Modest Effects of Low-frequency Electrical Stimulation on Patients with Chronic Insomnia in an Open Trial

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Background and Objective The purpose of this study was to investigate the effects of low-frequency transcutaneous electric nerve stimulation (TENS) on chronic insomnia. Treatment options in patients with chronic insomnia are limited to medications, and cognitive behavioral therapy.

Methods Fifty-four chronic insomniacs received TENS with low-frequency, applied on trapezius muscles for at least 30 minutes to 1 hour before sleeping, more than 5 days weekly, for 4 weeks. The Pittsburgh Sleep Quality Index, Insomnia Severity Index, Epworth Sleepiness Scale, Hospital Anxiety and Depression Scale, and quantitative electroencephalography at waking state, were obtained pre and post treatment.

Results Poor sleep quality and insomnia severity decreased significantly, and relative delta power in the occipital region, also decreased after TENS. Overall treatment response rate was 57.5%, and predictive factors of treatment response were daytime sleepiness, as well as depressive and anxious mood. Relative delta power in occipital region of responders significantly decreased over time, while that of non-responders did not change. This seemed to be associated with insomnia symptom improvement, and resulting daytime alertness.

Conclusions Low-frequency electrical stimulation, was modestly effective in chronic insomnia patients. Our results provide an alternative option of insomnia treatment, for future study.

Key Words EEG, Insomnia, Electrical stimulation, Transcutaneous electric nerve stimulation.

INTRODUCTION

Insomnia is a common symptom in adults. Estimated prevalence of insomnia symptom was 10-48%, and that of insomnia disorder was 6-22%, in epidemiological studies [1]. Insomnia is likely to become chronic. A longitudinal study reported that 74% of insomniacs complained of persistent symptoms after 1 year, and 46% continued to suffer from insomnia after 3 years [2]. It was also observed that insomnia was persistent, even after 10 years [3]. Although adverse health outcomes including cardiovascular disease, cognitive decline, depression and suicidal risk are also associated with chronic insomnia [4-7]. Treatment options for patients with chronic insomnia, have been limited to medications and cognitive behavioral therapy.

The most widely used medications for insomnia, are benzodiazepines and benzodiazepine-receptor agonists. These medications are safe and effective short-term treatment for acute insomnia. However, elevated risk of dependency, development of tolerance, rebound insomnia on discontinuation, and risk of cognitive decline, must be considered with long-term use [8,9]. Cognitive behavioral therapy for insomnia (CBT-I) has effectiveness equal to pharmacotherapy during acute treatment, and is more effective than pharmacotherapy, for long-term treatment. However, in-person encounters with therapists, and willingness of patients to parent...
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Participants
Patients age 55 or older with chronic insomnia, were recruited from the sleep clinic at Seoul National University Bundang Hospital (SNUBH) November 2015–October 2016. Insomnia disorder was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders-5. Patients had been taking medications for insomnia, for more than 6 months. We included patients whose depressive or anxiety symptoms, were resolved and stable. Medical history and prescriptions was retrospectively collected and reviewed, through electronic charts in SNUBH. None of the patients showed other sleep disorders, major psychiatric disorders, dementia, substance use disorders, or history of brain injury. The study was approved by the Institutional Review Board of SNUBH (E-1509/314-001), and the Korea Food and Drug Administration (approval number 747). All participants were informed of the purpose and procedures of this study, and provided with written consent forms, before participating in this study.

Study Protocol
Low-frequency electrical stimulation
The CR-9® medical device for TENS manufactured by Crown Medical, Inc. (Seoul, South Korea) was used. The device is marketed, for relief of muscular pain. The CR-9 electrical stimulator produces low-frequency electrical waves with bipolar pulse repeated frequency of 400 Hz, pulse duration of 100 microseconds, and current amplitude < 1 mA (peak output voltage ranges from 0.3 to 0.64 V). Current is transmitted from the device through wires that terminate in a conductive nickel plate, with a number of transcutaneous electrodes. The plates are attached to the back and neck skin, to stimulate trapeziums muscles. Patients were required to wear the jacket for at least 30 minutes to 1 hour before taking sleep pills, more than 5 days weekly, for 4 weeks. This protocol was developed by increasing micro-amperage and number of sessions and lowering frequency, based on a recent pilot study that failed to identify significant efficacy of CES [12]. After using the device for 2 weeks, patients were required to visit the hospital, for examination of adverse reaction and vital signs. At the visit, their adherence to the TENS protocol was verified, by examining their written sleep diary. Every adverse reaction after using the electrical stimulator was recorded, using codes specified in the World Health Organization (WHO) adverse reaction terminology (WHO-ART) version 92, updated by the Uppsala monitoring center.

