Tropical Journal of Pharmaceutical Research December 2024; 23 (12): 2017-2023
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v23i12.6

Original Research Article

Treatment of peripheral neuropathy in type 2 diabetes with epalrestat combined with sulodexide

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Sent for review: 5 December 2023 *Revised accepted: 10 December 2024*

Abstract

Purpose: *To analyze the efficacy of epalrestat combined with Sulodexide in the treatment of diabetic peripheral neuropathy in type 2 diabetes.*
Methods: *A total of 140 patients with type 2 diabetic peripheral neuropathy, who were treated at the Zhanjiang Central People's Hospital between February 2022 and February 2023, were selected as subjects. They were randomly divided into two groups using a computer-generated random number table. The control group (n = 70) received epalrestat treatment, while the study group (n = 70) was treated with a combination of epalrestat and Sulodexide11. Efficacy, nerve conduction velocity, levels of inflammatory factors and oxidative stress markers were compared between groups.*
Results: *After treatment, total effective rate in study group was 97.14 %, which was higher than that of control group (85.71 %; p < 0.05). Sensory nerve conduction velocity (SCV) and motor nerve conduction velocity (MCV) of the common peroneal nerve and median nerve in study group were significantly faster than those in control group (p < 0.05). Levels of serum high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), procalcitonin (PCT) and tumor necrosis factor-α (TNF-α) in study group were significantly lower than those in control group (p < 0.05). Total antioxidant capacity (T-AOC) and superoxide dismutase (SOD) levels in study group were higher than those in control group, while malondialdehyde (MDA) level was lower than control group (p < 0.05).*
Conclusions: *Epalrestat combined with Sulodexide in treatment of diabetic peripheral neuropathy in type 2 diabetes improves efficacy, accelerates nerve conduction velocity, reduces inflammatory factor levels and decreases oxidative stress response. Further studies are necessary to accurately verify the combination therapy value using epalrestat and Sulodexide in treating peripheral neuropathy associated with type 2 diabetes.*

Keywords: *Epalrestat, Sulodexide, Type 2 diabetic peripheral neuropathy, Nerve conduction velocity, Inflammatory factors, Oxidative stress*

Tropical Journal of Pharmaceutical Research is indexed by Scopus, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Type 2 diabetes mellitus is a very common metabolic disease in endocrinology characterized by prolonged course and many complications, peripheral neuropathy is one of the common complications, with numbness of limbs, sensory deficits and pain as main manifestations [1-2]. Patients with peripheral neuropathy in type 2 diabetes mellitus have a poor prognosis and the focus of treatment is on controlling blood glucose, anti-oxidative stress neurotrophic nutrition, etc [3].

Epalrestat, a commonly used drug in the treatment of type 2 diabetic peripheral

neuropathy, is an aldose reductase inhibitor that inhibits glucose metabolism, prevents its conversion into large amounts of sorbitol and reduces damage caused by sorbitol to patient's neurological function [4]. Although the effect of epalrestat in the treatment of type 2 diabetic peripheral neuropathy has been recognized, effect of single drug use is limited.

Sulodexide is a vasoprotective agent made from extraction of porcine intestinal mucosa and promotes improvement of vascular endothelial function. However, the effect of combined application with epalrestat needs to be investigated [5]. In recent years, patients with type 2 diabetic peripheral neuropathy at Zhanjiang Central People's Hospital have been treated with a combination of epalrestat and Sulodexide. This study analyzes the efficacy of epalrestat and Sulodexide combination treatment in the management of diabetic peripheral neuropathy in type 2 diabetes.

METHODS

General information

A total of 140 patients diagnosed with type 2 diabetic peripheral neuropathy, who were treated at Zhanjiang Central People's Hospital, Zhanjiang, China, from February 2022 to February 2023, were selected as subjects and subsequently divided into groups using the computer-generated Random Number Table method. In control group, there were 32 females and 38 males, with an average age of 59.88 ± 6.12 years (range: 31 - 73 years). Duration of type 2 diabetes ranged from 2 to 14 years and averaged 8.90 ± 1.22 years, while duration of peripheral neuropathy varied from 1 to 7 years, with a mean of 3.42 ± 0.50 years. In the study group, a total of 70 individuals comprised 34 females and 36 males with an average age of 59.67 ± 6.39 years (range: 30 - 75 years). Duration of type 2 diabetes in this group spanned from three to fourteen years and an average duration of 8.95 ± 1.29 years. Similarly, the period for peripheral neuropathy extended between one and eight years (average: 3.44 ± 0.59) years.

