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A RANDOMIZED COMPARATIVE STUDY OF EFFICACY AND SAFETY OF EPALRESTAT AND METHYLCOBALAMIN IN PATIENTS WITH DIABETIC NEUROPATHY

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ABSTRACT

INTORDUCTION: Diabetic neuropathy is a common complication in nearly 50% of over all diabetes population. Recently Epalrestat and Methylcobalamin are widely used in clinical practice to manage diabetic neuropathy. This study was aimed to compare the efficacy and safety of Epalrestat and Methylcobalamin in patients with diabetic neuropathy.

METHODS: A total number of 110 patients with diabetic neuropathy were divided into two groups; group A administered with 150 mg of Epalrestat and group B administered with 1500 mcg of Methylcobalamin once daily basis. The treatment period was 12 weeks with monitoring on week 4, 8 & 12 of the study. At base line and at follow up visits parameters like pain intensity by VAS pain score, loss of sensation, burning sensation, numbness, muscle cramps, spontaneous pain, weakness, dizziness, loss of sensation of heat & cold assessed by MNSI & HbA1C.

RESULTS: A significant improvement in all the efficacy parameters was observed with Epalrestat treatment compared to methylcobalamin treatment. Epalrestat treatment is associated with very few adverse events. Patients as well as physicians reported that the Epalrestat treatment is better-quality in efficacy and safety parameters compared to Methylcobalamin.

CONCLUSION: The present study concludes that Epalrestat has superior efficacy and safety profile than Methylcobalamin in the treatment of diabetic neuropathy.

KEYWORDS : Epalrestat, Methylcobalamin, Mnsi & Diabetic Neuropathy

INTRODUCTION:

Diabetes is a national as well as global epidemic disease in terms of incidence, healthcare costs and overall complications as reported by the Center for Disease Control (CDC).[1] According to recent estimates, approximately 285 million people worldwide (6.6%) in the 20–79 year age group have diabetes in 2010 and by 2030, 438 million people (7.8%) of the adult population, is expected to have diabetes.

Diabetes is a multifaceted disease associated with neurological, vascular, immunological and metabolic complications. Long standing hyperglycemia is believed to be the major cause of these complications. Although strict glycemic control reduces the occurrence and progression of diabetes related complications, this approach alone does not completely eliminate complications. Diabetic neuropathy is a common complication that develops in about 50% of people with diabetes.[2] Diabetic neuropathy appears relatively early in the disease process. The prevalence of up to 7% is reported in South Indian patients even at the time of diagnosis of diabetes. [3] Diabetic neuropathy has widespread occurrence and devastating effects.

The precise pathogenesis of diabetic neuropathy is unclear despite recent advances. Polyol pathway of glucose metabolism has been considered as one of the major mechanisms in the pathogenesis of diabetic neuropathy.[3,4] Conversion of glucose to sorbitol by the enzyme aldose reductase is the rate limiting step of polyol pathway. Increased activity of polyol pathway due to hyperglycemia and subsequent accumulation of excess sorbitol explains the neuronal damage in diabetes.[5] Aldose reductase is enhanced in the presence of hyperglycemia resulting in an increase in the intracellular osmotic pressure, the intracellular depletion of myoinositol, a reduction in Na^+K^+ATPase activity, and the enhancement of protein saccharification causing numbness and pain via neurocyte hypofunction.

