Original Research Article

Comparative analysis of nerve conduction in median nerve and efficacy of gabapentin vs amitriptyline in patients of peripheral neuropathic pain in case of diabetes mellitus

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Abstract

Background: Pain is the most disturbing symptom of diabetic peripheral neuropathy. Almost 30-50% of patients with diabetes mellitus develop peripheral neuropathies. Distal symmetric sensorimotor polyneuropathy (DSPN) is most common type. Gabapentin and Amitriptyline are the two most commonly used drugs in pain associated with this condition. **Aim of the study:** The aim of this study was to compare the effect of Gabapentin and Amitriptyline on improvement of nerve conduction in median nerve and to compare efficacy of both drugs in subjects of Type 2 diabetes mellitus with peripheral neuropathic pain. **Material and methods:** A prospective, open, randomized, parallel group, comparative study was conducted in 60 patients coming to Department of Medicine, Rajindra Hospital attached to Government Medical College Patiala, to evaluate the effect of Gabapentin and Amitriptyline on improvement of nerve conduction in median nerve in patients with diabetic peripheral neuropathic pain. The patients fulfilling the inclusion criteria were included in the study after taking written informed consent. The patients were divided into two groups of 30 cases each by simple randomization. Group I patients received Gabapentin 300 mg HS by oral route. Group II patients received Amitriptyline 25 mg HS by oral route. Improvement in conduction in median nerve by assessing sensory nerve conduction velocity and symptomatic improvement by using Visual analogue scale (VAS), was compared at the baseline and at the end of 4 months. All the observations thus made were statistically analysed using appropriate tests. **Results:** Baseline characteristics of the patients in two groups such as age, sex, duration of diabetes, blood sugar level were similar ($p>0.05$). The mean age in group I and group II was 53.40±8.41 years and 57.17±8.55 years, respectively. There was statistically significant improvement in nerve conduction velocity in median nerve in both groups. NCV improved by 14.52 % in group I (gabapentin) and 9.40 % in group II (amitriptyline) at the end of follow up period i.e. four months, but there was no statistically significant difference between the two drugs in improving nerve conduction (mean difference= 1.73±0.01, $p=0.342$). There was statistically significant reduction in mean VAS score from baseline in both groups. The mean difference between two drugs in reducing VAS score (0.46±0.10, $p=0.015$) favored Gabapentin. **Conclusion:** In this study, we concluded that both drugs significantly improved nerve conduction and it was comparable in both the groups. Gabapentin treated patient's mean VAS score at the study end point, was significantly lower compared with the Amitriptyline treated patient's end-point score. There was significant reduction in blood sugar 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.

Key Word: Diabetic peripheral neuropathic pain, Gabapentin, Amitriptyline, Nerve conduction, Efficacy

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INTRODUCTION

Chronic sensorimotor polyneuropathy is the most common painful diabetic neuropathy. According to existing studies, about one third of diabetic patients are affected with diabetic neuropathy.[1] DPN was defined by Toronto Consensus Panel on Diabetic Neuropathy as a 'symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and micro-

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vessel alterations as a result of chronic hyperglycaemia exposure and cardiovascular risk covariates.' Diabetic peripheral neuropathy is frequently subclinical and can be diagnosed by an abnormality of nerve conduction tests. Nerve conduction testing is the first objective quantitative indication of the condition.[2] DPN is insidious in onset and it starts in the toes and gradually moves proximally. It starts affecting upper limbs once it is well established in the lower limbs.[3] DPNP is characterized by burning-type pain, tingling ('pins and needles' or paraesthesia), and numbness in limbs.[3] These symptoms tend to get worse at night and disturb sleep which often leads to anxiety and reduction in individual's ability to perform daily activities.[4] Nerve conduction studies are abnormal due to any pathological changes in structure of nerve. They are considered gold standard for the diagnosis of all neuropathies. The velocity at which an impulse is conducted along a motor (or) sensory nerve can be measured with great accuracy.[5] In a study conducted in India, normative values for median sensory nerve conduction velocity value for males was found out to be 56.93 ± 3.47 m/s and for females was 56.20 ± 3.38 m/s.[6] Routine nerve conduction studies include evaluation of motor function of the median, ulnar, peroneal, and tibial nerves, and sensory function of median, ulnar, radial, and sural nerves. Nerve conduction studies are the most reliable, accurate, and sensitive measure of the ability of peripheral nerves to conduct electrical impulses.[7] Classes of drugs and individual agents with effectiveness in treating DPNP include TCAs, anticonvulsants, SNRIs and opioids.[8]

