Am J Transl Res 2025;17(4):2898-2906
www.ajtr.org /ISSN:1943-8141/AJTR0161571

Original Article

Therapeutic effects of mecobalamin combined with epalrestat on diabetic peripheral neuropathy: reduction of inflammatory factors and improvement in electromyogram indices

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Received October 29, 2024; Accepted March 19, 2025; Epub April 15, 2025; Published April 30, 2025

Abstract: Objective: To evaluate the clinical efficacy of mecobalamin combined with epalrestat in treating diabetic peripheral neuropathy (DPN) and its effects on inflammatory factors and electromyogram (EMG) indices. Methods: Data from 100 DPN patients treated at Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People's Hospital between June 2021 and December 2022 were retrospectively analyzed. Among them, the control group was 45 patients treated with mecobalamin alone. 55 patients treated with epalrestat, in addition to mecobalamin, were the observation group. Outcomes compared between the two groups included the changes in inflammatory factors, EMG indices, oxidative stress markers, blood glucose levels before and after treatment, clinical efficacy, and the incidence of adverse reactions. Results: The observation group showed a significantly higher overall response rate than the control group ($P<0.05$). After treatment, the observation group exhibited lower levels of C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), and matrix metalloproteinase-9 (MMP-9) than control group (all $P<0.05$). The observation group also demonstrated higher motor nerve conduction velocity (MCV) and sensory nerve conduction velocity (SCV) of the median nerve and nervus peronaeus communis compared to the control group (all $P<0.05$). Additionally, the observation group showed lower levels of propylene glycol and higher levels of superoxide dismutase compared to the control group (both $P<0.05$). Fasting blood glucose and 2-hour postprandial blood glucose levels in the observation group were significantly lower than those in the control group ($P<0.05$). Both groups exhibited a decrease in Michigan Diabetic Neuropathy Scores post-treatment compared to pre-treatment, with the observation group scoring lower than the control group ($P<0.05$). No difference was found between the 2 groups in the incidence of adverse reactions ($P>0.05$). Conclusion: Mecobalamin combined with epalrestat substantially alleviates DPN, improves electromyogram indices, and reduces inflammatory factors and oxidative stress response, without increasing adverse reactions.

Keywords: Mecobalamin, epalrestat, diabetic peripheral neuropathy, inflammatory factors, electromyogram indexes

Introduction

Diabetic peripheral neuropathy (DPN) is one of the most common complications in patients with diabetes and a major cause of disability [1]. DPN typically develops during the course of diabetes mellitus (DM) and is associated with damage to the peripheral nervous system [1]. However, due to variations in screening methods and diagnostic criteria, the precise epidemiologic data for DPN remain unclear [2]. It has been reported that around 10-20% of patients already have developed DPN at the time of their DM diagnosis, with the incidence of DPN ranging from 30% to 90% within 5, 10, and 20 years post-diagnosis [3].

The pathogenesis of DPN is not fully understood and is thought to result from the interplay of multiple factors, including metabolic disorders, vascular damage, insufficient neurotrophic support, abnormal cytokine levels, oxidative

https://doi.org/10.62347/XUBX8834

stress, and immune factors [2]. Glucose autooxidation leads to the formation of reactive oxygen species, causing cellular oxidative stress and mitochondrial dysfunction. In clinical practice, non-pharmacologic treatments such as physical exercise are used along with medications that improve microcirculation, including pentoxifylline, aldose reductase inhibitors like epalrestat, antioxidants such as alpha-lipoic acid, and neurotrophic repair agents like methylcobalamin for the prevention and treatment of DPN [3, 4]. While there are many drugs available for the therapy of DPN, their efficacy varies [5]. Therefore, individualized treatment tailored to the specific needs of patients is critical for improving clinical outcomes and alleviating symptoms [6]. As a typical neurotrophic drug, mecobalamin can reduce symptoms by repairing nerve tissue and accelerating axonal regeneration and myelination [7]. Mecobalamin has demonstrated favorable efficacy and safety in treating DPN. Additionally, epalrestat, a representative aldose reductase inhibitors, can effectively block the polyol pathway and reduce the production of carboxymethyl lysine, thus exerting therapeutic effects [8]. It also demonstrates preventive and therapeutic benefits in DPN treatment. However, the efficacy of these two drugs in combination is uncertain.

