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Original Article

Internal Medicine Section

Evaluation of Efficacy and Safety of Epalrestat (150 mg) Compared to Epalrestat (50 mg) in Patients Suffering from Diabetic Peripheral Neuropathy

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ABSTRACT

Introduction: Epalrestat is currently the only Aldose Reductase Inhibitor (ARI) approved to treat symptoms of Diabetic Peripheral Neuropathy (DPN). The efficacy and safety of Epalrestat 50 mg TDS have been established in clinical practice, however compliance is challenging.

Aim: To evaluate efficacy and safety of Epalrestat Sustained Release (SR) (150 mg) compared to Epalrestat Immediate Release (IR) (50 mg) in patients suffering from DPN.

Materials and Methods: A total of 100 patients with DPN were enrolled in the study, after fulfilling the inclusion and exclusion criteria into two groups of fifty each. Each patient received tablet Epalrestat SR 150 mg once daily or Epalrestat IR 50 mg thrice daily orally for 12 weeks were follow-up at the end of 4, 8, and 12 weeks for evaluation. Primary outcome measure was percent change in Modified Neuropathy Disability Score (MNDS) in both groups from baseline. Secondary outcomes were mean change in pain intensity, numbness in Upper Limb (UL); Lower Limb (LL), cramping and dizziness on VAS score in both groups from baseline. Statistical analysis was done using Student's paired and unpaired t-test, Fisher's-exact-test, and repeated measures ANOVA test.

Results: Epalrestat SR treatment showed clinically significant improvements in MNDS Score and symptoms of neuropathy when compared with Epalrestat IR tablet. Mean MNDS in Epalrestat SR group was reduced to 6.38, 4.28, 1.86 after 4, 8 and 12 weeks of treatment respectively ($p<0.001$). At the end of 12 weeks, mean pain severity was reduced to 1.68 in Epalrestat SR group and 2.68 in Epalrestat IR group respectively on VAS ($p<0.0001$). UL numbness was reduced to 0.54 in Epalrestat SR group and to 1.14 in Epalrestat IR group after 12 weeks of treatment which was statistically significant. Similar statistically significant decline was observed in numbness of LL at the end of 12 weeks of treatment (Epalrestat SR: 1.46 and Epalrestat IR: 2.12). Cramping and dizziness also showed improvement in both Epalrestat groups ($p>0.05$). The most common reported adverse events were headache, diarrhoea and vomiting.

Conclusion: Epalrestat SR is a better alternative to Epalrestat IR in the treatment of DPN.

Keywords: Aldose reductase inhibitor, Diabetes mellitus, Hyperglycaemia

INTRODUCTION

Peripheral neuropathy affects up to 50% of diabetic patients. DPN is responsible for significant morbidity, increased mortality, and impaired quality of life [1]. Reliability of the neurological scores for evaluation neuropathy in Type 2 Diabetic Mellitus (T2DM) patient, revealed that MNDS had 92 % sensitivity and 77% diagnostic efficacy [2]. It is the best neuropathic end point in large prospective study [3].

Currently, plethora of drugs developed which prevents nerves damage. The most effective drugs would be inhibitors of nerve damage process like Aldose Reductase Inhibitor (ARI). These drugs could offer the advantage of being effective even with persistent hyperglycaemia [4].

Duloxetine and pregabalin, have been approved in US for painful DPN [5], whereas Epalrestat is marketed in Japan [6]. Epalrestat is a non competitive inhibitor of aldose reductase, the rate-limiting enzyme in the polyol pathway [7]. Epalrestat was assessed in clinical trials at doses of 50 mg TDS [8].

A study using neuropathy symptoms scores on Visual Analogue Scale (VAS) showed that Epalrestat 50 mg TDS improved the symptoms of DPN and has better efficacy compared to Methylcobalamine [9]. Another study showed that Epalrestat 50 mg TDS improved subjective symptoms of neuropathy and highly effective and safe agent for the treatment of DPN [10]. A multicentric trial evaluating Epalrestat 50 mg TDS, concluded that Epalrestat is well tolerated and can effectively delay the progression of DPN and ameliorate the associated symptoms [11].

Better effectiveness of SR formulation is explained by the virtue of its prolonged and controlled release rate leading to minimisation of the peak and trough effect in plasma, steady state plasma concentration, not missing the doses and patient convenience when compared with IR formulation [12].

