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Comparative Analysis of Efficacy and Safety of Gabapentin Vs Amitriptyline in Patients of Peripheral Neuropathic Pain in Case of Diabetes Mellitus

Rajneet Kaur[1], Vijay K. Sehgal[2*], R. P. S. Sibia[3], Avneet Kaur[4], Avnish Kumar[5]

[1]Post Graduate Resident, Department of Pharmacology, Government Medical College, Patiala – 147001, Punjab, India
[2]Professor and Head, Department of Pharmacology, Government Medical College, Patiala – 147001, Punjab, India; vijayksehgal@yahoo.com
[3]Professor and Head, Department of Medicine, Rajindra Hospital, Patiala – 147001, Punjab, India
[4]MBBS Final Professional, Government Medical College, Patiala – 147001, Punjab, India
[5]Professor and Head, Department of Physiology, Government Medical College, Patiala – 147001, Punjab, India

Abstract

Introduction: Diabetes mellitus frequently leads to development of peripheral neuropathies in almost 30-50% of patients and the most common type of neuropathy associated with this condition is Distal Symmetric Sensorimotor Polyneuropathy (DSPN). Gabapentin and Amitriptyline are two drugs frequently used for the treatment of neuropathic pain associated with type 2 diabetes. **Aim of the study:** The aim of this study was to compare efficacy and safety of Gabapentin and Amitriptyline 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 efficacy and safety of Gabapentin and Amitriptyline 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. Therapeutic efficacy of both drugs, by using Michigan Neuropathy Screening Instrument (MNSI) was compared at the baseline and at the end of 4 months. Any adverse drug reactions of the respective drug observed in patient were also noted. 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 were similar ($p>0.05$). The mean age in group I and group II were 53.40±8.41 years and 57.17±8.55 years, respectively. There was statistically significant reduction in mean MNSI scores in questionnaire part and physical examination part in both the groups. Also, there was statistically significant difference between the two drugs in reducing mean MNSI score. Mean difference between two drugs in reducing MNSI score in history part (0.77±0.16, $p<0.01$) and physical examination part (0.75±0.19, $p<0.01$) favoured Gabapentin. No. of adverse drug reactions reported were significantly higher in Amitriptyline group, p value (<0.05) for the difference in ADRs between two drugs was statistically significant. **Conclusion:** In this study, we concluded that both drugs lead to improvement in signs and symptoms of diabetic neuropathy. Gabapentin was proved to be more efficacious than Amitriptyline. Gabapentin treated patient's mean MNSI score at the study end point was significantly lower as compared to the Amitriptyline treated patient's end-point score. Adverse drug reactions reported in our study were mild in both the groups and a significantly higher number of adverse effects were reported in the amitriptyline group. Dizziness and somnolence were two most commonly reported adverse drug reactions.

Keywords: Amitriptyline, Diabetic Peripheral Neuropathic Pain, Efficacy, Gabapentin, Nerve Conduction, Safety

**Author for correspondence*

1. Introduction

Diabetes mellitus is a major cause of morbidity and mortality and leads to development of peripheral neuropathy in almost up to 50% of the patients. Chronic sensor imotor distal symmetrical polyneuropathy is the most common type of neuropathy associated with this condition.[1]

Risk factors implicated for the development of Diabetic Peripheral Neuropathy (DPN) are poor glycaemic control, duration of diabetes, obesity, hyperlipidaemia, elevated albumin excretion rates.[1] DPN was defined by Toronto Consensus Panel on Diabetic Neuropathy as a 'symmetrical, length-dependent sensor imotor polyneuropathy attributable to metabolic and micro vessel alterations as a result of chronic hyperglycaemia exposure and cardiovascular risk covariates.[2]

DPNP is characterized by burning-type pain, tingling ('pins and needles' or paraesthesia), and numbness in limbs. It starts in the toes and gradually moves proximally. It affects upper limbs after it is well established in the lower limbs.[3]

A careful clinical examination of diabetic patients by examining pinprick, temperature, 10-g monofilament pressure sensation at the distal halluces, and vibration perception (using a 128-Hz tuning fork), and ankle reflexes is required for the diagnosis of diabetic peripheral neuropathic pain. Physical examination of feet should be performed for calluses, ulcers and deformities. Different scoring systems have been developed for screening of DPN.[4]