MATERIALS AND METHODS

Study Design: In this prospective, open, randomized, parallel group, comparative study, 60 patients of Diabetic Peripheral Neuropathic Pain (DPNP) attending the outpatient Department of Medicine, Rajindra Hospital, Patiala were included. The patients fulfilling the inclusion criteria and having none of the exclusion criteria were enrolled in the study after obtaining written informed consent. Inclusion and exclusion criteria was as following:

Inclusion Criteria:

1. Age in the range of 18 to 65 years
2. Gender- male or female
3. Patients with established diagnosis of Type 2 Diabetes mellitus
4. Clinically relevant Diabetic Peripheral Neuropathic Pain
5. Patient willing to sign informed consent form

Exclusion criteria:

1. Patient already on treatment of neuropathy of different cause such as Vit B_{12} deficiency, alcohol intoxication, malignancies etc.
2. Presence of renal, hepatic or cardiovascular insufficiency
3. Patients with epilepsy, uncontrolled hypertension and substance abuse
4. Current/ previous diagnosis of psychiatric disorder
5. Pregnant and lactating females
6. Patient taking such drugs for any other disease which are known to cause drug interactions with AMI or GBP
7. Patient taking drugs which can cause neuropathy
8. Patient taking any other analgesic drug during study period
9. Patients allergic to any of the components of study drugs.
10. Patient not willing to give consent

Study Sequence: In this prospective, open, randomized, parallel group, comparative study, 60 patients of diabetic peripheral neuropathic pain were included. A written informed consent was obtained from patients after explaining them about study drugs and procedure. After taking a thorough history and clinical examination patients were divided into two groups of 30 subjects each through simple randomization method and followed up over a period of four months. Group I patients received Gabapentin at a dose of 300 mg HS and subsequent therapeutic response in patients were noted. Group II patients received Amitriptyline at a dose of 25 mg HS and subsequent therapeutic response was noted.

Study Parameters

Patients were assessed for clinical improvement on the basis of:

1. Nerve conduction in median nerve
2. Visual Analogue Scale

Improvement in nerve conduction was assessed by measuring nerve conduction velocity in median nerve (sensory part) at baseline and at the end of follow up period i.e. four months. Comparison of efficacy by VAS scores was done at baseline and four months.

Nerve conduction study: This test was carried out in department of Physiology. NCS was done in median nerve using computer based electrodiagnostic equipment Neuro-perfect.

Visual analogue scale[9]: It was used to assess the intensity of pain. It comprised of a horizontal line (called horizontal visual analogue scale), 10 cm in length. Patients were asked to mark the intensity of pain on the scale.

RESULTS

The data was entered in Microsoft excel and compiled and was statistically analysed using appropriate tests and presented graphically. Statistical analysis was performed using SPSS software version 21.0 Chicago, Illinois, USA. P values of <0.05 was considered as statistically significant.