Epalrestat is a carboxylic acid derivative that acts as aldose reductase inhibitor. Epalrestat is proven to have beneficial effects in diabetic neuropathy in many controlled clinical trials. In hyperglycemia, Epalrestat significantly reduces intracellular sorbitol accumulation by an uncompetitive aldose reductase inhibition. Epalrestat improves motor and sensory nerve conduction velocity and subjective neuropathy symptoms in patients with diabetic neuropathy.[5-8]

Methylcobalamin is one of the biologically active forms of vitamin B12. It is used in the treatment of peripheral neuropathy, diabetic neuropathy, and as a preliminary treatment for amyotrophic lateral sclerosis. Unlike cyanocobalamin, methylcobalamin is active in the spinal fluid. Due to this property, it is able to help heal the damaged nerve cells and restores normal functions. In clinical studies, Methylcobalamin showed improvement in the somatic and autonomic symptoms with regression of signs of diabetic neuropathy such as pain and paresthesia.[9,10]

Recently Epalrestat and Methylcobalamin are widely used in clinical practice to manage diabetic neuropathy. Hence, this study was undertaken to evaluate the efficacy and safety of Epalrestat and Methylcobalamin in patients with diabetic neuropathy.

PATIENTS AND METHODS:

STUDY DESIGN:

Single blind prospective randomized comparative study.

SAMPLE SIZE:

A total number of 110 patients from the out- patient and in-patient department in Karpaga Vinayaga Institute of Medical Sciences & Research Centre, Chinnakolambakkam, Kanchipuram District- 603 308, Tamil Nadu, who were on Diabetic neuropathy were included.

STUDY PERIOD:

The study was conducted over period of 12 months from March 2016 to February 2017.

STUDY SITE:

The study was carried out in Karpaga Vinayaga Institute of Medical Sciences & Research Centre, Chinnakolambakkam, Kanchipuram District- 603 308, Tamil Nadu.

STUDY PROTOCOL:

For this study, about 110 diabetic patients with symptoms of neuropathy will be randomly divided into two groups by block randomization method, i.e., Group A (55 patients) will receive 150 mg of Epalrestat per day, Group B (55 patients) will receive 1500 mcg of Methylcobalamin per day. They have been planned to treat with drugs for a period of 12 weeks and they will be asked to come for follow up on 4, 8 & 12 weeks.

A total of 110 diabetic patients with neuropathy symptoms were

enrolled in our study program. The patients were observed for age, sex, family history, blood pressure, weight & height were recorded. The patients were asked to monitor their blood glucose level, both fasting and postprandial and glycosylated hemoglobin at the initial visit to the hospital and after 3 months of treatment.

INCLUSION CRITERIA:

1. Diabetic patients, both type 1 & type 2 with symptoms of neuropathy.
2. Age – 20 to 65 years.
3. HbA1C ≤ 9% ± 0.5% variation in the previous 3 months.
4. Patients on continued conventional therapy for Diabetes Mellitus.

EXCLUSION CRITERIA:

1. Patients having alcoholic neuropathy.
2. Patients having Foot ulcer.
3. Patients having Carpal tunnel syndrome.
4. Patients having Cerebrovascular sequelae.
5. Patients having hepatic and renal impairment.
6. Patients taking anti-epileptic and anti- depressant drugs.
7. Patients on any other medications that affects symptoms of neuropathy.

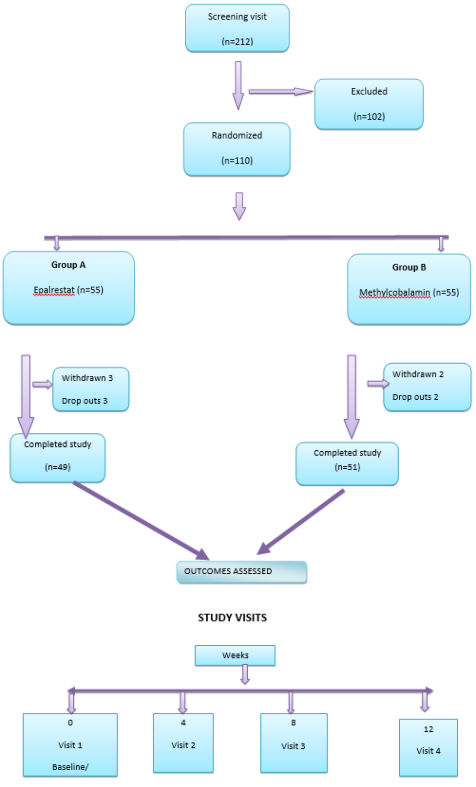
ETHICAL CONSIDERATION:

All the investigational procedures and protocols used in this study were reviewed & approved by the Institutional Ethical Committee (IEC Reference No: 22/2016) and were in accordance with the CONSORT guidelines.

