Original Article
Clinical efficacies of electroacupuncture combined with epalrestat and α-lipoic acid in patients with diabetic peripheral neuropathy and its effects on nerve conduction velocity and oxidative stress

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Abstract: Objective: To investigate the clinical efficacies of electroacupuncture (EAP) combined with epalrestat and α-lipoic acid (α-LA) in patients with diabetic peripheral neuropathy (DPN) and its effects on nerve conduction velocity and oxidative stress (OS). Methods: A prospective study was conducted on 138 patients with DPN, who were divided into the control group (treated with epalrestat + α-LA, n = 69) and observation group (treated with EAP + epalrestat + α-LA, n = 69). Clinical efficacy was observed 14 days after treatment. Nerve conduction function, Visual Analogue Scale score and OS factors were measured in both groups. Results: The total effective rate in the observation group was significantly higher than that in the control group (P = 0.036). After treatment, motor nerve conduction velocity and sensory nerve conduction velocity of the median nerve and common peroneal nerve in both groups were significantly improved compared with those before treatment, and the improvement in the observation group was significantly better than that in the control group (all P < 0.05). There were opposite trends in the neurological function score and degree of neuralgia (all P < 0.05). After treatment, malonaldehyde and superoxide dismutase in the two groups were significantly decreased and increased respectively compared with those before treatment (both P < 0.05), and the improvement of the two indicators in the observation group was significantly better than that in the control group (P < 0.001). Conclusion: EAP combined with epalrestat and α-LA in the treatment of DPN can improve clinical efficacy, promote nerve repair and improve the state of OS, which is worthy of clinical application.

Keywords: Electroacupuncture, diabetic peripheral neuropathy, clinical efficacy, neurological function, oxidative stress

Introduction
Diabetes mellitus (DM) is a metabolic disease characterized by elevated blood glucose. With the development of modern society and increased processing of the diet, the incidence of DM is increasing annually [1, 2]. DM is mainly caused by increased blood glucose, wherefrom the body changes under the influence of long-term hyperglycemia, resulting in multiple complications [3]. Diabetic peripheral neuropathy (DPN) is the most common complication of DM, with an incidence of 30% [4, 5]. The early symptoms of DPN are not obvious; with the progression of this disease, limb disorders, and pain or loss of sensory function may occur [6]. Its pathogenesis is mainly related to the occurrence of oxidative stress (OS) and the promotion of the secretion of inflammatory factors in vivo under the effect of hyperglycemia [7]. Therefore, the treatment of DPN mainly focuses on symptom improvement based on the patient’s glycemic control. Epalrestat is an aldose reductase inhibitor, which can effectively reduce endothelial cell function damage [8]. Besides, α-lipoic acid (α-LA) is an antioxidant that can improve the state of OS [9]. Clinically, the combined application of the two drugs has a certain effect on DPN, but there are some patients still have poor effects or no obvious improvement of symptoms [10]. In recent years, it has been found that the application of electroacupuncture (EAP) in the treatment of DPN has achieved certain clinical results [11]. There
EAP combined with epalrestat and α-LA in DPN patients

There is currently no observation on the efficacy of EAP combined with epalrestat and α-LA in the treatment of DPN. Thus, this study explored the therapeutic effects and mechanism of EAP combined with epalrestat and α-LA in the treatment of DPN.

Materials and methods

Clinical information

A total of 138 patients admitted to the Department of Endocrinology of The Second Affiliated Hospital of Hainan Medical University from January 2017 to June 2019 were selected for a prospective study. Those patients were divided into a control group (treated with epalrestat + α-LA, n = 69) and an observation group (treated with EAP + epalrestat + α-LA, n = 69) according to a random number grouping method. The study was approved by the Hospital Ethics Committee of The Second Affiliated Hospital of Hainan Medical University, and all the included patients or their family members signed the consent form.

Inclusion criteria and exclusion criteria

The included patients, aged 18-76 years old, were in line with DM and DPN standards [12]. Additionally, patients with severe cardiac, renal, pulmonary dysfunction, other neuropathy and malignant tumors were excluded. Patients who were allergic to drugs were also excluded.