OBSERVATIONS

The present study was a prospective, open, randomized, parallel group, comparative trial conducted in 60 patients attending the outpatient Department of Medicine, Rajindra Hospital, Patiala. This study was conducted over a period of four months. Patients with clinically relevant diabetic peripheral neuropathic pain were included in the study. Observations were as follows-

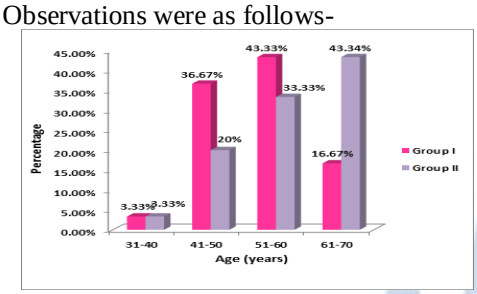

Figure 1: Age Wise Distribution In Group I Vs Group II

The present study included 30 patients of Diabetic peripheral neuropathic pain in each group of different age groups. Mean age (± SD) calculated in Group I and Group II was 53.40±8.41 and 57.17±8.55 years, respectively. P-value (0.091) for the difference in age range between two groups was not significant.

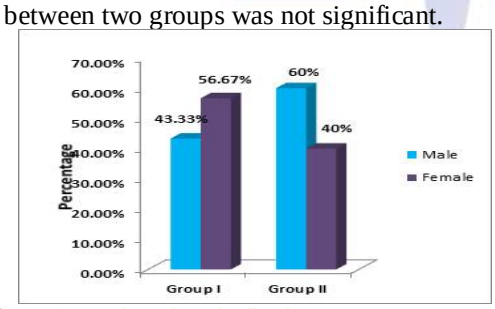

Figure 2: Gender Wise Distribution In Group I Vs Group II

The total number of males who participated in this study were 31 (51.66%) and the total number of females were 29 (48.33%). Group-wise gender distribution in Group I was: males 13 (43.33%) and females 17 (56.67%) and in Group II was: males 18 (60%) and females 12 (40%). P-value (0.197) for the difference in gender distribution between two groups was not significant.

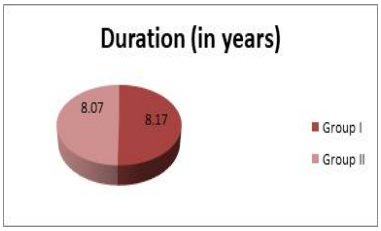

Figure 3: Duration Of Diabetes In Both Groups

Mean (± SD) duration of diabetes calculated in Group I was 8.17±3.36 years and in Group II was 8.07±3.24 years. P-value (0.907) for the difference in duration of diabetes between two groups was not significant.

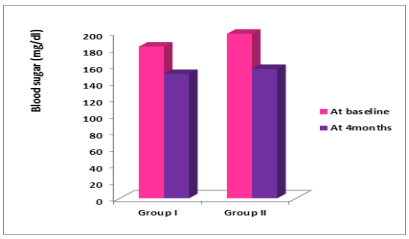

Figure 4.1: Comparison Of Blood Sugar (Mg/Dl) In Group I And Group Ii (With In Group Comparison)

Mean RBS (±SD) calculated in Group I at baseline and four months was 182.70±37.65 mg/dl and 149.70±26.70 mg/dl, respectively. Mean difference was calculated as 33.00±10.95 mg/dl. p value (<0.001) for the difference in random blood sugar levels at baseline and four months in Group I was significant. Mean RBS (±SD) calculated in Group II at baseline and four months was 198.20±30.18 mg/dl and 155.80±22.95 mg/dl, respectively. Mean difference was calculated as 42.40±7.23 mg/dl. p value (<0.001) for the difference in random blood sugar levels at baseline and four months in Group II was significant.

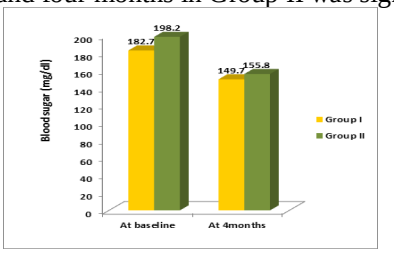

Figure 4.2: Comparison Of Blood Sugar (Mg/Dl) In Group I Vs Group Ii (Between Group Comparison)

Mean RBS (±SD) calculated at baseline in Group I and Group II was 182.70±37.65 mg/dl and 198.20±30.17 mg/dl, respectively. Mean difference was calculated as 15.50±7.48 mg/dl. p value (0.084) for the difference in random blood sugar levels at baseline in both groups was not significant. Mean RBS (±SD) calculated at four months in Group I and Group II was 149.70±26.70 mg/dl and 155.80±22.95 mg/dl, respectively. Mean difference was calculated as 6.10±3.75 mg/dl. p value (0.347) for the difference in random blood sugar levels at four months in both groups was not significant.

