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Comparison of Carbamazipine and Amitryptyline for the Reduction of Diabetic Neuropathic Pain: A Randomized Clinical Trial

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Abstract

Background: D*iabetic neuropathy is very difficult to treat.* ***Objective:*** *The purpose of the present study was to compare the efficacy and safety of carbamazepine and amitryptyline for reduction of diabetic neuropathic pain.* ***Methodology:*** *This was a randomized controlled trial conducted in the department of Neurology including Neuropathy Clinic of BSMMU and in collaboration with department of Endocrinology, BSMMU, Dhaka from January 2012 to December 2013 for a period of two (2) years. Adult diabetic patients presented with neuropathic pain with symmetrical involvement of distal limbs from indoor and outpatient department of Neurology including Neuropathy clinic as well as indoor and outpatient department of Endocrinology, BSMMU were enrolled in the study population. The study population was divided into two groups named as group A and group B. The group A was experimental group. In this group, patients were treated with oral carbamazepine 400mg/day in two divided doses for initial 2 weeks, then 600mg/ day in three divided doses for further 4 weeks. The group B was control group. In this group, patients were treated with oral amitriptyline 25mg/ day at night for initial 2 weeks, then 50mg/day taking at night for further 4 weeks. During trial, three follow ups were taken at 2 weeks interval and encountered the clinical response by pain score (VAS) and the side effects. The first follow up after 2 weeks of treatment; the second follow up was after 4 weeks of treatment and the third follow up was after 6 weeks of treatment.* ***Result:*** *A total number of 110 cases clinically diagnosed as painful diabetic polyneuropathy, then 56 cases randomly selected for Group A and 54 cases randomly selected for Group B. During follow up of 6 weeks, 2 case of Group A developed skin rash for which they discontinued drug. From rest of cases, 2 from Group A and 4 from Group B were dropped out. Because they did not come for follow up. So finally 52 cases for Group A group and 50 cases for Group B group were studied. A total of 102 patients were included in the study. They were divided into four Groups according to their age. The mean age was found 52.17(±10.02) years in Group A and 53.41(±8.82) years in Group B. The mean (±SD) of percent improvement in Group A and Group B were 41.11(±11.29) vs. 31.76(±19.14) (P<0.05). Dizziness and Drowsiness were found in Group A as 33.3% and 37.0%. But in Group B dryness of mouth and constipation were found as 46.3% and 7.4%.* ***Conclusion:*** *In conclusion carbamazepine produced greater improvements than amitriptyline in relieving pain and paresthesia associated with diabetic neuropathy.*

Keywords: *Diabetic neuropathy; carbamazepine; amitriptyline; pain; paresthesia*

Introduction:

Diabetic neuropathic pain is difficult to treat and patients rarely experience complete pain relief. It is a frustrating problem for both providers and patients[1]. Drugs from several different pharmacological classes have been shown to be safe and effective in alleviating neuropathic pain. These include tricyclic antidepressants (TCAs), anticonvulsants, sodium-channel blockers, and topical agents[2].

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Carbamazepine (CBZ) produces significant pain reduction in patients suffering from painful diabetic neuropathy with a number needed to treat (NNT) of 3.3 based on several study[3]. The number needed to harm (NNH) for CBZ is 3.4 for minor side-effects and NNH of 24 for severe effects[4]. The common side-effects of CBZ are drowsiness, diplopia, blurred vision, nausea and vomiting. In treatment of the elderly population with this drug, one must be aware of possible cardiac disease, water retention, decreased osmolality and hyponatremia complications[5].

Tricyclic antidepressants (TCA) have been established to reduce pain independent of their effect on mood[6]. These drugs block the reuptake of norepinephrine and serotonin which are the two neurotransmitters that are implicated in nociceptive modulation; furthermore it also inhibits sodium channels. TCAs are effective for both constant and lancinating, paroxysmal pain[7]. Based on the evidence of several controlled studies in patients with painful diabetic neuropathy, these drugs are very effective[8-9]. In this context this present study was undertaken to compare the efficacy and safety of carbamazepine and amitryptyline for the reduction of diabetic neuropathy pain.

