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Comparative Study of Efficacy between Pregabalin and Epalrestat in Diabetic Peripheral Neuropathic (Dpn) Pain

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Abstract

Diabetic neuropathies are a family of nerve disorders caused by diabetes. People with diabetes can, over time, develop nerve damage throughout the body. A total of fifty patients having diabetic neuropathic pain are recruited based on the inclusion and exclusion criteria. At first visit, patients are randomly assigned to one of the two treatment groups either Epalrestat or Pregabalin. Statistical analysis using student unpaired t-test. The scales used are Dallas pain questionnaire scale, Pain drawing scale, Lower extremity function scale; Biothesiometry score and plasma glucose post prandial. In the Dallas pain questionnaire scale, Pain drawing scale, Lower extremity function right and left toe scale in visit II and visit III are is P>0.05 significant value. In the Biothesiometry score right and left toe scale the 'p' value is <0.05, it has found that the reduction of diabetic neuropathy between two treatment groups during visit III is statistically differs. The plasma glucose post prandial the 'p' value is 0.0445 and it is <0.05, it has found that the reduction of PGPP between two treatment groups during visit II and III is statistically differs. The study concludes that there was rapid reduction of pain scores in pain rating scale; biothesiometry scores and reduction of PGPP levels are more in Pregabalin therapy when compared to Epalrestat therapy. The above information indicates that the efficacy observed for diabetic peripheral neuropathic pain relief, was more with Pregaballin therapy at a dose of 150 mg daily.

Keywords: Diabetic neuropathy, Epalrestat, Pregabalin, Dallas pain questionnaire

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INTRODUCTION

Diabetic neuropathy has been defined as a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes without other causes for peripheral neuropathy. It includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system [1]. People with diabetes who smoke and drink alcohol are more likely to develop neuropathy. Some elderly diabetics with neuropathy also develop a condition called diabetic myopathy (muscle wasting), in which the small muscles of the foot, as well as some other muscles, become thinner and weaker [2]. Diabetic neuropathies are a family of nerve disorders caused by diabetes. People with diabetes can, over time, develop nerve damage throughout the body. Some people with nerve damage have no symptoms. Others may have symptoms such as pain, tingling, or numbness—loss of feeling in the hands, arms, feet, and legs. Nerve problems can occur in every organ system, including the digestive tract, heart, and sex organs [3]. The neuropathic disorder includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system. Diabetes is the second most common cause of neuropathy after leprous neuritis [4].The manifestations of diabetic neuropathy closely mimic chronic inflammatory demyelinising poly neuropathy, alcoholic neuropathy, and other endocrine neuropathies, it is necessary to exclude all other causes of peripheral nerve dysfunction [5]. Autonomic neuropathies affect the nerves that regulate vital functions, including the heart muscle and smooth muscles [6].Focal neuropathy is subdivided into mono neuropathy (cranial neuropathy, radiculopathy (intercostals neuropathy)) or multifocal neuropathy (asymmetric proximal lower limb motor neuropathy—diabetic amyotrophy) which are all comparatively rare [7]. Regular foot exams are important to identify small infections and prevent foot injuries from getting worse. If foot injuries go unnoticed for too long, amputation may be required [8]. The diagnosis of chronic DPN involves the exclusion of non diabetic causes. It should include serum B12, thyroid function, blood urea nitrogen, and serum creatinine. A combination of typical symptomatology and distal sensory loss with absent reflexes, or the signs in the absence of symptoms, is highly suggestive of DPN [9].

METHODOLOGY

STUDY DESIGN

A randomized, open label, prospective single centre study, to compare the efficacy of Epalrestat and Pregablin, for 10 weeks in patients with diabetic peripheral neuropathic pain (DPNP).