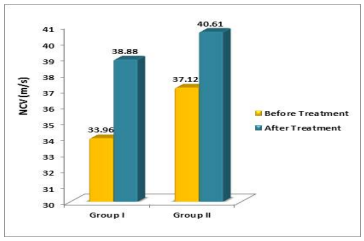

Figure 5.1: Comparison Of Ncv (M/S) In Group I And Group Ii Before And After Treatment (With In Group Comparison)

Mean NCV (±SD) calculated in Group I before and after treatment was 33.96±7.08 m/s and 38.88±6.95 m/s, respectively. Mean difference was calculated as 4.93±0.13 m/s. Nerve conduction velocity improved by 14.52 % after treatment. p value (<0.001) for the difference in NCV at baseline and 4 months in Group I was significant. Mean NCV (±SD) calculated in Group II before and after treatment was 37.12±7.31 m/s and 40.61±7.02 m/s, respectively. Mean difference was calculated as 3.49±0.29 m/s. Nerve conduction velocity improved by 9.40 % after treatment. p value (<0.001) for the difference in NCV at baseline and 4 months in Group II was significant.

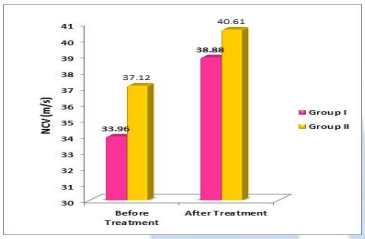

Figure 5.2: Comparison Of Ncv (M/S) In Group I Vs Group Ii Before And After Treatment (Between Group Comparison)

Mean NCV (±SD) calculated at baseline in Group I and Group II was 33.96±7.08 m/s and 37.12±7.31 m/s, respectively. Mean difference was calculated as 3.16±0.23 m/s. p value (0.094) for the difference in NCV at baseline in Group I vs Group II was not significant. Mean NCV (±SD) calculated after treatment in Group I and Group II was 38.88±6.95 m/s and 40.61±7.02 m/s, respectively. Mean difference was calculated as 1.73±0.01 m/s. p value (0.342) for the difference in NCV at 4 months in Group I vs Group II was not significant.

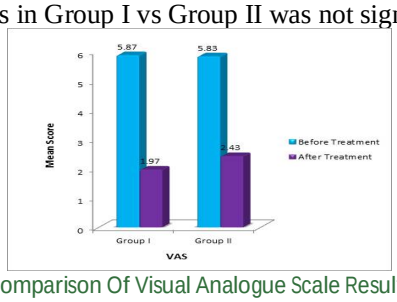

Table 6.1: Comparison Of Visual Analogue Scale Results In Group I And Group Ii Before And After Treatment (With In Group Comparison)

Mean VAS score (±SD) calculated in Group I before and after treatment was 5.87±1.01 and 1.97±0.67, respectively. Mean difference was calculated as 3.90±0.34. VAS score reduced by 66.44% after treatment. p value (<0.001) for the difference in VAS score at baseline and four months was significant. Mean VAS score (±SD) calculated in Group II before and after treatment was 5.83±1.02 and 2.43±0.77, respectively. Mean difference was calculated as 3.40±0.25. VAS score reduced by 58.32% after treatment. p value (<0.001) for the difference in VAS score at baseline and four months was significant.