Methodology

Study Population and Setting: This study was designed as randomized controlled trial and was conducted from January 2012 to December 2013 for a period of two (2) years. This study was carried out in the department of Neurology including Neuropathy Clinic and in collaboration with department of Endocrinology at Banghabandhu Sheikh Mujib Medical University, Dhaka. Adult diabetic patients presented with neuropathic pain with symmetrical involvement of distal limbs from indoor and outpatient department of Neurology including Neuropathy clinic as well as indoor and outpatient department of Endocrinology were enrolled in the study population. Diabetic patients having neuropathic pain with symmetrical involvement of distal part of limbs for at least 6 months, pain score 4 or more using a visual analog scale (0 = no pain, 10 = worst pain possible) and all adult diabetic patients of both sexes between the age of 18-65 years. Patient with history of drug hypersensitivity reaction, impaired hepatic and renal function, pregnant women, lactating mother, patient treated by antidepressant, antiepileptic drugs within one month of commence of study, alcohol or substance abuser, patients with cognitive impairment, mood disorder, patients with cardiovascular disease like ischemic heart diseases, heart failure, heart block, arrhythmia, patients with urinary outflow obstruction, prostatism, glaucoma, known case of malignancy, connective tissue disease were excluded from this study.

Randomization and Blinding: The study population was included by purposive sampling technique after fulfilling the inclusion and exclusion criteria. Participants were randomized in two groups named as group A and group B by lottery. For unbiased randomization, two cards were provided. One marked with X and another marked with Y. Selected subjects were invited to draw a card blindly. Card drawn was marked with X, the subject was allocated for oral Carbamazepine and card drawn marked with Y was given oral amitriptyline. Carbamazepine receiver was fallen into group A and amitriptyline receiver was fallen into group B.

Allocation and Intervention: Before starting medication, it was sincerely explained about side effect of drug to each subject. Each subject in group A was treated with oral Carbamazepine. Starting dose was 400mg/day in two divided dose. After two weeks dose was increased to 600mg/day in three divided doses. Dose was not allowed to increase if intolerable side effect developed. Each subject in group B was treated with oral amitriptyline. Starting dose was 25mg/day, single dose given at night. After two weeks, dose increased to 50mg/day, single dose, given at night. Dose was not allowed to increase when intolerable side effect developed.