Methods

Control group: Patients were required to increase their vegetable intake, and reduced alcohol and simple sugar intake. Overweight or obese patients (body mass index > 25) were encouraged to lose weight and increase daily activity (moderate activity for at least 20 min a day). On the basis of blood glucose control, 50 mg of oral epalrestat (Yangtze River Pharmaceutical Group, China) was added, three times a day before meals. Moreover, patients were treated with intravenous drip infusion of α-LA injection (Jiangsu Shenlong Pharmaceutical Co., Ltd., China; 12 mL: 300 mg) and 0.9% normal saline (Double-Crane Pharmaceutical Co., Ltd., China; 100 mL) for 30 min once per day, lasting for 14 days.

Observation group: The same treatment was given in the observation group. Besides, EAP was performed. The patients were treated with EAP at Ganshu, Pishu, Shenshu, Zusanli, Quchi, Neiguan, Yanglingquan, Taixi and Taichong on both sides. The procedure of acupuncture was as follows. The patients were kept sitting position, the acupuncture points were routinely disinfected, and disposable sterile acupuncture needles (0.3 mm×40 mm; Suzhou Acupuncture Goods Co., Ltd., China) were used for acupuncture treatment. Ganshu: Oblique insertion 0.5-0.8 Cun; Pishu: straight insertion 0.5-1.0 Cun; Shenshu: straight insertion 0.5-1.0 Cun; Zusanli: straight insertion 1.0-1.5 Cun; Quchi: straight insertion 1.0-1.5 Cun; Neiguan: straight insertion 0.5-1.0 Cun; Yanglingquan: straight insertion 1.0-1.5 Cun; Taixi: straight insertion 0.5-1.5 Cun; Taichong: straight insertion 0.5-1.0 Cun. After inserting the needle into each point, the needle was lifted, inserted and twisted in order to make the acupuncture point produce needing sensation. The procedure of EAP was as follows. After getting needing sensation produced by acupuncture, the single-side Quchi-Neiguan and Yanglingquan-Taichong were set as the EAP point. And 6805-D electroacupuncture apparatus (Shantou Medical Equipment Factory Co., Ltd., China) was used for electric stimulation with disperse-dense wave (4 Hz of disperse wave, 20 Hz of dense wave, and 6 s of disperse-dense cycle). The intensity of electrical stimulation was set according to the patient’s tolerance and EAP was conducted for 30 min/time, once a day, lasting for 14 days.

Outcome measures

Primary outcome measures: (1) Electromyograph was adopted to measure motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) of the median nerve and common peroneal nerve before treatment and 14 days after treatment [12]. (2) Toronto clinical scoring system (TCSS) was used to measure neurological function, with the highest score of 19 points. A higher score indicated more severe neurological injury [13]. (3) Visual Analogue Scale (VAS) was used to record the scores of neuralgia before treatment and 14 days after treatment [14]. (4) After 14 days of treatment, the efficacy was evaluated according to the diagnostic criteria of clinical efficacy of DPN, which was divided into markedly effective, effective and ineffective [12]. The total effective rate = Number of cases of (markedly effective + effective)/total number of cases * 100%.
Secondary outcome measures: After admission, 5 mL of venous blood was taken at 8 am in a fasting condition before and after treatment. Serum enzyme-linked immunosorbent assay was adopted to determine malonaldehyde (MDA; ml058112-1, Shanghai Enzyme-linked Biotechnology Co., Ltd., China) and superoxide dismutase (SOD; ml063052-1, Shanghai Enzyme-linked Biotechnology Co., Ltd., China).

Statistical analysis

SPSS 17.0 software was used for statistical analysis. The measurement data in line with normal distribution were expressed by mean ± standard deviation (x ± sd), and those in line with homogeneity of variance were tested by t test. Paired t test was used for intra-group comparison, and independent t test was adopted for comparison between groups; and were expressed as t. Count data were expressed as n/%; the comparison was performed by Pearson Chi-square test and expressed as χ². P < 0.05 indicated a statistically significant difference.

Results

Comparison of general information and baseline data

During the treatment, one patient in the observation group withdrew from the study due to sudden myocardial infarction. There was no difference in general information and baseline data between the two groups (all P > 0.05), as shown in Table 1.

Comparisons of nerve conduction velocity (NCV), neurological function score and degree of neuralgia

After treatment, MNCV and SNCV of the two groups were significantly improved compared with those before treatment, and the improvement of the observation group was significantly better than that of the control group (P < 0.001). See Table 2. There were opposite trends in the neurological function score and degree of neuralgia (both P < 0.001), as shown in Tables 3, 4.
EAP combined with epalrestat and α-LA in DPN patients

Comparison of clinical efficacy

The total effective rate in the observation group was significantly higher than that in the control group (94.12% vs 82.61%, P < 0.05). See Table 5 and Figure 1.