This study aimed to evaluate the clinical efficacy of mecobalamin combined with epalrestat in treating DPN and their effects on inflammatory factors and electromyogram indices, with the goal of providing further insight for clinical treatment.

Materials and methods

Case selection

Data from 100 DPN patients treated at Quzhou Affiliated Hospital of Wenzhou Medical University and Quzhou People's Hospital between June 2021 and December 2022 were retrospectively analyzed. Among them, 45 patients treated with mecobalamin were assigned to the control group, while 55 patients who received epalrestat in addition to mecobalamin were assigned to the observation group. This study was conducted with approval from the Medical Ethics Committee of Quzhou Affiliated Hospital of Wenzhou Medical University and Quzhou People's Hospital.

Inclusion criteria: (1) Patients who met the diagnostic and treatment consensus-related criteria for DPN [6]; (2) Patients presenting with clinical manifestations such as decreased knee tendon and Achilles tendon reflex, or sensory disorders (e.g., burning, pain); (3) Patients with complete clinical data, including examination records and past medical history; (4) patients who had not received antioxidants, such as vitamin C or vitamin E; (5) Patients with detailed and comprehensive clinical data.

Exclusion criteria: (1) Patients with neuropathy caused by factors other than diabetes; (2) Patients with ulcers of the skin or mucous membrane; (3) Patients with active bleeding; (4) Patients with a history of allergies to the medications used in this study.

Therapeutic regimen

Both groups received routine treatment and intervention upon admission. The control group was treated with mecobalamin (approval number: H20031126). Each patient typically received an oral dose of 0.5-1.0 mg of mecobalamin three times a day, with the dosage adjusted based on the patient's age and the severity of their condition. The observation group received epalrestat (approval number: H2017-1215) in addition to mecobalamin treatment. Epalrestat (50 mg) was administered 30 minutes before meals, three times a day. Both groups were treated for 8 weeks. Close monitoring of patients' medication reactions was conducted, and any anomalies were promptly addressed to ensure the treatment's efficacy.

Quantification of inflammatory factors

Fasting blood samples (5 mL) were collected from each patient in the early morning before and after treatment. The samples were centrifuged for 5 minutes at 3,500 rotations per minute (r/min) with a radius of 8 cm. The isolated serum was stored at -20°C. Serum levels of C-reactive protein (CRP) was determined using immunoturbidimetry (Roche Diagnostics GmbH, Germany); procalcitonin (PCT) levels were determined using chemiluminescence (Beijing Lanjie Ke Technology Co., Ltd., China); and interleukin-6 (IL-6) and matrix metalloproteinase-9 (MMP-9) levels were quantified by enzyme-linked immunosorbent assay (ELISA) (Beijing Lanjie Ke Technology Co., Ltd., China).

Electromyogram indexes

Motor nerve conduction velocity (MCV) and sensory nerve conduction velocity (SCV) of the median nerve and nervus peronaeus communis were determined in both groups before and after treatment using a POSEIDON electromyographic evoked potential instrument (Shanghai Haishen Medical Electronic Instrument Co., Ltd., China).

Oxidative factors

Blood samples were collected from the elbow vein of fasting patients in both groups before and after treatment. The samples were centrifuged at 3,000 rpm for 15 minutes to isolate serum. Serum superoxide dismutase (SOD) levels were measured using spectrophotometry (Nanjing Jiancheng Bioengineering Institute, China), and serum propylene glycol (MDA) levels were determined using the thiobarbituric acid method. Reagent kits for these assays were purchased from Nanjing Jiancheng Bioengineering Institute, and the procedures were followed according to the instructions.

Blood glucose

Fasting blood samples were collected from the elbow vein of patients in both groups before and after treatment. The samples were centrifuged at 3,000 rpm for 15 minutes to isolate serum. Serum fasting blood glucose (FBG) and 2-hour postprandial blood glucose (2hPG) levels were measured using a fully automatic blood glucose analyzer (Roche Diagnostics GmbH, Germany).

