Direct current electrical stimulation of acupuncture needles for peripheral nerve regeneration: an exploratory case series

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ABSTRACT

Objective To examine the therapeutic effect of a novel therapeutic method based on electroacupuncture with intermittent direct current (DCEA) and associated adverse events in patients with peripheral nerve damage and a poor clinical prognosis.

Methods In seven older patients with peripheral nerve damage (neurapraxia 2, axonotmesis 4, neuromesis 1), an acupuncture needle connected to an anode electrode was inserted proximal to the site of the injury along the route of the nerve, while the cathode electrode was inserted into the innervated muscle, and DCEA was performed (100 Hz for 20 min, weekly). Muscular paralysis was evaluated weekly with manual muscle testing, the active range of motion of joints related to the muscular paralysis and, when necessary, needle electromyography. Adverse events were also recorded during the course of the treatment.

Results Complete functional recovery was observed in the two cases with neurapraxia and two with axonotmesis, while one axonotmesis case achieved improvement and the other showed reinnervation potential without functional recovery. No improvement was observed in the neuromesis case. Pigmentation of the skin where the anode needle was inserted occurred in three cases. Although there was no definite causal link, one case showed excessive formation and resorption of bone in the area close to the cathode needle site.

Discussion Accelerated nerve regeneration caused by DCEA may contribute to recovery. The skin pigmentation and callus formation suggest that the shape of the anode electrode, current intensity and other factors should be examined to establish a safer treatment method.

INTRODUCTION

In previous studies of rat models of sciatic nerve crush injury, we have examined the effects of a novel therapeutic method based on electroacupuncture with intermittent direct current (DCEA) on peripheral nerve regeneration. In these animal studies, after crushing the sciatic nerve in the femoral region (axonotmesis), insulated acupuncture needles (insulated with acrylic resin to 0.5 mm from the tip) were inserted along the course of the sciatic nerve at 1 cm distal and 1 cm proximal to the injured site. The needles were used as electrodes to compare the effects of DCEA in two experimental groups: (1) distal cathode, proximal anode and (2) distal anode, proximal cathode; and two control groups: (3) no electrical stimulation given to the acupuncture needles and (4) no treatment given. The results clearly showed that DCEA with a distal cathode accelerated peripheral nerve regeneration.1 2 Based on the results of these basic animal studies, DCEA with the cathode distal to the nerve injury site was applied clinically in this study to treat seven cases of motor paralysis due to peripheral nerve damage. Adverse events and symptoms were observed during the course of the treatment. This study was performed with the approval of the Meiji University of Integrative Medicine Ethics Committee.

METHODS

Subjects

The subjects, who gave informed consent after receiving an explanation of the details of the study, were seven older patients with motor paralysis due to peripheral nerve injury. Case details including the injured peripheral nerve, cause, duration of symptoms (from onset to the start of DCEA), age and motor disorder are shown in table 1.

DCEA method

The injured peripheral nerve and location of the injury were determined after verifying onset conditions, motor disorder and extent of sensory impairment, performing needle electromyography (n-EMG), verifying the location of the Tinel sign, and screening for other diseases with similar symptoms. An acupuncture needle (30 mm long, 0.3 mm in diameter) was inserted along the route of the injured peripheral nerve proximal to the site of the injury and at a location where stimulation could be felt in an area commanded by...
Another acupuncture needle with different diameter (30 mm long, 0.25 mm in diameter) was inserted in the belly of paralysed muscle distal to the motor point. When there was more than one paralysed muscle, the muscle causing the most serious functional problems was selected. DCEA was performed using the inserted needles as electrodes, with the needle inserted proximal to the injury site along the route of the nerve acting as the anode and the needle inserted in the paralysed muscle as the cathode (Ohm Pulser LFP-7000; Zen Iryoki, Fukuoka, Japan). The treatment was performed once a week for 20 min with monophasic square pulse wave of which the duration was 200 μs which delivered at a rate of 100 pulses/s. Electrical current output was adjusted at a minimum intensity at which the patients were able to perceive spreading sensation to the innovated area of the target nerve but not to cause uncomfortable sensation.