Sample size: 50

Medication used for the study: - Epalrestat [10], Pregabalin [11]

INCLUSION CRITERIA

- Males or females 18-75 years of age
- Diabetes mellitus (type I or type II)
- No change in medications for reducing blood sugar within 4 weeks before screening
- Experiencing daily pain due to diabetic neuropathy for at least 6 months but not more than 5 years
- Neuropathic pain must begin in the feet, with relatively symmetrical onset.
- Able to communicate intelligibly with the investigator and study coordinator
- Keeping all appointments for clinic visits, tests, and procedures

EXCLUSION CRITERIA

Any clinically significant neurologic disorders (with the exception of diabetic peripheral neuropathic pain).

Any clinically significant or unstable medical or psychiatric condition that would interfere with the patient's ability to participate in the study

- Prior renal transplant or current renal dialysis
- Pernicious anemia
- Untreated hypothyroidism
- Amputations due to diabetes mellitus (with the exception of toes)
- Known or at high risk of hepatitis B or C infection
- Known or at high risk of human immunodeficiency virus (HIV) infection
- Any anticipated need for surgery during the study
- Known seizure disorder
- Any malignancy in the past 2 years (with the exception of basal cell carcinoma)
- Pain that cannot be clearly differentiated from, or conditions that interfere with the assessment of diabetic neuropathic pain.
- Use of anticonvulsants, antidepressants, or prescription membrane-stabilizing agents
- History of substance abuse or dependence within the past year, excluding nicotine and caffeine
- Frequent and/or severe allergic reactions with multiple medications
- Participation in any clinical trial within 30 days before screening

ETHICAL COMMITTEE APPROVAL

Ethical committee approval was sought from Institutional Review Board, Arthur Asirvatham Hospital, Madurai and Tamilnadu.

MATERIALS AND METHODS

A total of fifty patients having diabetic neuropathic pain are recruited based on the inclusion and exclusion criteria. At first visit, patients are randomly assigned to one of the two treatment groups either Epalrestat or

Pregabalin. Before initiating the therapy baseline parameters are recorded in patient's proforma and pain scores are recorded in pain rating scales namely, Dallas pain questionnaire and pain drawing scale, lower extremity function scale by asking questions and vibration potential evaluation and monofilament (biothesiometry) scores are recorded.

Patients are advised to take drugs up to10 weeks. At second visit, after 5th week, pain scores are recorded by asking questions to the study patients and vibration potential evaluation and monofilament (biothesiometry) scores are recorded. At third visit, after 10th week, same pain rating scales are used to measure the pain scores and vibration potential evaluation and monofilament (biothesiometry) scores are recorded. Finally pain scores and biothesiometry scores are used to compare the efficacy of Epalrestat and Pregablin.

STATISTICS

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using Graph Pad Instat DTCG (GPI v3.0).Using these software frequencies, percentages, means, standard deviations, student unpaired t- test and 'p' values were calculated. Student unpaired t- test was used to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS AND DISCUSSION

Demographic characteristics of patients

The descriptive analysis of study showed that, out of 50patient 62% of them were males and 38% were females. It indicates that males are more prone to diabetic neuropathy. Regarding age group distribution the patient who had age group between 50-59 was had more incidences of diabetic neuropathies. The study showed that 56% of patient had the family history of DM and 44% of them do not had family history of DM. it indicates that the patient having the family history of DM are more prone to diabetic neuropathy.

CLINICAL CHARACTERISTICS

Dallas pain questionnaire scale during visit II

Regarding to Dallas pain questionnaire during the visit II there is a percentage reduction of pain score is more with Pregabalin (group B mean-50.8, SD-18.6%) when compared to Epalrestat (group A mean-32.5, SD-16.8%). Since the 'p' value is 0.0017 and it is >0.05, it has found that the reduction of pain between two treatment groups by using DPQ during visit II is statistically differs.(Table 1)

D.P.Q SCALE	GROUP A		GROUP B	
	MEAN	S.D	MEAN	S.D
VISIT - I	27.6	12.8	32.8	11.4
VISIT – II	18.7	9.7	16.5	8.9
CHANGE DURING VISIT – II	8.9	6.3	16.4	7.1
PERCENTAGE CHANGE DURING VISIT – II	32.5	16.8	50.8	18.6
p		0.0017	SIGNIFICANT	

