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TO COMPARE THE EFFICACY AND SAFETY OF GABAPENTIN AND PREGABALIN FOR PERIPHERAL NEUROPATHY IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT
Diabetic neuropathies are nerve damaging disorders and occurs in ~ 50% of individuals with long – standing type 1 and type 2 Diabetes Mellitus. Clinical features of diabetic neuropathy are mild tingling sensation in one or two of the toes in some case and in other cases, patients may be affected with severe pain and numbness in foot, sensory loss and dysesthesia. There are very less studies done in this field and no pattern of efficacious drugs is set in literature, although drugs are used to give symptomatic relief and to decrease the progress of disease but their ADR profile is also not clearly understood. Keeping these problem in mind, study was planned to evaluate efficacy and safety of Gabapentin & Pregabalin in Diabetic neuropathic patients. Total 60 patients were enrolled in the study. Neuropathy Symptom Score (NSS) & Neuropathy Deficit Score (NDS) were used to evaluate efficacy at 0, 30 and 90 days of treatment. ADRs were noted for monitoring safety at 30 and 90 days of treatment. Mean Difference of Gabapentin was more than Pregabalin after applying NSS & NDS. While Mean ADR Score was less in Gabapentin compare to pregabalin. P-value was significant after comparing both drugs. Gabapentin was more efficacious than Pregabalin after evaluating NSS and NDS value. More number of ADR were seen in Pregabalin compared to Gabapentin. Hence Gabapentin was more efficacious and safer drug for Diabetic neuropathy.

KEYWORDS: Diabetic Neuropathy, Neuropathy Symptom Score, Neuropathy Deficit Score.

INTRODUCTION
Diabetes mellitus is a group of metabolic disorder in which there is increased blood glucose level i.e. hyperglycaemia. Diabetes mellitus is of 2 types. Type 1 is insulin dependent and type 2 is insulin independent. In 2000, there were 170 million cases all over the world and is supposed to reach 366 million by 2030.[1] More than 7.1% of Indians adult population that is approximately 62 million people are affected by diabetes mellitus. This is the leading cause of morbidity and mortality worldwide.[2]

Most commonly caused neuropathy by diabetes is peripheral neuropathy. This neuropathy affects mainly peripheral nerves mainly of legs which lead to sensation impairment, deformed foots, infections and ulcers leading to amputation. Neuronal ischemia caused by narrowing of micro vessels is the main cause of neuropathy. Diabetic neuropathy may present with mild tingling sensation in toes and mild to severe pain, numbness and dysesthesia. Pain presented may be dull or achy, burning or pricking.[3] The diagnostic basis of diabetic neuropathy are symptoms, signs, medical history and physical examination. Examination includes muscle tone, strength, tendon reflexes and sensitivity to touch, temperature, and vibration. Other tests being conducted are filament test, nerve conduction studies, electromyography, quantitative sensory testing and autonomic testing.

Most commonly used drugs in treatment of diabetic neuropathy are Tricyclic antidepressants, gabapentin and pregabalin. Though TCAs are drugs of choice for treatment but there is a long list of adverse effects.[4] Therefore, we prefer gabapentin or pregabalin over them. Gabapentin and Pregabalin are GABA analogs which act on voltage- gated Calcium channels. Sedation, peripheral oedema, dizziness and drowsiness are the common side effects of gabapentin and pregabalin.

In Europe, pregabalin was approved for treatment of neuropathic pain in 2004. And in US it was approved for neuropathic pain as well as herpetic neuralgia in 2005.[5] The European Federation of Neurological Societies

recommends pregabalin as a first line treatment of diabetic neuropathic pain, post herpetic neuralgic pain, and central neuropathic pain.[6]

Likewise, gabapentin was also approved for treatment of neuropathic pain in Europe but post herpetic neuralgia in US.[7] But very few approx. 10% people taking it for fibromyalgia get relief.[8] But in case of post herpetic neuralgia and diabetic neuropathy, there are strong evidences of its effectiveness.[9] It reduces pain, therefore, helpful in reducing uses of opioids in surgery and in neuropathic pain due to malignancies.[10] According to Rudroju et. al. study, gabapentin was shown to be more effective treatment followed by other drugs like pregabalin, duloxetine, amitriptyline, venlafaxine and placebo.[11] Another trial conducted by Devi et al in 2012 comparing gabapentin and pregabalin showed no significant difference between the treatments of neuropathy.[12],[13] The major problem in the treatment of diabetic neuropathy is the lack of active-controlled studies that also assess combination therapy. Extensive literature search did not reveal any study which compares safety and efficacy of pregabalin and gabapentin in adult population with diabetic neuropathy. Therefore, this study was done in a tertiary care hospital to compare therapy of peripheral neuropathy in adults with type II diabetes mellitus.

