parts, history and physical assessment were assessed at baseline, 4, 8 and 12 weeks. History contains 15 "yes or no" questions (>4 correlates DPN). Physical assessment includes foot inspection, ulceration, vibration, muscle stretch reflexes and monofilament testing. It consist of total score of 10 (>2 correlates DPN). Adverse events if any were recorded. The blood sample was sent for laboratory investigations at monthly intervals for fasting blood glucose level, blood urea, serum creatinine, SGOT and SGPT. If the patient did not tolerate the drug or did not get relief in symptoms, he/she was excluded from the study and alternative treatment was given. Although study was till 12 weeks, all patients received further treatment for diabetic peripheral neuropathy from the Medicine outpatients department.

Statistical Analysis: All patients who were randomized were considered for safety analysis. Data were analyzed by repeated measures analysis of variance (ANOVA) and paired t test for intragroup comparison and by unpaired t test for intergroup comparison. Post hoc analysis was done by Tukey’s honestly significant difference (HSD) test. Categorical data in baseline demographic profile were analyzed by chi-square test. ‘p’ value < 0.05 was considered to be statistically significant.

Results

The demographic profile was comparable between the groups with respect to age, gender, height, weight, body mass index and baseline clinical characteristics [Table1].

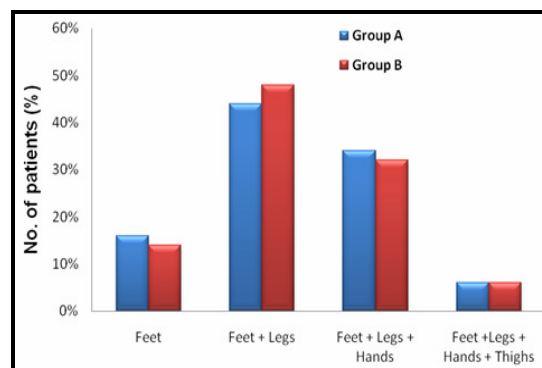
Table-1: Demographic profile of patients in both the groups (n=50 in each group)

Demographic Profile		Group A	Group B
Age		53.48 ± 8.99	55.54 ± 9.07
Sex	Male	27 (54%)	21 (42%)
	Female	23 (46%)	29 (58%)
Height(meters)		1.61 ± 0.082	1.64 ± 0.083
Weight (Kg)		72.18 ± 14.49	77.36 ± 15.74
BMI		27.77 ± 4.25	28.5 ± 4.99
Duration of Diabetes (in months)		78 ± 62.42	70 ± 62.86
Duration of Pain in months		10.9 ± 13.97	9.42 ± 10.99
S. Creatinine (mg/dl)		0.81 ± 0.15	0.83 ± 0.17
S. Cholesterol (mg/dl)		206.54±38.77	201.12±40.01
NPRS Score		7.46 ± 1.23	7.28 ± 1.26
MNSI H/o) Score		6.42 ± 1.44	6.3 ± 1.29
MNSI (PA) Score		6 ± 1.65	5.8 ± 1.65
FBS levels (mg/dl)		159.18±39.29	156.3 ± 43.94

Values are expressed as mean ± SD (standard deviation) while categorical values are expressed as actual number of patients and their percentage.

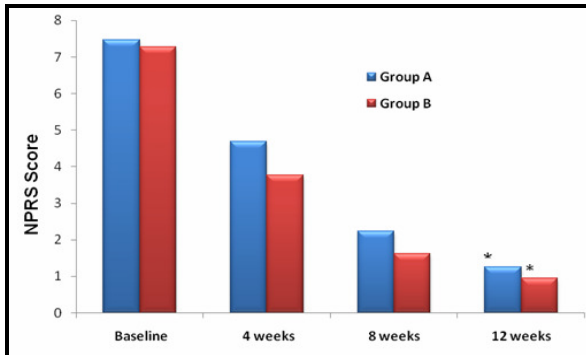
Regarding distribution of neuropathic pain in various parts of the body, the common sites of pain in DPN were feet, legs, hands and thigh. Majority of patients in both the groups had pain in their extremities viz. feet and legs (44% in group A and 48% in group B) [Fig 1].

Fig-1: Pain distribution in both the groups



Efficacy was measured by using 11-point numeric pain rating scale and MNSI score. On comparing both the treatment groups, the mean pain score reduction as per 11-point numeric pain rating scale was statistically significant at 4 weeks ($p=0.0025$), 8 weeks ($p=0.0109$) and 12 weeks ($p=0.0412$) in between the two groups [Figure 2].