STUDY EVALUATION:

Informed consent was obtained after a detailed explanation of the study purpose and methods. Patients were received Epalrestat or Methylcobalamin. The treatment period was 12 weeks and both the medications were administered once daily. This is a single blind study; therefore patients were unaware of treatment given to them. Patients were monitored on 4th, 8th and 12th weeks of the study. Patient's demographic data and medical history were recorded at screening visit. Physical examinations were recorded at screening and 12th week of follow up visit. Systemic examination and vital examination were recorded at every follow up visit. Figure 1. showing the disposition of patients by flow chart method.

Figure 1. Flow chart showing the disposition of patients
TRIAL FLOW CHART



EFFICACY PARAMETERS:

1. VAS scale of pain intensity based on 10 point scoring method - mild, moderate, severe, very severe, worst, shown in Table 1.
2. Loss of sensation, burning sensation, numbness, muscle cramps, spontaneous pain, weakness, dizziness, loss of sensation of heat & cold assessed by Michigan neuropathy screening instrument score method. (Patient Version and Physician Version)
3. HbA1C at baseline & at the end of treatment.

Table.1: Visual Analog Scale (VAS) Pain intensity scoring system

Score	Symptoms
0	No pain
1-2	Mild pain
3-4	Moderate pain
5-6	Severe pain
7-8	Very severe pain
8-10	Worst pain

SAFETY PARAMETERS:

1. Adverse events like skin rash, hot flushes, etc.,
2. FBS at baseline & at the end of treatment.
3. PPBS at baseline & at the end of treatment.
4. LFT at baseline & at the end of treatment.
5. RFT at baseline & at the end of treatment.
6. CBC at baseline & at the end of treatment.

STATISTICAL ANALYSIS:

Statistical analysis was done with the help of Graph Pad Prism Instat Version 3 (USA). Basic statistical evaluation including Mean, Median, and Standard Deviation (SD) will be calculated from the raw data. Efficacy variables such as diabetic neuropathy symptoms, pain intensity were assessed by VAS Pain scoring method. Muscle strength, muscle cramps, prickling feelings, burning pain, sensitive to touch, ulceration and ankle reflexes were assessed by Michigan neuropathy screening instrument (MNSI) score method. Chi-square test and one way ANOVA followed by Tukey-Kramer multiple comparison test were used where ever applicable.

OBSERVATION AND RESULTS:

Out of 212 screened patients, 102 were excluded and 110 were enrolled based on the inclusion and exclusion criteria. The reasons for exclusion were:

a. Patients with Foot ulcer (31)
b. Patients having alcoholic neuropathy (33)
c. Patients having hepatic impairment (29)
d. Patients taking antidepressants (09)

The 110 recruited patients were randomized into 2 groups A and B consisting of 55 patients each. Patients of group A received Epalrestat and group B received Methylcobalamin. In Group A- three patients were withdrawn from the study due to 2 patients had diabetic foot ulcer complication with standard therapy which required additional care and therapy and 1 patient had abnormal laboratory parameters especially HbA1C. In Group B- two patients were withdrawn from the study due to 2 patients had developed with symptoms of chronic kidney failure which requiring additional care and therapy. In group A and B, 3 and 2 patients respectively, who were failed to follow up due to personal reason. At the out set, In Group A and B, 49 and 51 patients respectively who were completed the study. The results at the end of the study are detailed.

The demographic profiles of the patients enrolled in the study as per the inclusion and exclusion criteria are shown in Table 2. The enrolled patients were in the age group of 20- 65 yrs with the mean age of 53.87 yrs for the Group A and 53.61 years for the Group B. Other parameters are also listed in Table 2.