Table 1: Dallas pain questionnaire (dpq) at visit-II

Dallas pain questionnaire scale during visit III

According to Dallas pain questionnaire during the visit III there is a percentage reduction of pain score is more with Pregabalin (group B mean-84.1%, SD-8.4%) when compared to Epalrestat (group A mean-40.6%, SD-40.6%). The 'p' value is 0.0001 and it is >0.05, it has found that the reduction of pain between two treatment groups by using PDS during visit II is statistically differs.(Table 2)

D.P.Q SCALE	GROUP A		GROUP B	
	MEAN	S.D	MEAN	S.D
VISIT - I	27.6	12.8	32.8	11.6
VISIT – III	15.4	10.4	5.4	3.6
CHANGE DURING VISIT – III	12.5	12	27.4	9.3
PERCENTAGE CHANGE DURING VISIT – III	40.6	40.6	84.1	8.1
p		0.0001	SIGNIFICANT	

Table 2: Dallas pain questionnaire (dpq) at visit-III

Pain drawing scale during visit II

Pain drawing scale during the visit II shows that there is a percentage reduction of pain score is more with Pregabalin (group B mean-40.26%, SD-13.69%) when compared to Epalrestat (group A mean- 21.5%, SD-14.57%). The 'p' value is 0.0001 and it is >0.05, it has found that the reduction of pain between two treatment groups by using PDS during visit II is statistically differs. (Table 3)

Pain drawing scale during visit III

Regarding to Pain drawing scale during the visit III there is a percentage reduction of pain score is more with Pregabalin (group B mean-70.67%, SD-18.01%) when compared to Epalrestat (group A mean- 29.97%, SD- 19.48%). The 'p' value is 0.0001 and it is >0.05, it has found that the reduction of pain between two treatment groups by using PDS during visit III is statistically differs. (Table 4)

PDS	GROUP A		GROUP B	
	MEAN	S.D	MEAN	S.D
VISIT – I	5	1.19	5.32	1.25
VISIT – II	3.96	1.21	3.24	1.09
CHANGE DURING VISIT – II	1.04	0.68	2.08	0.64
PERCENTAGE CHANGE DURING VISIT – II	21.5	14.57	40.26	13.69
p		0.0001	SIGNIFICANT	

Table 3: Pain drawing scale (pds) at visit-II

PDS	GROUP A		GROUP B	
	MEAN	S.D	MEAN	S.D
VISIT – I	5	1.19	5.32	1.25
VISIT – III	3.4	0.87	1.68	1.11
CHANGE DURING VISIT – III	1.6	1	3.64	0.81
PERCENTAGE CHANGE DURING VISIT – III	29.97	19.48	70.67	12.01
p		0.0001	SIGNIFICANT	

Table 4: Pain drawing scale (pds) at visit-III

Lower extremity function scale during visit II

According to Lower extremity function scale during the visit II there is a percentage reduction of pain score is more with Pregabalin (group B mean-49.4%, SD-24.6%) when compared to Epalrestat (group A mean-26.5%, SD- 24.6%). The 'p' value is 0.0004 and it is >0.05, it has found that the reduction of pain between two treatment groups by using LEFS during visit II is statistically differs. (Table 5)

LEFS	GROUP A		GROUP B	
	MEAN	S.D	MEAN	S.D
VISIT – I	47	11.4	41.2	10.5
VISIT – II	57.4	9.9	59.5	10.3
CHANGE DURING VISIT – II	10.4	6.7	18.4	5.8
PERCENTAGE CHANGE DURING VISIT – II	26.5	24.6	49.4	24.6
p		0.0004	SIGNIFICANT	

