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Rujul Jain, Surya Kumar Singh
Department of Endocrinology and Metabolism, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

Study of Epalrestat in diabetic distal symmetric polyneuropathy and correlation of its therapeutic efficacy with erythrocyte sorbitol levels: A step towards precision medicine

ABSTRACT

Background. Diabetic Distal Symmetric Polyneuropathy (DSPN), despite being the most common and a disabling diabetic complication, remains difficult to treat. It has led to rekindle our interest in Epalrestat which has the potential to alter the natural history of the disease. The present study was designed to evaluate the efficacy of Epalrestat in DSPN and to correlate its therapeutic efficacy with baseline erythrocyte sorbitol levels.

Methods. One hundred patients with duration of diabetes more than five years and Diabetic Neuropathy Symptom Score (DNSS) ≥ 1 were included. They were divided into two groups of 50 patients each: Group 1 (received Epalrestat 150 mg Tablet once a day), Group 2 (received placebo). Baseline Diabetic Neuropathy Symptom Score (score out of 4), Numeric Pain Intensity Scale (NPIS; score out of 10), monofilament score (score out of 10), Vibration Perception Threshold (VPT) by Sensitometer and erythrocyte sorbitol levels (by ELISA) were recorded. Same parameters were repeated at three months follow up visit.

Results. The mean improvement in DNSS score was 2.39 ± 1.1 in group 1 vs 0.57 ± 1.04 in group 2; P < 0.01. Similarly there was a significant difference in improvement in monofilament score in the two groups (2.82 ± 1.41 in group 1 vs 0.12 ± 0.93 in group 2; p< 0.01), in NPIS score (2.61 ± 1.26 in group 1 vs 0.41 ± 0.81 in group 2; P < 0.01). Average VPT score improved by 3.48 ± 2 in group 1 vs 0.34 ± 1.14 V in group 2; P < 0.01). Improvement in VPT score with Epalrestat was correlated with baseline erythrocyte sorbitol levels (correlation coefficient of 0.911; P < 0.0001).

Conclusions. Epalrestat was overall more effective than placebo in improving the symptoms as well as in improving the quantitative sensory nerve function measured by sensitometer. The improvement in all the parameters positively correlated with baseline erythrocyte sorbitol levels. Sorbitol levels can be a useful tool in predicting the response to drug. (Clin Diabetol 2021; 10; 4: 354–358)

Key words: diabetic peripheral neuropathy, Epalrestat, sorbitol, vibration perception threshold.

Introduction

Diabetes Mellitus (DM) and its various complications have contributed enormously to the burden of morbidity and mortality worldwide. Diabetic peripheral neuropathy (DPN) is the most prevalent diabetic complication, having a lifetime occurrence rate of 50% and also seen in around 8% of newly detected diabetic patients [1]. DPN incurs a huge health burden on the society by increasing the risk of foot ulceration and consequent amputation with a significant lowering of quality of life [2]. But despite enormous health conse-

Address for correspondence:
SK Singh
Department of Endocrinology and Metabolism
Institute of Medical Sciences
Banaras Hindu University, Varanasi, India
e-mail: sksendocrine@yahoo.com
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quences, still there are not many therapeutic options available for treating DPN, quite unlike other diabetic microvascular complications.

A host of biochemical pathways affecting a multitude of metabolic factors have been implicated in the pathogenesis of DPN. Among many, polyol pathway plays an important role in the pathogenesis of nerve fiber damage [3]. Aldose reductase (AR) enzyme plays a key role in nerve tissue damage through NADPH dependent production of sorbitol from glucose thereby altering the redox status and cellular osmolarity of the nerve tissue leading to cellular damage [4]. Epalrestat is one of the commercially available aldose reductase inhibitors (ARIs).