Outcome measures

Primary outcome measures: (1) The changes in inflammatory factors were compared between the two groups before and after treatment. (2) The changes in electromyogram indexes were compared before and after treatment. (3) The clinical efficacy was compared between the two groups. Ineffective: No alleviation of symptoms or worsening of symptoms, with no changes in electromyographic results or limb reflex. Effective: Alleviation of conscious symptoms and an increase in nerve conduction velocity as measured by electromyography, with recovery of limb reflex to 50%-80%. Markedly effective: Significant alleviation of conscious symptoms, a substantial increase in nerve conduction velocity or complete recovery of nerve conduction velocity as shown by electromyographic results, and obvious recovery of limb reflex. The overall response rate (%) = number of cases with markedly effective treatment + number of cases with effective treatment/total number of cases ×100.00%. (4) The levels of MDA and SOD before and after treatment were compared between the two groups. (5) The severity of neuropathy was assessed using the Michigan Diabetic Neuropathy Score (MDNS) before and after treatment. The MDNS ranges from 0 to 46 points, where higher scores indicate more severe peripheral neuropathy. An MDNS score >6 was considered abnormal.

Secondary outcome measures: (1) The clinical baseline data of the two groups were compared, including age, gender, body mass index (BMI), course of DM, history of hypertension, history of hyperlipidemia, smoking history, and history of alcoholism. (2) FBG and 2hPG levels were compared between the two groups. The incidence of adverse reactions in the two groups was counted.

Statistical methods

Data visualization was performed using Graph Pad Prism 9.0 (GraphPad Software, Inc. USA). Measured data were expressed as mean ± standard deviation (mean ± SD). Normally distributed measured data were analyzed using the t-test, and inter-group comparisons were conducted using the independent-samples t-test. Counted data were expressed as percentages and analyzed using the chi-square test. A *P*-value of <0.05 was considered significant.

Results

Comparison of baseline data between the two groups

There were no significant differences between the two groups in terms of age, gender, BMI, course of DM, history of hypertension, history of hyperlipidemia, smoking history, or history of alcoholism (P>0.05, **Table 1**).

Comparison of clinical efficacy between the two groups

Comparison of clinical efficacy between the two groups revealed a significantly higher overall

Table 1. Comparison of baseline data between the two groups

Group	Control group (n=45)	Observation group (n=55)	*P* value
Age			0.414
≥60 years old	26	36	
<60 years old	19	19	
Gender			0.159
Male	35	35	
Female	10	20	
BMI			0.550
≥25 kg/m^2	11	11	
<25 kg/m^2	34	44	
Course of diabetes mellitus			0.320
≥8 years	20	30	
<8 years	25	25	
History of hypertension			0.834
Yes	16	18	
No	29	37	
History of hyperlipidemia			0.407
Yes	5	10	
No	40	45	
History of smoking			0.159
Yes	35	35	
No	10	20	
History of alcoholism			0.322
Yes	7	5	
No	38	50	

Note: BMI: Body mass index.

Table 2. Comparison of treatment efficacy between the two groups

Group	Markedly effective	Effective	Ineffective	Overall response
Control group (n=45)	18	17	10	35 (77.78%)
Observation group (n=55)	30	22	3	52 (94.54%)
χ^2				6.153
P value				0.013

response rate in the observation group than the control group (P=0.013, **Table 2**).

Comparison of inflammatory factors between the two groups before and after treatment

The levels of CRP, PCT, IL-6 and MMP-9 were compared between the two groups before and after treatment. Before treatment, levels were comparable in the two groups (P>0.05). After treatment, the levels of CRP, PCT, IL-6 and MMP-9 significantly decreased in both groups (P<0.0001, **Figure 1**), with the observation group showing significantly lower levels than the control group (P<0.0001, **Figure 1**).

Comparison of electromyogram indices between the two groups before and after treatment

The MCV and SCV of median nerve and nervus peronaeus communis were compared between the two groups before and after treatment. Before treatment, there were no significant differences in MCV or SCV between the two groups (P>0.05). However, after treatment, MCV and SCV increased significantly in both groups (both P<0.0001, **Figure 2**), with higher MCV and SCV observed in the observation group compared to the control group (both P<0.05, **Figure 2**).