Sleep diary and questionnaires
Each subject completed a sleep diary, the morning following each nightly electrical stimulation session. Check lists for the diary included sleep latency, time in bed, awake after sleep on-

METHODS
set, intensity and duration of using stimulator, and medication dose. Demographic characteristics and sleep questionnaires, including the Pittsburgh Sleep Quality Index (PSQI) [20], Insomnia Severity Index (ISI) [21] and Epworth Sleepiness Scale (ESS) [22], were completed before and after electrical stimulation protocol. Vital signs including blood pressure and pulse rate, were checked. As individual mood or pain state can influence insomnia symptoms, the Hospital Anxiety and Depression Scale (HADS) [23] and Numerical Rating Scale (NRS) [24], were also completed.

QEEG
QEEG at waking state was measured twice before and after the electrical stimulation period. The EEG was recorded in a sitting position for 15 minutes, and subjects were instructed to relax. For the first 7 minutes, subjects kept their eyes closed. For the next minute, subjects opened their eyes, and for the last 7 minutes, subjects kept their eyes closed. Subjects were observed by an examiner, to monitor and prevent drowsiness. EEG electrodes were placed according to the international 10–20 system at FP1, FP2, F3, F4, F7, F8, C3, C4, P3, P4, T3, T4, T5, T6, O1, and O2, with an average reference. Recording of EEG started when electrical impedance of all electrodes was below 5 kΩ, and EEG signals were sampled at 1,000 Hz and digitalized. High pass filter was set to 100 Hz, with low pass filter set to 0.3 Hz. An artifact-free 120-s EEG recording with the eyes closed (24 epochs of 5-s EEG segments), was selected by visual analysis, and artifacts comprised muscle activity, small body movements, eyelid movements, and micro-sleep. Spectral analysis for EEG data was performed, by the fast Fourier transform. Absolute power values of 5 bands at each electrode were computed; delta (1.0–4.0 Hz), theta (4.0–8.0 Hz), alpha (8.0–12.0 Hz), beta (12.0–25.0 Hz), and high beta (25.0–30.0 Hz). Relative power values were computed as percentage of absolute power, and grouped into 5 cerebral regions; frontal, central, parietal, temporal, and occipital area. Relative power was selected as a first principle analysis, for decreasing individual patient variation, as well as source of bias between twice recordings.

Statistical Analyses
Per protocol analysis with exclusion of drop-outs was performed, due to no EEG data at post-treatment to compare. All results are reported as mean ± standard deviation (SD). The Kolmogorov-Smirnov test was used, to confirm normality of all data. Independent t-test or χ² test, and the Mann-Whitney U test, were used for comparison of demographic characteristics between completers and drop-out. Except the drop-outs, the overall effect of low-frequency electrical stimulation on insomnia was analyzed, using paired t-test or Wilcoxon signed rank test by estimating significant difference of PSQI, ISI, and ESS scores and EEG power values between, before, and after treatment. Cohen’s d was calculated, for estimating an effect size. QEEG data from subjects with changed medication dose were not included in EEG analyses, because benzodiazepines or other sleep-promoting agents can change awaking EEG. Partial correlation coefficients adjusting age, sex, alcohol use, and smoking were computed, to examine the association between sleep, and EEG parameters.

Responders were defined when PSQI, ISI, or ESS scores decreased more than 1 SD, or dosage of medication, was reduced after treatment. Predictors of treatment response were estimated, using multivariable logistic regression analysis. We also compared group-by-time interaction of relative EEG power between responders and non-responders, by using 2-way analysis of covariance (ANCOVA) for each cortical region. All significance tests were 2-sided, and p-value was set at < 0.05. SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA) was used for all analysis.