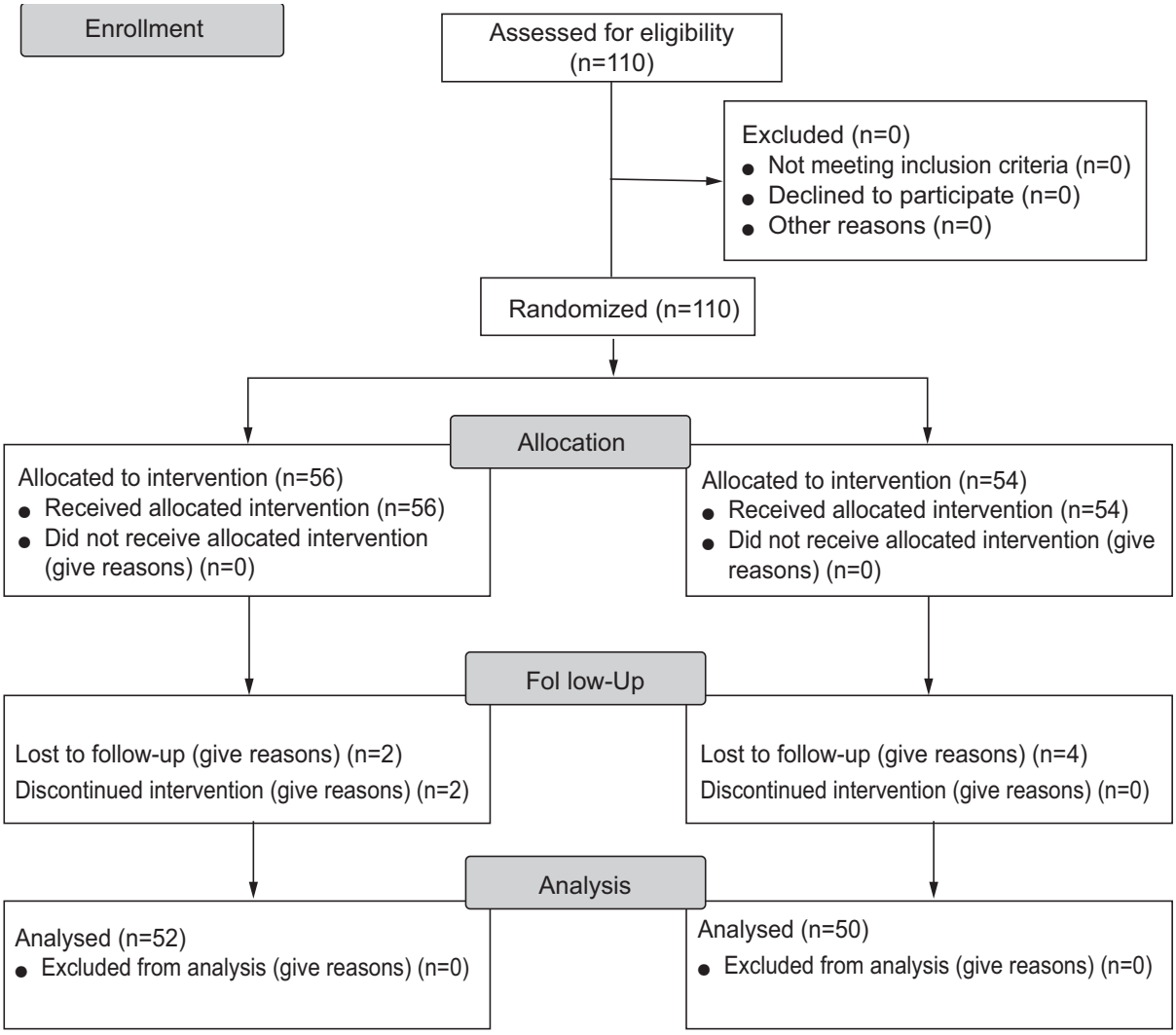

Fig.-1: *CONSORT Flow Chart*

Follow up and Outcome Measures: During the study period, three follow up were taken at 2 weeks interval and encountered the clinical response by pain score (VAS) and the side effects. The first follow up was after 2 weeks of treatment; the second follow up was after 4 weeks of treatment and the third follow up was after 6 weeks of treatment. Pain score was measured by using VAS (0-10) before starting medication and during follow up visit. Selected subject was asked to make a mark on VAS. Thus pain score was recorded in data information sheet. Dizziness, drowsiness, unsteadiness, nausea and vomiting, blurred vision and double vision, uncommon side effect include behavioral change, depression, unusual bleeding, anemia, jaundice, skin rash, itching, toxic epidermal necrolysis and Stevens-Johnson syndrome, water retention were recorded as common side effects of carbamazepine. Dry mouth, drowsiness, blurred vision, constipation, nausea, difficulty in passing urine, postural hypotension and confusion or delirium were the common side effect of amitriptyline.

Statistical Analysis: Data were analyzed by computer with the help of SPSS version 21.0 software package. All data was recorded systematically in a preformed data collection sheet and expressed the quantitative variables as mean+SD. It was analyzed for categorical variables by using chi-squared test and for continuous

variable t-test used. For all statistical tests, we considered p value <0.05 as statistically significant. Prior to the commencement of this study, the research protocol was approved by the Institutional Review Board (IRB) of BSMMU, Dhaka.

Results:

A total number of 110 cases clinically diagnosed as painful diabetic polyneuropathy, then 56 cases randomly selected for Group A and 54 cases randomly selected for Group B. During follow up of 6 weeks, 2 case of Group A developed skin rash for which they discontinued drug. From rest of cases, 2 from Group A and 4 from Group B were dropped out. Because they did not come for follow up. So finally 52 cases for Group A group and 50 cases for Group B group were studied. Table 1 shows the age distribution of both Groups. A total of 102 patients were included in the study. They were divided into four Groups according to their age. The mean age was found 52.17(10.02) years and range were (25-65) years in Group A and mean age was 53.41(8.82) years and range were (25-65) years in Group B. Most of the study patients were > 55 years age Group in both Group A and Group B (48.1% vs 60%). In this table shows no significant difference in age distribution among both Groups (Table 1).

