Does transcutaneous Vagus Nerve Stimulation (tVNS) reduce pain intensity in chronic low back pain patients? A randomized controlled pilot study

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ABSTRACT

Background: Low back pain, if poorly treated, is responsible for a decline in patients’ quality of life. In addition to medication and exercise therapy, transcutaneous vagus nerve stimulation (tVNS) emerges as one of the modalities for chronic pain. Currently, studies on the effect of tVNS on pain intensity, particularly in chronic low back pain cases, are still scarce. This study aims to examine the effect of tVNS in addition to exercise treatment on patients with chronic low back pain.

Methods: Twenty-two patients were randomly assigned to one of two groups: the control group, which included eleven patients who received only exercise therapy, and the intervention group, which included eleven patients who received exercise therapy with tVNS as an additional therapy. The demographic data of the participants and the results of the Numerical Pain Rating Scale (NPRS) were used as outcome measures. Data were collected before and after the two-week treatment period. Safety and adverse events were monitored throughout the study.

Results: The mean NPRS decreased in both groups, with the intervention group decreasing from 5.45 to 1.73 (p < 0.001) and the control group decreasing from 5.82 to 3.27 (p < 0.001). Although the intervention group’s average NPRS score decreased more than the control groups, no significant difference was found (p=1.04). Following Cohen’s D, the effect size of the intervention group was more significant (2.22) than that of the control group (1.62).

Conclusion: These findings imply that tVNS should be considered an additional therapy for chronic low back pain patients. During the study, no side effects were discovered.

Keywords: Low Back Pain, Pain Intensity, NPRS, tVNS.


INTRODUCTION

Chronic low back pain, typically lasting for at least 12 weeks, is reported to be the leading cause of disability worldwide and emerges as the main problem for well-being and the economy.1 In addition to causing disability, low back pain decreases individuals’ productivity, lowering their overall quality of life. The Global Burden of Disease Study from 2017 reported that low back pain is among the top ten disability-causing diseases.2 In general, the prevalence of low back pain ranges between 60 and 70% in industrialized countries (annual prevalence of 15–45% and 5% incidence in adult age). Prevalence rises and peaks between 35 and 55 years of age. The prevalence of low back pain in Indonesia comprises 18%, increases with aging, and is frequently reported in the middle and fourth decades.3 The incidence was reported to be around 3–17%, based on patients’ visits to several Indonesian hospitals.4 Around 30 to 40% of people with chronic LBP also suffer from depression, which is reported to aggravate the pain and possibly worsen patients’ disabilities.5

Low back pain management includes both medication and non-medication treatments. The former includes the administration of analgesics, including opioids, non-steroidal anti-inflammatory drugs, steroids, muscle relaxants, and antidepressants. Meanwhile, the latter involves education, exercise therapy, manual manipulative therapy, traction, orthosis, transcutaneous electrical nerve stimulation (TENS), massage, and yoga.6 Along with the development of depression and epilepsy management in the last decade, transcutaneous vagus nerve stimulation (tVNS) has been introduced as one of the modalities for chronic pain. The benefits of this treatment have been confirmed in fibromyalgia, migraine, and cluster headache.6,7 Several studies involving epilepsy and depressed patients reported that their pain was relieved after receiving tVNS.8

Electrical stimulation to the auricular branch of the vagal nerve (ABVN) innervating the ear is an easy and accessible target for therapy. In recent years, numerous studies have proven the safety and tolerability of this method,
including its effect on the neuropsychiatric population’s central and peripheral nervous systems and behaviors.⁸ tVNS exhibits the potential to overcome various conditions, including neurological, psychological, inflammatory, and cardiovascular conditions. tVNS was approved by the Food and Drug Administration (FDA) in 2012 as a treatment for chronic pain.⁹ tVNS is methodologically similar to TENS for the treatment of musculoskeletal pain. The distinction is that the former refers to certain ear anatomy thought to be innervated by ABVN, typically located at the acusticus externus (tragus), cymba conchae, and cavum conchae. The stimulation is given using a square-type monophasic wave at a frequency between 1-30Hz, pulse width 80-500 μs, 0.5 – 6 mA intensity, adjusted to the patient’s tolerance or below the patient’s pain threshold for 20-30 minutes. The frequency dosage recommended by FDA is 20–30 Hz.¹⁰

The mechanism of tVNS in addressing chronic pain, including chronic LBP, is carried out through its pain-modulating effect on serotonergic and noradrenergic pathways, as indicated by the activities in locus corelues and nucleus raphe in functional magnetic resonance imaging (fMRI) and the somatosensory response of vagus nerve on far-field brainstem evoked potentials during tVNS. Additionally, tVNS has an anti-inflammatory effect through the hypothalamus-pituitary-adrenal (HPA) axis and an anti-inflammatory cholinergic mechanism that is responsible for inhibiting pain at the peripheral level through its anti-inflammatory effect.⁸ It also inhibits TNF-α release that hinders peripheral and central sensitization.¹¹ tVNS is expected to be one of the non-invasive modalities for chronic low back pain by relieving pain and improving patients’ quality of life.