Table 5: Lower extremity function scale (lefs) at visit-II

Lower extremity function scale during visit III

Regarding to scale Lower extremity function during the visit III there is a percentage reduction of pain score is more with Pregabalin (group B mean-87.8%, SD-52.5%) when compared to Epalrestat (group A mean-35.6%, SD- 27.9%). The 'p' value is 0.0001 and it is >0.05, it has found that the reduction of pain between two treatment groups by using LEFS during visit III is statistically differs.(Table 6)

LEFS	GROUP A		GROUP B	
	MEAN	S.D	MEAN	S.D
VISIT – I	47	11.4	41.2	10.5
VISIT – III	61.8	11.3	22.4	4.8
CHANGE DURING VISIT – III	14.8	9.7	31.3	7.5
PERCENTAGE CHANGE DURING VISIT – III	35.6	27.9	87.8	52.5
p		0.0001	SIGNIFICANT	

Table 6: Lower extremity function scale (lefs) at visit-III

Biothesiometry score on right toe during visit II

Regarding to Biothesiometry score on right toe during the visit II there is a percentage reduction of diabetic neuropathy is more with Pregabalin (group B mean-24.3%, SD-15.8%) when compared to Epalrestat (group A mean- 14.8%, SD- 14.3%). The 'p' value is 0.0463 and it is <0.05, it has found that the reduction of diabetic neuropathy between two treatment groups during visit II is statistically differs. (Table 7)

BIO – RT	GROUP A		GROUP B	
	MEAN	S.D	MEAN	S.D
VISIT – I	40.5	8.5	40.2	6.9
VISIT – II	33.7	6	29.7	4.9
CHANGE DURING VISIT – II	6.8	6.3	10.5	7.2
PERCENTAGE CHANGE DURING VISIT – II	14.8	14.3	24.3	15.8
p		0.0463	SIGNIFICANT	

Table 7: Biothesiometry on right toe at visit-II

Biothesiometry score on right toe during visit III

Regarding to Biothesiometry score on right toe during the visit III there is a percentage reduction of diabetic neuropathy is more with Pregabalin (group B mean-36.7%, SD-15.8%) when compared to Epalrestat (group A mean- 14.8%, SD- 14.3%). The 'p' value is 0.0006 and it is <0.05, it has found that the reduction of diabetic neuropathy between two treatment groups during visit III is statistically differs. (Table 8)

Biothesiometry score on left toe during visit II

Regarding to Biothesiometry score on left toe during the visit II there is a percentage reduction of diabetic neuropathy is more with pregabalin (group B mean-24.4%, SD-13.6%) when compared to epalrestat (group A mean- 14.6%, SD- 11.6%). The 'p' value is 0.0151 and it is <0.05, it has found that the reduction of diabetic neuropathy between two treatment groups during visit II is statistically differs. (Table 9)

BIO – RT	GROUP A		GROUP B	
	MEAN	S.D	MEAN	S.D
VISIT – I	40.5	8.5	40.2	6.9
VISIT – III	31.4	6.3	24.6	2.8
CHANGE DURING VISIT – III	9.1	7.4	15.5	7.1
PERCENTAGE CHANGE DURING VISIT – III	20.5	15.7	36.7	13.5
p		0.0006	SIGNIFICANT	

Table 8: Biothesiometry on right toe at visit-III

BIO – LT	GROUP A		GROUP B	
	MEAN	S.D	MEAN	S.D
VISIT – I	44.5	8.4	45.2	7.3
VISIT – II	37.3	5.6	33.6	5.1
CHANGE DURING VISIT – II	7.2	5.9	11.7	7
PERCENTAGE CHANGE DURING VISIT – II	14.6	11.6	24.4	13.6
p		0.0151	SIGNIFICANT	