Evaluation methods
Before the first treatment, five of the seven cases underwent n-EMG examinations of paralysed muscles; the other two cases had already had motor function determined to some degree. During the course of the treatment, n-EMG examinations were repeated when necessary. The EMG test was performed and assessed by a physician who had experience of more than 30 years. For all cases, manual muscle testing (MMT) was performed on paralysed muscles once weekly and the active range of motion (AROM) of related joints was evaluated. AROM was taken as the angle of mobility from a completely relaxed state measured against gravity. Range of motion (ROM) and MMT were evaluated by a therapist who had more than 20 years clinical experience in the field. Adverse events during treatment were monitored by interviewing patients, skin observation in the treated area and x-ray radiographs when necessary.

RESULTS (COURSE OF SYMPTOMS AND ADVERSE EVENTS OF EACH CASE)
All cases except one (Case 3) showed no limitation in their passive ROM (PROM) in the joint evaluated for the recovery. All cases except one (Case 3, who underwent PROM exercise by physiotherapist) had trained with self-management ROM exercise prior to the study and continued at their home during the study period.

Case 1
During the course of treatment, ankle dorsal flexion and pronation MMT and AROM scores improved (figure 1 and table 2). However, no improvement was seen in MMT and AROM scores for great toe extension (figure 1 and table 2). During the treatment, pigmentation of the skin where the anode acupuncture needle was inserted was observed (figure 2 and table 2), but there was no pain or other subjective symptoms at the insertion site.

Case 2
Ankle dorsal flexion/pronation, and great toe extension MMT and AROM scores were improved by treatment. After 1 month of treatment, ankle dorsal flexion and great toe extension MMT scores were both 5, and AROMs were 45° and 40°, respectively. After 2 months of treatment, recovery of ankle pronation was complete with MMT and AROM of 5° and 5°, respectively. No adverse events were observed during or after the treatment (table 2).
Case 3
At the start of the treatment, MMT and AROM scores for abduction of the shoulder were 1° and 0° (PROM was 90°), respectively, but after 2 months of treatment the scores improved to 2° and 50°, respectively (table 2). However, a suggestion of an adverse event occurring during the second month of treatment led to treatment discontinuation. Following anterior dislocation of the shoulder, this case suffered paralysis of the axillary nerve, but x-rays taken to verify the course of repositioning showed formation and resorption of bone in the area close to the cathode acupuncture needle insertion site. There was no clear causal relationship, but since it was possibly due to the influence of DCEA, the patient was advised and then requested treatment discontinuation. Four months after discontinuing the treatment, a plain x-ray showed a tendency for reduced bone formation but there was still some remaining bone resorption (figure 2 and table 2). From the beginning of treatment to 4 months after discontinuing treatment, no other adverse events were observed.

Case 4
During the course of treatment, ankle dorsal flexion/pronation, and great toe extension MMT and AROM scores improved. After 3 months of treatment, recovery was complete with MMT scores of 5 for ankle dorsal flexion, pronation and great toe extension and ROMs of 60°, 10° and 50°, respectively. No adverse events were observed during or after treatment (table 2).

Case 5
The patient’s ulnar nerve in the region of the wrist joint had been completely cut by glass. Epineurial suture was performed at another hospital and 14 months later the patient received treatment at our hospital. However, after 9 months of treatment, no improvement in finger adduction and abduction had been observed. From the start of treatment to the present time, no adverse events were observed (table 2).