Table 2: Demographical characteristics of study population

Parameters	Group A (n=49)	Group B (n=51)	Chi-Square test independence p-value
Age (Yrs)			
Mean SD	53.87 14.4	53.61 11.24	0.846 (NS)
Range	20-65	20-65	-
Gender, n (%)			
Men	32 (65%)	28 (55%)	0.775 (NS)

Women	17 (35%)	23 (45%)	0.775 (NS)
BMI			
Baseline	25.49 2.34	25.65 2.52	0.750 (NS)
4th Visit	25.50 2.65	25.59 2.65	0.625 (NS)

Chi-square test independence p-value shows NS with respect to patient's age, gender and BMI.

PHYSICAL AND LABORATORY EXAMINATION:

All parameters including pulse rate, blood pressure, and respiratory rate were with in normal limits at baseline. Laboratory investigations for FBS, PPBS, HbA1C, AST concentration, ALT concentration, Serum Albumin, Serum Total Bilirubin, Serum Creatinine, Serum Urea, Urine Albumin and Urine Sugar were with in normal limits. The above laboratory investigations did not show any significant change in either group.

DISCUSSION:

Diabetic neuropathies are nerve disorder; it is a common complication of diabetes caused by hyperglycaemia which can damage nerve fibers to whole body. Depends upon the types of nerves involved, which is categorized as peripheral, autonomic, proximal and focal neuropathies. The exact mechanism of diabetic neuropathy remains unknown. Several reports suggested that a variety of molecules are involved in the development of diabetic neuropathy, such as protein kinase C, polyol, aldose reductase, advanced glycation end products, reactive oxygen species, cytokines. More over, some risk factors like metabolite, autoimmune, inherited traits and life style, may contribute to the development of diabetic neuropathy. Methylcobalamin has an extended record as a nerve and it has been used in the treatment of neuropathy for a long time. Epalrestat is a relatively newer addition in this category that has gained the acceptance of the healthcare society as an effective treatment option for diabetic neuropathy, potentially preventing or ameliorating long term diabetic complications.[11]

Present study was conducted to compare the efficacy and safety of epalrestat, methylcobalamin alone in treatment of patients with diabetic neuropathy. We have evaluated most common diabetic neuropathy complications including VAS scale of pain intensity based on 10 point scoring method. The result of pain intensity scores were shown in Table 4.

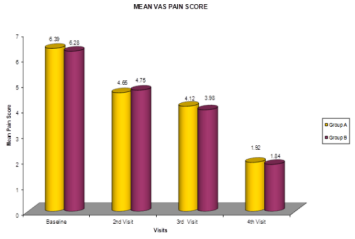
TABLE 4: Shows the pain intensity scores (Visual Analog Pain Score Method)

Visit		Group A (n=49)	Group B (n=51)
Baseline/ Visit 1	Mean Score	6.39***	6.28***
	S.D	0.60	0.59
Visit 2	Mean Score	4.65 ΔΔΔ	4.75 ΔΔΔ
	S.D	0.43	0.45
Visit 3	Mean Score	4.12 ΨΨΨ	3.98 ΨΨΨ
	S.D	0.42	0.38
Visit 4	Mean Score	1.92	1.84
	S.D	0.11	0.13

Data represented as mean with S.D (n=49 & 51), which represents mean VAS pain Score. *** denotes $p<0.001$, Base line (Visit 1st) compared with visit 2nd, 3rd and 4th visit, ΔΔΔ denotes $p<0.001$, visit 2nd compared with visit 3rd and 4th. ΨΨΨ denotes $p<0.001$, visit 3rd compared with visit 4th. (One-way ANOVA followed by Tukey-Kramer multiple comparisons test)

The graphical representation of Mean VAS Pain score were shown in Figure 2.