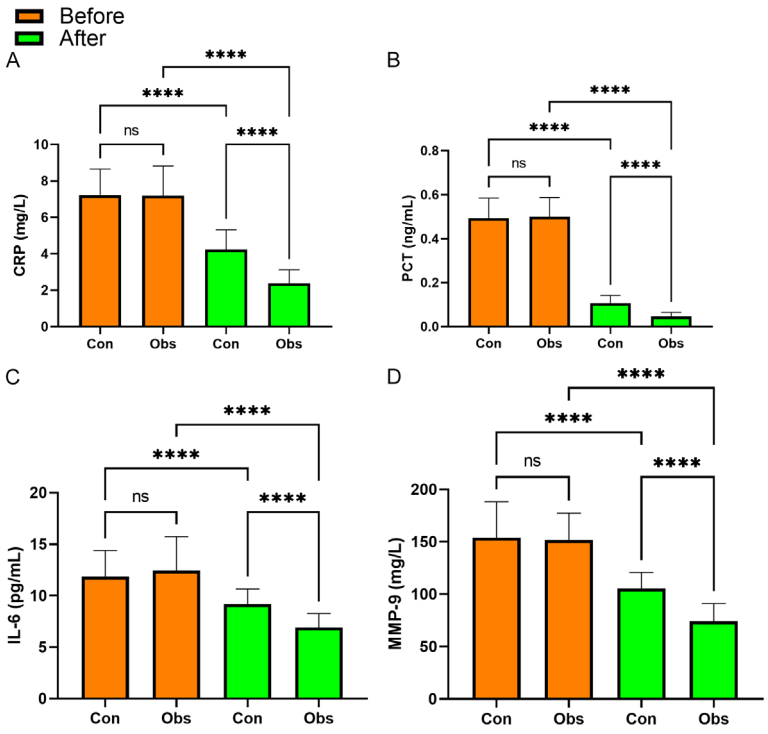

Figure 1. Comparison of inflammatory factors between the two groups before and after treatment. A: Changes in CRP in the two groups before and after treatment. B: Changes in PCT in the two groups before and after treatment. C: Changes in IL-6 in the two groups before and after treatment. D: Changes in MMP-9 in the two groups before and after treatment. Notes: ns P>0.05, ****P<0.0001. CRP: C-reactive protein; PCT; procalcitonin; IL-6: interleukin-6; MMP-9: matrix metalloproteinase-9.

Typical changes in electromyogram indices are displayed in Supplementary Figure 1.

Comparison of oxidative stress between the two groups before and after treatment

Before treatment, there were no significant differences in MDA or SOD levels between the two groups (P>0.05). After treatment, both groups exhibited a significant decrease in MDA and an increase in SOD (P<0.05). The observation group showed significantly lower MDA levels and significantly higher SOD levels compared to the control group (P<0.05, **Figure 3**).

Comparison of blood glucose levels between the two groups before and after treatment

Before treatment, there were no significant differences in FBG or 2hPG levels between the two groups (P>0.05). After treatment, both groups showed an decrease in FBG and 2hPG levels, with the observation group having significantly lower levels of FBG and 2hPG compared to the control group (both P<0.05, **Figure 4**).

Comparison of MDNS between the two groups

Before treatment, there was no significant difference in the MDNS between the two groups (P>0.05). After treatment, both groups showed a notable decrease in MDNS, with the observation group scoring significantly lower than the control group, (P<0.05, **Figure 5**).

Adverse reactions

Analysis of adverse reactions revealed no difference between the control group and observation group in terms of incidence (P>0.05, **Table 3**).

Discussion

As one of the prevalent chronic complications of DM, diabetic peripheral neuropathy (DPN) shows a relatively high incidence [9]. In recent years, due to changes in lifestyle and diet, the incidence of DM has progressively increased, consequently leading to a corresponding increase in the incidence of DPN [10]. The onset of DPN is often subtle and progresses slowly, which can result in irreversible damage, adversely affecting the health and quality of life of patients [11]. Timely and effective therapy and intervention are crucial for promoting patient recovery and improving prognosis. Therefore, this study aimed to evaluate the clinical efficacy of mecobalamin combined with epalrestat in treating DPN.