RESULTS

Safety Reports
The process of this study is summarized in Fig. 1. Among 54 patients with chronic insomnia at baseline, 10 patients dropped out because of adverse reactions (n = 4), withdrawal of consent (n = 5), and a car accident reportedly unrelated with use of the device (n = 1). Tolerability data were available for 54 subjects, and adverse reactions were reported in 11 cases (20%); chest pressure sensation (n = 2), chest ache (n = 1), application site irritation (n = 1), rash pruritic (n = 1), itching (n = 1), nervousness (n = 2), hypoglycemia (n = 1), and fatigue (n = 1). Discomfort in the chest area was due to Velcro-type of the accessory device, for attaching and tightly securing the TENS device to the body. Although skin-related adverse reaction to the metal electrode was recognized as a common problem, 2 subjects withdrew because of this problem. Decreased sleep quality due to nervousness in 2 subjects was their main reason for exiting the study. Adverse reactions were tolerable, and self-limiting after several days, for remaining participants.

Effectiveness on Insomnia
There was no difference in demographic factors including sex, age, insomnia duration and other psychiatric disorders, anxiety and depressive symptoms, perceivable pain, subjective sleep quality and daytime sleepiness between completers and dropouts. Forty four (81.5%) patients completed the study protocol; 40 (14 men, 35%; mean age 65.3 ± 8.4) were included in the final analysis. The remaining 4 patients had poor quality QEEG data. At baseline, 38 participants were taking at least one benzodiazepine drug continuously (n = 34) or intermittently (n = 4), with 2 people taking mirtazapine (n = 1) or anti-histamine (n = 1).

Mean duration of device use was 23.1 ± 4 days. Mean dura-
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Aim of daily usage was 39.7 ± 9.3 minutes. Mean current intensity was 137.1 ± 20.3 μA at the neck and 138.8 ± 20.9 μA at shoulder. Low-frequency electrical stimulation produced significant improvement in PSQI (12.53 ± 3.65 to 11.05 ± 3.73, Cohen’s d = 0.403, p < 0.001) and ISI score (13.48 ± 7.24 to 11.72 ± 5.98, Cohen’s d = 0.265, p = 0.006). Sleep diaries revealed treatment-related improvement of sleep quality, in terms of sleep latency reduction (51.94 ± 33.21 to 35.59 ± 22.55 minutes, p < 0.001, Cohen’s d = 0.576) and increased total sleep time (309.88 ± 80.1 to 334.5 ± 81.93 minutes, p = 0.005, Cohen’s d = 0.304).

Table 1. Comparison of sleep, mood, and pain variables between before and after low-frequency electrical stimulation

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>p-value</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQI</td>
<td>12.53 ± 3.65</td>
<td>11.05 ± 3.73</td>
<td>&lt; 0.001</td>
<td>0.403</td>
</tr>
<tr>
<td>ISI</td>
<td>13.48 ± 7.24</td>
<td>11.72 ± 5.98</td>
<td>0.006</td>
<td>0.265</td>
</tr>
<tr>
<td>Sleep diary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep latency</td>
<td>51.94 ± 33.21</td>
<td>35.59 ± 22.55</td>
<td>&lt; 0.001</td>
<td>0.576</td>
</tr>
<tr>
<td>Time in bed</td>
<td>406.25 ± 72.91</td>
<td>430.5 ± 65.46</td>
<td>0.021</td>
<td>0.350</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>309.88 ± 80.1</td>
<td>334.5 ± 81.93</td>
<td>0.005</td>
<td>0.304</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>77.23 ± 17.65</td>
<td>78.62 ± 18.76</td>
<td>0.86</td>
<td>0.076</td>
</tr>
<tr>
<td>ESS</td>
<td>4.23 ± 4.45</td>
<td>4.75 ± 4.12</td>
<td>0.24</td>
<td>0.121</td>
</tr>
<tr>
<td>HADS</td>
<td>14.28 ± 8.68</td>
<td>14.1 ± 8.17</td>
<td>0.53</td>
<td>0.021</td>
</tr>
<tr>
<td>NRS</td>
<td>2.68 ± 2.41</td>
<td>2.95 ± 2.39</td>
<td>0.44</td>
<td>0.112</td>
</tr>
</tbody>
</table>

PSQI: Pittsburgh Sleep Quality Index, ISI: Insomnia Severity Index, ESS: Epworth Sleepiness Scale, HADS: Hospital Anxiety and Depression Scale, NRS: Numerical Rating Scale.