Comparison of MDA and OS factors

After treatment, MDA and SOD in the two groups were significantly decreased and increased respectively compared with those before treatment (both P < 0.05), and the improvement of the two indicators in the observation group was significantly better than that in the control group (P < 0.001). See Table 6.

Discussion

With the continuous increase in the number of DM patients, the number of DPN patients is

Table 2. Comparison of nerve conduction velocity (x ± SD, cm/s)

<table>
<thead>
<tr>
<th>Item</th>
<th>Median nerve</th>
<th>Common peroneal nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MNCV</td>
<td>SNCV</td>
</tr>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation group (n = 68)</td>
<td>37.35 ± 2.17</td>
<td>35.12 ± 2.09</td>
</tr>
<tr>
<td>Control group (n = 69)</td>
<td>37.86 ± 2.29</td>
<td>34.99 ± 2.12</td>
</tr>
<tr>
<td>After treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation group (n = 68)</td>
<td>43.62 ± 2.17***</td>
<td>45.87 ± 2.89***</td>
</tr>
<tr>
<td>Control group (n = 69)</td>
<td>40.26 ± 2.03***</td>
<td>41.97 ± 2.41***</td>
</tr>
</tbody>
</table>

Note: Compared within group before and after treatment, ***P < 0.001; compared with control group after treatment, ##P < 0.001. MNCV: motor nerve conduction velocity; SNCV: sensory nerve conduction velocity.

Table 3. Comparison of neurological function score (x ± SD, score)

<table>
<thead>
<tr>
<th>Item</th>
<th>Observation group (n = 68)</th>
<th>Control group (n = 69)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>11.34 ± 2.43</td>
<td>11.45 ± 2.29</td>
<td>0.273</td>
<td>0.786</td>
</tr>
<tr>
<td>After treatment</td>
<td>6.76 ± 1.55</td>
<td>8.05 ± 1.69</td>
<td>4.654</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>t</td>
<td>13.101</td>
<td>9.923</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Comparison of degree of neuralgia (x ± SD, score)

<table>
<thead>
<tr>
<th>Item</th>
<th>Observation group (n = 68)</th>
<th>Control group (n = 69)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>5.32 ± 1.44</td>
<td>5.46 ± 1.52</td>
<td>0.553</td>
<td>0.581</td>
</tr>
<tr>
<td>After treatment</td>
<td>1.53 ± 0.73</td>
<td>2.34 ± 1.03</td>
<td>5.304</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>t</td>
<td>19.362</td>
<td>14.110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Comparison of clinical efficacy (n, %)

<table>
<thead>
<tr>
<th>Item</th>
<th>Markedly effective</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Total effective rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group (n = 68)</td>
<td>35 (51.47)</td>
<td>29 (42.65)</td>
<td>4 (5.88)</td>
<td>64 (94.12)</td>
</tr>
<tr>
<td>Control group (n = 69)</td>
<td>27 (39.13)</td>
<td>30 (43.48)</td>
<td>12 (17.39)</td>
<td>57 (82.61)</td>
</tr>
<tr>
<td>χ²</td>
<td></td>
<td></td>
<td></td>
<td>4.398</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td>0.036</td>
</tr>
</tbody>
</table>