Studies on the effect of tVNS on chronic LBP, compared to the control group not receiving tVNS, have not been published. To the author’s knowledge, no studies have been conducted to investigate the effect of tVNS on LBP patients in terms of pain reduction, has been reported. Based on the evidence on the benefits of tVNS on pain cases and chronic low back pain cases, particularly chronic musculoskeletal pain, the author conducted this study aiming to examine the effect of tVNS on the pain intensity of chronic LBP patients in Dr. Soetomo General Hospital, Surabaya, Indonesia.

METHOD

A randomized controlled trial was conducted at the medical rehabilitation polyclinic of Dr. Soetomo General Hospital, Surabaya. The population of this study comprised all chronic low back pain patients who underwent outpatient therapy at the medical rehabilitation polyclinic of Dr. Soetomo General Hospital since January 2021. Inclusion criteria included patients aged 18-55 years old, diagnosed with chronic non-organic mechanical LBP ≥ 3 months to ≤ 1 year without showing signs of red flags, and the NPRS pain score was ≥ 4. The exclusion criteria included the history of taking analgesics in addition to paracetamol and NSAIDs, the consumption of new analgesic in the past 2 weeks, the use of other modalities in the past 1 week, history of pain, trauma, and skin disorders (scorch or open wound) at the ears, history of face pain, the use of metal implants including pacemakers, pregnancy, history of heart disease (heart rhythm disturbance, coronary heart disease), history of neurological disorders (including convulsions or epilepsy), history of moderate-to-severe depression (HDRS score ≥ 17), history of vasovagal syncope, history of metal allergies of skin, alcohol and drug dependence, a disorder of communication and obesity (grade II) (BMI ≥ 30 kg/m² according to ASIA classification).

This study used consecutive sampling, followed by randomization, to divide the participants into control and intervention groups. The data were taken randomly before and after the treatment (pre and post-test) (pre-test and post-test with open trial single-blind randomized controlled trial). The number of subjects in this study was eleven for each group. The approval of the ethics committee was given by the Clinical Research Ethics Committee at Dr. Soetomo Academic General Hospital (0411/KEPK/IV/2022). Written informed consent forms were obtained from all patients to indicate their consent for inclusion in the study. The assessment was performed twice in both groups during the study, before and after the intervention. The control and intervention group received exercise therapy based on ACSM Guidelines 2018, which included core strengthening exercises (abdominal drawing in and cat and camel exercise), stretching exercises (pelvic tilt, single and double knee to chest), posture correction and breathing exercises.¹² Exercises are given two days a week for two weeks, led by a physiotherapist, with each practice session lasting 30 minutes. Based on this study protocol, the intervention group received the same exercises as the control group, under the single physiotherapist’s supervision for both groups, without knowing which group the participants were in. The intervention group received additional tVNS therapy, which was administered transcutaneously using a transcutaneous electrical stimulation device with special electrodes placed on the skin of the ears (cymba conchae). The stimulation frequency was 25 Hz, the pulse width was 250 microseconds, the intensity was based on the patient’s tolerance, and the duration was 20 minutes. It was given five times a week for two weeks by the research doctor based on the previous study protocol.¹³¹⁴

The clinical outcome in the form of pain intensity in both groups was assessed using the Numerical Pain Rate Scales (NPRS), which was utilized to assess respondents’ perceptions of the level of pain that they felt before and after the intervention, as indicated by the way the respondents reported pain levels with a pain scale ranging from 0 to 10 (scale 0 = no pain, scale 10 = the most intense pain imaginable).¹⁵ The participants’ demographic data were also used as secondary outcome measures. Safety and adverse events were monitored throughout the study.