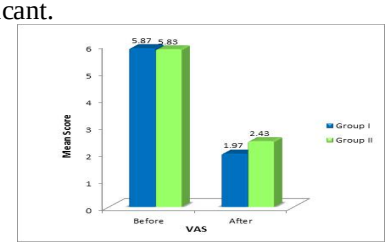

Table 6.2: Comparison Of Visual Analogue Scale Results In Group I Vs Group Ii Before And After Treatment (Between Group Comparison)

Mean VAS score (±SD) calculated at baseline in Group I and Group II was 5.87±1.01 and 5.83±1.02, respectively. Mean difference was calculated as 0.47±0.01. p value (0.899) for the difference in VAS score at baseline in Group I vs Group II was not significant. Mean VAS score (±SD) calculated after treatment in Group I and Group II was 1.97±0.67 and 2.43±0.77, respectively. Mean difference was calculated as 0.46±0.10. p value (0.015) for the difference in VAS score at four months in Group I vs Group II was significant.

DISCUSSION

Diabetes mellitus is associated with a number of chronic sequelae and around 50% of people with DM go on to develop polyneuropathy.[9] The main treatment for DSP with PDN is treatment of painful symptoms.[10]The primary objective of the present study was to compare improvement in sensory nerve conduction velocity in median nerve at the end of four months in patients of DPNP. The salient observations made in this study and their comparison with other studies is discussed as under:

Demographic Characteristics

Age and Gender wise distribution of patients: In present study, maximum number of patients were in age range 41-65 years. The mean age of presentation in Group I and Group II was 53.40±8.4 and 57.17±8.55 years, respectively. The number of patients presenting with DPN increased towards higher age ranges. Both groups were comparable to each other in age wise distribution of patients (p value=0.091). Out of the 60 subjects enrolled in this study, total number of males were 31 (51.66%) and the total number of females were

29 (48.33%). Group-wise gender distribution in Group I was: males 13 (43.33%) and females 17 (56.67%) and in Group II was: males 18 (60%) and females 12 (40%). Difference in gender distribution in both groups was not significant showing equal preponderance of both genders (p value= 0.197).

Duration of Type 2 Diabetes mellitus: In present study, mean (± SD) duration of diabetes calculated in Group I was 8.17±3.36 years and in Group II was 8.07±3.24 years. P-value (0.907) for the difference in duration of diabetes between two groups was not significant. In a study conducted by Moghtaderi *et al* in 2006, study group included 97 males and 79 females. The disease duration was 7.08±4.5 years in men and 5.91±3.2 years in women.[11] These findings are comparable to the mean duration of diabetes in our study.