Table 9: Biothesiometry on left toe at visit-II

Biothesiometry score on left toe during visit III

Regarding to table Biothesiometry score on left toe during the visit III there is a percentage reduction of diabetic neuropathy is more with Pregabalin (group B mean-40.9%, SD-11.4%) when compared to Epalrestat (group A mean- 19.17%, SD- 13.5%). The 'p' value is 0.0001 and it is <0.05, it has found that the reduction of diabetic neuropathy between two treatment groups during visit III is statistically differs. (Table 10)

BIO – LT	GROUP A		GROUP B	
	MEAN	S.D	MEAN	S.D
VISIT – I	44.5	8.4	45.2	7.3
VISIT – III	35.1	6.5	26.2	3.9
CHANGE DURING VISIT – III	9.4	7	19.1	7.1
PERCENTAGE CHANGE DURING VISIT – III	19.7	13.5	40.9	11.4
p		0.0001	SIGNIFICANT	

Table 10: Biothesiometry on left toe at visit-III

PGPP during visit II

In the table PGPP during the visit II it has observed that there is a percentage reduction of diabetic neuropathy is more with Pregabalin (group B mean-21.54%, SD-13.32%) when compared to Epalrestat (group A mean-9.82%, SD- 21.8%). The 'p' value is 0.0445 and it is <0.05, it has found that the reduction of PGPP between two treatment groups during visit III is statistically differs. (Table 11)

PGPP	GROUP A		GROUP B	
	MEAN	S.D	MEAN	S.D
VISIT – I	9.4	2.7	10.09	2.83
VISIT – II	8.06	1.44	7.68	1.53
CHANGE DURING VISIT – II	1.34	1.97	2.41	2.04
PERCENTAGE CHANGE DURING VISIT – II	9.82	21.8	21.54	13.32
p		0.0445	SIGNIFICANT	

Table 11: Comparison of PGPP of group A and B at visit II

PGPP during visit III

The table PGPP during the visit III shows that there is a percentage reduction of diabetic neuropathy is more with Pregabalin (group B mean-28.97%, SD-12.07%) when compared to Epalrestat (group A mean- 14.07%, SD- 21.24%). The 'p' value is 0.002 and it is <0.05, it has found that the reduction of PGPP between two treatment groups during visit III is statistically differs. (Table 12)

PGPP	GROUP A		GROUP B	
	MEAN	S.D	MEAN	S.D
VISIT – I	9.4	2.7	10.09	2.83
VISIT – III	7.71	1.5	6.93	1.26
CHANGE DURING VISIT – III	1.74	2.17	3.16	2.23
PERCENTAGE CHANGE DURING VISIT – III	14.07	21.24	28.97	12.07
p		0.002	SIGNIFICANT	

Table 12: Comparison of PGPP of group A and B at visit III

CONCLUSION

In this 10-week study, Pregabalin, at a dose of 150mg daily, was significantly more effective than Epalrestat at a dose of 150mg daily, in relieving diabetic neuropathic pain. Analysis of results obtained with pain questionnaires such as Dallas pain questionnaire, pain drawing scale and lower extremity function scale it was observed that, in diabetic neuropathic pain states, pain treatment with Pregabalin was significantly more effective than Epalrestat and their was improvements in the percentage reduction of pain scores indicates Pregabalin at a dose of 150mg daily, was significantly more effective than Epalrestat at a dose of 150mg daily, in relieving diabetic neuropathic pain.

In the biothesiometry scores analysis at 2nd and 3rd visit, the onset of pain relief was rapid, with significant efficacy was observed in the Pregabalin group at a dose of 150mg daily group than Epalrestat group at a dose of 150mg daily.

The study shows that there was rapid reduction of pain scores in pain rating scale; biothesiometry scores and reduction of PGPP levels are more in Pregabalin therapy when compared to Epalrestat therapy. The above information indicates that the efficacy observed for diabetic peripheral neuropathic pain relief, was more with Pregaballin therapy at a dose of 150 mg daily. The study emphasizes the importance of early reduction of peripheral neuropathy among diabetic patients using simple affordable tools and methods to reduce mortality and diabetic peripheral neuropathy.

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