Statistical Analysis

IBM SPSS Statistics 21.0 and MS-Excel 2007 are utilized for statistical analysis and calculations. To compare the NPRS pain scale before and after treatment in each group (control and treatment), a paired t-test will be carried out if the data are distributed normally, or the Wilcoxon signed rank test would be performed if the data are not distributed normally.
To compare the post-test scores and the difference in scores between the treatment and control groups, a paired t-test will be applied if the data are distributed normally. The Mann–Whitney test will be performed if the data are not distributed normally. The p-value is considered significant when p < 0.05. The effect size calculation (Cohen's d) is applied to compare the efficiency of reducing the NPRS pain scale between the intervention and control groups.

RESULTS

The characteristics of participants from both groups are displayed in Table 1. The mean age of patients in the control group comprised 44.91 ± 10.07 years old (age range 31-55 years old), while in the intervention group, it was 40.73 ± 10.68 (age range 21-55 years old). There was no significant difference in participants’ ages between the two groups (p=0.356). The average body weight of the control and intervention groups was 67.91 ± 14.80 kg (range 50-93 kg) and 67.09 ± 11.97 kg (range 52-86 kg), respectively. Similarly, no significant difference was found in participants’ BMI between the two groups (p=0.606) was found. The average body weight of the control and intervention groups comprised 166.64 ± 9.26 cm (range 144-178 cm) and 164.64 ± 8.64 cm (range 159-177 cm), respectively. No significant difference in participants’ height between the two groups (p=0.611) was found. The mean BMI of the control and intervention groups was 24.84 ± 3.63 kg/m² (range 19.4-29.68 kg/m²) and 24.92 ± 3.59 kg/m² (range 18.7-29.5 kg/m²), respectively. There was no significant difference in participants’ BMI between the two groups (p=0.961).

The NPRS score was assessed at the beginning and end of the study. Table 2 shows the total NPRS of the control and intervention groups before and after treatment. The intervention group had a pre-treatment NPRS of 5.45 ± 1.12 and a post-treatment NPRS of 1.73 ± 1.27, as shown in the table. The parametric statistical test (paired t-test) result showed that the intervention group’s total NPRS improved significantly (p < 0.001). The total NPRS of the control group before and after treatment was 5.82 ± 1.07 and 3.27 ± 1.61, respectively. The parametric statistical test (paired t-test) result showed that the intervention group’s total NPRS improved significantly (p < 0.001). The intervention group’s mean delta NPRS (i.e., receiving additional tVNS for 2 weeks (10x)) was 3.73 ± 1.67, while the control group was 2.55 ± 1.57. The independent t-test result showed no significant difference in NPRS between the two groups (p = 0.104). The intervention’s effect size was calculated using Cohen’s d for both groups. The control group’s effect size was 1.62, indicating a large effect on NPRS improvement, whereas the intervention group’s effect size was 2.22, indicating a more significant effect than the control group.

DISCUSSION

The pre-test and post-test NPRS scores exhibited a statistically significant improvement in the intervention group receiving tVNS and exercise therapy (p < 0.001). This finding is in line with the study conducted by Kutlu N et al. involving patients with chronic fibromyalgia, showing that the intervention group indicated a significant improvement as denoted by Visual Analog Scale (VAS) after receiving pain score exercise therapy with additional tVNS. tVNS is given to the tragus and concha in both ears at 10 Hz for less than 500 microseconds. The intensity was adjusted to patients’ sensory threshold for 30 minutes, and each session was performed five times a week for four weeks. The exercise therapy included stretching, body reinforcement, upper and lower extremities, and posture correction, performed five times a week for four weeks. This study demonstrated that adding tVNS to exercise therapy may significantly improve pain. An RCT on systemic lupus erythematosus with musculoskeletal pain VAS ≥ 4 and fatigue also reported the early improvement of pain using tVNS after four weeks.

Table 1. Demographic data of the control group and intervention group.

<table>
<thead>
<tr>
<th>Category</th>
<th>Control Group (n = 11)</th>
<th>Intervention group (n = 11)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (81.8)</td>
<td>8 (72.7)</td>
<td>0.611a</td>
</tr>
<tr>
<td>Female</td>
<td>2 (18.2)</td>
<td>3 (27.3)</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>44.91 ± 10.07</td>
<td>40.73 ± 10.68</td>
<td>0.356b</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>67.91 ± 14.80</td>
<td>67.09 ± 11.97</td>
<td>0.888c</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.64 ± 9.26</td>
<td>164.64 ± 8.64</td>
<td>0.606d</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.84 ± 3.63</td>
<td>24.92 ± 3.59</td>
<td>0.961e</td>
</tr>
</tbody>
</table>

Notes: Data are presented as number (percentage) and mean ± standard deviation. The p-value is based on Chi-square test and independent t-test. Significant at p-value < 0.05. Abbreviation: BMI, body mass index.