The present study was planned to evaluate and compare the efficacy and safety of Epalrestat 150 mg SR tablet Once Daily (OD), with Epalrestat IR 50 mg TDS in patients of DPN.

MATERIALS AND METHODS

A randomised, double blind, double dummy, parallel group, two arm, comparative, prospective study was carried out in the Department of Medicine in collaboration with the Department of Pharmacology at tertiary care hospital from December 2011. The study duration was 24 weeks, which includes 12 weeks of recruitment period. This study was conducted in compliance with the protocol approved by the Institutional Ethical Committee (IEC). Written Informed consent was obtained from all the study participants.

Keeping power of study 80%, alpha 5% and dropout of 10%; total of 100 patients (n=100) satisfying the inclusion and exclusion criteria were enrolled in the study were randomly allocated into two groups of fifty (n=50) each, using a computer generated randomisation chart.

Group A: Epalrestat SR (150 mg) OD before lunch for 3 months orally (n=50).

Group B: Epalrestat IR (50 mg) 1 tablet thrice daily before meals for 3 months orally (n=50).

This was double dummy trial, hence patients in Group A received one tablet of Epalrestat 150 mg and two placebo tablet while in Group B patients received one tablet of Epalrestat 50 mg thrice daily.

Inclusion criteria: 1) Patients of either sex in the age group between 18 to 70 years; 2) Diabetic patients stabilised on antidiabetic medication (on stable dose of antidiabetic drugs for the last 4 weeks) with stable glycaemic control (HbA1c <7.5%±0.5% variation in the previous 3 months) presenting with subjective symptoms of peripheral neuropathy with MNDS >2, 3) Subjects who provided a written informed consent and will abide by the study requirements.

Exclusion criteria: 1) Patients with Stage 3 (N3) [13] i.e., disabling neuropathy or presence of symptoms/signs of foot ulcer; 2) Patients with diabetic neuropathy requiring hospitalisation for management of neuropathy/diabetic complications/any other disease condition; 3) Patients presenting with primary cause of neurologic disorders other than diabetes (alcoholic neuropathy, carpal tunnel syndrome, sequelae of cerebrovascular disease); 4) Patients presenting with arteriosclerosis obliterans (ankle brachial pressure index of <0.8); 5) Patients with known hypersensitivity to any of the ingredients; 6) Patients with severe cardiac, hepatic, gastrointestinal, renal, pulmonary and skin diseases; 7) Patients with history of alcohol/drug abuse; 8) Pregnant and lactating females; 9) Patients receiving other experimental medications for diabetic neuropathy, prostaglandin E1 preparations, or any other medication that affects symptoms of diabetic neuropathy.

Evaluation

The medical history and symptoms including cause, type, site and duration of pain were recorded in the Case Report Form (CRF). In addition, other symptoms of neuropathy i.e., numbness of UL and LL, cramping, and dizziness were also recorded in the CRF. Each symptom was recorded on VAS where in 0= indicates normal and 10= severe intensity of the symptom. The general examination and systemic examination findings were recorded as normal/abnormal.

MNDS Score [2] is based on evaluation of following parameters:

1. Vibration perception threshold using 128 Hz fork placed on apex of big toe;
2. Temperature perception on dorsum of foot using beaker containing warm water followed by ice;
3. Pin prick proximal to big toe nail with sharp and blunt edge, for above three parameters normal response is scored as 0 and abnormal response as 1;
4. Achilles tendon reflex: If reflex is present=0, present with reinforcement=1 and absent=2. Score ranges from 0 to 10 for both right and left extremities.

The parameters for clinical evaluation i.e., each symptom score and MNDS were assessed on day 30, day 60 and day 90. Evaluation of symptom scores was done by grading of symptoms as absent or present. Severity of symptoms was recorded on VAS from 0 to 10.

Safety measures: Laboratories investigations were done at baseline and 90 days after the study.

1. Investigations:

- Haematological; Complete blood count
- Serological: Liver function tests (SGOT, SGPT), serum proteins, A/G ratio, serum bilirubin, Fasting blood sugar, Blood urea nitrogen and serum creatinine
- Urine examination to detect presence of albumin and sugar.