Although the precise pathogenesis of DPN is not fully understood, it is widely believed to be primarily triggered by prolonged high blood glucose levels in patients [12]. With a growing understanding of DM, it has become clear that the development of peripheral neuropathy is linked to various factors, such as metabolic pathways and growth factors. Currently, pharmacologic therapy remains the primary treatment of DPN [13]. Among these treatments,

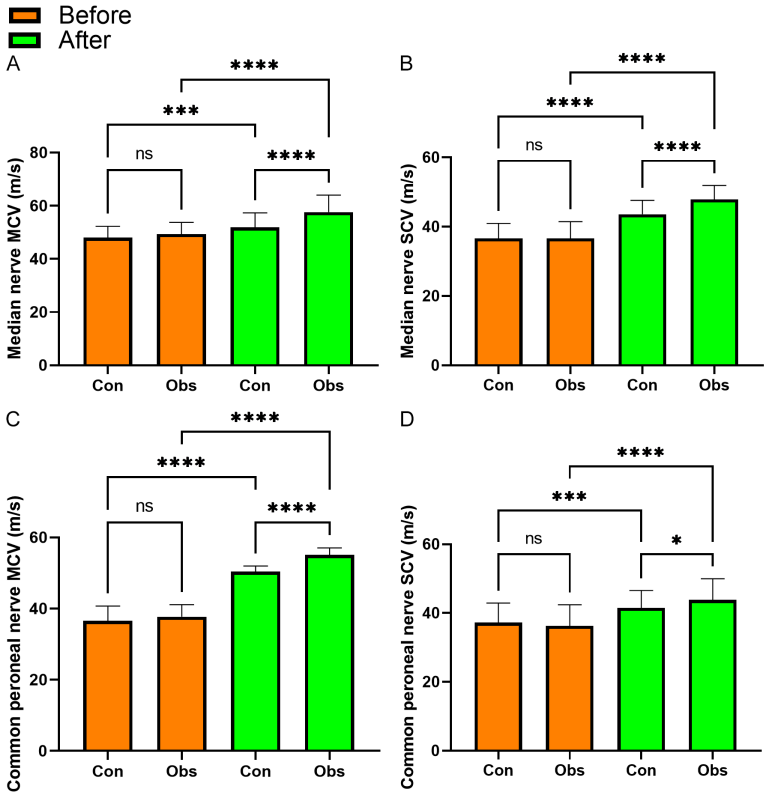

Figure 2. Comparison of electromyogram indices between the two groups before and after treatment. A: Changes in MCV of median nerve in the two groups before and after treatment. B: Changes in SCV of median nerve in the two groups before and after treatment. C: Changes in MCV of nervus peronaeus communis in the two groups before and after treatment. D: Changes in SCV of nervus peronaeus communis in the two groups before and after treatment. Notes: ns P>0.05, *P<0.05, ***P<0.001, ****P<0.0001. MCV: motor nerve conduction velocity; SCV: sensory nerve conduction velocity.

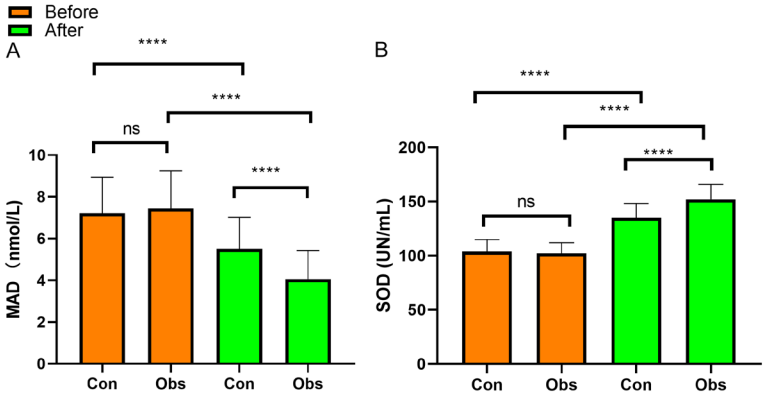

Figure 3. Comparison of oxidative stress between the two groups before and after treatment. A: Changes in MDA levels before and after treatment in both groups. B: Changes in SOD levels before and after treatment in both groups. Notes: ns P>0.05, ****P<0.0001. MDA: propylene glycol; SOD: superoxide dismutase.