Ethical approval

The study received approval from the Medical Ethics Committee of Zhanjiang Central People's Hospital (approval no. 21-ZJ-112) and was performed in accordance with the Declaration of Helsinki [6].

Inclusion criteria

Patients were included based on criteria for Diagnosis of type 2 diabetes mellitus outlined in "Chinese Guidelines for Prevention and Treatment of Type Two Diabetes Mellitus" [7] and confirmed through neuro-electrophysiological examination for peripheral neuropathy. In addition, patients between 18 – 75 years, without medications that could potentially influence study outcomes taken within thirty days before enrollment, having a Michigan Neuropathy Screening [8] score equal to or greater than two as well as complete medical records and provided signed informed consent were included.

Exclusion criteria

However, patients with severe liver or renal insufficiency, allergies related to study medications, history indicating traumatic neurological impairment, presence of severe cardiovascular or cerebrovascular diseases, malignant tumors, cognitive impairments and mental disorders were excluded.

Treatments

Upon admission, all patients received standard treatments including antidiabetic medications or insulin injections alongside dietary management. Once the hypoglycemic effect met established criteria, control group was orally administered 50 mg epalrestat (Yangzijiang Pharmaceutical Group Nanjing Aling Pharmaceutical Co., LTD.; H20040840) three times daily before meals. In addition to this regimen, study group received Sulodexide (ALFA WASSERMANN S.p.A.; H20140119) twice daily. Patients were assessed after 8 weeks of continuous treatment.

Evaluation of parameters/indices

Clinical efficacy

After treatment, the efficacy of treatment was assessed based on criteria formulated in the Clinical Disease Diagnosis Basis for Cure and Improvement Standards [9]. If symptoms such as coldness, numbness and pain in the patient's limbs fully disappeared after treatment and the nerve conduction velocity was increased by 5 m/s compared with the value before treatment or had been restored to the normal level then, the effect is significantly effective. On the other hand, if symptoms such as coldness, numbness and pain in the patient's limbs significantly improved and the nerve conduction velocity was increased by less than 5 m/s compared with that before treatment, it is effective. However, if there are no changes in symptoms of coldness, numbness

and pain in the patient's limbs, or they were even aggravated and nerve conduction velocity was not accelerated, it is said to be ineffective. Total effective rate represents the summation of the components "*significantly effective* and *effective*" relative to the overall number of patients.

Nerve conduction velocity

Sensory nerve conduction velocity (SCV) and motor nerve conduction velocity (MCV) of common peroneal and median nerves were determined and recorded by myoelectric evoked potential apparatus (Shanghai Jumo Medical Equipment Co., Ltd., Model MEB-9400C) before and after treatment.

Inflammatory factor levels

Before and after treatment, levels of serum ultrasensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6), procalcitonin (PCT) and tumor necrosis factor-alpha (TNF-α) were assessed in both groups. Fasting peripheral venous blood (5 mL) was drawn from each patient, centrifuged at 3000 r/min for 10 min and serum levels of inflammatory factors determined by enzyme-linked immunosorbent assay.

Oxidative stress indicators

Total antioxidant capacity (T-AOC), glutathione peroxidase (GSH-PX), superoxide dismutase (SOD) and malondialdehyde (MDA) levels were determined in both groups before and after treatment. Serum levels of T-AOC were determined by thiobarbituric colorimetric assay while MDA and SOD levels were determined by the xanthine oxidation method. The assays were conducted by utilizing a specialized glutathione peroxidase assay kit (Beyotime, Shanghai, China).

Statistical analysis

Data analyses were performed using SPSS version 20.0 software and measurement data were subjected to *t*-tests while n (%) shows count data analyzed via chi-square tests. Values of $p < 0.05$ indicate that differences are statistically significant.

RESULTS

Clinical efficacy

After treatment, the total effective rate in the study group was higher than that in control group ($p < 0.05$) as shown in Table 1.

Nerve conduction velocity

There was no significant difference in nerve conduction velocity between both groups before treatment ($p > 0.05$) but after treatment, nerve conduction velocity in both groups was significantly faster than before and the SCV and MCV of the peroneal and median nerves in study group were significantly faster than those in control group ($p < 0.05$) as shown in Table 2.

Inflammatory marker levels

Before treatment, there was no significant difference in levels of inflammatory factors between groups ($p > 0.05$). However, post-treatment levels of inflammatory indicators improved significantly in comparison with pre-treatment levels. Furthermore, levels of serum hs-CRP, IL-6, PCT and TNF-α also decreased in study group compared to control ($p < 0.05$; Table 3).