The Michigan Neuropathy Screening Instrument (MNSI) is one such scoring system used widely for the assessment of distal symmetrical peripheral neuropathy in diabetes. It includes two separate assessments, a 15-item self-administered questionnaire and score is derived by summing the abnormal responses, and a lower limb examination that includes inspection of feet and assessment of vibratory and pressure sensation and ankle reflexes and score is derived by assigning points for abnormal findings.[5]

Management of the patient with DPNP includes lifestyle modification, adequate glycaemic control and pharmacological treatment for pain relief. The current approach is to achieve and maintain near-normal glycaemia (HbA1c) as an initial step.[1]

Various classes of drugs that are effective in treatment of DPNP include TCAs, anticonvulsants, SNRIs and opioids. The Toronto Consensus Panel on Diabetic Neuropathy recommended that a Tricyclic Antidepressant (TCA), a Serotonin–Norepinephrine Reuptake Inhibitor (SNRI) or an α2δ agonist should be considered for first line treatments.[6]

Diabetes mellitus is a widely prevalent chronic metabolic disorder and peripheral neuropathy is a major long term complication associated with it.[1] The need for this study arises because generally symptoms of peripheral neuropathy are ignored by patients until it leads to excruciating pain and further complications. Gabapentin and Amitriptyline are two drugs most commonly prescribed for this condition.[7] In India, very few studies have been conducted to compare Gabapentin and Amitriptyline. So in the present study, efficacy and safety of Gabapentin and Amitriptyline was compared.

2. Materials and Methods

2.1 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 were 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.

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 Group II patients received Amitriptyline at a dose of 25 mg HS, subsequent therapeutic response along with any Adverse Drug Reactions (ADRs) observed in patients was noted.

2.2 Study Parameters

Patients were assessed for clinical improvement on the basis of Michigan Neuropathy Screening Instrument score. Comparison of efficacy by MNSI score was done at baseline and four months.

2.3 Michigan Neuropathy Screening Instrument

MNSI has two parts history and physical examination. The history part consists of questionnaire which was self-administered by patient. Responses were added to obtain total score. Physical examination was performed and total score was calculated.[8]

2.4 Adverse Drug Reactions

Any side effects of GBP and AMI in patients on treatment were observed to compare the safety of both drugs.