Various studies have been conducted to evaluate the efficacy and safety of ARIs in prevention and treatment of DSPN with contrasting results. The Aldose Reductase Inhibitor–Diabetes Complications Trial (ADCT) was a large 3-year trial which showed promising results [5] but a subsequent meta-analysis showed no overall benefit. [6] Judging from the novel mechanism by which Epalrestat works, it is imperative to rekindle interest in this drug for treatment of DPN. It is possible that ARIs are effective in DSPN only when baseline erythrocyte sorbitol levels are raised and the drug decreases sorbitol levels during the course of the treatment. This study was designed to evaluate the efficacy of Epalrestat in Diabetic Symmetrical Peripheral Neuropathy (DSPN) and whether erythrocyte sorbitol levels can be used as predictor of response to Epalrestat in DSPN.

Material and methods

This study was conducted in the Department of Endocrinology and Metabolism, University Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.

Selection of subjects

Subjects with diabetes and peripheral neuropathy were included in the study after obtaining their informed consent. All diabetic patients with duration of diabetes ≥ 5 years were screened for symptoms of peripheral neuropathy by Diabetic Neuropathy Symptom Score (DNSS) (Supplemental table 1) and simultaneously Vibration Perception Threshold (VPT) was checked by sensitometer (Dhansai Lab, Mumbai). DNSS score ≥ 1 and VPT > 25 volts (V) was taken as evidence of peripheral neuropathy.

The study was an open-label and prospective randomized controlled trial in 100 patients with diabetic peripheral neuropathy. The randomization was done through a computer generated random sequence. The enrolled patient population was divided into two groups of 50 patients each: Group 1 (received Epalrestat 150 mg Tablet once a day for 12 weeks) and Group 2 (received placebo). Each participant was given verbal information and was asked to report if they experienced any side effects related to the use of the treatment. All the patients received standard diabetes care and glycemic management was optimized. Three patients (1 patient in group 1 and 2 patients in group 2) were lost to follow up.

The study was reviewed and approved by the Ethics and Drug Trials committee of the institute. The trial was registered with Clinical Trial Registry of India as CTRI/2018/01/011527.

Inclusion Criteria: Duration of diabetes more than 5 years, Diabetic Neuropathy Symptom score 1(Supplemental table 1) and VPT > 25 Volts

Exclusion Criteria: Duration of diabetes less than 5 years, patients having active foot ulcer, subjects on drugs causing peripheral neuropathy or affecting sorbitol levels like Isoniazid, Amiodarone, Laxatives, anti-retroviral drugs etc., chronic alcohol consumption, subjects with estimated glomerular filtration rate (eGFR) less than 60 ml/min, subjects with chronic liver disease, subjects with vitamin B12 deficiency.

Tools for comparison

All study subjects underwent assessment of various parameters at baseline and at 12 weeks. Neuropathy symptoms were assessed by Diabetic Neuropathic Symptom Score. Pain was recorded as 0–10 on numeric pain intensity scale. A neurological examination for neuropathy was done for each patient. Monofilament testing at five sites on each foot (big toe, 1st metatarsal head, 3rd metatarsal head, 5th metatarsal head, and heel) was done at baseline and at 12 weeks.

Vibration perception threshold testing

VPT was tested using Sensitometer, Dhansai Laboratory, Mumbai. After explaining the procedure properly to the subject, the probe was applied to greater toe, 1st metatarsal, 3rd metatarsal, 5th metatarsal and heel of both the feet with the patient in supine position in a quiet room. The vibration was increased gradually from minimum voltage and transition from no vibration to the onset of perceiving vibration was taken as the vibration perception threshold score. The Yes/No method was used. The VPT was tested on five areas on each foot. An average of all the values was taken as VPT of the subject. The VPT was measured in volts. A voltage more than 25 V was taken as presence of neuropathy.