Comparisons between Responders and Non-Responders

When comparing mean dose of drugs for 3 days pre and post electrical stimulation treatment, benzodiazepine drugs dose in
6 patients decreased after treatment (1.9 ± 1.7 vs. 1.1 ± 1.1; dose equivalent of lorazepam). A total of 23 patients showed treatment response (57.5% response rate). When we compared change of sleep variables in sleep diaries between responders and non-responders, sleep latency decreased (44.46 ± 26.9 to 30.26 ± 17.55 minutes, p < 0.001, Cohen’s d = 0.625) and total sleep time increased (308.7 ± 82.2 to 347 ± 77.66 minutes, p = 0.001, Cohen’s d = 0.479) in responders (Table 2). Response was predicted by increasing baseline ESS score [odds ratio (OR) = 1.79, 95% confidence interval (CI) = 1.09–2.95, p = 0.021], and baseline HADS score (OR = 1.36, 95% CI = 1.02–1.81, p = 0.038), after adjusting for age, sex, other psychiatric disorders, insomnia duration, and amount and intensity of treatment (Table 3). QEEG data also showed group-by-time interactions between responders and non-responders. Relative delta power of insomnia patients significantly decreased in the occipital region, compared to power before treatment (15.1 ± 9.4 to 12.7 ± 12.9, Cohen’s d = 0.238, *p < 0.05).

Table 2. Comparison of sleep, mood, and pain variables between before and after low-frequency electrical stimulation between responders and non-responders

<table>
<thead>
<tr>
<th></th>
<th>Responders (n = 23)</th>
<th>Non-responders (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
</tr>
<tr>
<td>PSQI</td>
<td>13 ± 3.84</td>
<td>10.61 ± 3.96</td>
</tr>
<tr>
<td>ISI</td>
<td>15.27 ± 7.73</td>
<td>11.5 ± 6.05</td>
</tr>
<tr>
<td>Sleep diary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep latency</td>
<td>44.46 ± 26.9</td>
<td>30.26 ± 17.55</td>
</tr>
<tr>
<td>Time in bed</td>
<td>405.22 ± 74.64</td>
<td>425 ± 60.13</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>308.7 ± 82.2</td>
<td>347 ± 77.66</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>77.67 ± 20.02</td>
<td>83 ± 19.37</td>
</tr>
<tr>
<td>ESS</td>
<td>6.09 ± 4.92</td>
<td>5.96 ± 4.59</td>
</tr>
<tr>
<td>HADS</td>
<td>16.7 ± 8.95</td>
<td>15.74 ± 8.56</td>
</tr>
<tr>
<td>NRS</td>
<td>3.01 ± 2.44</td>
<td>3.33 ± 2.55</td>
</tr>
</tbody>
</table>

*Cohen’s d was used. Responders were defined when PSQI, ISI, or ESS scores decreased more than one standard deviation or if the dosage of medication was reduced after treatment.

PSQI: Pittsburgh Sleep Quality Index, ISI: Insomnia Severity Index, ESS: Epworth Sleepiness Scale, HADS: Hospital Anxiety and Depression Scale, NRS: Numerical Rating Scale.
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in the occipital region, after adjustment for age, alcohol use, smoking, treatment duration, time and intensity (F = 5.8, p = 0.024). Relative delta power in the occipital area significantly decreased in responders (16.5 ± 9.7 to 10.9 ± 8.9), compared to non-responders (13.7 ± 9.1 to 14.5 ± 11.9) (Fig. 3).

DISCUSSION

Data demonstrate that low-frequency TENS is a safe and effective method, for treatment of chronic insomnia, without change in pain and mood state. TENS also induced decreased relative delta power, in the occipital area after 4 weeks of use. This reduction seemed to be associated with improvement of the insomnia symptom, and resulting daytime alertness. Predictors for treatment responses are daytime sleepiness, and a depressive-anxious mood, before starting TENS. Adverse reactions were relatively tolerable, and self-limited during the study period.