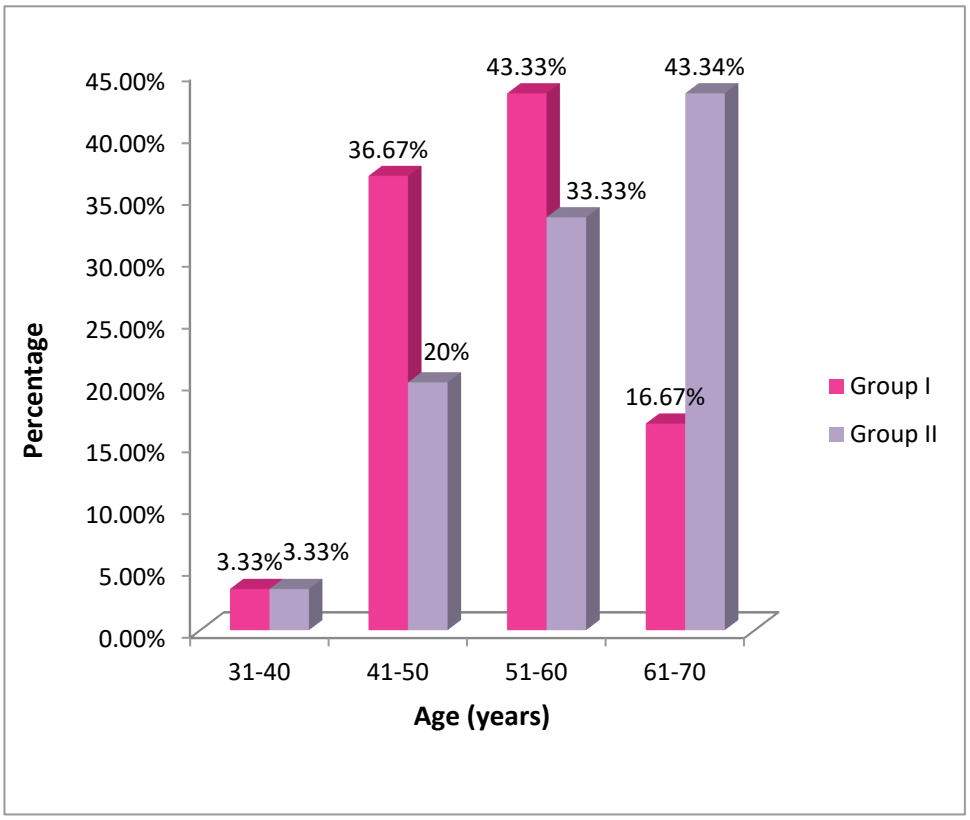

Figure 1. Age wise distribution in group I vs group II.

3. 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.

4. 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-

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 as shown in (figure 1).

The total no. of males who participated in this study was 31 (51.66%) and the total number of females was 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 as shown in (figure 2).

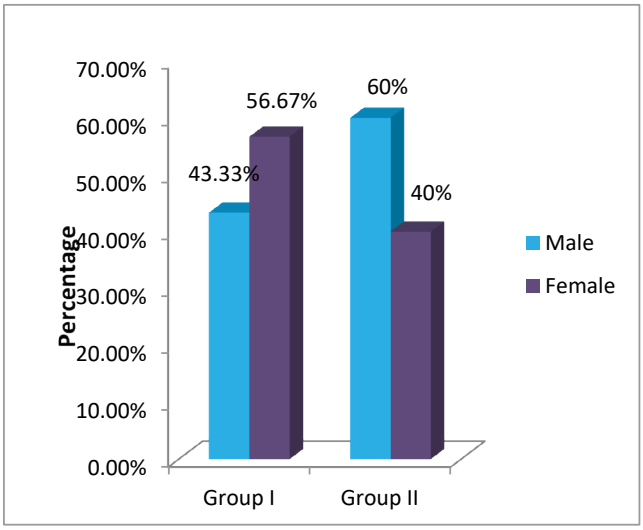

Figure 2. Gender wise distribution in group I vs group II.

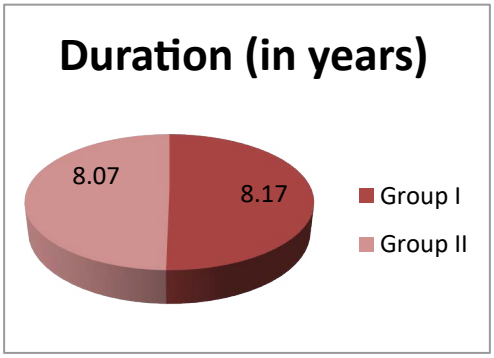

Figure 3. Duration of diabetes in both groups.

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 as shown in (figure 3).

Mean MNSI score for history part calculated in Group I before and after treatment was 5.80±1.06 and 2.43±0.97, respectively. Mean difference was calculated as 3.37±0.09. MNSI score reduced by 58.10% after treatment. Mean MNSI score (±SD) calculated in Group II before and after treatment was 6.27±1.01 and 3.20±1.13, respectively. Mean difference was calculated as 3.07±0.11. MNSI score reduced by 48.96% after treatment. p value (<0.001) for the difference in MNSI score at baseline and four months in both Group I and Group II was significant as shown in (figure 4.1).

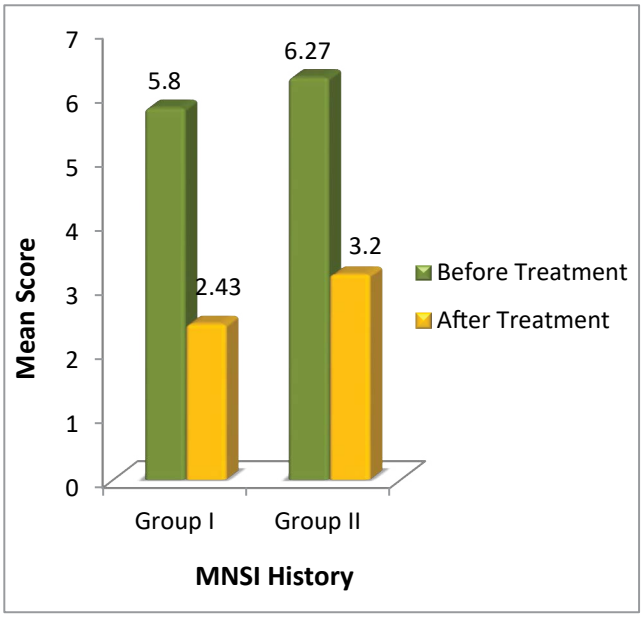

Figure 4.1. Comparison of MNSI score (history part) in group I and group II before and after treatment (with in group comparison).

