A Pilot Randomized Controlled Trial of Transcutaneous Electrical Nerve Stimulation for Patients With Acute Tinnitus

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Abstract
Background: This pilot study aimed to evaluate the feasibility effectiveness and safety of transcutaneous electrical nerve stimulation (TENS) for patients with acute tinnitus.

Methods: A total of 46 eligible patients with acute tinnitus were entered and included in this randomized controlled trial. All the included patients were equally and randomly divided into a verum TENS group and a sham TENS group, each group 23 participants. All patients received parenteral intramuscular therapy of 1 ml Vitamin B12 weekly for a total of 4 weeks. In addition, they also underwent verum or sham TENS 30 min daily, 3 times weekly for 4 weeks. The primary efficacy endpoint was measured by the Tinnitus Handicap Inventory (THI), 12-Item Short Form Health Survey (SF-12) questionnaire, and adverse events. All outcome efficacy endpoints were measured at baseline and after 4 weeks of treatment.

Results: After 4-week treatment, the patients undergoing verum TENS showed statistically efficacy of symptoms relief, as measured by the scales of THI (P < .01), TQ (P < .01), and THI (P < .01), and improvement of quality of life, as assessed by the SF-12 (P < .01), compared with patients receiving sham TENS. In addition, no adverse events related to the treatment were recorded in either group.

Conclusions: The results of this study showed that verum TENS may benefit patients with acute tinnitus after 4 weeks of treatment.

Abbreviations: SF-12 = 12-Item Short Form Health Survey, TENS = transcutaneous electrical nerve stimulation, THI = Tinnitus Handicap Inventory, TQ = Tinnitus Questionnaire, TSS = Tinnitus Severity Scale.

Keywords: acute tinnitus, effectiveness, safety, transcutaneous electrical nerve stimulation

1. Introduction
Tinnitus is a common and disturbing condition.[1–21] It characterizes as the perception of sound or noise that has no external source.[3–4] It has been reported that about 5 to 10 percent of patients suffer from such condition.[5–6] This rate can increase up to 30% among the elderly,[5] and often becomes chronic condition, which may result in the anxiety, depression, insomnia, and poor quality of life in patients with such condition.[7–10]

Presently, no highly effective management was recommended for tinnitus, although a variety of therapies are utilized to treat this condition. These therapies consisted of medications, hearing aids, retraining therapy, behavioral therapy, cochlear implant therapy, acupuncture, and electrical stimulation, such as transcutaneous electrical nerve stimulation (TENS).[11–21] Of these management, TENS is regarded as one of the most potential candidates with safe, non-invasive, and effective intervention.[19–21] However, there is still insufficient data to effectively support that TENS can manage acute tinnitus specifically.

In the present study, we hypothesized that verum TENS therapy for acute tinnitus specifically after 4 weeks treatment would be superior to the effectiveness of sham TENS intervention. Thus, we designed this pilot randomized sham-controlled trial to evaluate the feasibility effectiveness of verum TENS therapy for the treatment of patients with acute tinnitus.

2. Methods/design

2.1. Study design
This pilot study was approved by the Medical Ethics Committee of The People’s Hospital of Yanan and Yanan University Affiliated Hospital. It was conducted from June 2017 to May 2018 at both centers. A total of 46 patients with acute tinnitus were recruited from 2 centers in this study. The first center of The People’s Hospital of Yanan recruited 20 patients, and the second center of Yanan University Affiliated Hospital included 26 patients. All patients in both centers were randomly allocated to a
verum TENS group and a sham TENS group at a 1:1 rate. They all received parenteral intramuscular therapy of 1 ml Vitamin B12 weekly for a total of 4 weeks. Moreover, subjects in the verum TENS group underwent real TENS therapy. The participants in the sham TENS group received sham TENS intervention. Patients in both groups were treated 30 min daily, 3 times weekly for a total of 4 weeks.

2.2. Patients

Patients were included if they met the following criteria:

1. all included patients were diagnosed as acute tinnitus;
2. male or female aged between 18 to 75 years old;
3. have a history of tinnitus less than 6 consecutive months;
4. not caused by any kinds of medications; and
5. written informed consent was provided by each individual.