2. Recording of adverse events and serious adverse events (At baseline and 90 days after the study).

STATISTICAL ANALYSIS

Statistical analysis was performed with the help of the Graphpad Prism 5. Student's paired t-test used for comparing quantitative data within the study groups before and after study. For comparing quantitative data between the study groups after therapy, Student's unpaired t-test was applied. Comparison of qualitative data between the study groups was done using chi-square test with Yates correction or Fisher's exact-test with two-tailed p-value where applicable. Comparison of quantitative data obtained at multiple time intervals was done using repeated measures ANOVA test, with Tukey's Multiple Comparison test for selected pairs as the post-test. Statistical significance is indicated by: *p<0.05: Statistically significant; **p<0.001: statistically highly significant.

RESULTS

Total 100 participants were randomly allocated into two groups. Both groups were similar in all baseline parameters at the start of study as shown in [Table/Fig-1].

Parameters	Epalrestat SR; (n=50) Mean±SEM	Epalrestat IR; (n=50) Mean±SEM	p-value
Age*(years)	50.02±1.11	51.00±0.00	0.51
Sex† Male, Female	27, 23	21, 29	0.31
Weight*(kg)	73.38±0.82	73.34±0.62	0.96
Height*(m)	1.61±0.00	1.60±0.00	0.69
BMI*(kg/m^2)	28.30±0.28	28.46±0.27	0.68
Duration of DM (Years)*	12.12±0.56	12.18±0.48	0.93
Duration of PDN (Years)*	8.88±0.34	8.86±0.38	0.96
HbA1c* (%)	6.83±0.03	6.82±0.03	0.69
MNDS Score*	8.52±0.10	8.68±0.08	0.23
Pain Intensity ‡*	6.68±0.53	6.66±0.53	0.97
Numbness in UL‡*	3.20±0.61	3.24±0.59	0.96
Numbness in LL‡*	5.86±0.57	5.64± 0.60	0.79
Cramping ‡*	4.08±0.60	2.56±0.56	0.06
Dizziness ‡*	1.22±0.43	2.12±0.51	0.18

[Table/Fig-1]: Demographical characteristics of the study population.
*Unpaired t-test, †Fisher's exact-test p>0.05 Not Significant ‡Symptoms intensity noted on VAS Score in Mean±SEM (Standard Error of mean) UL: Upper limb; LL: Lower limb

MNDS: As shown in [Table/Fig-2] both the treatment groups showed significant reduction in score during the entire treatment period. Mean Score in Epalrestat SR group was reduced to 6.38, 4.28, 1.86 after 4, 8 and 12 weeks of treatment respectively (p<0.001). Similarly mean score reduction was also statistically significant in Epalrestat IR group to 2.28 after 12 weeks (p<0.001). When compared both groups, it was statistically significant after 8 week (p-value=0.003) and 12 weeks of treatment (p-value=0.01).

Duration in weeks	Epalrestat SR (Mean±SEM)	Epalrestat IR (Mean±SEM)	p-value
Baseline	8.52±0.10	8.68±0.08	0.23
4	6.38±0.11†	6.60±0.09†	0.14
8	4.28±0.10†	4.74±0.11†	0.003*
12	1.86±0.08†	2.28±0.14†	0.010*

[Table/Fig-2]: Comparison of MNDS score.
SEM: Standard error of mean; Using unpaired t-test *p<0.05; †p-significant within group using paired t-test

In patients of Epalrestat SR group the score was reduced to <2 in 92% of patient While in case of Epalrestat IR only 38% of the patients returned to <2 score after 12 week of treatment which could be attributed to steady state plasma concentration and or patient's compliance for TDS doses [Table/Fig-3].

Duration in weeks	Epalrestat SR group			Epalrestat IR group		
	0-2 n (%)	3-6 n (%)	7-10 n (%)	0-2 n (%)	3-6 n (%)	7-10 n (%)
Baseline	0 (0)	1 (2)	49 (98)	0 (0)	1 (2)	49 (98)
4	0 (0)	22 (44)	28 (56)	0 (0)	14 (28)	36 (72)
8	0 (0)	50 (100)	0 (0)	1 (2)	48 (96)	1 (2)
12	46 (92)	4 (8)	0 (0)	19 (38)	31 (62)	0 (0)

[Table/Fig-3]: Percentage change in MNDS score.