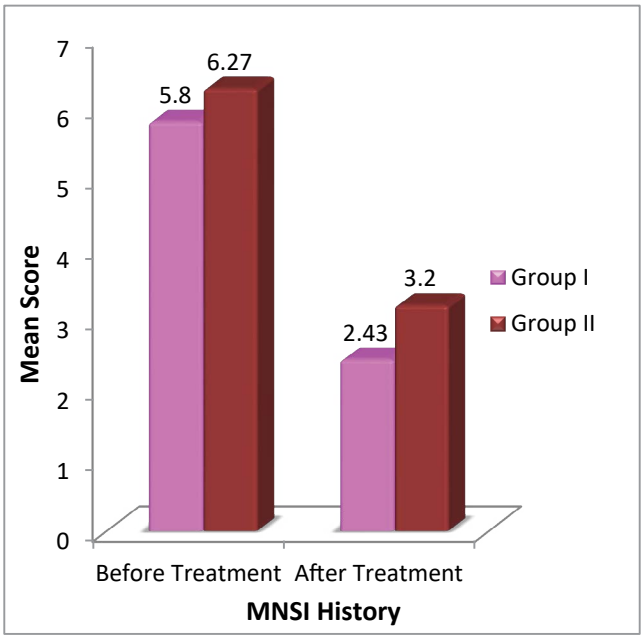

Figure 4.2. Comparison of MNSI score (history part) in group I vs group II before and after treatment (between group comparison).

Mean MNSI score for history part calculated at baseline calculated at baseline in Group I and Group II was 5.83±1.06 and 6.27±1.01, respectively. Mean difference was calculated as 0.47±0.05. p value (0.087) for the difference in MNSI score at baseline in Group I vs Group II was not significant.

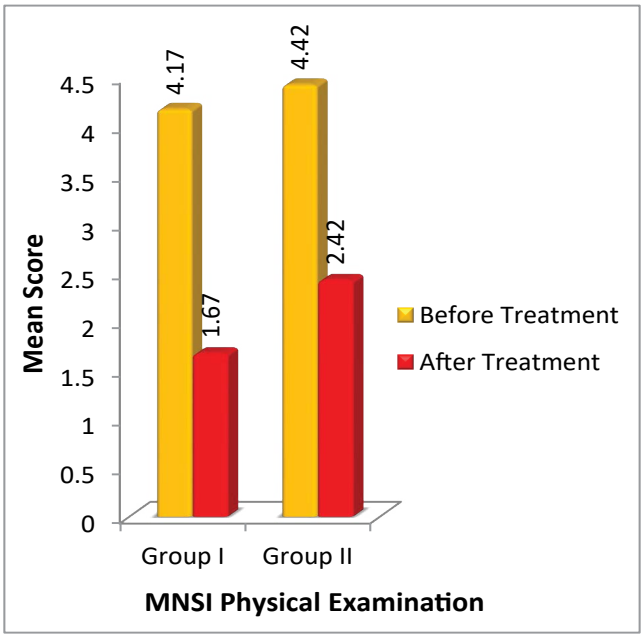

Figure 4.3. Comparison of MNSI score (physical examination part) in group I and group II before and after treatment (with in group comparison).

Mean MNSI score for history part calculated after treatment in Group I and Group II was 2.43±0.97 and 3.20±1.13, respectively. Mean difference was calculated as 0.77±0.16. p value (<0.01) for the difference in MNSI score at four months in Group I vs Group II was significant as shown in (figure 4.2).

Mean MNSI score for physical examination part calculated in Group I before and after treatment was 4.17±0.91 and 1.67±0.76, respectively. Mean difference was calculated as 2.50±0.15. MNSI score reduced by 59.95% after treatment. Mean MNSI score (±SD) calculated in Group II before and after treatment was 4.42±1.04 and 2.42±0.95, respectively. Mean difference was calculated as 2.00±0.10. MNSI score reduced by 45.25% after treatment. p value (<0.001) for the difference in MNSI score at baseline and four months in both Group I and Group II was significant as shown in figure (4.3).

