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SAFETY AND EFFICACY OF PREGABALIN WITH NORTRIPTYLINE AND GABAPENTIN WITH NORTRIPTYLINE IN DIABETIC NEUROPATHY AND RADICULOPATHY

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ABSTRACT
Objective: To study and evaluate the safety and efficacy associated with use of pregabalin with nortriptyline and gabapentin with nortriptyline, in patients with diabetic neuropathy and radiculopathy and their respective ADR. **Background:** Diabetic neuropathy and radiculopathy are common cause of disability. Diabetic neuropathy is the most common complication associated with DM that affects approximately one third of people with DM type 1 / type 2. Anticonvulsant medications are now considered the best treatment option with fewer adverse effects and in this study we compare the safety and efficacy of pregabalin and gabapentin in combination with antidepressant drug nortriptyline. **Methodology:** A hospital based prospective study was conducted in Neurology Out- Patient Department of Aster Prime Hospital, Hyderabad, India. Patient details were collected using data collection forms. Patients were counseled about the disease. Visual analogue score (VAS) and Modified MAC NAB criteria of spine questionnaire was used. **Results:** Out of 150 patients, 45 patients were treated with pregabalin with nortriptyline and 105 patients were treated with gabapentin with nortriptyline and using SPSS software which incorporates mean, standard deviation method, t test and chi square test, results were calculated. Results obtained illustrate that pregabalin with nortriptyline was associated with less adverse effects and is considered to be more safe and efficacious when compared with gabapentin with nortriptyline. **Conclusion:** It is crucial to find an effective and an equally safe treatment to reduce the further risk of co morbidities associated with diabetic neuropathy and radiculopathy.

KEYWORDS: Diabetic neuropathy, Radiculopathy, Pregabalin, Gabapentin, Nortryptiline.

INTRODUCTION
Diabetic neuropathy is the most common complication associated with diabetes mellitus that affects approximately one third of people with diabetes mellitus type 1 / type 2. But it occurs more commonly in people with type 2 diabetes. Radiculopathy (nerve root dysfunction) is a common condition that affects more than 5% of the population, with an equitable distribution between men and women. According to the International Diabetes Federation, 382 million people worldwide are currently affected by diabetes[1], which is one of the leading causes of neuropathy.[2]

Diabetic neuropathy is nerve damage caused by diabetes. It is believed that this is dua to a micro vascular lesion involving small blood vessels that supply blood to the nerve (vas nervorum) in addition to the macrovascular condition. The extent of neuropathy increases with the duration of diabetes mellitus. Different types of radiculopathy includes peripheral neuropathy (distal symmetric polyneuropathy)- damage to the nerves that usually affects the legs and feet and can sometimes affect the hands and arms, autonomic neuropathy is damage to nerves that control your internal organ. Focal neuropathy is a condition that damages a single nerve, mainly the nerves of the hand, head, leg and torso. The most common cause of focal neuropathy is "CARPAL TUNNEL SYNDROME", proximal neuropathy is a rare and disabling type of nerve injury to the hip, buttocks, or thigh. There is a high prevalence of autonomic neuropathy (50-60%)[3][4] And is associated with significant mortality and morbidity. When the nerve roots of the spine are punctured or damaged, the resulting symptoms are called radiculopathy. Radiculopathy is classified into lumbar, cervical, thoracic. Lumbar Radiculopathy is, irritation and compression of one or more roots occur in the lumbar area of spine. Cervical radiculopathy is compression of

cervical nerve roots which may include pain, sensory deficits, motor deficits, diminished reflexes. Thoracic radiculopathy is the pain and resulting symptoms associated with compression of the nerve or nerve roots of the thoracic spine.[9]

Early detection and control of diabetes and other co existing risk factors for neuropathy (e.g., hypertension, smoking, alcohol abuse) can help prevent, delay, or slowdown the progression of diabetic neuropathy.[5,6,7]

MATERIALS AND METHOD

- A 6 months survey study was conducted in Neurology department of Aster prime hospital Hyderabad. A minimum of 150 patients were selected as subjects for the study. Data was collected in data collection form which included Patient detail like age, gender, medical history, medication history and social history, current medications (drugs prescribed, brand/generic, dose, route, frequency and duration), lab reports, and diagnosis of patient. Prescription details like consultation date, patient identification number, and treatment given. SPSS statistical method was used.
- Visual analogue score (VAS) and Modified MAC NAB criteria of spine questionnaire was used to assess the efficacy of treatment. Patients were also counseled about the disease.