epalrestat, an aldose reductase inhibitor, can effectively and selectively inhibit aldose reductase activity, reduce the accumulation of sorbitol and fructose in peripheral nerve cells, and correct polyol metabolism imbalances, thus helping to accelerate the recovery of inositol activity and Na+-K+-ATPase function [14]. Moreover, epalrestat can inhibit the protein kinase C signaling pathway, enhance endothelial cell nitric oxide production, and suppress neutrophil-endothelial cell adhesion and the expression of endothelial adhesion factors in high-glucose environments. Ultimately, this process leads to an improvement in nerve conduction velocity and nerve function [15, 16]. On the other hand, mecobalamin, a derivative of vitamin B12, is more easily absorbed by nerve cells than vitamin B12 itself. It accelerates lipids, proteins, and nucleic acid metabolism in nerve cells, promoting nerve function repair, axon regeneration, and myelin formation, which helps alleviate neurological symptoms [17, 18]. This study compared the efficacy of mecobalamin and epalrestat on DPN patients. The results of our study indicate that the combination of mecobalamin and epalrestat produces a significant therapeutic effect in treating DPN, without increasing the incidence of adverse reactions in patients.

Type 2 diabetic peripheral neuropathy (DPN) impairs MCV and SCV, compromising sensory function and worsening patients' quality of life [19]. Studies have shown that during the progression of DPN, patients produce a large number of cytokines, which regulate and stimulate systemic inflammatory responses [20]. These inflammatory factors pro-

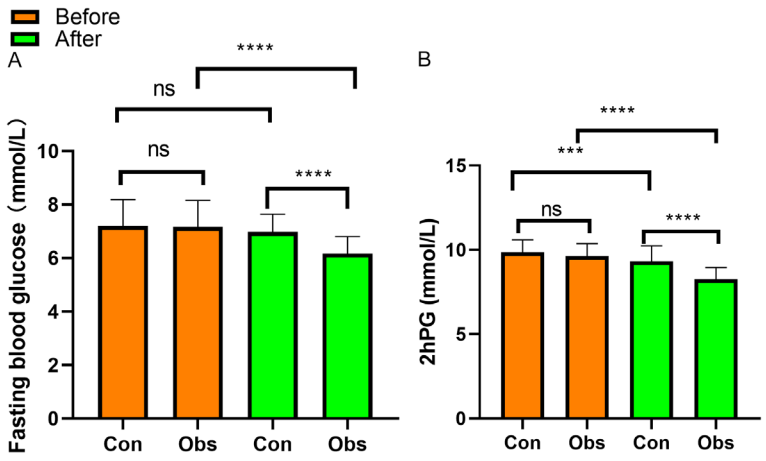

Figure 4. Comparison of blood glucose levels between the two groups before and after treatment in patients. A: Changes in fasting blood glucose levels before and after treatment. B: Changes in 2-hour postprandial blood glucose levels before and after treatment. Notes: ns P>0.05, ***P<0.001, ****P<0.0001. 2hPG: 2-hour postprandial blood glucose.

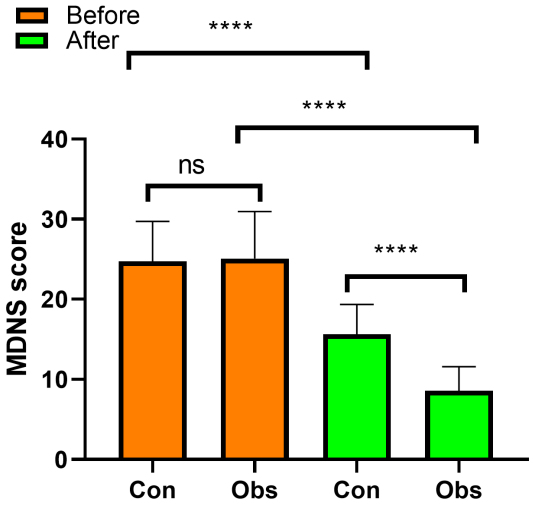

Figure 5. Comparison of MDNS between the two groups before and after treatment. Notes: ns P>0.05, ****P<0.0001. MDNS: Michigan Diabetic Neuropathy Score.

