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Electroacupuncture Is Not Effective in Chronic Painful Neuropathies

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Abstract

Objective. To investigate the analgesic efficacy of electroacupuncture (EA) in patients with chronic painful neuropathy.

Design. Double-blind, placebo-controlled, cross-over study. Inclusion criteria were diagnosis of peripheral neuropathy, neuropathic pain (visual analog scale > 4) for at least 6 months, and stable analgesic medications for at least 3 months.

Patients. Sixteen patients were randomized into two arms to be treated with EA or pseudo-EA (placebo).

Interventions. The protocol included 6 weeks of treatment, 12 weeks free of treatment, and then further 6 weeks of treatment. EA or pseudo-EA was performed weekly during each treatment period.

Outcome Measures. The primary outcome was the number of patients treated with EA achieving at least 50% of pain relief at the end of each treatment compared with pain intensity at baseline. Secondary outcomes were modification in patient's global impression of change, depression and anxiety, and quality of life.

Results. Eleven patients were randomized to EA and five patients to pseudo-EA as the first treatment.

Only one patient per group (EA and pseudo-EA) reported 50% of pain relief at the end of each treatment compared with pain intensity at baseline. Pain intensity did not differ between EA (5.7 ± 2.3 at baseline and 4.97 ± 3.23 after treatment) and pseudo-EA (4.9 ± 1.9 at baseline and 4.18 ± 2.69 after treatment). There was no difference between patients who received EA as the first treatment and patients initially treated with placebo. There was no change in the secondary outcomes.

Conclusions. Our results do not support the use of EA in this population of painful neuropathy patients. Further studies in larger groups of patients are warranted to confirm our observation.

Key Words. Acupuncture; Electroacupuncture; Neuropathic Pain; Painful Neuropathy; Peripheral Neuropathy; Treatment

Introduction

Neuropathic pain is a relatively common condition occurring in about 4–5% of the population [1]. However, treatment options are limited due to the variable and unpredictable responses, while optimum dose for any drug may vary from patient to patient. Recent meta-analysis reported that current treatments can achieve 30–50% reduction in pain intensity in only 25–50% of patients [2–4]. Peripheral neuropathies are a frequent cause of chronic neuropathic pain that can severely affect patients' quality of life [5–8] and increase the socioeconomic costs [9]. Etiological therapies are available only in few specific conditions, such as in patients with neuropathies of immune-mediated, hypothyroid, dyslipidemic, iatrogenic, and compressive origin.

Acupuncture has a history of over 3,000 years [10] and it has been used for centuries in Asian countries to treat different disorders, including pain syndromes, hemiplegia, psychological illnesses, and obesity. In 1996, the Food and Drug Administration approved acupuncture as a medical device, and this technique has spread to treat several conditions, such as low back pain, myofascial pain, headache, sciatica, shoulder problems, tennis elbow syndrome, migraine, and osteoarthritis of the knee [11]. In China, the two most important indications for acupuncture are Bell's palsy and cerebrovascular accidents [12]. Among all these disorders, pain alleviation has been accepted worldwide. The mechanism of acupuncture analgesia, albeit poorly understood, has been attributed to the modulation of endogenous opiates, growth factors, gamma aminobutyric acid (GABA), and cytokines [13–17], and influence of serotoninergic descending pain inhibitory pathway [18]. However, the recent guidelines of the

American Society of Anesthesiologists Task Force and American Society of Regional Anesthesia and Pain Medicine recommended acupuncture as adjuvant to conventional therapy only for nonspecific, noninflammatory low back pain [19]. Acupuncture and electroacupuncture (EA) are considered safe, although minor side effects have been be reported, including bruising, mild discomfort, and rarely fainting, nausea, and vomiting. The procedure carries higher risk in patients with heart disease, neutropenia, and compromised immunity, whereas EA is contraindicated in patients with pacemaker [20].

There are two different strategies in performing acupuncture therapy: manual and EA. The latter combines the therapeutic effects of transcutaneous electric nerve stimulation and manual acupuncture. EA is most used, particularly for pain, because it can be standardized by waveform, length, and frequency of stimulation. Indeed, it has been suggested that different frequencies of stimulation can modulate the release of different neuropeptides and pain mediators. Low-frequency (2–15 Hz) EA engages centrally mediated endorphin, enkephalin, serotonergic, and noradrenergic analgesia, and may engage opioid-mediated immunomodulation [20]. High-frequency (>100 Hz) EA engages segmental-spinal opioids (dynorphin, enkephalin) and non-opioid (GABA, glycine) analgesia [21]. Thus, low-frequency stimulation is most often used for treating acute pain, whereas high-frequency stimulation is most often used in chronic pain.