Patients were excluded if they had received TENS, acupuncture, or electroacupuncture 3 months before this study; cardiac pacemaker; diseases that can cause tinnitus, such as otosclerosis; severe psychiatric disorders; cancer or severe mental disorders; pregnancy and lactation. They were also excluded if they had received medications for the treatment of acute tinnitus 3 months before the study, or during the study period.

2.3. Randomization and blinding

Forty-six patients with acute tinnitus were randomly allocated to the verum TENS group and sham TENS group in a 1:1 ratio. Randomization is conducted by a block randomization using a computerized number generator with SAS package 8.1 (SAS Institute Inc., Cary, NC, USA). The allocation information was concealed in sequentially numbered, opaque, sealed envelopes. The researchers, outcome assessors, and data analysts were masked to the treatment allocation information.

2.4. Intervention schedule

In this study, patients in both groups received parenteral intramuscular therapy of 1 ml Vitamin B12 (2500 mcg) weekly for a total of 4 weeks, according to the previously published study.[22]

Additionally, TENS therapy is performed by a LH202H Han Electrostimulator (Jinghua Wei Industry Development Company, Beijing, China). A pair of electrodes was placed on the left and right C2 nerves dermatomes. The negative electrode was placed at the opposite to the tinnitus side. If patients suffered from acute tinnitus on both sides, then the negative electrode was placed on the left side. It can generate pulses of disperse-dense wave and a frequency of 2/100Hz. Each individual was treated 30 min daily, 3 times weekly for a total of 4 weeks. Sham TENS intervention was applied by the same electrostimulator at the same location, session, and total treatment duration, but without electrical power.

2.5. Outcome measurements

The primary efficacy endpoint was severity of tinnitus. It was measured by the Tinnitus Severity Scale (TSS)[23] and Tinnitus Questionnaire (TQ) sum scores.[24] TSS consists of 6 numeric rating scales. Of these, scale 1 ranges from 0 to 5, and scales 2 to 6 vary from 0 to 10, with a higher score, indicating a severe tinnitus. TQ sum score range from 0 to 84, with a higher score, indicating a severer distress. The secondary efficacy endpoints were measured by the Tinnitus Handicap Inventory (THI),[25] the 12-Item Short Form Health Survey (SF-12) questionnaire,[26] and adverse events during the treatment period. The THI scale ranges from 0 to 100; with a higher score, indicating a greater handicap. The SF-12 includes physical and mental components; each item ranges 0 to 100, with a higher score, indicating a better quality of life. All the outcomes were measured at baseline and after 4 weeks of treatment.

2.6. Statistical analysis

The outcome values were conducted by using SAS package 8.1 (SAS Institute Inc., Cary, NC, USA). The minimum size of each group was estimated at 20 participants with α=0.5, β=0.8. Assuming a 15% drop-out rate, the required sample size of this study was therefore estimated to be 46 patients, with 23 assigned to each group.

All outcome data were analyzed by intention-to-treat (ITT) principle. The Mann-Whitney U test or Fisher two-tailed exact test was used to compare the primary and secondary outcome measurements. The value of P<.05 was set to have the statistical significance.

3. Results

In total, 57 patients with acute tinnitus were admitted and entered the study (Fig. 1). Of these participants, 11 did not meet the inclusion criteria. Thus, 46 patients were randomly divided into the verum TENS group or sham TENS group in a ratio of 1:1. ITT approach was utilized to analyze all the primary and secondary efficacy outcomes. No patients withdrew or lost to follow-up visit (Fig. 1).

The characteristics of all included patients at baseline are listed in Table 1. In addition, the primary and secondary efficacy outcomes were also measured at baseline (Table 1). There were no significant differences in all characteristics, as well as the primary and secondary outcome measurement at baseline between 2 groups.