Erythrocyte sorbitol measurement

Erythrocyte sorbitol levels were measured by Human Sorbitol Dehydrogenase (SDH) Elisa kit (Sincere Biotech

Table 1. Baseline characteristics of the study groups

Parameter	Epalrestat (group 1) n = 50	Placebo (group 2) n = 50	P value
Age (years)	50.4 ± 13.5	51.12 ± 12.84	0.785
Duration of diabetes (years)	10.08 ± 4.8	10.46 ± 5.08	0.890
DNSS score (out of 4)	4.78 ± 2.42	4.7 ± 2.24	0.006
Monofilament test (out of 10)	3.88 ± 2.43	3.64 ± 2.51	0.133
Numeric pain intensity scale (out of 10)	8.12 ± 1.19	8.04 ± 1.15	0.049
VPT (average) (in Volts)	32.05 ± 5.75	31 ± 6.36	0.275
HbA1c (%)	9 ± 1.61	8.99 ± 1.75	0.934
Erythrocyte sorbitol levels [ng/mL]	16.15 ± 4.9	16.02 ± 4.6	0.720

Co., Beijing, China) as per the protocol provided by the manufacturer. Absorbance of each well was read at the wavelength of 450 nm in ELISA reader (BIOTEK, India).

Statistical analysis

Quantitative variables were compared using Independent t test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups. Qualitative variables were correlated using Chi-Square test/Fisher's exact test. Spearman rank correlation coefficient was used to assess the correlation of various parameters with erythrocyte sorbitol levels. A p value of <0.05 was considered statistically significant.

Results

Baseline parameters

Both the study groups were comparable in terms of age and duration of diabetes. The study population in both the groups was evenly distributed across all age groups. Overall the duration of diabetes ranged from 5 years to 26 years. The mean duration of neuropathy symptoms was 4 years in both the study groups. Both the study groups were comparable in terms of mean HbA1c and erythrocyte sorbitol levels at the baseline (Table 1).

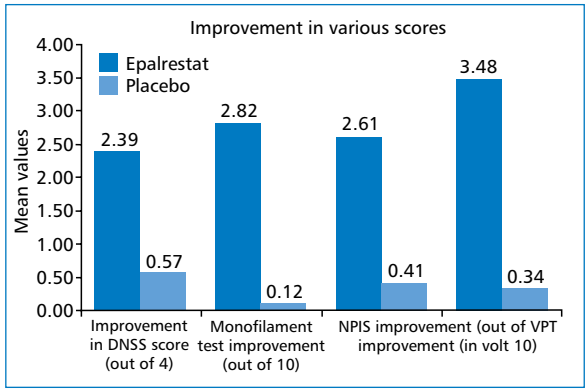

Figure 1. Comparison of two study groups

Comparison of Epalrestat and placebo

The mean improvement in DNSS score was 2.39 ± 1.1 in group 1 vs 0.57 ± 1.04 in group 2; $P < 0.01$. Similarly there was a significant difference in improvement in monofilament score and NPIS score in the two groups. Average VPT score improved by 3.48 ± 2 vs in group 1 vs 0.34 ± 1.14 V in group 2; $P < 0.01$) (Figure 1). Mean HbA1c was around 7.2% in both the groups at follow up visit (Table 2).

Table 2. Follow up characteristics of the study groups

Parameter	Epalrestat (group1) n = 49	Placebo (group2) n = 48	P value
DNSS score (out of 4)			
Follow up visit	2.39 ± 1.1	0.57 ± 1.04	< 0.001
Monofilament test (out of 10)			
Follow up visit	2.82 ± 1.41	0.12 ± 0.93	0.002
Numeric pain intensity scale (out of 10)			
Follow up visit	2.61 ± 1.26	0.41 ± 0.81	< 0.001
VPT (average) (in Volts)			
Follow up visit	28.7 ± 5.33	30.81 ± 6.67	0.116
HbA1c (%) Follow up visit	7.2 ± 1.18	7.17 ± 1.24	0.997
Erythrocyte sorbitol levels [ng/mL] Follow up visit	11.79 ± 3.09	14.59 ± 4.24	< 0.001