Severity of pain on VAS: About 76% of patients in both treatment groups presented with pain. Significant improvement was noted in Epalrestat SR and Epalrestat IR group. Intergroup comparison at the end of 12 weeks, showed highly significant reduction in pain severity (p-value=0.001) as shown in [Table/Fig-4].

Duration in weeks	Epalrestat SR (Mean±SEM)	Epalrestat IR (Mean±SEM)	p-value
Baseline	6.68±0.53	6.66±0.53	0.97
4	4.84±0.40†	5.08±0.41†	0.68
8	3.24±0.28†	3.90±0.32†	0.12
12	1.68±0.16†	2.68±0.24†	0.001*

[Table/Fig-4]: Comparison of pain Intensity.
†p: Significant within group using repeated measures anova with tukey's multiple comparison test

Numbness in UL on VAS: Total 19 (38%) patients in Epalrestat SR and 18 (36%) patients in Epalrestat IR group complained of numbness in UL, which was improved during and after the treatment. UL numbness in Epalrestat SR group was reduced from 3.20 to 1.46 after 8 weeks and to 0.54 after 12 weeks of treatment (p<0.0001). Similar reduction in numbness was observed in Epalrestat IR group from mean baseline 3.24 to 1.78 after 8 weeks and to 1.14 after 12 weeks of treatment (p-value=0.001).

However, numbness score of Epalrestat SR group showed greater improvement as compared to Epalrestat IR group after 12 weeks of treatment (p-value=0.01) as shown in [Table/Fig-5].

Duration in weeks	Epalrestat SR (Mean±SEM)	Epalrestat IR (Mean±SEM)	p-value
Baseline	3.20±0.61	3.24±0.59	0.96
4	2.04±0.39	2.42±0.44	0.52
8	1.46±0.28†	1.78±0.33†	0.46
12	0.54±0.11†	1.14±0.22†	0.01*

[Table/Fig-5]: Comparison of numbness in UL.
(†p: Significant within group using repeated measures anova with tukey's multiple comparison test)

Numbness in LL on VAS: A total of 68% of patients in Epalrestat SR group and 64% of patients in Epalrestat IR group, complained of numbness in LL which was improved during and after the treatment.

As depicted in [Table/Fig-6], mean numbness score in Epalrestat SR group was reduced to 4.36, 2.92, and 1.46 after 4, 8, and 12 weeks of treatment respectively (p-value<0.0001).

Duration in weeks	Epalrestat SR (Mean±SEM)	Epalrestat IR (Mean±SEM)	p-value
Baseline	5.86±0.57	5.64±0.60	0.79
4	4.36±0.43†	4.18±0.46	0.77
8	2.92±0.29†	3.10±0.35†	0.69
12	1.46±0.17†	2.12±0.27†	0.04*

[Table/Fig-6]: Comparison of numbness in LL.
(†p: Significant within group using repeated measures anova with tukey's multiple comparison test)

Similar reduction also observed in Epalrestat IR group from 5.64 to 3.10 after 8 weeks and to 2.12 after 12 weeks of treatment (p-value<0.0001). Intergroup comparison in numbness showed greater reduction in Epalrestat SR group after 12 weeks of treatment compared to Epalrestat IR group (p-value=0.04).

Cramping on VAS: [Table/Fig-7] shows that reduction in cramping on VAS was significant in both treatment groups, however intergroup comparison was statistically non significant during entire treatment period.

Duration in weeks	Epalrestat SR (Mean±SEM)	Epalrestat IR (Mean±SEM)	p-value
Baseline	4.08±0.60	2.56±0.56	0.06
4	2.90±0.44	1.98±0.43	0.14
8	1.86±0.29†	1.32±0.29	0.19
12	0.74±0.14†	0.76±0.19†	0.93

[Table/Fig-7]: Comparison of cramping.
(†p: Significant within group using repeated measures anova with tukey's multiple comparison test)

Epalrestat SR treated patient had mean baseline cramping score of 4.08 which was reduced significantly to 1.86 after 8 weeks and 0.74 after 12 weeks of treatment (p-value<0.0001). However, reduction in symptom of cramping score on VAS was highly significant only after 12 weeks of treatment i.e., from mean baseline 2.56 to 0.76 in Epalrestat IR group.