Oxidative stress markers

There were no significant differences in oxidative stress indicators between the two groups before treatment ($p > 0.05$) but they improved significantly after treatment in both groups compared with those before treatment. Total antioxidant capacity and SOD levels were higher in study group than control group, while the MDA levels were lower than that in control group ($p < 0.05$; Table 4).

Table 1: Comparison of clinical efficacy between two groups

Group	Significant effective	Effective	Ineffective	Total effective rate
Control group	27(38.57)	33(47.14)	10(14.29)	60(85.71)
Study group	36(51.43)	32(45.71)	2(2.86)	68(97.14)
x^2 value	-	-	-	5.833
P-value	-	-	-	0.016

Table 2: Comparison of nerve conduction velocity between two groups

Group	Common peroneal nerve				Median nerve			
	SCV		MCV		SCV		MCV	
	Pre-treatment	***Post-treatment***	***Pre-treatment***	***Post-treatment***	***Pre-treatment***	***Post-treatment***	***Pre-treatment***	***Post-treatment***
Control group	37.17±5.59	42.25±5.19[a]	37.47±4.19	51.12±4.22[a]	37.55±5.15	44.12±4.68[a]	47.99±5.06	52.76±5.53[a]
Study group	37.11±5.68	44.78±5.91[a]	37.50±4.12	55.86±4.29[a]	37.43±5.30	49.11±4.72[a]	47.9 ±5.18	55.77±5.68[a]
T	0.063	2.691	0.043	6.590	0.136	6.281	0.092	3.177
P-value	0.950	0.008	0.966	<0.001	0.892	<0.001	0.926	0.002

[a] Compared to the baseline within this group, $p < 0.05$

Table 3: Comparison of inflammatory markers levels between two groups

Group	hs-CRP		IL-6		PCT		TNF-α	
	Pre-treatment	**Post-treatment**	**Pre-treatment**	**Post-treatment**	**Pre-treatment**	**Post-treatment**	**Pre-treatment**	**Post-treatment**
Control group	7.17±1.63	4.21±1.18[a]	11.85±2.63	9.25±1.68[a]	0.53±0.11	0.12±0.04[a]	42.02±8.13	36.68±5.11[a]
Study group	7.22±1.55	2.56±0.93[a]	11.90±2.53	8.20±1.55[a]	0.50±0.16	0.08±0.03[a]	42.09±8.02	19.93±2.67[a]
T	0.186	9.188	0.115	3.843	1.293	6.693	0.051	24.307
P-value	0.853	<0.001	0.909	<0.001	0.198	<0.001	0.959	<0.001

[a] Compared to the baseline within this group, $p < 0.05$

Table 4: Comparison of oxidative stress markers between two groups

Group	T-AOC		SOD		MDA	
	Pre-treatment	*Post-treatment*	*Pre-treatment*	*Post-treatment*	*Pre-treatment*	*Post-treatment*
Control group	14.96±3.61	16.63±3.52[a]	73.35±10.22	78.26±11.36[a]	5.73±1.06	4.96±1.02[a]
Study group	15.02±3.52	21.76±3.60[a]	73.41±10.11	92.05±15.13[a]	5.81±1.19	3.61±1.00[a]
T	0.100	8.525	0.035	6.098	0.420	7.907
P-value	0.921	<0.001	0.972	<0.001	0.675	<0.001

[a] Compared to the baseline within this group, $p < 0.05$

DISCUSSION

In recent years, the incidence of type 2 diabetes mellitus has been steadily increasing, with peripheral neuropathy emerging as a prevalent complication among patients. This condition not only exacerbates patient's overall health and complicates treatment efforts but also directly impacts their quality of life and work [10]. Type 2 diabetic peripheral neuropathy is characterized by symptoms such as limb coldness, numbness and pain. As the disease progresses, motor nerve function is impaired which, in severe cases, leads to limb infections, ulcers or tissue necrosis. Studies indicate that timely professional intervention for patients suffering from type 2 diabetic peripheral neuropathy enhances prognosis by alleviating symptoms and inhibiting disease progression [11]. However, monotherapy with epalrestat exhibits limited targeting capabilities and requires further enhancement in efficacy. Consequently, exploring appropriate combination therapies has become a focal point of some studies [11,12].