Efficacy Parameters

Nerve conduction velocity: In our study, both drugs had shown statistically significant improvement in sensory nerve conduction velocity in median nerve. NCV improved by 14.52 % (mean diff.= 4.93±0.13, p<0.001) in group I (gabapentin) and 9.40 % (mean diff.= 3.49±0.29, p<0.001) in group II (amitriptyline) at the end of follow up period i.e. four months. Mean of NCV in group I and group II at baseline was 33.96±7.08 m/s and 37.12±7.31 m/s, respectively (p value= 0.094, not significant) indicating that both groups were comparable for baseline NCV. Mean of NCV in group I and group II after treatment was 38.88±6.95 m/s and 40.61±7.02 m/s, respectively (p=0.342, not significant) indicating that improvement caused by both drugs in NCV was comparable. Although both drugs caused statistically significant improvement in nerve conduction from baseline value, but there was no statistically significant difference in improvement between the two drugs (mean difference= 1.73±0.01). In most of the published literature, electrophysiological testing of nerves was done to screen and diagnose early onset of DPN. We have evaluated SNCV in median nerve across the time to see improvement in neuropathy. Nerve conduction velocity is an expression of the physiological and pathological state of the nerve.[5] The results of our study in case of Gabapentin group are similar to studies conducted earlier in which Gabapentin showed significant improvement in nerve conduction.[12,13] However in contrast to some studies[12,14], where no significant improvement in NCV was shown by Amitriptyline, our study reported significant improvement in NCV in Amitriptyline group as well. The results in case of Amitriptyline group differed from these studies[12,14] as in our study significant improvement in NCV was shown in Amitriptyline group, this can be attributed to significant glycemic control during the study duration. There exists a strong evidence in published literature that glycemic control prevents deterioration in nerve conduction.[15,16] In our study, statistically significant improvement was noticed in random blood sugar levels at 4 months (p <0.001, highly significant) in both the groups. Baseline blood sugar levels were comparable for both the groups. Percentage reduction (21.39 %) in blood sugar was higher in group II as compared to group I but difference was not statistically significant. Many studies in the past have established that lowering of blood glucose retards the deterioration in nerve conduction velocity observed in the diabetic nerve.[15,16,17,18] Similarly in a study conducted by Kikkawa *et al* in 2004 to investigate acute changes in nerve conduction associated with glycemic control, it was shown that four weeks after the start of Insulin treatment, there was a significant improvement in minimal F-wave latencies of the median (P< 0.001) and tibial (P < 0.001) nerves, and in distal latencies (P = 0.01) and sensory nerve conduction velocities (P < 0.001) of the median nerves. This study suggested that glycemic control quickly alters the speed of nerve conduction.[15] In a study conducted by Huang CC *et al* in 2005, it was shown that SPCV (sum of % change in velocity) was significantly inversely correlated with mean HbA1c. It concluded that hyperglycemia is the most important etiology for electrophysiologic progression in type 2 diabetic patients and a mean HbA1c of more than 8.5% will result in significant deterioration in electrophysiology.[19] In concordance with the existing evidence, significant glycemic control in our study can be expected to have an impact on nerve conduction. In a study conducted by Shahabuddin S *et al* in Aurangabad India in 2013, normative values for SNCV in median nerve were established as 56.93 ± 3.47m/s for males and 56.20 ± 3.38 m/s for females.[6] So in concordance with this study, mean of NCV in both groups in our study was less than the established normative data thus indicating neuropathy. In a study conducted by Misra A *et al* in 2014, thirty six patients of peripheral neuropathy were divided into two groups; group 1 received Ondansetron 8 mg per day while group 2 received Amitriptyline 25 mg per day. NCV showed improvement in Ondansetron group with less number of adverse effects as compared to that of Amitriptyline. Also NCV in Amitriptyline group demonstrated worsening in one of the parameters, F-waves, in left tibial nerve.[14] In contrast, our study had shown a statistically significant improvement in sensory NCV in Amitriptyline group. In a study conducted by Rajesh M *et al* in 2015, comparison of pre-drug (0 week) and post-drug (12th week) values showed significant improvement in both latency and conduction velocity in the Pregabalin and Gabapentin treated groups, in both motor and sensory nerves. The improvement in the

Amitriptyline treated group was not found to be statistically significant in either motor or sensory nerves.[12] In contrast, our study had shown improvement in SNCV in both Gabapentin and Amitriptyline groups. A study was conducted by Sabet R *et al* in 2017 to determine the efficacy of gabapentin on nerve conduction studies in patients with mild CTS. Group A received naproxen alone while group B received both gabapentin (100-300 mg) and naproxen for two months. SNCV of the median nerve showed no significant improvements in group A ($p>0.05$), whereas for group B, SNCV was significantly improved at two months after treatment ($p<0.001$).[13] These findings are similar to our study. In another study conducted by Kumar A in Haryana India in 2017, normative conduction velocity in the right median nerve was 52.58 ± 6.62 m/s and in the left median nerve was 52.48 ± 5.92 m/s. In our study, conduction velocity in diabetic nerves was lesser than the normative values.[20] In a study conducted by Nilabh *et al* in 2018 in patients of PIVD treated with gabapentin over a period of six weeks, a significant improvement in nerve conduction parameters i.e. amplitude, latency and conduction velocity in all the motor and sensory nerves included in the study was established. Mean difference in NCV in various nerves before and after treatment ranged from 2.52±0.57 m/s to 5.5±1.69 m/s ($p<0.001$)[21] which is comparable to improvement in our study i.e. 4.93±0.13 m/s in Gabapentin group.