Figure 1. Comparison of clinical efficacy. Compared with control group, *P < 0.05.
also increasing [15]. DPN, the most common complication of DM, can impact a variety of nerves such as motor, sensory and autonomic nerves. Its impact on nerves is manifested as sensory disorders of the limb and motor disorders of the muscle, seriously affecting the life quality of patients [16]. NCV is the gold standard for the diagnosis of DPN. Patients will have pain during the long-term detection of NCV, thus the neurological function score is also used to evaluate the degree of neuropathy. A study has reported that the application of EAP in the treatment of sciatic nerve injury can improve the sciatic nerve function and make it recover faster thermal sense and touch [17]. Another study has indicated that the application of EAP can promote the recovery of nerve conduction function in patients with DPN; after acupuncture, the conduction of nerve velocity is increased and the growth of microvessels at the nerve injury site is promoted, so as to improve the state of nerve ischemia and hypoxia [18]. Research has proved that a significant curative effect depends on the selection of acupuncture and moxibustion sites for the treatment of DPN in the lesioned area [19]. After DPN modeled rats were treated with EAP, it was found that apoptosis of the sciatic nerve was reduced, which alleviated sciatic nerve injury [20]. In this study, it was also shown that the improvement of nerve function and the recovery of nerve conduction function in the observation group were better than those in the control group, which was related to the promotion of nerve repair by EAP. Severe pain occurs in patients with DPN due to hyperalgesia and hypersensitivity caused by neuropathy [21, 22]. Previous studies have shown that the application of EPA can improve chronic neuralgia and effectively relieve pain caused by DPN [23, 24]. A study has reported that low-frequency EPA has a better effect on the pain caused by DPN than high-frequency treatment. In this study, the pain caused by DPN was significantly alleviated in the observation group, which was consistent with the above research results. The judgment of clinical efficacy of DPN is mainly reflected by the improvement of nerve function and the reduction of pain symptoms. The above two indicators were improved in the observation group, suggesting that the neurological recovery of observation group is superior to that of the control group.

During the development of DM, free radicals may be increased while antioxidant capacity may be weakened through non-enzymatic glycosylation of protein, self-oxidation of glucose, activation of protein kinase, glycosylation of antioxidant enzymes and improvement of polyol pathway activity, which may lead to OS. OS refers to a stress state in which the body generates a large number of mitochondrial reactive oxygen species after being stimulated, leading to a decrease in antioxidant capacity. Once OS occurs in DPN patients, the progression of diabetes will be promoted by the sensitivity reduction of peripheral tissues to insulin and the damage to islet β cells [9]. Particularly, SOD and MDA are both important indicators to measure OS [25]. SOD, mainly distributed in cells and body fluids, is an important scavenger of reactive oxygen species, which functions in maintaining the balance of oxidation and antioxidation. It can protect cells from damage by breaking down hydrogen peroxide and lipid peroxide, as well as preventing lipid peroxidation. MDA, a product of lipid peroxidation, is also regarded as a risk factor of DPN. It is the material basis of cell membrane damage, whose content reflects the severity of lipid peroxidation in vivo and the cell damage [25]. CRP is an acute phase protein synthesized by liver cells. When the body is stimulated by inflammation, CRP level changes rapidly, which can well reflect the degree of inflammation [26]. TNF-α and IL-6 are important inflammatory indicators.

### Table 6. Comparison of MDA and OS factors (x ± SD)

<table>
<thead>
<tr>
<th>Item</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observation group (n = 68)</td>
<td>Control group (n = 69)</td>
</tr>
<tr>
<td>MDA (mg/L)</td>
<td>23.68 ± 2.82</td>
<td>23.89 ± 3.46</td>
</tr>
<tr>
<td>SOD (ng/L)</td>
<td>121.15 ± 5.16</td>
<td>124.76 ± 5.48</td>
</tr>
</tbody>
</table>

Note: Compared within group before and after treatment, ***P < 0.001; compared with control group after treatment, ###P < 0.001. OS: oxidative stress; MDA: malonaldehyde; SOD: superoxide dismutase.
in the inflammatory response, which are closely related to blood coagulation and vascular endothelial injury [27, 28]. Research has reported that the occurrence of DPN is closely associated with the production of inflammatory factors under the state of OS [29, 30]. Under the action of inflammatory factors, neuropathy can be aggravated and disease progression can be promoted [31, 32]. This study showed that EAP for the treatment of DPN can effectively reduce the level of inflammatory factors [33]. Another study indicated that EAP might inhibit inflammatory factors by inhibiting the release of TNF-α by macrophages [34]. What’s more, acupuncture can effectively regulate the NF-κB signaling pathway and reduce neuronal apoptosis to achieve an anti-inflammatory effect [35]. In this study, it was also found that the level of oxidation factors in the observation group was improved significantly, and the improvement of OS state was conducive to the recovery of nerve function, which might be related to the above mechanism of action.

However, there are still limitations in this study. With a small sample size and short follow-up time, we are aware that a multicenter randomized controlled study with larger sample size and long follow-up time are needed, and the mechanism of acupuncture improving DPN remains to be explored in the future.

In summary, EAP combined with epalrestat and α-LA in the treatment of DPN can promote nerve repair and improve the state of OS, which is worthy of clinical application.

Disclosure of conflict of interest

None.

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References