STUDY CRITERIA

Inclusion criteria

- Patients who were diagnosed with diabetic neuropathy and radiculopathy of both genders.
- Patients who were prescribed pregabalin with nortriptyline or gabapentin with nortriptyline.
- Patients who were willing to give verbal informed consent for the study.

Exclusion criteria

- Pregnant women, as there is no evidence for the use of drugs pregabalin and gabapentin in pregnancy. (Category C).
- Patients who are not willing to give verbal informed consent for the study.
- In patients or the hospitalized patients and Post-operative patients.

Table 1

TABLE: TITLES FOR COLLECTING DATA
Patient Details: IP No., age, DOA, DOD, BMI, history, co morbidities
lab findings like CBP, MRI, CT SCAN,
Provisional diagnosis, Final diagnosis
Drug prescribed and time, dose, duration of treatment (Pregabalin-NT or Gabapentin-NT)
Non pharmacological treatment
Adverse effect : drowsiness, sedation, swelling etc
Efficacy of drug : VAS score BT, AT (2weeks, 4weeks, 6weeks, 8weeks)

RESULTS AND DISCUSSION

Table 1: Age Distribution.

Age Interval (yrs)	N	Percentage (%)
21-30	9	6
31-40	**43**	**29**
41-50	37	25
51-60	35	23
61-70	20	13
>70	6	4

Mean ± SD is 48.01±12.79

Table 2: Treatment Group.

Group	Male		Female	
	N	%	N	%
I (45)	26	58	19	42
II (105)	50	48	55	52

Table 3: Group wise Age Distribution.

Group	N	Percentage (%)	Mean ± SD	P value
I	45	30	47.31±12.82	0.6612
II	105	70	48.31±12.82	

P value calculated by Independent t test

Statistically significant difference was not found in the age between the groups.

Table 4: Diagnosis Wise Distribution.

S. No	Diagnosis	N	
		Group I	Group II
1	Cervical disc prolapse	11	31
2	Diabetic neuropathy	5	11
3	Lumbar disc disease	29	63

Table 5: Comparison of VAS Score before and After Treatment in Group I.

Review	Minimum	Maximum	Mean ± SD	P value
BT	5	10	7.91±1.45	<0.0001
AT	0	8	3.08±1.90	

P value calculated by Dependent t test.

Statistically significant difference was found in the VAS score of before and after treatment of Group I.

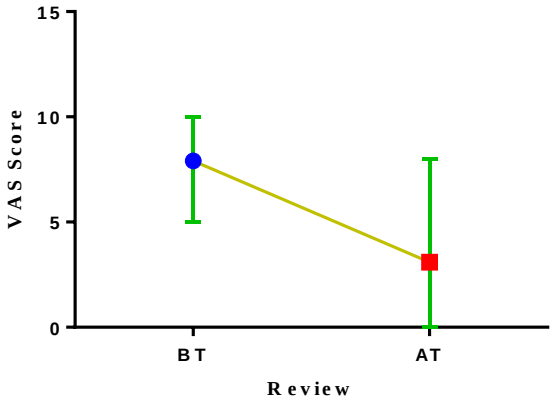

Figure 1: Comparison of VAS Score before and After Treatment in Group I.

Table 6: Comparison of VAS Score before and After Treatment in Group II.

Review	Minimum	Maximum	Mean ± SD	P value
BT	5	10	8.12±1.39	<0.0001
AT	0	10	4.86±2.82	

P value calculated by Dependent t test.

Statistically significant difference was found in the VAS score of before and after treatment of Group II.

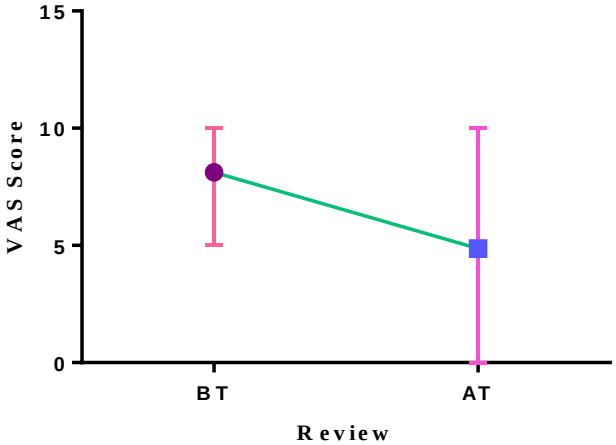

Figure 2: Comparison of VAS Score before and After Treatment in Group II.

Table 7: Comparison of Modified MAC NAB Score before and After Treatment in Group I.