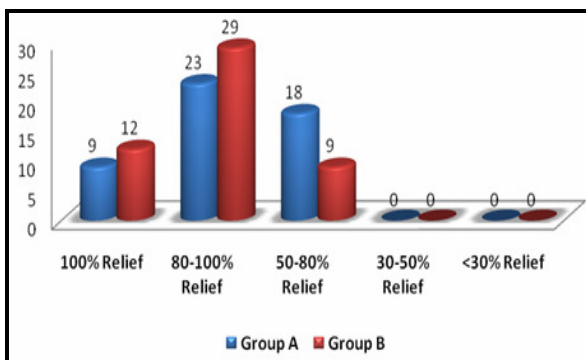
Fig-2: Numeric Pain Rating Scale (NPRS) score at baseline, 4, 8 and at 12 weeks in both the groups



*Denotes $p < 0.05$ as compared to baseline

In group A (amitriptyline) out of total 50 patients, 9 patients had full (100%) relief, 23 patients reported 80-100 percent relief while 18 patients had 50-80 percent relief at 12 weeks. Similarly in group B (gabapentin) out of total 50 patients, 12 patients had full (100%) relief, 29 patients had 80-100 percent relief while 9 patients had 50-80 percent relief at end of 12 weeks [Figure 3].

Fig-3: Percentage of Pain Relief (PPR) in both the groups

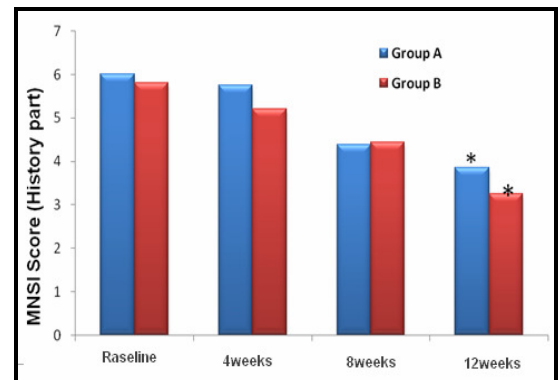


The mean MNSI score reduction was statistically not significant at 4 weeks ($p=0.092$) and 8 weeks ($p=0.844$); statistically significant at 12 weeks ($p=0.019$) in between groups [Figure 4].

There was statistically significant ($p < 0.0001$) reduction in fasting blood glucose levels in both

the groups at the end of 12 weeks but in between the groups the FBS levels were comparable.

Fig-4: MNSI Score at baseline, 4, 8 and 12 weeks



*Denotes $p < 0.05$ as compared to baseline

Safety analysis: Side effects were mild and there were no serious adverse effects reported in either of the treatment groups. In group A out of 50 patients, total 18 patients had side effects where as in group B out of 50 patients, only 7 patients reported side effects. In group A, 16 percent patients had complaints of sedation, 14 percent complained of dry mouth as well as alteration of taste, 12 percent complained of lethargy, 8 percent patients complained of headache, 6 percent complained of dizziness and 4 percent complained of weight gain, dyspepsia and anorexia after taking amitriptyline. However, none of the patients were withdrawn from the study. While in group B, 10 percent patients complained of sedation while only 2 percent patients complained of dizziness, lethargy, dry mouth, taste alteration and headache [Tab-2].

Table-2: Adverse effects reported in both the groups

Adverse effects	Group A: n (%)	Group B: n (%)
Sedation	08 (16 %)	05 (10 %)
Dry Mouth	07 (14 %)	01 (2 %)
Taste Alteration	07 (14 %)	01 (2 %)
Lethargy	06 (12 %)	01 (2 %)
Headache	04 (8 %)	01 (2 %)
Dizziness	03 (6 %)	01 (2 %)
Weight Gain	02 (4 %)	0
Dyspepsia	02 (4 %)	0
Anorexia	02 (4 %)	0

Discussion

The baseline demographic characteristics considered in this study include age, gender, height, weight, BMI, duration of diabetes, pain and positive family history of diabetes of the patients. These were comparable in both the groups. Randomized studies in India and from other countries also have included patients with a mean age similar to this study [18-20]. Mean BMI of the patients was slightly higher as compared to another study [20] but patients fall in the category of overweight in both the studies. This shows that overweight diabetic patients are more likely to develop neuropathy symptoms.

The present study shows wide variation in duration of diabetes of the patients from other studies. [18-21]. As compared to other studies duration of diabetes was less which may be because some patients from rural areas presented for the first time with neuropathic symptoms and were diagnosed with diabetes. This shows that many people in rural areas are not aware of diabetic symptoms and they directly visit the clinic only when they develop symptoms of neuropathy. The most common presenting symptom of patients in our study was numbness, burning, tingling and allodynia which was similar to other studies [6, 19]. Distribution of pain was more in feet and legs in our study which was comparable to another study [19].