Mean MNSI score for physical examination part calculated at baseline in Group I and Group II was 4.17±0.91 and 4.42±1.04, respectively. Mean difference was calculated as 0.25±0.13. p value (0.327) for the difference in MNSI score at baseline in Group I vs Group II was not significant.

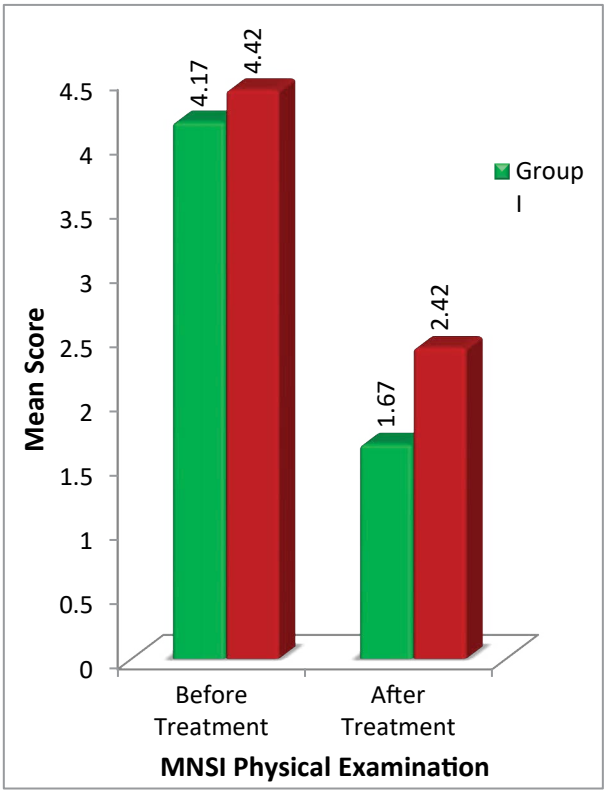

Figure 4.4. Comparison of MNSI score (physical examination part) in group I vs group II before and after treatment (between group comparison).

Table 1. Adverse drug reactions in group I and II

Adverse effects	Group I (n = no. of patients)	Group II (n = no. of patients)
Dizziness	8 (26.66%)	14 (46.66%)
Somnolence	6 (20%)	13(43.33%)
Headache	4(13.33%)	4(13.33%)
Nausea	3 (10%)	3(10%)
Vomiting	1 (3.33%)	3(10%)
Constipation	1 (3.33%)	4(13.33%)
Dry mouth	0	7(23.33%)
Sweating	0	2(6.66%)
Blurred vision	0	1(3.33%)
Weight gain	1 (3.33%)	4(13.33%)
P value	<0.05	

Mean MNSI score for physical examination part calculated after treatment in Group I and Group II was 1.67±0.76 and 2.42±0.95, respectively. Mean difference was calculated to be 0.75±0.19. p value (<0.01) for the difference in MNSI score at four months in Group I vs Group II was significant as shown in figure (4.4).

As shown in (table 1), no. of adverse drug reactions reported were significantly higher in Amitriptyline group, p value (<0.05) for the difference in ADRs between two drugs was statistically significant. The most commonly reported side effects were dizziness 8 (26.66%) cases in group I and 14 (46.66%) cases in group II and somnolence 6 (20%) cases in group I and 13 (43.33%) cases in group II. Dry mouth was also reported among 7 (23.33%) patients in group II.

5. Discussion

The primary objective of the present study was to compare reduction in MNSI score with pharmacological treatment 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:

5.1 Demographic Characteristics

5.2.1 Age and Gender Wise Distribution of Patients

In present study, maximum number of patients was 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 was 31 (51.66%) and the total number of females was 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).

5.2 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.[9] These findings are comparable to the mean duration of diabetes in our study.

6. Efficacy

6.1 Michigan Neuropathy Screening Instrument Score

In our study both groups were comparable for baseline MNSI score in history part (mean difference = 0.47±0.05, p = 0.087) and physical examination part (mean difference = 0.25±0.13, p = 0.327) and difference was not statistically significant.