MATERIAL AND METHODS

Aims and Objective

1. To compare the efficacy of Gabapentin and pregabalin used in treatment of peripheral neuropathy.
2. To evaluate the safety profile of various drugs used in treatment of peripheral neuropathy.

Types of Study

This Prospective Study was conducted on already diagnosed cases of Type II DM with peripheral neuropathy.

Place of Study

The study was conducted in department of Medicine and department of Pharmacology TMMC & RC, Moradabad, U.P.

Study design

On the basis of inclusion and exclusion criteria, the patient attending the OPD of medicine department was enrolled.

Informed consent was taken from every patient before enrolling him or her in the study.

The Ethical clearance was taken from the Institute's Ethical committee before starting this study.

Sample size was 60. 30 patients each, after randomization, shall be included in each of the following group of therapy.

Group A- Gabapentin
Group B- Pregabalin
The dose of the medications was titrated as per the treatment guideline.

Inclusion criteria

- Patients more than 30yrs and less than 70yrs of age and of both sex were included in this study.
- Patients of DM who were diagnosed with peripheral neuropathy on basis of American Diabetes Association (ADA) criteria.
- Patient who have not taken any treatment for Neuropathic pain in the past 6 months are included in the study.

Exclusion criteria

- Patient suffering from serious infection i.e. T.B, HIV and other immunocompromised conditions was not included in this study.
- Pregnant and Lactating females were excluded from the study.
- Patients having any other major medical or surgical illness were also excluded from the study.
- Patients suffering from Neuropathic pain of aetiology other than DM II were excluded from study.

Assessment Criteria

Detailed history regarding the duration and treatment of diabetic peripheral neuropathy was recorded.

Each patient was assessed on day 0, followed by assessment on day 30 and day 90 on the basis of neuropathy symptoms score(NSS) and neuropathy deficit score(NDS).

Separate records were maintained for different groups of drugs so that their efficacy and safety can be compared.

Safety of the drugs was assessed by the number of adverse effect caused by the individual or combination of drugs.

ADRs was recorded on ADR Record sheet on day 30 and day 90.
Symptoms of diabetic neuropathy was assessed by following Score:

- Neuropathy Symptom Score (NSS)
- Neuropathy Deficit Score (NDS)

On the basis of neuropathy symptom score patient will be divided into three grades:
Grade I (mild symptoms = 3-4)
Grade II (moderate symptoms = 5-6)
Grade III (Severe symptoms = 7-10)

NDS is calculated by ankle reflex, pinprick sensation, temperature sensation and vibration sense are tested with tuning fork.

Similarly, on the basis of neuropathy deficit score patient will be divided into three grades: -
Grade I (mild neuropathic deficits = 3-5)
Grade II (moderate neuropathic deficits = 6-8)
Grade III (severe neuropathic deficits = 9-10)

Statistical Analysis: Data was analyzed and tabulated with the help of using SPSS v20 software and Microsoft excel software.

RESULTS

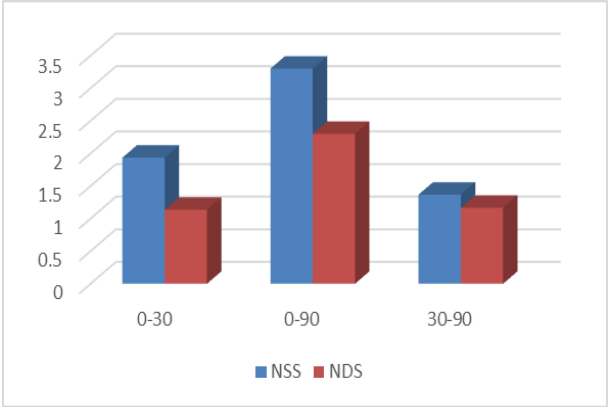
In our study, 60 patients were enrolled and divided into two groups Total 30 Patients in GROUP A were treated with GABAPENTIN and 30 patients in GROUP B treated with PREGABALIN.

Demographic Distribution

After evaluation of result we came to know that 59% female and 41% male were suffering from diabetes neuropathy. The most common age group affected with diabetic neuropathy was 41-50 years followed by 51-60 years and 61-70 years.