Efficacy: The evaluation of efficacy of the study drugs was based on improvement in neuropathic sign and symptoms of the patients by the NPRS score, percentage of pain relief, MNSI score at baseline, 4, 8 and 12 weeks. The baseline mean pain score as per NPRS scale and MNSI score was similar to another study which also used both the scales to evaluate the efficacy [20, 22]. In our study, DPN patients who received amitriptyline showed significant reduction in mean pain score as assessed on NPRS scale and PPR (4-point scale) across the time. These findings were in concordance with published literature [6,19,21, 23-24] where evaluation of pain was confirmed by similar well established pain-evaluation scores.

This study shows statistically significant difference in reduction in mean pain score between the two groups. At the end of the study it was seen that gabapentin reduces pain more

significantly than amitriptyline at 4, 8 and 12 weeks ($p < 0.05$) as per NPRS scale. This shows that Gabapentin relieves pain faster than amitriptyline. Another study by Dallochio et al conducted on 25 patients for 12 weeks had showed similar significant difference ($p = 0.026$) in pain reduction in Gabapentin and Amitriptyline groups.^[21] While a cross over study by Morello et al on twenty five patients for six week, with a one week washout period between treatment arms reported no significant difference in pain relief as per mean pain score and global pain score between the Gabapentin and Amitriptyline groups ($p = 0.26$) [19]. This difference in the results may be due the difference in the sample size as the sample size was larger in the present study.

In present study, 23 patients in group A and 29 patients in group B got 80-100 percent pain relief whereas 18 patients in group A and 9 patients in group B got only 50-80 percent relief. This shows that gabapentin more efficiently reduces the neuropathic pain than amitriptyline. These results are similar to a study in which the duration of treatment was same (12 weeks) [21] as in our study whereas differ from another study in which duration of treatment was for 6 weeks [19]. In this study, neuropathy status was evaluated at baseline, 4, 8 and 12 weeks using well established MNSI score. In our study we found significant reduction in MNSI scores between the two groups. This shows that Gabapentin improves neuropathy symptoms better than amitriptyline. These results are similar to the study conducted for 12 weeks in which paraesthesia score was compared [19].

Evaluation of this MNSI scoring shows improvement in the signs of neuropathy like vibration sensation, ulcer healing and touch sensation on long term treatment. Other studies have used MNSI scoring to screen and diagnose, we have evaluated MNSI scoring across the time to see improvement in sign and symptoms of neuropathy. The proper management of DPN includes adequate glycemic control and optimum pharmacotherapy of neuropathic sign and symptoms. There was significant reduction in FBS levels over the study period and thus the

reduction in the glycemic burden can be expected to contribute to the pain relief and may have effect on the efficacy assessment [19, 25]. This is consistent with yet another published report [22].

Safety Analysis: The management of patients with diabetic neuropathic pain is challenging and often difficult to treat with current drug regime. During the entire study period all patients were closely monitored for any adverse effects both according to the adverse effect checklist and by voluntary reporting of the patients. Overall, both the study drugs were well tolerated with no significant laboratory or safety findings. There was not any severe adverse event in our study. The adverse effect profile in this study was generally consistent with the previous studies [18-24]. Adverse events reported in our study were mild in both the groups and no discontinuation of drug was required. In total, 18 patients in group A and only 7 patients in group B reported adverse effects. There were a significantly higher number of adverse events reported in the amitriptyline group which were consistent with the other studies done earlier [18-19, 21]. There were no significant changes in the renal and liver function during the study period which were consistent with the other studies [24].

Strength of the study: Several strengths of our study needs to be highlighted. We have used the standard validated scales and scores for the diagnosis of diabetic peripheral neuropathy and for assessing pain relief. These have been used by other studies also. We have evaluated MNSI

score for assessing sign and symptoms of neuropathy. To the horizon of our knowledge, very few studies have assessed the sensory parameters.

Limitations of the study: We had several limitations. Firstly, this was an open label study without any blinding. Secondly, the follow-up of patients was only for 12 weeks and therefore, the long term efficacy and safety of the drugs could not be assessed. Lastly, though our study sensitized our fraternity to identify and fill up lacunae regarding prescribing practices to manage DPN, yet this was only a revelation of a single centre with limited external validity.

Future directions of the study: In our next phase of studies, we will try to cover three tier level of health system i.e. primary, secondary and tertiary level health care hospitals with multicentre data collection.

Conclusions

To sum up, it was found that both Gabapentin and Amitriptyline produce significant pain relief in patients with diabetic peripheral neuropathy. Gabapentin monotherapy produced rapid onset of pain relief and it also shows improvement in neuropathic sign and symptoms on long term treatment and relatively it has minor and potentially avoidable adverse effects. Amitriptyline is associated with more adverse effects which is an important factor to keep in mind.

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