Table 2 Summary of the results

<table>
<thead>
<tr>
<th>Case</th>
<th>Duration of treatment (months)</th>
<th>Action tested</th>
<th>Manual muscle testing (Points)</th>
<th>Active range of motion</th>
<th>Note</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>Ankle dorsiflexion</td>
<td>4</td>
<td>40°</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Great toe extension</td>
<td>0</td>
<td>0°</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ankle pronation</td>
<td>3</td>
<td>15°</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Ankle dorsiflexion</td>
<td>5</td>
<td>45°</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Great toe extension</td>
<td>5</td>
<td>40°</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ankle pronation</td>
<td>5</td>
<td>5°</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>Abduction of arm</td>
<td>2</td>
<td>50°</td>
<td>Treatment discontinuation</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Ankle dorsiflexion</td>
<td>5</td>
<td>60°</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Great toe extension</td>
<td>5</td>
<td>50°</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ankle pronation</td>
<td>5</td>
<td>10°</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>Finger adduction/abduction</td>
<td>0</td>
<td>0°</td>
<td>Reinervation potential (−)</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>Ankle dorsiflexion</td>
<td>5</td>
<td>55°</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
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<td>Great toe extension</td>
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<td>50°</td>
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</tr>
<tr>
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<td>Great toe extension</td>
<td>0</td>
<td>0°</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ankle pronation</td>
<td>0</td>
<td>0°</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

NA, not applicable.
Case 6
During the course of treatment, ankle dorsal flexion/pronation, and great toe extension MMT and ROM scores improved. After 6 months of treatment, the MMT scores for ankle dorsal flexion/pronation were both 5 and AROMs were 55° and 10°, respectively. After 16 months of treatment, functional recovery was complete with MMT and AROM scores for great toe extension being 5° and 50°, respectively (figure 1 and table 2). During the treatment, pigmentation of the skin was observed where the anode acupuncture needle was inserted (figure 2 and table 2). However, there was no pain or other subjective symptoms at the insertion site.

Case 7
This patient began treatment at this hospital more than 12 months after the injury. Evaluation before the first treatment showed MMT and AROM scores for ankle dorsal flexion/pronation, and great toe extension of 0° and 0°, respectively. An n-EMG examination revealed only fibrillation potential (denervation potential) in the tibialis anterior. After 13 months of treatment, MMT and AROM scores for ankle dorsal flexion/pronation and great toe extension had not changed, but an n-EMG examination verified reinnervation potential (figure 3 and table 2). To date, after 48 months of treatment, an n-EMG examination verified reinnervation potential in the tibialis anterior but no improvement has been observed in MMT and AROM scores for ankle dorsal flexion/pronation and great toe extension. During the treatment, pigmentation of the skin was observed where the anode acupuncture needle was inserted (figure 2 and table 2). However, there was no pain or other subjective symptoms at the insertion site.

DISCUSSION
During the course of treatment, complete motor function recovery was observed in the two cases of possible neuapraxia (cases 2 and 4) with complication of diabetes mellitus as pre-existing disease. Among the seven cases, axonotmesis was suspected in four, with complete functional recovery (except some muscles) observed in two of them (cases 1 and 6). One of the four suspected axonotmesis cases (case 7) did not start treatment until over a year after injury, during which time no functional improvement was observed. At the time of treatment commencement, only fibrillation potential (denervation potential) was detected, but 13 months after the start of DCEA treatment, reinnervation potential was observed. In the remaining suspected axonotmesis case (case 3), the suggestion of an adverse event occurring 2 months after starting

Figure 2 Adverse events caused after treatment. The observed adverse events were pigmentation of the skin at the anode insertion site of case 1, 6 and 7 (upper). Bone formation/resorption at the cathode insertion site was verified in case 3 (lower).
treatment led to treatment discontinuation, although up to that point functional improvement was observed. There was also one case (case 5) with neurotmesis, who had received epineurial suture at another hospital. When treatment was started 14 months later, no functional improvement was observed and even after 9 months of treatment there was still no functional improvement. These results show that, apart from the case of neurotmesis with the delayed treatment after injury, clinical benefit for functional and/or electrophysiological improvement and recovery was observed with this method in six of the seven cases. Since no comparison was made with untreated cases as a control group in this study, the observed improvements could have been due to the natural course of recovery. However, the functional and electrophysiological improvement and recovery observed in older patients with poor prognoses for axonotmesis, who had shown virtually no improvement over an extended period, indicates the possible effectiveness of DCEA.