Figure 2: Shows the graphical representation of Mean VAS Pain Score



Loss of sensation, burning sensation, numbness, muscle cramps, spontaneous pain, weakness, dizziness, loss of sensation of heat & cold assessed by Michigan neuropathy screening instrument score method, which was shown in Table 5 and HbA1C at baseline & at the end of treatment were analysed.

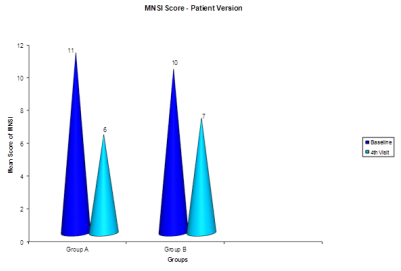
TABLE 5: Shows the Michigan Neuropathy Screening Instrument (MNSI) score- Completed by the person with diabetes.

Visit		Group A (n=49)	Group B (n=51)
Baseline/ Visit 1	Mean Points	11***	10***
	S.D	1.63	1.19
End of 4th week	Mean Points	06	07
	S.D	0.58	0.52

Data represented as mean with S.D (n=49 &51), which represents mean points of MNSI. *** denotes $p<0.001$, Base line (Visit 1st) compared with visit 4th visit (One tail P value with Unpaired t test).

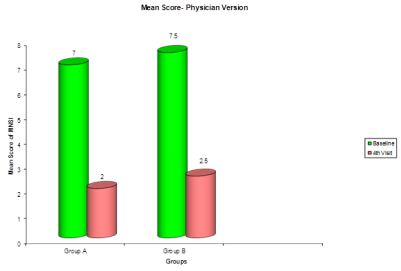
The graphical illustration of MNSI Score – Patient version shown in Figure 3,

Figure 3: Shows the graphical representation of MNSI Score- Patient Version



In figure 4, explains the graphical representation of Michigan Neuropathy Screening Instrument (MNSI) Score- Physician version.

Figure 4: Illustration of graphical representation of Michigan Neuropathy Screening Instrument (MNSI) Score.



The results of the present study reveal that Epalrestat monotherapy group showed a very good improvement and comparably moderate improvement respectively in diabetic neuropathy symptoms over the baseline. All the evaluated neuropathy symptoms showed statistically significant (P<0.01) in group A. Despite the fact that, epalrestat group symptomatic relief was achieved much earlier with reduction in score values and was better compared to Methylcobalamine Group.

Improvement in diabetic neuropathy patients was investigated in terms of VAS (Visual analog scale) pain intensity score, MNSI (Michigan neuropathy screening instrument) score and HbA1C levels. In group A significant ($p<0.001$) reduction in pain score (4.12) was observed at 8th week onwards while compared to baseline and very good reduction in pain score (1.92) was observed at 12th week of therapy. Both groups had significant ($p<0.001$) reduction in MNSI score by patient version, especially group A were shown to have very good reduction (Mean Score Value: 6) compared to group B. Similarly, both groups had significant ($p<0.001$) reduction in MNSI score by health professional version, especially group A were shown to have very good reduction (Mean Score Value: 2.0) compared to group B. The MNSI diabetic patient version score was evaluated on the basis of higher score out of maximum 13 points indicates more neuropathic symptoms as well as MNSI physician version score grater than 2 points out of 10 point scale

were considered neuropathic.[12] The data were explained in Table 6,

TABLE 6: Shows the Michigan Neuropathy Screening Instrument (MNSI) Score - Completed by Health Professionals

Visit		Group A (n=49)	Group B (n=51)
Baseline/ Visit 1	Mean Score	7.0***	7.5***
	S.D	0.68	0.78
End of 4th week	Mean Score	2.0	2.5
	S.D	0.17	0.19

Data represented as mean with S.D (n=49 &51), which represents mean score of MNSI- Completed by health professional. *** denotes $p<0.001$, Base line (Visit 1st) compared with visit 4th visit (One tail P value with Unpaired t test).