Improvement of sleep quality after electrical stimulation was found by subjective reports and EEG measurements. Decrease of sleep latency and increase of total sleep time were observed in participants, as well as decrease of insomnia severity, indicated by scores of the questionnaires. This finding is consistent with the result of a randomized case-control study using CES, reporting decrease of sleep latency and wake-up time, after sleep-onset with electrical treatment [25]. The authors also found significant increase of slow wave sleep and total delta sleep through polysomnography, which could contribute to treatment-related improvement for insomniacs. Contrary to the positive role of delta during sleep, increased delta waves at wakefulness has been documented, in a wide array of pathological conditions, such as brain tissue damage and cognitive decline [26]. Delta waves at wakefulness also indicate increased fatigue and mental dullness, typically resulting from insomnia. We found significant decrease of relative delta power at wakefulness, associated with subjective reduction of insomnia severity. Also, difference in decrease of relative delta power between responders and non-responders in this study, could suggest that decreased delta power at wakefulness was a treatment effect from TENS. Kennerly [27] reported a similar result.

Table 3. Multivariable logistic regression analysis for response of low-frequency electrical stimulation

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI Lower limit</th>
<th>95% CI Upper limit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.21</td>
<td>0.97</td>
<td>1.52</td>
<td>0.096</td>
</tr>
<tr>
<td>Sex</td>
<td>1.01</td>
<td>0.06</td>
<td>18.73</td>
<td>0.99</td>
</tr>
<tr>
<td>Other psychiatric disorder</td>
<td>3.50</td>
<td>0.16</td>
<td>75.07</td>
<td>0.42</td>
</tr>
<tr>
<td>Insomnia duration</td>
<td>0.99</td>
<td>0.97</td>
<td>1.00</td>
<td>0.13</td>
</tr>
<tr>
<td>Baseline PSQI</td>
<td>0.74</td>
<td>0.43</td>
<td>1.27</td>
<td>0.27</td>
</tr>
<tr>
<td>Baseline ESS</td>
<td>1.79</td>
<td>1.09</td>
<td>2.95</td>
<td>0.021</td>
</tr>
<tr>
<td>Baseline ISI</td>
<td>1.09</td>
<td>0.79</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Baseline HADS</td>
<td>1.36</td>
<td>1.02</td>
<td>1.81</td>
<td>0.038</td>
</tr>
<tr>
<td>Baseline NRS</td>
<td>0.85</td>
<td>0.48</td>
<td>1.51</td>
<td>0.59</td>
</tr>
<tr>
<td>Treatment duration (days)</td>
<td>1.11</td>
<td>0.73</td>
<td>1.68</td>
<td>0.62</td>
</tr>
<tr>
<td>Treatment time (min)</td>
<td>0.94</td>
<td>0.80</td>
<td>1.09</td>
<td>0.39</td>
</tr>
<tr>
<td>Treatment intensity (mean)</td>
<td>2.02</td>
<td>0.33</td>
<td>12.52</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Responders were defined when PSQI, ISI, or ESS scores decreased more than one standard deviation or if the dosage of medication was reduced after treatment.

PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale, ISI: Insomnia Severity Index, HADS: Hospital Anxiety and Depression Scale, NRS: Numerical Rating Scale, OR: odds ratio, CI: confidence interval.

Fig. 3. Comparison of delta power in the occipital region over time between responders and non-responders. Two-way analysis of covariance was used after age, alcohol use, smoking, treatment duration, time, and intensity were adjusted (p = 0.024, F = 5.806). Responders were defined if PSQI, ISI or ESS scores decreased more than 1 standard deviation, or if medication dosage was reduced after treatment. PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale, ISI: Insomnia Severity Index.
of EEG that a 20-minute session of CES induced changes of cortical activity at wakefulness, including decreased delta and theta frequency, and increased alpha frequency. TENS applied at the trapezius muscles, could induce significant change in brain activity, as CES does.

Overall response rate of low-frequency TENS, was 57.5% in chronic insomniacs. When comparing with response rate of CES with insomniacs that range from 42% to 81% [28,29], the response rate in this study is acceptable. Higher anxious and depressive mood are associated with better treatment responses of insomnia after using TENS, although no statistically significant change in anxious and depressive moods over time was evident, between responders and non-responders. The negative mood may affect a person's feeling or cognition of sleep at night, and contribute to expectation of relief from insomnia, by participating in this study. Indeed, individuals with comorbid symptoms of insomnia and depression have more worry, dysfunctional beliefs, and rumination about sleep, than those with only an insomnia symptom [30].