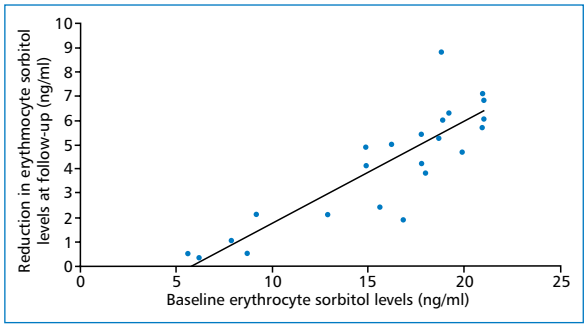

Figure 2. Correlation between baseline erythrocyte sorbitol levels and reduction in sorbitol levels after three months of Epalrestat

Correlation of efficacy of Epalrestat with erythrocyte sorbitol levels

Reduction in sorbitol level with Epalrestat correlated positively with baseline sorbitol levels (r = 0.867; p<0.0001) (Figure 2). Improvement in various parameters with Epalrestat was positively correlated with baseline erythrocyte sorbitol levels and improvement in VPT showed best correlation (r= 0.911; p<0.0001) with baseline erythrocyte sorbitol levels (Figure 3).

Discussion

Aldose reductase (AR), an aldo-keto reductase enzyme has been shown to be involved in the pathogenesis of chronic microvascular diabetic complications [4]. ARIs have received a great deal of attention lately as an attractive therapeutic option for management of various long-term diabetic complications. There is a renewed interest in these drugs, of which only Epalrestat is available in India [7]. The clinical efficacy of Epalrestat in DSPN is still not clear.

Our study showed that Epalrestat was overall more effective than placebo in improving the symptoms of DSPN as well as in improving the quantitative sensory nerve function measured by sensitometer. No major adverse events related to Epalrestat were noted in the study subjects. The higher the erythrocyte sorbitol levels at baseline, the greater was the decrease after Epalrestat treatment. Interestingly, improvement in various parameters with Epalrestat also correlated with baseline erythrocyte sorbitol levels.