Review	Modified MAC NAB Score				P value
	Poor	Fair	Good	Excellent	
BT	32	12	1	0	<0.0001
AT	1	4	24	16	

P value calculated by Chi square test.
Statistically significant difference was found before and after treatment in Group 1.

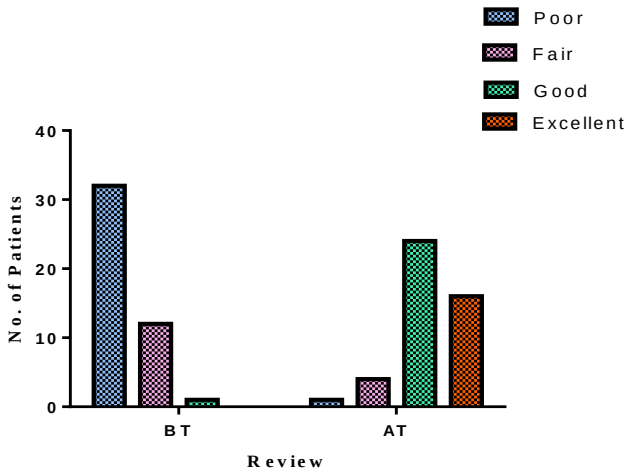

Figure 3: Comparison of Modified MAC NAB Score before and After Treatment In Group I.

Table 8: Comparison of Modified MAC NAB Score before and After Treatment in Group II.

Review	Modified MAC NAB Score				P value
	Poor	Fair	Good	Excellent	
BT	73	29	3	0	<0.0001
AT	21	22	46	16	

P value calculated by Chi square test.
Statistically significant difference was found before and after treatment in Group 2.

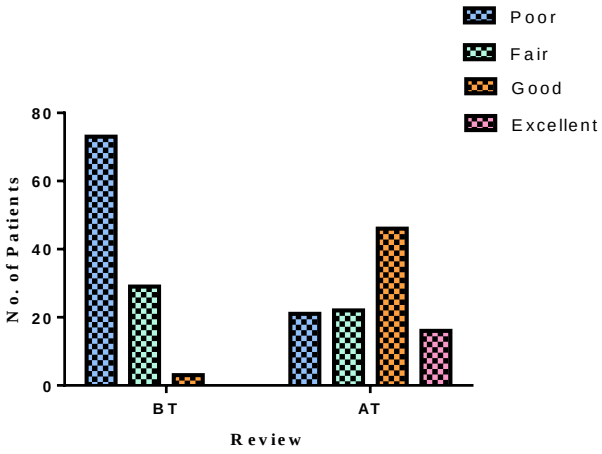

Figure 4: Comparison of Modified MAC NAB Score before and After Treatment In Group II.

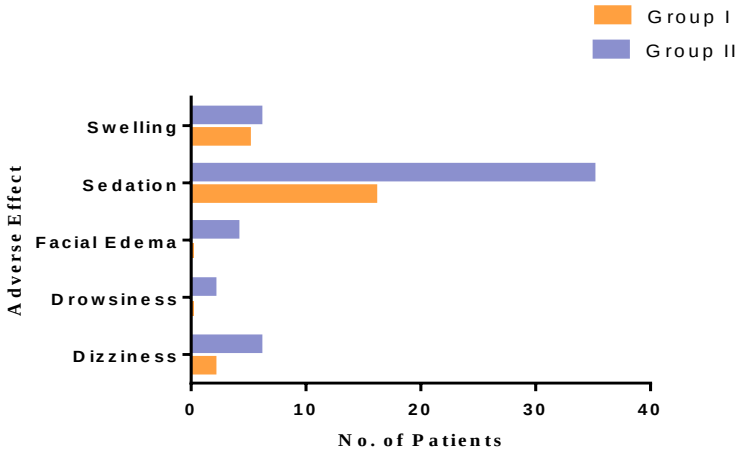

Figure 5: Proportion of Adverse Effects.

DISCUSSION

Patients were divided into 2 groups i.e.:

- Group I- Pregabalin with Nortriptyline
- Group II- Gabapentin with Nortriptyline
- And the results were calculated using SPSS version 17.
- Out of 150 patients, 76 patients were males with 50.6% and 74 patients were female with 49.4%. *(P value <0.05 is considered significant since the Confidence interval is 95%).*