Table-I

Distribution of the respondents by age Groups (n=102)

Age (years)	Group A (n=52)	Group B (n=50)	p value*
25-34 (n=5)	4(7.7%)#	1 (2.0%)	0.411[ns]
35-44 (n=12)	6(11.5%)	6(12.0%)	
45-54 (n=30)	17 (32.7%)	13 (26.0%)	
>55 (n=55)	25(48.1%)	30 (60.0%)	
Total	52(100%)	50(100%)	
Mean (±SD)	52.17±10.02	53.41±8.82	

ns=non significant; *Chi square test was done to measure the level of significance

Table II shows the response of Group A and Group B on DPN patients in term of pain. Before starting the medication pain Scales of both Groups were moderate and there was no significant difference (p>0.05) i.e 5.20 (0.86) vs 5.06 (0.82). But after trial from 1st follow up to 3rd follow up significant differences in pain reduction were observed in Group A than Group B. [1st follow up 4.40 (0.80) Vs 4.81 (0.85), p = 0.011; 2nd follow up 3.73 (0.86) Vs 4.07 (0.84), p = 0.041; 3rd follow up 3.00 (0.45) Vs. 3.41 (0.10), p =0.007] (Table 2).

Table-II

Distribution of the respondents by Visual Analog Scale (VAS) score in Both Groups during premedication and three Follow up (FU) in post-medication (n=102)

VAS	Group A (n=52)	Group B (n=50)	P value
Pre-Medication	5.20±0.86	5.06±0.82	0.361
Post-Medication 1st FU	4.40±0.80	4.81±0.85	0.011
Post-Medication 2nd FU	3.73±0.86	4.07±0.84	0.041
Post-Medication 3rd FU	3.00±0.45	3.41±0.10	0.007

mean (±SD); Independent Sample t test was done to measure the level of significance

The percent improvement of visual analog scale score of pre-medication and post-medication was measured. There was highly significant difference between Group A and Group B. The mean (±SD) of percent improvement in Group A and Group B were 41.11(±11.29) vs. 31.76(±19.14) and the median were 41.67 vs. 31.67 (Table III).

Table III

Distribution of the respondents by Percent Improvement of Visual Analog Scale score in Post-Medication (n=102)

Percent Improvement	Group A (n=52)	Group B (n=50)	p value
Mean (±SD)	41.11±11.29	31.76±19.14	0.0001
Median	41.67	31.67	

Mann-Whitney U test was done to measure the level of significance

Table IV shows the distribution of side effects in post-medication. There found dizziness, drowsiness, dryness of mouth, nausea and constipation as side effects. Dizziness and drowsiness were found in Group A as 33.3% and 37.0%. But in Group B dryness of mouth and constipation were found as 46.3% and 7.4%.

Table-IV

Distribution of Respondents by side effects in post-Medication periods in between two Groups (n=102)

Side Effects	Group A (n=52)	Group B (n=50)	p value
Dizziness			
Yes	18(33.3%)	0(0.0%)	0.0001[s]
No	34(66.7%)	50(100.0%)	
Drowsiness			
Yes	18(35.5%)	13(27.8%)	0.288[ns]
No	34(64.5%)	37(72.2%)	
Dryness of Mouth			
Yes	0(0.0%)	23(46.3%)	0.0001[s]
No	52(100.0%)	27(53.7%)	
Nausea			
Yes	3(7.4%)	2(5.6%)	0.647[ns]
No	49(92.6%)	48(94.4%)	
Constipation			
Yes	0(0.0%)	2(7.4%)	0.153[ns]
No	52(100.0%)	48(92.6%)	
Unsteadiness			
Yes	2(3.0%)	0(0%)	0.475[ns]
No	50(97.0%)	50(100.0%)	

s=significant, ns=not significant; P value reached from chi square test

Discussion:

Painful diabetic polyneuropathy significantly affect on the quality of life, sleep, mood, mobility, ability to motor activities and social behaviors of patients[6]. High prevalence of diabetes and consequently painful neuropathy limits the daily activities of the patients[9]. For a long time amitriptyline has been considered as a first line treatment for the pain management of diabetic neuropathic patients.

This randomized clinical trial was conducted in the departments of neurology including neuropathy clinic as well as Department of Endocrinology, BSMMU, Dhaka from January 2012 to December 2013. Total 110 adult diabetic patients who complain neuropathic pain with symmetrical involvement of distal limbs were enrolled in this study. In which 56 patients were treated with oral carbamazepine in Group A and 54 patients Group B were treated with oral amitriptyline. Two cases in group A withdrew from the study due to development of side effect. Another 2 cases from group A and 4 cases from group B failed to follow up. Finally analyzed the data of 52 patients from group A and 50 patients of group B. Detail information was collected by a data collection sheet and followed up the patients for 6 weeks to evaluate their clinical response and side effects.