Visual analogue scale: In our study both groups were comparable for baseline VAS score (mean difference=0.47±0.01, p=0.899) and difference was not statistically significant. Mean reduction in VAS score at baseline and after treatment in group I and group II was 3.90±0.34 ($p<0.001$) and 3.40±0.25 ($p<0.001$) indicating that both gabapentin and amitriptyline caused statistically significant reduction in pain .The mean difference between two drugs in reducing VAS score (0.46±0.10, p=0.015) favored Gabapentin. Similar to present study, in a randomized, double-blind crossover study conducted by Max MB *et al* in 1987, Amitriptyline was found to be superior to placebo in relieving burning pain and lancinating pains. Patients able to tolerate higher amitriptyline doses reported greater relief.[22] The similar results were reported in a study conducted by Backonja *et al* in 1999, in which gabapentin monotherapy was efficacious for the treatment of pain and sleep interference associated with diabetic peripheral neuropathy. Gabapentin exhibited positive effects on mood and quality of life, with mild and well tolerated side effects.[23]In a similar study conducted by Dallocchio *et al* in 2000 to compare the efficacy and tolerability of gabapentin and amitriptyline monotherapy in painful diabetic neuropathy, Gabapentin produced greater pain reductions than amitriptyline (P = 0.026). Decreases in paresthesia scores also were in favor of gabapentin (P = 0.004). Adverse events were more frequent in the amitriptyline group than in the gabapentin group: they were reported by 11/12 (92%) and 4/13 (31%) of patients, respectively (P = 0.003).[24] In a similar study conducted by Chandra *et al* in 2010, to compare efficacy of Amitriptyline and Gabapentin in DPN, Gabapentin improved neuropathy symptoms better than amitriptyline at the end of 12 weeks ($p=0.019$).[25] In a study conducted by Rajgopal *et al* in 2017 to compare efficacy and safety of gabapentin and amitriptyline, there was significant decrease in the VAS score in both the groups from baseline at the end of the study period.[26] The results of our study are in concordance with the existing evidence.

CONCLUSION

Diabetic peripheral neuropathy is defined as a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycaemia exposure and cardiovascular risk covariates. The diagnosis of DPN can only be made after a careful clinical examination, different scoring systems have been developed for monitoring progression or response to intervention in clinical trials. Nerve conduction studies remain the most reliable, accurate, and sensitive measure of peripheral nerve function. These have long been a gold standard for the diagnosis of all neuropathies. Management of the patient with DPNP includes lifestyle intervention, glycaemic control and pharmacological therapy for pain relief. Tricyclic anti-depressants and anti-convulsants are considered the first treatment for diabetic neuropathic pain. The present study was done to compare the efficacy of Gabapentin and Amitriptyline. Improvement in SNCV in median nerve was assessed at the end of four months. Evaluation of efficacy of the study drugs was based on improvement in VAS score at baseline and four months. There was statistically significant improvement in nerve conduction velocity in median nerve in both groups. NCV improved by 14.52 % in group I (gabapentin) and 9.40 % in group II (amitriptyline) at the end of follow up period i.e. four months. Although there was statistically significant improvement in nerve conduction from baseline value, but there was no statistically significant difference between the two drugs in improving nerve conduction (mean difference= 1.73±0.01, p=0.342), thus proving them to be comparable in terms of improvement in nerve conduction. There was statistically significant reduction in mean VAS score from baseline in group I (3.90±0.34, $p<0.001$) and group II (3.40±0.25, $p<0.001$) indicating that both gabapentin and amitriptyline caused statistically significant reduction in pain. The mean

difference between two drugs in reducing VAS score (0.46±0.10, p=0.015) favored Gabapentin.

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