Dizziness on VAS: In Epalrestat SR group, dizziness score was reduced from 1.22 to 0.32 after 12 weeks of treatment which was statistically significant (p-value<0.0001). Similar reduction in dizziness score was observed as early as after 4 week of treatment in Epalrestat IR group from baseline to 1.54. This reduction was subsequently statistically highly significant after 8 weeks (1.14) and 12 weeks (0.68) of treatment. Intergroup comparison at each follow-up visit showed no statistical significance in dizziness in both the groups (p-value=0.12) as revealed in [Table/Fig-8].

Duration in weeks	Epalrestat SR (Mean±SEM)	Epalrestat IR (Mean±SEM)	p-value
Baseline	1.22±0.43	2.12±0.51	0.18
4	0.84±0.30	1.54±0.37†	0.15
8	0.56±0.21†	1.14±0.28†	0.10
12	0.32±0.14†	0.68±0.18†	0.12

[Table/Fig-8]: Comparison of dizziness.
(†p: Significant within group using repeated measures anova with tukey's multiple comparison test)

Adverse Effects (AEs): AEs related to the drug were reported in 7 (14%) patients in Epalrestat SR group as compared to 12 (24%) patients in Epalrestat IR group as shown in [Table/Fig-9]. No serious AEs were reported in any of the study groups.

Type of AE	Epalrestat SR	Epalrestat IR
Headache	3	5
Vomiting	1	3
Diarrhoea	2	1
Elevated liver enzymes	1	3

[Table/Fig-9]: Nature and incidence of adverse effects.

DISCUSSION

Clinical trials conducted with 150 mg of Epalrestat may improve subjective symptoms in patient with Type 1 or Type 2 diabetes with established neuropathy [14-17].

Our study showed that in both the treatment groups, significantly reduced MNDS at the end of study. Vibration Perception Threshold (VPT) and Achilles tendon reflex, both are component of MNDS score. Maladkar M et al., Sharma SR and Sharma N and Hotta N et al., evaluated VPT and Achilles tendon reflexes separately, not

as a part of MNDS [9-11]. Sharma SR and Sharma N noted that baseline VPT in Epalrestat group was 8.01 which increased by 0.57 after three months of therapy [10]. Maladkar M et al., noted that at the end of 12 weeks, significantly more patients (53.9%) from the Epalrestat group had normal tendon reflexes compared to 33.9 % from the comparator group [9]. These finding are in accordance with present study when above two parameters are considered separately.

Pain reduced significantly in both the treatment groups. Similar results in relief of pain after 12 weeks of treatment were noted by Maladkar M et al., Sharma SR and Sharma N and Hotta N et al., [9-11]. Maladkar M et al., noted that 19.1% of patients in Epalrestat group, had relief from pain compared to 7.8% relieved patients in comparator group, which is statistically significant (p-value<0.05) [9]. Significant improvement of spontaneous pain was reported by Sharma SR and Sharma N in both UL and LL, after three months treatment with Epalrestat [10].

Numbness in UL and LL on VAS was significantly reduced in both treatment groups in the present study. These results are in accordance with the observations obtained by Hotta N et al., Maladkar M et al., Sharma SR and Sharma N and Steele JW et al., which showed that the Epalrestat group exhibited significantly greater amelioration of the numbness of UL, and LL [8-10,14].

Our study showed reduction in cramping on VAS, which was statistically significant in both treatment groups (Epalrestat SR: 0.74; Epalrestat IR: 0.76) however intergroup comparison was statistically non significant. A similar result for reduction in cramping was observed by Maladkar M et al., [9].

In this study, both groups showed, dizziness score on VAS was reduced after 12 weeks of treatment which was statistically significant. Similar reduction in dizziness was noted by Hotta N et al., Sharma SR and Sharma N and Hotta N et al., [8,10,11].

AEs attributed to Epalrestat were previously reported in 2.5% of the subjects in a 12-month Study [8] and 3.0% in a 12-week study [18]. The most frequent AEs in present study were reported in Epalrestat IR group, while Epalrestat SR showed better tolerability. None of the patients in Epalrestat SR group missed study dose and showed complete treatment adherence.

LIMITATION

It is imperative to do much more studies in greater number of patients over longer period of time for evaluating the efficacy and safety of epalrestat SR.

CONCLUSION

Epalrestat SR showed clinically and statistically more improvement in DPN, and comparable AEs profile. We conclude that Epalrestat 150 mg SR is a better alternative to Epalrestat 50 mg IR in the treatment of DPN.

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