Two explanations of the mechanism involved in the promotion of nerve regeneration by DCEA using a cathode located distal to the nerve injury site have been proposed. One is that neural adhesion molecules, nerve growth factor and other nerve growth and nutritional factors move electrophoretically towards the cathode resulting in a concentration gradient that stimulates nerve regeneration. The other is that axonal injury causes an influx of Ca²⁺ ions into the proximal end of the severed axon. It is known that during the time taken for the open wound to close, the pathological condition of dieback occurs. However, it is thought that using a distal cathode suppresses the influx of Ca²⁺ ions, which could possibly inhibit dieback.

Almost all of the cases referred to in this clinical study were treated with DCEA several months to more than a year after being injured, so it is likely that the wound of the severed axon had already closed, which would reduce the possibility of DCEA being involved in the inhibition of dieback. It is thought that the beneficial effect of DCEA on peripheral nerve regeneration seen in this study could have been due to the aforementioned electrophoretic movement to the cathode of the neural adhesion molecules, the neurotrophic and neurogrowth factors required for nerve regeneration.

In terms of adverse events, pigmentation of the skin where the anode acupuncture needle was inserted was observed in three of the seven cases. It is known that electrolysis occurs during direct current electrical stimulation with an anodic electrode made of a material with a high tendency to ionisation. The major components of the needles used in this study were iron (73%), chromium (17%) and nickel (8%). Iron has the highest ionisation tendency, followed by nickel and chromium. It is not clear which of these components is involved in the pigmentation, but it is possible that iron, which has the highest ionisation tendency and is the major component, is the main cause. It is known that during electrolysis, Fe³⁺ ions are released and that Fe³⁺ ions are similar to haemosiderin, a natural metabolic product of haemoglobin. Also, Fe³⁺ ions have been observed in histological images to be phagocytosed by macrophages, and since the metabolic pathways exist, it is thought they can be easily resolved. These findings indicate that Fe³⁺ ions are probably not particularly harmful to the human body but more detailed research should be conducted in the future. However, because there were only seven cases with no controls, whether pigmentation of the skin was a result of needling, or a specific phenomenon may be issue of further investigations. In the case in which a plain x-ray radiograph showed formation and resorption of bone in the area close to where the cathode acupuncture needle was inserted, no causal relationship was seen. There have been many reports of the promotion of bone formation by direct and alternating current stimulation, and clinical studies of the electrical stimulation of external fixators have been conducted. Taking this into consideration, it is possible that DCEA was involved in this case of bone formation. Animal studies should be performed to examine these possibilities in detail.

Future studies should focus on methods of treatment that promote nerve regeneration without causing adverse events. In this study, one adverse event was pigmentation of the skin at the anode insertion site. This was observed in three of the seven cases, but these cases received stronger electrical stimulation than the four cases that did not show any skin pigmentation. Since the strength of stimulation in this study was set to the minimum intensity at which the patients could perceive, it is thought that the sensitivity of the three cases with pigmentation could have been low, resulting in application of a larger total current. On the other hand, there are also reports of animal studies examining axonal regeneration by direct current stimulation that indicate the effectiveness of weak electric current. In light of this, to improve the DCEA method, studies should be conducted to examine the frequency,

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**Figure 3** Case 7 treatment course. The graphs show needle electromyography results. Reinnervation potential was verified after 13 months of treatment.
stimulation time and degree of stimulation in order to establish the optimal and minimum current required for nerve regeneration. In addition, since acupuncture needles could be broken under some stimulation conditions if iron, nickel and chromium dissolve as a result of electrolysis, changing to a surface anode electrode could be examined.

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Competing interests  None.

Ethics approval  This study was conducted with the approval of the ethics committee of the Meiji University of Integrative Medicine.

Provenance and peer review  Not commissioned; externally peer reviewed.

REFERENCES

Summary points
▶ Direct current EA stimulates nerve regeneration in animals.
▶ We gave courses of direct current EA to 7 patients with peripheral nerve damage.
▶ Good results were seen in 4 patients, and some change in 2 more.
Direct current electrical stimulation of acupuncture needles for peripheral nerve regeneration: an exploratory case series
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