mote the release of vascular endothelial growth factor, reducing blood flow to nerve tissue, ultimately leading to ischemic necrosis of nerve tissue and impaired neurological function [13]. In this study, after treatment, the MCV and SCV of median nerve and nervus peronaeus communis in the observation group increased greatly, while the levels of CRP, PCT, IL-6 and MMP-9 decreased significantly. These results suggest that patients with type 2 DPN experience a chronic inflammatory response, and the combination of mecobalamin and epalrestat can effectively suppress this inflammatory response and improve nerve conduction velocity. This effect may be attributed to the polyol pathway, where aldose reductase converts glucose into sorbitol, leading to increased sorbitol expression and stress response, which in turn raises inflammatory markers such as CRP, PCT, IL-6 and MMP-9. As an aldose reductase inhibitor, epalrestat can substantially inhibit aldose reductase activity, limiting glucose-to-sorbitol conversion and consequently lowering inflammatory markers (CRP, PCT, IL-6 and MMP-9). In addition, pancreatic kallikrein can inhibit phospholipase A2, block platelet aggregation, prevent thrombosis, and promote increased nerve blood flow, alleviating hypoxia and ischemia, which in turn enhances nerve conduction velocity. Epalrestat, as a sugar reductase inhibitor, effectively inhibits the polyol pathway, reduces aldose reductase activity, and decreases the accumulation of sorbitol and inositol in nerve tissue, thereby improving MCV. In this study, after treatment, the MDNS score decreased significantly in both groups, indicating that combination therapy alleviates neuropathy symptoms.

Additionally, SOD and MDA levels, key indicators of oxidative stress response, improved in both groups after treatment, with more pronounced improvements in the combination therapy group. This suggests that the combination therapy effectively addresses oxidative stress imbalance in patients. In conclusion, the combination of methylcobalamin and epalrestat exhibited synergistic effects, reducing inflammatory markers, improving nerve conduction velocity, and mitigating oxidative stress. Notably, the observation group demonstrated lower FBG and 2hPG levels compared to the control group, indicating superior glycemic control with combination therapy. These results demonstrate that the combination of methylcobalamin and epalrestat reduces inflammatory markers, improves electromyographic indicators, and decreases oxidative stress reactions in patients with type 2 DPN.

Table 3. Comparison of adverse reactions between the two groups

Group	Nausea	Vomiting	Dizziness	Fever	Diarrhea	Total adverse reactions
Control group (n=45)	2	2	1	2	1	8 (18.89%)
Observation group (n=55)	2	2	3	4	3	14 (25.45%)
χ^2	0.042	0.042	0.673	0.351	0.673	0.850
P value	0.837	0.837	0.411	0.553	0.411	0.357

This study has confirmed the clinical efficacy of mecobalamin combined with epalrestat in the treatment of DPN through retrospective research. However, there are several limitations. First, the study did not include long-term follow-up data, so further research is needed to determine whether the combination of these two drugs affects long-term patient outcome. Second, the relatively small size in this study may have introduced bias in the analysis of the results. We plan to conduct additional experiments in future research to strengthen the conclusions.

Conclusion

Mecobalamin combined with epalrestat can substantially alleviate diabetic peripheral neuropathy. This pproach effectively reduces the levels of inflammatory factors and improve electromyogram indices, while decreasing the oxidative stress response, without increasing adverse reactions.

Disclosure of conflict of interest

None.