Mean reduction in MNSI score in history part in group I and group II was 3.37±0.09 (p<0.001) and 3.07±0.11 (p<0.001), respectively. Mean reduction in MNSI score in physical examination part in group I and group II was 2.5±0.15 (p<0.001) and 2.00±0.10 (p<0.001), respectively. This indicated that both gabapentin and amitriptyline cause statistically significant improvement in signs and symptoms of neuropathy.

The mean difference between two drugs in reducing MNSI score in history part (0.77±0.16, p<0.01) and physical examination part (0.75±0.19, p<0.01) favored Gabapentin.

In a study conducted by Mete et al in 2008, the mean score of the patients obtained in the MNSI questionnaire

form was 6.7±2.7. Diabetic peripheral neuropathy was diagnosed in patients with a physical examination score ≥2.5.[10] Similarly in our study baseline mean MNSI questionnaire score and physical examination score in group I was 5.80±1.06 and 4.17±0.91, respectively and in group II was 6.27±1.01 and 4.42±1.04, respectively.

Similar results were reported in a study conducted by Chandra *et al.,* in 2010 to compare efficacy of Amitriptyline and Gabapentin in DPN, there was significant reduction in MNSI scores between the two groups. Gabapentin improved neuropathy symptoms better than amitriptyline at the end of 12 weeks (p = 0.019).[11]

Evaluation of this MNSI scoring shows improvement in the signs of neuropathy like vibration sensation, dry skin and touch sensation. Other studies have used MNSI scoring to screen and diagnose, we have utilised MNSI scoring to see improvement in sign and symptoms of neuropathy.

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).[12]

The results of our study are in concordance with the existing evidence.

6.2 Safety Analysis

In our study, no. of adverse drug reactions reported were significantly higher in Amitriptyline group, p value (<0.05) for the difference in ADRs between two drugs was statistically significant, indicating that Gabapentin is a safer drug as compared to Amitriptyline. Most commonly reported side effects were dizziness 8 (26.66%) cases in group I and 14 (46.66%) cases in group II and somnolence 6 (20%) cases in group I and 13 (43.33%) cases in group II. Dry mouth was also reported in 7 (23.33%) cases among group II. Overall both drugs were well tolerated, side effects were mild. None of the side effects lead to withdrawal or exclusion of any patient.

Similar results were reported in a study conducted by Serpell *et al.,* in 2001 to evaluate the efficacy and safety of gabapentin in the treatment of neuropathic pain, it was reported that Gabapentin was well tolerated and the most common adverse events were mild to moderate dizziness and somnolence.[13]

In a study conducted by Sator-Katzenschlager *et al.,* in 2005 to compare the efficacy and side effects of gabapentin, amitriptyline, and their combination, it was reported that the incidence of minor side effects which prevented a further increase in the daily drug dosage was lower in the gabapentin group than in the two other groups throughout the observation period, the difference reaching statistical significance after three months (P < 0.05).[14] This establishes the results of our study.

The present study was fraught with a few limitations. First of all, the duration of the study was limited with limited patient enrolment. Further, the data was cross-sectional and therefore the causal relationship between the drugs and peripheral neuropathy could not be firmly established. Another limitation was the region-specific nature of the research data. So, the results cannot be generalized to other population groups.

Further studies with a larger sample size and longer duration are, therefore, warranted. The studies with a multicentric patient enrolment will help in the generalization of data to larger populations and improve external validity in the general population and different settings.

7. Conclusion

The present study was done to compare the efficacy and safety of Gabapentin and Amitriptyline. Evaluation of efficacy of the study drugs was based on improvement in neuropathic sign and symptoms of the patients by MNSI score, at baseline and four months.

In this study we concluded that both drugs lead to improvement in signs and symptoms of diabetic neuropathy. Gabapentin was proved to be more efficacious than Amitriptyline. Gabapentin treated patient's mean MNSI score at the study end point was significantly lower as compared to the Amitriptyline treated patient's end-point score. Adverse events reported in our study were mild in both the groups and no discontinuation of drug was required. There were a significantly higher number of adverse events reported in the Amitriptyline group as compared to Gabapentin group. Dizziness and somnolence were two most commonly reported adverse drug reactions in both the groups. Dry mouth was also

reported in Amitriptyline group. Overall, both the study drugs were well tolerated and there was not any severe adverse event in our study.

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