There is no known study on such a type of clinical trial in painful diabetic neuropathic patients in Bangladesh. It is a little endeavor to evaluate the efficacy of carbamazepine and amitriptyline in the treatment of painful diabetic polyneuropathy in Bangladesh. Carbamazepine is the first anticonvulsant studied for the treatment of diabetic neuropathy[9]. In the present study it has given significant relief of neuropathic pain compared with amitriptyline on day 14, 28 and 42 ($P<0.001$). Mean percent reductions of pain are 15.1±9.53 and 4.9±7.01 in day 14, 28.19±13.0 and 19.6±11.9 in day 28 and 41.1±11.3 and 31.8±19.1 in day 42 in group A and group B respectively. In every follow up efficacy of carbamazepine has found more than that of amitriptyline ($p>0.001$); however, both drugs have ability to reduce pain. Wilton[10] has also found carbamazepine as a significant pain reliever in their clinical trial and has compared carbamazepine with placebo and has recorded pain score on day 10 and 14 and has found statistically significant improvement in carbamazepine group and the result is comparable with findings of this present study. A double blind, 6-wk, placebo-controlled, crossover trial of 30 patients has been conducted by Rull et al[11] and has found that carbamazepine relieves sensory symptoms in 93% with diabetic neuropathy which is superior to the results with placebo. In another double-blind, placebo-controlled, crossover trial conducted by Wilton[10], 40 patients have received either carbamazepine or placebo for 1 wk and have reported their pain using a 10-cm analog scale. Carbamazepine has provided significant relief of diabetic peripheral neuropathy pain compared with placebo on day 10 and day 14 ($P < 0.05$). Observers have also noted a statistically significant decrease in pain in favor of carbamazepine.

In Gomez-Perez et al[12] study 200 mg carbamazepine has been compared with 10 mg nortriptyline/ 0.5 mg fluphenazine in a double-blind, randomized, crossover, double-placebo trial involving 16 patients with diabetic peripheral neuropathy. Carbamazepine has reduced pain by 28.7% in the first 2 week and by 49% in the second 2 week compared with baseline values ($P < 0.001$ at week 4). Nortriptyline-fluphenazine has reduced pain by 38.2% in the first 2 week and by 66.6% in the second 2 week compared with baseline values ($P < 0.001$). However, there is no statistically significant difference between treatments. Adverse events are more common with nortriptyline/ fluphenazine than with carbamazepine.

In the present study dizziness, drowsiness, dryness of mouth, nausea and constipation were frequently reported side effects. In group A dizziness (33.3%) and drowsiness (37.0%) and in group B dryness of mouth (46.3%) and constipation (7.4%) were found as frequent complaints. Dizziness was found significantly common in carbamazepine ($P<0.001$) and dryness of mouth in amitriptyline ($P<0.001$) group. There are several limitations with use antiepileptic drugs. Carbamazepine did not gain popularity because of its adverse effects which ranged from somnolence, dizziness and gait disturbance. In earlier studies, hematopoietic issues were addressed but no patients were excluded because of them. Dizziness and somnolence were the most frequent tolerable adverse effects. Various side effects have been reported with the use of anticonvulsant drugs varying from dizziness, diplopia to life threatening rashes, blood dyscrasias and hepatotoxicity[9]. In the present study in carbamazepine group patients reported more dizziness (33.3%) and drowsiness (37.0%) and in amitriptyline group dryness of mouth (46.3%) and constipation (7.4%). Dizziness was found significantly common in carbamazepine ($P<0.001$) and dryness of mouth in amitriptyline ($P<0.001$) group.

In one retrospective cohort study of 143 patients with trigeminal neuralgia (TGN) in which long term effect over 16 years of CBZ was evaluated[13]. The drug was effective initially with few mild side effects in 99 patients (69%). Twenty five percent patients failed to respond to CBZ and 6% were intolerant to CBZ due to rash, nausea and thirst and water intoxication in 6, 1 and 1 patient respectively which necessitated cessation of the drug. This study has thus confirmed the efficacy of CBZ for the treatment of TN and proved that it may continue to be effective for many years.

Conclusion

It has been concluded that carbamazepine has produced greater improvements than amitriptyline in relieving pain and paresthesia associated with diabetic neuropathy. Additionally, carbamazepine has better tolerated than amitriptyline. These findings suggest that carbamazepine may be of benefit in treating the painful peripheral neuropathy associated with diabetes.

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