1. The ages of the patients in our study ranged between 21-70 years with Mean ± SD: 48.01±12.79. Out of 150 patients, 35%(N=52) belonged to the age group of 21-40 years; 25% (N=37) were between 41-50 years of age; 23% (N=35) were between 51-60 years of age; 13% (N=20) were between 60-70 years of age; 4%(N=6) were above 70 years of age.
2. Group I(N=45) consisted of 58% males (N=26) and 42% females (N=19) and Group II (N=105) constituted of 48% males(N=50) and 52% females (N=55).
3. Statistically significant difference was not found in the age between the groups. i.e group I and group II and 30% of the patients belonged to group I (N=45) and 70% of the patients belonged to group II (N=105).
4. Out of the total 150 patients who visited the opd, 42 patients were diagnosed with cervical disc prolapsed i.e. in group I, 11 patients were diagnosed, and in group II, 31 patients were diagnosed with cervical disc prolapsed. Diabetic neuropathy was seen in 16 patients with 5 patients belonging to group I and 11 belonging to group II. Highest no. of patients were diagnosed with lumbar disc disease i.e. 92 with 29 patients belonging to group I and 63 patients belonging to group II.
5. Comorbidities seen in the patient were as follows: 13 patients in group I and 27 patients in group II were affected with diabetes mellitus, hypertension was observed in 17 patients in group I and 34 patients in group II. migraine was seen only in group II patient's i.e. 2. Hypothyroidism affected 2 patients of group I and 3 patients of group II. osteoarthritis was seen in 2 patients of group I and 1 patient of group II.osteoporosis was observed in only 1 patient of each group. The co morbidity with which patients were affected the most was hypertension (N=51).
6. The VAS score observed in patients belonging to group I was as follows: before treatment, minimum score seen was 5 and maximum score was 10, with Mean ± SD = 7.91±1.45 and after treatment, minimum score seen was 0 and maximum score was 8, with Mean ± SD = 3.08±1.90. The P value calculated was <0.0001. This has been illustrated table-2, figure-1.
7. The VAS score observed in patients belonging to group II was as follows: before treatment, minimum score seen was 5 and maximum score was 10, withMean ± SD = 8.12±1.39 and after treatment minimum score seen was 0 and maximum score was 10, with Mean ± SD =4.86±2.82. The P value calculated was<0.0001. This has been illustrated table-3, figure-2.
8. All patients in group I were scrutinized for their modified MAC-NAB score and it was seen that before treatment, 32 patients were assigned to the category of the poor score, 12 were of the fair category score,1 patient was given score of good category and none of them were given score of excellent score. After treatment, no. of patients who were given poor category score -1. fair category score was given to 4 patients, while 24 patients were given score of good category and16 patients were assigned with the score of excellent category. The P value obtained was <0.0001. This has been illustrated table-4, figure-3.
9. Patients in group II were scrutinized for their modified MAC-NAB score and it was seen that before treatment, 73 patients were assigned to the category of the poor score, 29 were of the fair category score, 3 patient was given score of good category and none of them were given score of excellent score. After treatment, no. of patients who

were given poor category score -21.fair category score was given to 22 patients, while 46 patients were given score of good category and 16 patients were assigned with the score of excellent category. The P value calculated was <0.0001. This has been illustrated table-5, figure-4.

10. The incidence of adverse effects observed after treatment with the drugs were as follows: dizziness was seen in 2 patients of group I and 6 patients of group II, drowsiness was seen in 0 patients of groupI and2 patients of group II,while facial edema was seen in 0 patients of group I and 4 patients of group II.sedation was observed in 16 patients in group I and 35 patients of group II.swelling was seen 5 patients of group I and 6 patients of group II.The Adverse effect which was observed to be the highest in the patients was sedation (N=51). This has been illustrated in figure-5.

Based on the results obtained from our study we conclude that combination of pregabalin -NT is more safe and effective than gabapentin-NT. this provides a new insight to usual drug regimen prescribed in cases of diabetic neuropathy and radiculopathy.In our study we evaluate the potential of the combination of these drugs rather than using the drugs alone which was previously done in studies such as.[10,11,12]:

1) *Ralf Baron et.al*-The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy.[10]
2) *Prof Ian Gilrona et.al*,-Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial.[11]

CONCLUSION

With diabetes increasing substantially, by 2050 the prevalence of diabetic neuropathy will increase dramatically, with a concomitant increase in associated cardiovascular mortality and end-stage renal disease**.** it is crucial to find an effective and an equally safe treatment to treat the patient with radiculopathy and diabetic neuropathy.

Our analysis suggests that treat with Pregabalin with Nortriptyline was more superior to Gabapentin with Nortriptyline as the mean VAS score difference was greater in Pregabalin with Nortriptylinegroup when compared to group Gabapentin with Nortriptyline and the prevalence of Adverse drug reactions were less in patients with Pregabalin-NT than with Gabapentin-NT. The Modified mac nab criteria confirms that the VAS score difference was seen only due to the treatment given but not other causes.

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