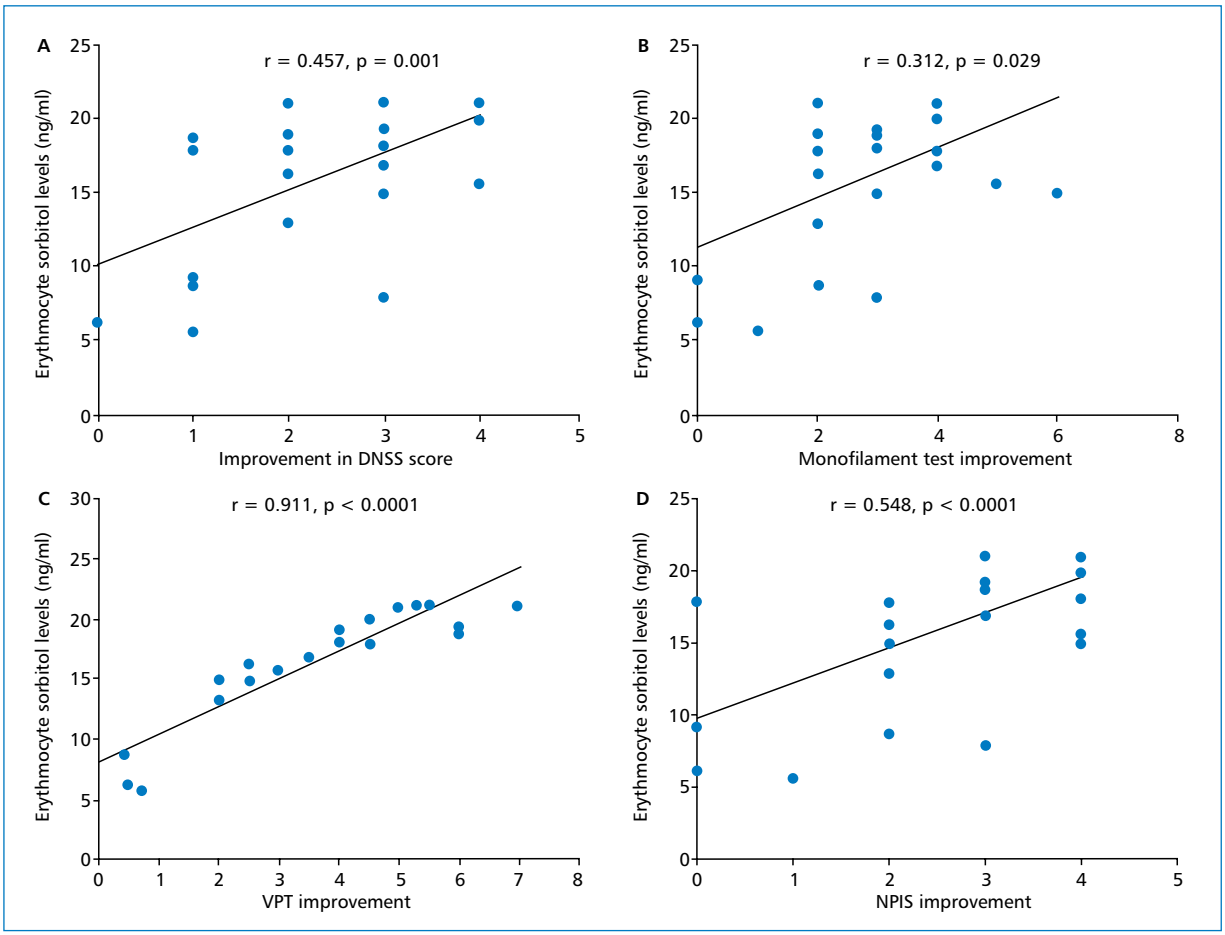

Figure 3. Showing correlation of improvement of (A) DNSS (B) monofilament (C) VPT (D) NPIS with baseline erthyrocyte sorbitol levels in patients of Epalrestat.

ADCT which was a 3-year trial comprising 289 and 305 patients respectively in the Epalrestat and placebo groups concluded that 150 mg daily Epalrestat appreciably prevented deterioration in median MNCV (median motor nerve conduction), MFWL (minimum F-wave latency) and VPT [5]. A Cochrane meta-analysis done in 2007 showed no statistically significant overall benefit of ARIs on neurological examination findings in diabetic polyneuropathy [6]. In an Indian study done by Sharma et al. in 2190 cases with diabetic neuropathy, it was shown that Epalrestat exerted an improvement in the subjective symptoms and nerve function tests. [8]. Ando et al. in a study concluded that decrease in erythrocyte sorbitol levels during Epalrestat administration was significantly correlated with baseline erythrocyte sorbitol levels [9].

It may be possible that the drug works more effectively only in those patients who have excessive sorbitol accumulation at baseline. Additionally, the role of genetics in making an individual more susceptible to express inappropriately high sorbitol for the same degree of hyperglycemia cannot be refuted. Differences in enzyme activity and kinetics of AR in individuals may account for the differential response to ARIs [9].

Strengths of our study: It was a prospective study. Our study used both clinical as well as quantitative sensory parameters to evaluate the efficacy of Epalrestat. Also the improvement in various parameters was correlated with baseline erythrocyte sorbitol levels.

Limitations of our study included limited duration of follow up period and failure to do nerve conduction studies (NCS) for evaluating the nerve function.

To conclude, our study shows that Epalrestat offers a ray of hope in ameliorating the symptoms of DSPN, which still remains one of the most difficult diabetic complications to treat. Erythrocyte sorbitol levels can be used to select the patients in which Epalrestat might work, thus paving the way for a personalized care strategy.

Conflict of interest

None.

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Supplemental table 1. Diabetic Neuropathy Symptom Score (Meijer et al.) [10]

Question asked	Yes	No	Score
Are you suffering unsteadines while walking?	1	0	1 or 0
Do you have a burning, aching pain, or tenderness at your legs or feet?	1	0	1 or 0
Do you have prickling sensation at your legs and feet?	1	0	1 or 0
Do you have places of numbness on your legs of feet?	1	0	1 or 0
Total	4	0	Between 4 and 0