Group A

In Group A difference between mean NSS at 0 to 30 days was 1.93, 30 to 90 days was 1.367 and 0- 90 days was 3.3 respectively. Mean NDS difference at 0-30 days was 1.13, 30-90 days was 1.167 and 0-90 days was 2.30. Graphical representation of the same is shown in the graph no 01.



Graph 01: Mean difference of Group A.

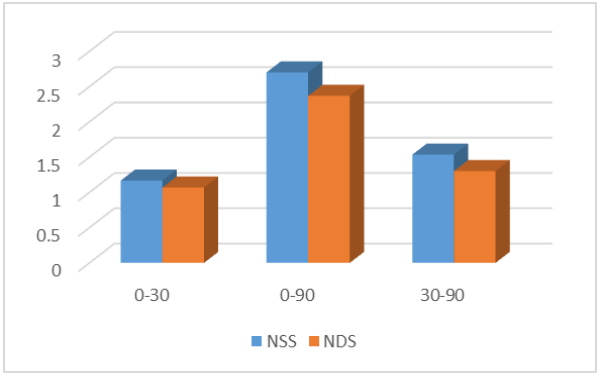
When we compare NSS at 0-30 days, 30-90 days and 0-90 days the t values were 10.102, 8.411 and 12.748 respectively. NDS was also compare at 0-30 days, 30-90 days and 0-90 days. The t values were 7.577, 5.178 and 8.736. As p-value is less than 0.05, hence it is significant which reject null hypothesis. (Table no.01).

Table. 01: Mean difference, std. error mean, t-value & p-value at different intervals of time.

Group A	Mean Difference	Std. Error Mean	t-value	p-value
NSS				
0-30 days	1.933	0.191	10.102	0.000
30-90 days	1.367	0.162	08.411	0.000
0-90 days	3.300	0.259	12.748	0.085
NDS				
0-30 days	1.133	0.150	07.577	0.000
30-90 days	1.167	0.225	05.178	0.003
0-90 days	2.300	0.263	08.736	0.004

Group B

At 0-30 days NSS with mean difference (WMD) of 1.16 was noted, at 30-90 days WMD was 1.53 and at 0-90 days WMD as 2.7 was noted. Mean NDS difference 0-30 days was 1.067, 30-90 days is 1.300 and 0-90 days was 2.367. Graphical representation of same are shown in graph no.02.



Graph 02: Mean difference of Group B.

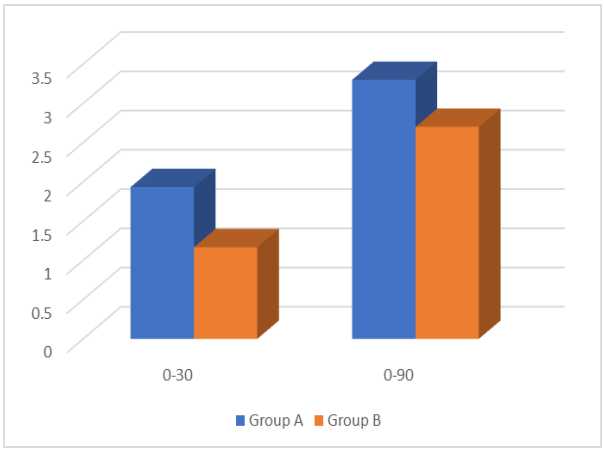
When NSS was compared at 0-30 days, 30-90 days and 0-90 days the t values were 7.30, 6.56 and 10.09 respectively. Similarly, NDS was compare at 0-30 days, 30-90 days and 0-90 days, and the t values were 7.89, 8.12 and 11.18. As p-value is less than 0.05, hence it is significant which reject null hypothesis. (Table.02).

Table. 02: Mean difference, std. error mean, t-value and p-values at different time intervals.

Group B	Mean Difference	Std. Error Mean	t-value	p-value
NSS				
0-30 days	1.167	0.160	7.309	0.000
30-90 days	1.533	0.234	6.565	0.006
0-90 days	2.700	0.268	10.090	0.020
NDS				
0-30 days	1.067	0.135	7.899	0.000
30-90 days	1.300	0.160	8.120	0.000
0-90 days	2.367	0.212	11.183	0.023