Our positive results follow the low-frequency TENS using more than 20 days and 30 to 60 minute sessions, conducted at < 1 mA (mean 137–138 μA) at the trapezius muscles. Selecting target regions is also crucial, as much as choosing proper duration, and degree of electrical stimulation. We had several reasons for determining these regions, for insomnia treatment in this study. Anatomical and functional innervation of cervical nerves within the trapezius muscles have been identified [31]. Moreover, psychological complaints regarding sleep disturbances, are a strong predictor of increased muscle response in the upper trapezius muscle [32]. High muscle tone in the trapezius muscle is usually observed, when insomniacs receive muscle relaxation therapy in sleep clinics.

The working mechanism of relieving insomnia by low-frequency TENS is unknown. But there are several possible hypotheses. First, neuromuscular effect of electrical stimulation has been suggested. People with physiological problems such as sleep disturbances, reportedly show increased muscle contractions when surface electromyography is recorded, bilaterally from the trapezius and deltoid muscle areas [32]. A positive relationship between muscle relaxation, and increased sleep quality is evident [33]. Effects of administering TENS on muscles have been reported, as increased muscle extension and decreased spasticity in patients with cerebral palsy [34], as well as increased muscular oxidative capacities, blood supply and skin temperatures, and inhibited pro-inflammatory cytokines [19,35-37]. Second, neurophysiological effects on the brain, could be induced by electrical stimulation. CES affects subcortical brain structures, such as the reticular activating system, thalamus, hypothalamus and limbic system, that regulate neurotransmitter function and hormone production, via the hypothalamic-pituitary axis, or modifies cortical activity [27]. Increased levels of serotonin, melatonin, cholinesterase and gamma-aminobutyric acid, and decreased cortisol in blood plasma, were reported after one 20-minute CES session [38]. Although we did not measure laboratory changes in this study, TENS may be helpful in inducing sleep and relaxation, because we performed electrical stimulation on participants' neck and shoulders near the head, similar to the application site of CES, and connected with cervical nerves [31]. A report described the effect of TENS on the brain, in which electrical low-frequency stimulation of the right hand, induced central neuroplastic changes of pain processing [39]. One study of TENS using single-photon emission computed tomography, reported improved brain perfusion in patients with brain lesions using electrical stimulation at the forearm [40].

Among several adverse reactions, we must consider 2 dropout cases due to nervousness, after using electrical stimulation for insomnia treatment. Decreased sleep quality due to nervousness could be explained by the paradoxical alerting reaction reported by some people, as remaining fully awake, because of paradoxical stimulation after the first or second week of CES use. Therefore, if some participants complain of nervousness and worsening sleep, it would be helpful not to use TENS immediately prior to sleep, but instead allow for a time gap between TENS and sleep, or changing the timing of TENS to morning, with decrease in frequency of use.

This study has several limitations. First, there was no control group using sham devices for estimating the placebo effect, compared to those using active electrical devices. We examined optimal dose and duration of TENS, for insomnia treatment from this pilot study. Further, studies will be conducted with a large-sample, randomized, double-blind and controlled design. Second, the definition of response group in this study, was relatively lenient. The degree of insomnia reduction by TENS was modest, because our participants had been taking sleeping pills for at least 6 months. Third, participants were age 55 or older, so the results cannot be generalized for all ages. Nevertheless, the strengths of our study were adjustment of confounders including pain, depression and anxiety, careful observation about change of participants' drug usage, and repeated examination of QEEG pre as well as post treatment.

In conclusion, low-frequency electrical stimulation was effective in decreasing insomnia severity in more than half of chronic insomnia patients, without crucial adverse reaction. Moreover, electrical stimulation contributed to reduced medication use for sleep in several patients. Daytime sleepiness, and depressive and anxious moods, which were predictors of treatment response and decreasing relative delta power in the occipital region, seemed to be associated with insomnia symptom improvement, and resulting daytime alertness. This study provides information that will be valuable, for future TENS studies. The hope is that TENS will prove to be an alternative therapeutic tool, for the relief of insomnia.
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Acknowledgments

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Conflicts of Interest

The authors have no financial conflicts of interest.

Authors’ Contribution

Conceptualization: Yoon IY. Data curation: Bang YR, Jeon HJ. Formal analysis: Bang YR, Yoon IY. Methodology: Yoon IY. Project administration: Bang YR, Jeon HJ. Yoon IY. Supervision: Yoon IY. Writing—original draft: Bang YR, Jeon HJ. Writing—original draft and editing: Yoon IY.

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