Results of all primary and secondary efficacy endpoints are summarized in Tables 2 and 3. They showed that patients in the Verum TENS group exerted better outcomes in TSS (P<.01, Table 2), TQ (P<.01, Table 2), THI (P<.01, Table 3), and SF-12 (P<.01, Table 3), compared with patients in the Sham TENS group.

During the 4-week treatment period, no adverse events related to the verum TENS or sham TENS intervention occurred in either group.

4. Discussion

It has been reported that tinnitus can greatly impact the quality of life in patients with it.[15] Many therapies are suggested to treat such condition. Of these, electrical stimulation is reported to treat tinnitus for more than 30 years.[27–29] It was gradually confirmed by several clinical studies.[20,29] TENS is one of the most important interventions of electrical stimulation. Previous studies found that TENS can treat tinnitus condition.[19–21] They found that TENS of the median nerve could not only modulate the tinnitus percept in some patients,[10] but also had an inhibitory effect by acting to the temporomandibular joint in patients with tinnitus.[11] Unfortunately, almost all of those studies provided quite low level of evidence to support this therapy. In the present...
### Figure 1. Flowchart of participant selection.

### Table 1

**Patient characteristic at baseline.**

| Characteristics                      | Verum TENS group (n=23) | Sham TENS group (n=23) | P value |
|--------------------------------------|-------------------------|------------------------|---------|
| Mean age (year)                      | 46.8 (11.6)             | 48.4 (13.1)            | 0.66    |
| Sex                                  |                         |                        |         |
| Male                                 | 14 (60.9)               | 17 (73.9)              | 0.35    |
| Female                               | 9 (39.1)                | 6 (26.1)               | 0.35    |
| BMI (kg/m²)                          | 22.5 (2.0)              | 21.9 (2.4)             | 0.36    |
| Tinnitus duration (months)           | 3.7 (1.4)               | 4.0 (1.6)              | 0.50    |
| Location of tinnitus                 |                         |                        |         |
| Left                                 | 5 (21.8)                | 7 (30.4)               | 0.50    |
| Right                                | 3 (13.0)                | 4 (17.4)               | 0.68    |
| Both                                 | 15 (65.2)               | 12 (52.2)              | 0.37    |
| Primary endpoint measurements        |                         |                        |         |
| TSS                                  | 22.8 (7.7)              | 21.1 (6.9)             | 0.43    |
| TQ                                   | 20.1 (4.5)              | 19.3 (8.4)             | 0.76    |
| Secondary endpoint measurement       |                         |                        |         |
| THI                                  | 31.8 (12.6)             | 30.2 (14.3)            | 0.69    |
| SF-12 (physical)                     | 77.6 (16.2)             | 79.3 (17.0)            | 0.72    |
| SF-12 (mental)                       | 80.1 (15.4)             | 81.6 (14.4)            | 0.73    |

Data are present as mean±standard deviation or number (%). BMI = body mass index, SF-12 = 12-Item Short Form Health Survey questionnaire, TENS = transcutaneous electrical nerve stimulation, THI = Tinnitus Handicap Inventory, TQ = Tinnitus Questionnaire, TSS = Tinnitus Severity Scale.
study, we applied the TENS to the location of the external pinna and tragus of each ear.

The results of the present pilot study confirmed our hypothesis that the effectiveness of verum TENS treatment is superior to the sham TENS for the treatment of patients with acute tinnitus after 4 weeks treatment. The results found that verum TENS may either significantly reduce the severity of acute tinnitus, as measured by the TSS, TQ, and THI, or greatly improve the quality of life in patients with acute tinnitus. These positive results indicated that verum TENS may have encouraging effectiveness for the treatment of acute tinnitus.

The present pilot study has 2 limitations. First, the sample size of this study is quite small, which may affect the results of this study. Second, this study only included 4 weeks treatment duration, which may quite short to assess the effectiveness of TENS. However, its effectiveness showed significantly positive after 4 weeks treatment, it may be because of the acute tinnitus with quite short disease duration.

5. Conclusion
The results of this study found that verum TENS may effectively treat acute tinnitus after 4-week treatment.

Author contributions
Conceptualization: Li Li, Hao Shi, and Min Wang.
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