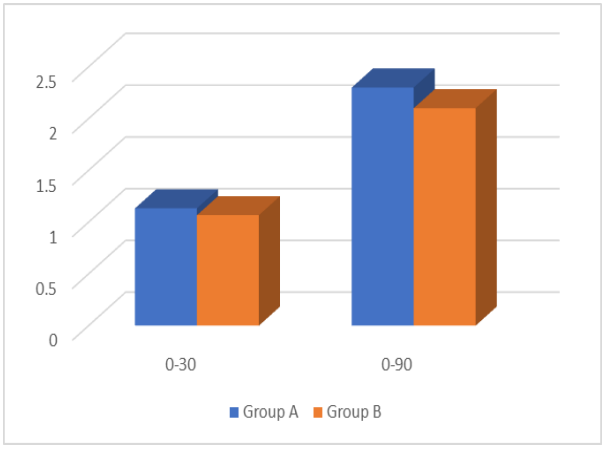
Comparison of efficacy between groups

On comparing mean NSS after 30 days, this was seen that Group A had highest mean difference 1.93 followed by Group B 1.16. After 90 days of treatment mean NSS difference for group A was 3.3 and for group B was 2.7. Graphical representation of same is shown graph number 03.



Graph 03: Comparison of mean score of NSS in between groups.

On comparing NDS as seen in graph below, after 30 days, efficacious group was A with mean difference score of 1.13 followed by Group B with mean difference in score 1.067. After 90 days of treatment the mean difference in NDS is 2.3 for group A followed by group B with score 2. Same is shown in the graph number 04.



Graph 04: Comparison of mean score of NDS in between groups.

Comparison of safety between groups

In group A Total number of ADR noted after 30 & 90 days were 41 and 42 with mean of 1.36 and 1.4. Common ADR were Drowsiness, Dizziness, Tremor, Tiredness, sedation and headache. In Group B total number of ADR noted after 30 & 90 days were 55 and 48 with mean of 1.83 and 1.6. Common ADR were Dry mouth, Dizziness, Sedation, Headache and Loss of Coordination. On Comparison of ADRs noted among both groups, after 90 days of treatment most safe group is Group A with mean ADR of 1.4 followed by Group B of mean ADR 1.6.

DISCUSSION

During our study, when we evaluated the demographic distribution of patients suffering from DPN, we came to know that out of 60 total patients enrolled, 59% were females and 41% were males. This depicts that in our study, there were more female patients than males. On analysis, Group A treated with gabapentin was more efficacious than group B treated with pregabalin. On the basis of safety profile, safer drug found was gabapentin than pregabalin.

Gilron I.et. al. in year 2009, a study focused about neuropathic pain, the prevalence of diabetic polyneuropathy is far more common in male i.e. 65% as compare to female with 35 %.[14] Likewise, in another Indian study done by A. Abhiijeet et.al. in year 2014 at Maharashtra says that the prevalence of Diabetic neuropathy is about 30 % in overall diabetic patients with 66 % were male and only 33 % were female.[15] Another study with the same result done by Karunanithi P. et al. in year 2014 shows that 62 % male and 38 % female were suffering from Diabetic neuropathy.[16] A recent study done by Gogia S. et.al. in year 2017 again indicates more prevalence of diabetic neuropathy in male (76.9 %) than females (23.1%).[17] None of the above study correlates with our study in gender wise distribution of Diabetic neuropathy among adults.

In reference with meta-analysis of 21 studies done by Rudroju N. et. al. in year 2013 clearly says that gabapentin was shown to be more efficacious than pregabalin, though it was not significant. Study further shows that gabapentin was most efficacious followed by pregabalin, amitriptyline and placebo.[18]

The meta-analysis done by Quilici S. et. al. in year 2009 which includes 11 studies, clearly shows that pregabalin is better than placebo as far efficacy is concerned. Also, same study says that pregabalin produce significant ADR in the form of somnolence & Dizziness which correlates with our study which says, Dizziness, headache and sedation are most common ADR noted in patient treated with pregabalin.[19]

The results of our study are different to recent study done by Axelerad D. et. al. in year 2014, the efficacy of the drugs pregabalin, gabapentin, sertraline and duloxetine were compared in the patients of diabetic peripheral neuropathy. Gabapentin and sertraline has the lesser effects in the neuropathy than pregabalin and duloxetine. These results are in contrast to the results achieved from our study which state that gabapentin is more efficacious than pregabalin in diabetic neuropathy.[20]

Limitations of study are small sample size, blinding was not done, comparison with placebo and less number of studies available in India. Our study was not funded and no financial help was taken from any source. These are main problem for deep evaluation and discussion.

CONCLUSION

In our study, we conclude that the efficacious group was Group A treated with Gabapentin followed by group B treated with pregabalin. Suppression of neuropathic signs and symptoms were seen in this group patients. When we compared safety profile, less number of ADRs were found in Gabapentin group compared to Pregabalin group. But, we strongly recommend more such studies with inclusion of large number of patients should be conducted to establish these results as guidelines in future.

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