With respect to HbA1C, group A shown very slight amount (7.56%) of reductions compared to baseline, which is not merely significant. The demographic profiles were not statistically significant. Blood glucose profiles like FBS, PPBS, HbA1C and BMI were measured before and after study, which also not significant. The serum profiles like AST, ALT, serum albumin and urine albumin & urine sugar were measured before and after study period, but which were not observed any significant difference. Serum urea, creatinine and total bilirubin were measured baseline and end of study, which were showed statistically not significant difference between and with in the groups at baseline and at the end of study.

Epalrestat helps to prevent neuronal degeneration by reducing the accumulation of toxic sorbitol and decreasing the oxidative stress while Methylcobalamin helps to recover neuronal injury. Methylcobalamin is one of the biologically active forms of vitamin B_{12}. It is used in the treatment of peripheral neuropathy, diabetic neuropathy, and as a preliminary treatment for amyotrophic lateral sclerosis. Unlike cyanocobalamin, methylcobalamin is active in the spinal fluid. Due to this property, it is able to help heal the damaged nerve cells and restores normal functions. In clinical studies, Methylcobalamin showed improvement in the somatic and autonomic symptoms with regression of signs of diabetic neuropathy such as pain and paresthesia.[13,14]

Epalrestat is a carboxylic acid derivative that acts as aldose reductase inhibitor. Epalrestat is proven to have beneficial effects in diabetic neuropathy in many controlled clinical trials. In hyperglycemia, Epalrestat significantly reduces intracellular sorbitol accumulation by an uncompetitive aldose reductase inhibition. Epalrestat improves motor and sensory nerve conduction velocity and subjective neuropathy symptoms in patients with diabetic neuropathy.[11,15,16] So, Epalrestat alone treated patients were more efficacious and well tolerated with safety for the management of diabetic neuropathy. Hyperglycemia promotes the synthesis of an endogenous protein kinase C activator, diacylglycerol. This excess protein kinase C activation induces ischemia and promotes vascular permeability and thickening of the basement memberane and causes neuropathy.[17-19] So, inactivation of protein kinase C indirectly reduces the risk of diabetic neuropathy.

The wellbeing and safety of both drugs was assessed based on the occurrence of adverse events reported by the patients who received the medicine. From our study, it was observed that nausea and vomiting (5.9%), gastric discomfort (7.8%) and diarrhoea (1.9%) was reported as ADR, in group B, 7.8% of patients suffered with gastric discomfort and 5.9% of patients suffered with nausea and vomiting, in group A, 4% of patients suffered with gastric discomfort, shown in Table 3. Both groups were well tolerated and do not generate any safety concern.

TABLE 3: Shows the frequency of various adverse drug reactions between the study groups.

S.No	Adverse drug reaction	Group A (n=49)	%	Group B (n=51)	%
01	Diarrhoea	-	0	1	1.9
02	Erythema	-	0	-	0
03	Gastric Discomfort	2	4	4	7.8
04	Head ache	1	2	-	0
05	Hepatic Dysfunction	-	0	-	0
06	Hot flush	1	2	1	1.9
07	Itching	-	0	1	1.9
08	Nausea & Vomiting	1	2	3	5.9
09	Skin rash	1	2	-	0
10	Swelling	-	0	1	1.9

CONCLUSION:

At the out set, this randomized single blind study concluded that Epalrestat, an aldose reductase, seems to be a better alternative than Methylcobalamin in the treatment of diabetic neuropathy. In present study, Epalrestat was clearly ahead of Methylcobalamin in efficacy parameters as a part of MNSI and VAS score. Epalrestat 150 mg /day was better tolerated than Methylcobalamin 1500 mcg/day for a period of 12 weeks therapy. There was no significant difference between baseline and end of study with respect to HbA1C levels in both groups. Epalrestat showed no serious adverse effects during study period. From our study, we can conclude that, Epalrestat has better efficacy and safety profile than Methylcobalamin in the treatment of Diabetic neuropathy.

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