There is no conclusive evidence that acupuncture or EA is effective in chronic neuropathic pain. The purpose of this study was to assess, in a double-blind, cross-over study, controlled vs placebo, the effectiveness of EA in reducing the intensity of neuropathic pain in a selected group of patients with painful neuropathy.

Patients and Methods

Patients aged 18–75 years with diagnosis of axonal polyneuropathy based on clinical and neurophysiological criteria, complaining of neuropathic pain at the lower limbs inadequately controlled by pharmacological treatment for at least 6 months, were considered. Inclusion criteria were visual analog scale (VAS) score > 4, stable analgesic intake for the last 3 months, and no condition known to hinder the assessment of efficacy and tolerability. VAS score was obtained by asking the patients to grade the mean severity of pain for the past 24 hours using a 10-cm line with no anchors, on which the ends indicate “no pain” and “worst possible pain.” Exclusion criteria were history of alcohol or drug abuse, history or presence of depression as assessed by the Beck Depression Inventory scale (patients with score > 13 were excluded from the study), and any condition at risk for EA (e.g., pacemaker). The study was approved by the local ethics committee. Patients were included after giving written informed consent. The study was performed between September 2007 and September 2009.

Patients were randomly assigned to EA or pseudo-electroacupuncture (pseudo-EA = placebo) as the starting treatment. They remained blind as to the type of treatment over the entire study period. To maintain the double-blind conditions, the examiners (PP, GL) were not informed of the type of treatment and assessed the efficacy and tolerability independently from the acupuncturists (MB, AS). Each patient underwent six sessions of EA for 30 minutes each at intervals of 5–7 days. EA was performed by delivering alternating current electrical stimuli (biphasic square wave generated by a stimulator device specific acupuncture) at low voltage (6 mV) and low frequency (2–10 Hz). Current intensity was graded on the sensory response of individual patients to a maximum of 70 mA. For analgesia in the lower limbs, the acupoints were 36St Zusanli and 6 M Sanyinjiao, whereas for feet, they were 3F Taichong and 60V Kunlun. Pseudo-EA was performed by applying the needle in neutral anatomical points, close to the acupoints, and delivering electrical stimulation with the same pattern as previously described [22]. At the end of the six sessions of EA or pseudo-EA, after a pause of 12 weeks, patients who had undergone EA were treated with pseudo-EA and vice versa. Both patients and examiners were kept blind on the type of treatment also during this second phase of the study.

The primary outcome was the number of patients treated with EA achieving at least 50% of pain relief at the end of each treatment compared with pain intensity at baseline. Secondary outcomes were changes in patient’s global impression of change (PGIC), depression and anxiety, and quality of life assessed by the SF-36 questionnaire administered at baseline and at the end of therapy.

Pain intensity was assessed by the VAS for pain. The scale was administered at the screening visit (baseline), at each treatment session immediately before the application of needles, at the end of the first and second treatment cycles, and at 15 and 30 days after the last session to assess the duration of analgesia. Adverse events and side effects were recorded. All patients were asked to maintain stable regimen of pretrial analgesics over the entire study.

Results

Sixteen subjects were included: nine female and seven male, with mean age of 64.9 years (range 43–75). Neuropathy was associated with diabetes in four patients, whereas it was idiopathic in 12 patients after screening for diabetes, impaired glucose tolerance, vitamin deficiencies, viral infections, systemic immune-mediated disorders, and malignancies.

Only one patient per group (EA and pseudo-EA) achieved 50% of pain relief after treatment compared with pain intensity at baseline. Pain intensity did not differ between patients treated with EA (5.7 ± 2.3 at baseline and 4.97 ± 3.23 after treatment) and those treated with pseudo-EA (4.9 ± 1.9 at baseline and 4.18 ± 2.69 after treatment). There was also no difference when we analyzed separately patients who received EA as the first

treatment and patients initially treated with pseudo-EA. There was no change in pain intensity comparing baseline and study end values when we pooled all the treatments (EA and pseudo-EA) as one group (5.0 ± 3.0 at baseline and 5.4 ± 2.2 at study end). PGIC did not significantly change compared with baseline, even when EA was administered as first or second treatment. Finally, there was no significant change in anxiety, depression, and quality of life and sleep before and after treatments.