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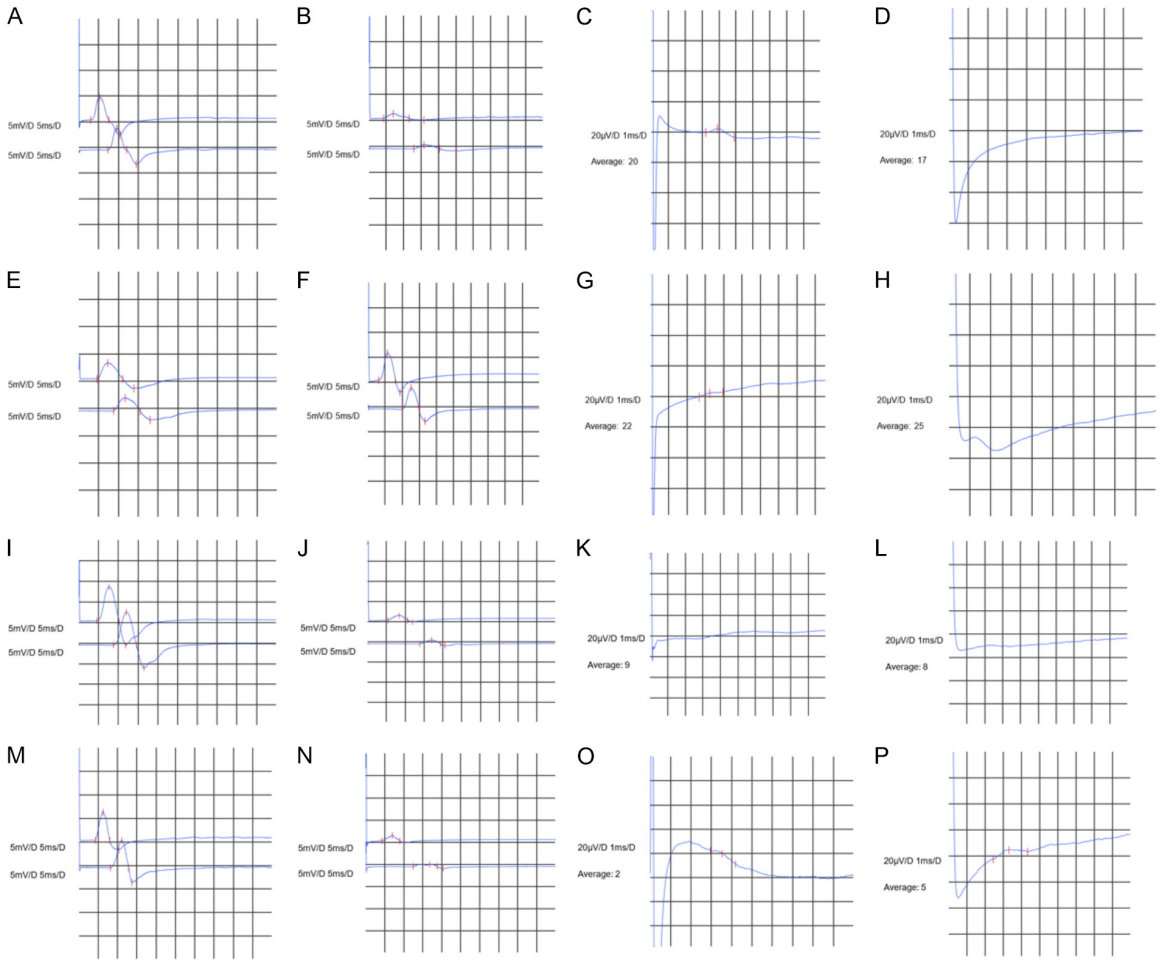

Supplementary Figure 1. Examples of changes in electromyogram indexes. A: Left median nerve (wrist-abductor pollicis brevis and elbow-wrist) in the control group before treatment. B: Left common peroneal nerve (ankle-extensor digitorum brevis and capitulum fibula-ankle) in the control group before treatment. C: Left median nerve (indicator finger-wrist) in the control group before treatment. D: Left common peroneal nerve (peroneus longus-dorsum of foot) in the control group before treatment. E: Left median nerve (wrist-abductor pollicis brevis and elbow-wrist) in the control group after treatment. F: Left common peroneal nerve (ankle-extensor digitorum brevis and capitulum fibula-ankle) in the control group after treatment. G: Left median nerve (indicator finger-wrist) in the control group after treatment. H: Left common peroneal nerve (peroneus longus-dorsum of foot) in the control group after treatment. I: Left median nerve (wrist-abductor pollicis brevis and elbow-wrist) in the observation group before treatment. J: Left common peroneal nerve (ankle-extensor digitorum brevis and capitulum fibula-ankle) in the observation group before treatment. K: Left median nerve (indicator finger-wrist) in the observation group before treatment. L: Left common peroneal nerve (peroneus longus-dorsum of foot) in the observation group before treatment. M: Left median nerve (wrist-abductor pollicis brevis and elbow-wrist) in the observation group after treatment. N: Left common peroneal nerve (ankle-extensor digitorum brevis and capitulum fibula-ankle) in the observation group after treatment. O: Left median nerve (indicator finger-wrist) in the observation group after treatment. P: Left common peroneal nerve (peroneus longus-dorsum of the foot) in the observation group after treatment.