Table 2. NPRS scores of both groups (Pre- and Post-treatment).

<table>
<thead>
<tr>
<th>NPRS (score)</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>p-value</th>
<th>Effect size (Cohens’d)</th>
<th>Δ score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>5.82 ± 1.07</td>
<td>3.27 ± 1.61</td>
<td>&lt;0.001</td>
<td>1.62</td>
<td>2.55 ± 1.57</td>
</tr>
<tr>
<td>Intervention Group</td>
<td>5.45 ± 1.12</td>
<td>1.73 ± 1.27</td>
<td>&lt;0.001</td>
<td>2.22</td>
<td>3.73 ± 1.67</td>
</tr>
<tr>
<td>p-value</td>
<td>0.449a</td>
<td>0.022a</td>
<td></td>
<td>0.014b</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Data are presented as mean ± standard deviation. The p-value is based on Paired t-test and Independent T-tests. Significant at p-value < 0.05. Abbreviation: NPRS, numerical pain rating scale.
effect of tVNS on relieving pain. Eighteen participants were assigned into two groups, a stimulation group and a sham stimulation group, in which tVNS was given to cymba concha at 25 Hz, a pulse width of 50 microseconds, and at the gradually increased intensity up to 15 mA or below the sensory threshold. Each participant received stimulation for an hour per day for four weeks, and 16 of 18 patients reported significant pain relief (p = 0.04). The study in Barcelona assessed the effect of tVNS on patients with RA, and it was measured using VAS. They reported nervous pain relief after receiving tVNS for 12 weeks (p < 0.001). Tarn J et al. examined the effect of tVNS on fatigue complaints and immune responses in patients with Primary Sjögren’s Syndrome. tVNS was given using a gammaCore device, which emits a low-voltage (1 millisecond, 5 kHz) with a burst wave frequency of 25 Hz for 90 seconds. tVNS was given 2 x 90 minutes a day for 26 days. The follow-up on the 28th day found that 12 of 15 patients reported relief in fatigue complaints.

This study found that the control group that received exercise therapy twice a week and carried it out for two weeks without tVNS therapy also showed significant improvements in NPRS pain scores. It indicated that exercises consisting of breathing exercises, posture correction, stretching exercises (single knee to chest, double knee to chest, and pelvic tilt), and strengthening core muscle exercises (abdominal drawing in and cat and camel) provide benefits for non-specific chronic low back pain relief, even with early assessment. Additionally, numerous studies showed that exercise is an effective modality in reducing chronic low back pain. A previous study showed that after six weeks of the intervention with 5 to 20 minutes of aerobic exercise, followed by 5 minutes of stretching exercise, and endurance exercise of 1-3 sets of 15 repetitions, carried out three times a week; there were changes in complaints of pain that decreased by 31% (p < 0.001). As conveyed by Câmara-Gomes LF et al., exercise also has an analgesic effect of reducing pain intensity in chronic low back pain patients. Strengthening exercises, posture correction, and stretching can reduce pain by utilizing a biomechanical approach. In addition, stretching exercises will stimulate free nerve endings sensitive to mechanical stimuli. Afferent pathways transmit these stimuli with a larger caliber and conduction velocity than nociceptive afferent pathways, which subsequently modulate the pain through a gate control mechanism.

Both groups showed positive effects on the improvement of the NPRS scores. However, there was no significant difference in the improvement of the NPRS scores before and after treatment between the intervention and the control group (p-value = 0.104). Clinical improvement in the control group that received training consisting of breathing exercises, posture correction, stretching exercises (single knee to chest, double knee to chest, and pelvic tilt), and strengthening core muscle exercises (abdominal drawing in, including cat and camel) indicated that in this study, exercise provided benefits for non-specific chronic low back pain in improving the pain complaints. The results of this study provide evidence related to the effects of early exercise therapy on chronic low back pain. Previous studies examining the effects of exercise therapy on chronic low back pain generally assessed the effects of exercise therapy after prolonged exercise. Taimela S et al. researched 125 patients with chronic low back pain. The result indicated that after 12 weeks of intervention with strengthening and stretching exercises, pain complaints decreased by 50% (p < 0.0001). Additionally, the research conducted by Leggett S et al. that involved 412 patients with chronic low back pain demonstrates that after eight weeks of intervention with strengthening, endurance, and stretching exercises, there was a 50% decrease in pain complaints as measured by the SF-36 (p < 0.0001).