Treatment was well tolerated and no side effect was recorded. Alternating current electrical stimulation was never referred to as unpleasant or painful. All patients maintained stable drug intake during the entire study period.

Discussion

Alternative medicine has become increasingly attractive in the Western world among physicians and patients suffering from different diseases. In particular, acupuncture is the most common approach in patients with chronic pain [23,24]. However, classical anatomy and physiology cannot be applied to the concepts of Chinese medicine on which the methodological bases of acupuncture are based. The mechanism of action of acupuncture analgesia has been extensively explored for the last 40 years. Different hypotheses have been proposed, but a unifying consensus has not been achieved. Until the 1990s, one of the most reliable theories, based on studies in animal models, claimed that low-frequency EA can stimulate the release of beta-endorphin, enkephalin, and endomorphin that activate δ- and μ-opioid receptors and of dinorphin that activates κ-opioid receptors [14,25–28]. The serotoninergic descending inhibitory pathway has also been suggested to be relevant to acupuncture analgesia. In particular, the injection of serotonin synthesis inhibitor or of 5-HT1/3 antagonists can decrease the analgesic effect of 2-Hz EA at both low and high frequencies (2 and 100 Hz), whereas EA analgesia is enhanced by 5-HT2 antagonists at high frequencies (100 Hz) [18,29–31]. Moreover, serotonin levels are increased in the spinal cord during EA [29].

Data on the effectiveness of acupuncture in controlled clinical trials are controversial. An extensive review of available clinical trials until 1990 by ter Riet et al. concluded that the effectiveness of acupuncture in the treatment of pain remained doubtful and the results are highly contradictory [32]. In 1997, a committee of the American National Institutes of Health concluded that there was sufficient evidence for acupuncture as a treatment for pain. The committee was strongly criticized, arguing that it was composed mainly of supporters of medical acupuncture and that reviews in the field tended to be written by enthusiasts often with the underlying assumption that it is a valuable therapy [33]. In 2000, a review of 51 clinical trials for a total of 2,423 patients with chronic pain confirmed the previous negative conclusions [34]. According to the authors, there was limited evidence that acupuncture can provide pain relief compared with patients who did not receive any treatment. A further review by Birch et al. [35] stated that acupuncture appears to be effective for postoperative dental pain, postoperative nausea and vomiting, and chemotherapy-related nausea and vomiting. In 2009, a meta-analysis of 13 studies on different types of pain in 3,025 patients [36] showed a minimal efficacy of EA when compared with pseudo-EA and untreated patients, but the effect was variable and cannot be distinguished from bias resulting from incomplete blinding. Moreover, the effect of placebo did not seem to be related to the method used, such as insertion of needles in non-acupuncture points or non-penetrating needles. Conversely, a recent study in patients with diabetic neuropathy reported a positive effect on numbness, spontaneous pain, rigidity, and altered temperature perception compared with placebo [37]. In a 10-week uncontrolled study on 46 patients with diabetic neuropathy, acupuncture induced pain relief in 77% of them and symptom resolution in 21% [38]. In another study, Walker [39] reported the efficacy of acupuncture performed once a week for 2–3 months in 90% of 40 patients in terms of pain, sleep, mobility, and mood improvement. The authors also reported a long-term effect, suggesting that a single cycle of treatment could be usually sufficient to reduce recurrent symptoms.

However, the number of randomized controlled clinical trials in homogeneous groups of patients with painful neuropathy is very limited. Two small studies on 11 and 23 patients showed pain relief [40,41], but in a larger randomized, placebo-controlled, multicenter clinical trial on 250 patients with HIV-associated painful neuropathy, acupuncture was not significantly more effective than placebo [42].

Our study did not show any of the efficacy of EA on neuropathic pain, sleep, and quality of life in a homogeneous group of patients with painful neuropathy. Although its major limitation is the small population of patients, the cross-over design used to undergo each patient blindly to both sham and true EA eliminated the bias of placebo effect. However, it has been suggested that placebo acupuncture is not suitable for comparison in randomized clinical trials because it is not completely inert [43]. In our study, this does not seem a relevant issue as neither EA nor pseudo-EA on neutral points allowed achieving significant pain relief. In conclusion, our results do not support the use of EA as analgesic treatment in patients with chronic painful neuropathy.

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