In this study, combination of epalrestat and Sulodexide for treating type 2 diabetic peripheral neuropathy demonstrated a significantly higher total effective rate in study group compared to control ($p < 0.05$), indicating that this combined approach improves outcomes for patients. epalrestat serves as a common reversible non-competitive inhibitor of aldose reductase in practice as it inhibits both aldose reductase activity and polyol metabolism while reducing neuronal damage caused by sorbitol accumulation. Additionally, it promotes Na+-K+-ATPase activity and facilitates timely recovery of inositol levels, thereby alleviating symptoms associated with type 2 diabetic peripheral neuropathy [12]. Sulodexide, on the other hand, is a natural glycosaminoglycan known for its antioxidative stress-reducing properties and anti-inflammatory effects. It boasts high bioavailability and affinity due to its rich content of anionic heparin sulfate components which adsorb substances on vascular endothelial surfaces thereby effectively enhancing vascular wall permeability to achieve therapeutic goals [13]. The synergistic effect produced by combining epalrestat with Sulodexide allows these agents to complement each other's strengths while enhancing therapeutic efficacy and ultimately relieving patient conditions.

Moreover, after treatment, both sensory conduction velocity (SCV) and motor conduction velocity (MCV) determination from common peroneal and median nerves were significantly faster in study group than those recorded in control group ($p < 0.05$). This suggests that combining epalrestat with Sulodexide accelerates nerve conduction velocities associated with type 2 diabetic peripheral neuropathy treatment outcomes. epalrestat obstructs polyol metabolic pathways preventing glucose conversion into sorbitol thus reducing sorbitol levels which mitigates edema within peripheral nerves and contributes positively towards restoring nerve function while improving axonal area alongside myelin sheath thickness. These factors culminate in enhanced nerve conduction velocities [14]. Furthermore, this combination therapy promotes rapid movement of skin-sulfated compounds along with heparin-like molecules protecting vascular endothelial functions while inhibiting oxidative stress responses alongside inflammatory reactions. This prevents mesangial cell proliferation along with extracellular matrix secretion thereby ameliorating hypercoagulable states within blood circulation while mitigating thrombosis risks and enhancing overall effectiveness against neurodegenerative processes.

Studies have identified autoimmune dysfunctions alongside metabolic disorders as contributing factors in developing progressive forms seen within type 2 diabetic peripheral neuropathies [15]. Elevated blood glucose causes an abnormal increase in oxygen free radicals and oxidative stress, which leads to complications. In this study, levels of serum hs-CRP, IL-6, PCT and TNF-α in study group after treatment were lower than control group ($p < 0.05$). Similarly, levels of T-AOC and SOD in study group were higher than in control group, while MDA levels were lower than that in the control group ($p < 0.05$). epalrestat combined with Sulodexide in treatment of type 2 diabetic peripheral neuropathy also

down-regulates levels of inflammatory factors and reduces oxidative stress. epalrestat directly acts on the protein kinase acid signaling pathway and inhibits it, which contributes to nitric oxide production in endothelial cells. At the same time, epalrestat inhibits high glucose-mediated adhesion of neutrophils to endothelial cells and down-regulates expression of endothelial adhesion factors.

Sulodexide also inhibits the expression of malondialdehyde and cell adhesion molecules, indirectly up-regulates superoxide dismutase levels, inhibits oxidative stress, delays the progression of the disease, regulates expression of platelet-derived growth factor and exhibits strong antithrombotic and anticoagulant ability. It prevents mesangial proliferation and proliferation of epithelial cells as well as smooth muscle tissue. Moreover, sulodexide is a heparin-like molecule, which can act on fibrin binding thrombin through heparin factor II, inhibits thrombosis and growth, releases a large amount of protein esterase, promotes lipoprotein enzyme activity and inhibits continuous progression of microangiopathy in diabetic patients [16]. Epalrestat combined with sulodexide regulates tyrosine kinase 2 and angiopoietin-2, reduces continuous phosphorylation of extracellular regulated protein kinase, prevents venous intimal hyperplasia, inhibits platelet aggregation, activates vascular wall fiber system and circulatory system, promote the improvement of blood circulation function and enhance the effect of anti-inflammatory and anti-oxidative stress. Thus, it down-regulates inflammatory factors and reduces oxidative stress.

Limitations of study

There is a presence of selection bias in cases of peripheral neuropathy associated with type 2 diabetes, as well as a small sample size and limited observation indicators.

CONCLUSION

Combination therapy of epalrestat and sulodexide demonstrates significant efficacy in the treatment of peripheral neuropathy associated with type 2 diabetes. This treatment not only improves outcomes and accelerates nerve conduction velocity but also reduces levels of inflammatory factors and oxidative stress reactions. Further studies are necessary to accurately verify the combination therapy value using epalrestat and Sulodexide in treating peripheral neuropathy associated with type 2 diabetes.

DECLARATIONS

Acknowledgements

None.

Funding

None provided.

Ethical approval

The study received approval from the Medical Ethics Committee of Zhanjiang Central People's Hospital (approval no. 21-ZJ-112).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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