When using the calculation following Cohen’s D, the effect size of the intervention group was more significant (2.22) than that of the control group (1.62). It indicated that adding tVNS therapy to the exercise therapy produced better clinical responses than the exercise therapy alone. These results were in line with the results attained from the previous research carried out by Kutlu N et al. mentioning that the addition of tVNS to exercise therapy provided clinical improvement in VAS pain and showed a better quality of life in the subjects with chronic pain due to fibromyalgia, but it was not statistically significant when compared with the exercise-only group. Due to the large effect of exercise therapy in this study, it is eventually difficult to distinguish the effect of adding tVNS to exercise therapy. Hence, it is necessary to study the effect of tVNS without exercise therapy compared to exercise therapy alone.

In the study conducted by Aranow C et al., it was found that tVNS in SLE patients reduced chronic pain complaints, which was better than the control group. A research involving patients with osteoarthritis of the hand also showed similar results, in which 18 subjects received tVNS stimulation, and 16 out of the 18 patients showed a significant improvement in pain complaints (p = 0.04). Based on some literature, the best location for tVNS stimulation is unclear. In this study, the stimulation locations were concha and cymba concha, with a frequency of 25 Hz. However, some of the best-suspected locations are concha, cymba concha, and tragus. A brain imaging study indicated that 25 Hz tVNS stimulation of the inner tragus and cymba concha resulted in significantly greater activation in the nucleus tractus solitarius (NTS) and locus coeruleus (LC) compared to the control site (ear lobe). The other research demonstrated that only stimulating cymba concha resulted in stronger activation in both NTS and LC than stimulating control sites.

This study reported the early effect of tVNS in addition to exercise therapy; tVNS
given to concha and cymba concha at 25Hz, a pulse width of 250 microseconds for 20 minutes, five times a week for two weeks was capable of clinically relieving pain intensity, compared to exercise therapy alone in terms of effect size. However, it is not statistically significant. In the study by Kutlu N et al., the intervention group receiving exercise therapy and tVNS exhibited no significant improvement in pain relief and quality of life compared to the control group receiving exercise therapy alone. When assessed using SF-36, the pain relief was significantly better in the group receiving tVNS and exercise therapies than in the group receiving only exercise therapy.13 In other research, tVNS was given to subjects suffering from chronic pain in SLE. It is administered to cymba concha at a frequency of 30 Hz, 300 microseconds, for five minutes daily for four days. The results indicated that it could significantly improve patients’ VAS scores at day-by-day follow-up on the fifth day if compared to the sham stimulation scores at day-by-day follow-up on the fifth day. The results indicated that it could significantly improve patients’ VAS scores at day-by-day follow-up on the fifth day if compared to the sham stimulation group (p-value = 0.049).14,16,19,20 In the study conducted by Courties A et al., patients with hand pain due to osteoarthritis of the hand were given tVNS on the cymba concha with a frequency of 25 Hz, a pulse width of 50 microseconds, and the intensity was increased to 15 mA and given for an hour per day for four weeks. The result showed that it provided significant pain relief.17 The research by Hein E et al. indicated that giving tVNS for 15 minutes, which was held five times a day for two weeks, has provided a significant therapeutic effect.18

The limitation of this study lies in the administration of the therapy carried out with exercise therapy, precluding this study from assessing the tVNS when given alone without combining it with other therapies. The follow-up was also relatively short (one day after treatment), making it impossible to compare the long-term benefits of tVNS and exercise therapy alone in this study. Based on a tVNS review, it is still unclear which located between the cymba concha, concha, and tragus is best and what frequency is best for tVNS stimulation in pain cases. This study also did not categorize each participant’s activity level in the group, which could be confounding because activity can influence low back pain. Future studies are necessary to confirm the effect of tVNS on LBP patients, comparing the intervention group that was given tVNS to the control group that received exercise therapy alone, with long term follow-up, followed by studies comparing stimulation at various locations, frequencies, and durations, and recruiting subjects based on activity level.

CONCLUSION
Adding tVNS therapy to exercise therapy was relatively safe and exhibited a greater effect size than the exercise therapy alone. Hence, tVNS therapy could serve as an additional therapy for LBP patients to improve clinical outcomes with no side effects observed.

CONFLICTS OF INTEREST
All authors – none to declare.

FUNDING
None to declare.

ETHICAL CLEARANCE
This study was approved by the Clinical Research Ethics Committee at Dr. Soetomo Academic General Hospital No. 0411/KEPK/IV/2022.

AUTHORS’ CONTRIBUTIONS
All authors contributed equally to this manuscript. The final manuscript was read and approved by all authors.

REFERENCES


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