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ORIGINAL RESEARCH **PAIN MANAGEMENT**

Effect of transcutaneous auricular vagus nerve stimulation in addition to exercises on disability in chronic low back pain patients: a randomized controlled study

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Abstract

Background & objective: Low back pain is a common problem, especially in the young and middle-aged working people, and is often very resistant to the conventional management. We evaluated the impact of transcutaneous auricular vagus nerve stimulation (tVNS), applied in conjunction with an exercise treatment program, on disability in chronic low back pain patients.

Methodology: The study was conducted from June to October 2022. Twenty-two patients aged 42.18 ± 9.91 y, with Numerical Pain Rating Scale (NPRS) score 5.64 ± 1.09 and Roland Morris Disability Questionnaire (RMDQ) score 10 ± 4.670, were randomly assigned to two groups. The control group received only exercise therapy (EXC group, n = 11), and the intervention group received exercise and tVNS therapy (EXC + tVNS group, n = 11). The primary outcome was RMDQ, measured before and after the intervention.

Result: The mean RMDQ was significantly improved in both groups. In the intervention group the improvement was from 9.45 ± 4.44 to 2.18 ± 2.71 (P = 0.000), in the control group it was from 10.55 ± 5.05 to 2.36 ± 2.06 (P = 0.001). Inter-group comparison showed no significant difference. The effect size of the control group (2.12) was similar with the intervention group (1.98).

Conclusion: Addition of 2-weeks tVNS to exercise therapy did not show superior effect on disability improvement compared to exercise only in chronic low back pain. Exercise alone was sufficient to improve the mean RMDQ.

Abbreviations: CLBP: Chronic low back pain; EXC: Exercise; tVNS: Transcutaneous auricular vagus nerve stimulation; NPRS: Numerical pain rating scale; RMDQ: Roland Morris disability questionnaire

Key words: Chronic low back pain; Disability; Exercise; Transcutaneous Auricular Vagus Nerve Stimulation

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1. Introduction

Chronic low back pain (CLBP), typically lasting for at least 12 weeks, is a crucial health problem that can impact functional capacity by limiting work activities. CLBP impacts economic status due to increased health costs and decreased productivity. The prevalence is higher in women (8.01%) than men (6.94%), and it increases with the increasing age (peak age 80-89 y). CLBP is also caused years lived with disability (YLDs) with an increase in prevalence from 42.5% in 1990 to 52.7% in 2017.[1,2] It has a big impact on both individuals as well as the society.[3] Activities of daily life (ADL) vary from basic to complex activities that allow independent living. LBP can cause disability, impaired function, reduced work productivity, a high rate of need for therapy in health facilities, and reduced quality of life.[4]

Roland Morris Disability Questionnaire (RMDQ) is a tool to measure a change in the degree of disability in LBP patients.[5] This questionnaire has a high test-retest reliability correlation and it is recommended as a questionnaire to assess function in LBP.[6] RMDQ consists of 24 yes/no statements that relate specifically to physical functioning to assess disability in patients with CLBP, the higher the score achieved, the greater the level of disability.[7]

Chronic pain management is best managed with a bio-psycho-social approach and therapy. Patients should receive information about the goals and effectiveness of exercise therapy in LBP and be advised to stay active.[8] Exercise can provide anti-inflammatory effects, improve immune function and control the level of inflammatory mediators.[9] The exercise has positive results, including reduced pain, increased function, and reduced time off. The most effective exercise is individually prescribed stretching and strengthening, done under supervision and compliance.[10]

Transcutaneous auricular vagus nerve stimulation is one of the modalities that is currently being developed and has been introduced for chronic pain. The benefits of this treatment have been confirmed in fibromyalgia and migraine.[11] Several studies involving epilepsy and depressed patients reported that their pain was relieved after receiving tVNS.[12] Auricular branch vagus nerve (ABVN) located in the conchae, cymba conchae, and tragus is the site of stimulation with the recommended frequency between 20−30 Hz according to Food and Drug Administration (FDA) and several groups have showed the safety and tolerability over the last decade.[13] The mechanism of tVNS in reducing chronic pain consist of pain-modulating effect on serotonergic and noradrenergic pathways, as indicated by activities in locus coeruleus and nucleus raphe in functional magnetic resonance imaging (fMRI). The anti-inflammatory effect of tVNS was found through the hypothalamus-pituitary-adrenal (HPA) axis, an anti-inflammatory cholinergic mechanism that is responsible for inhibiting pain at the peripheral level, that affects central and peripheral sensitization through TNF-α mechanism, and plays a role in the limbic area that influences psychological factor.[14]

We evaluated the impact of tVNS to exercise therapy on disability status in patients with CLBP. This study was design to test whether addition of tVNS to exercise therapy could reduce disability status better than exercise therapy alone in CLBP patients.

2. Methodology

A total of 22 CLBP patients who were under outpatient therapy since July 2021, were recruited from the medical rehabilitation polyclinic of Dr. Soetomo General Hospital, Surabaya, Indonesia. The inclusion criteria included age 18−55 y, diagnosed with chronic non-organic mechanical LBP for 3 months to 1 y, without

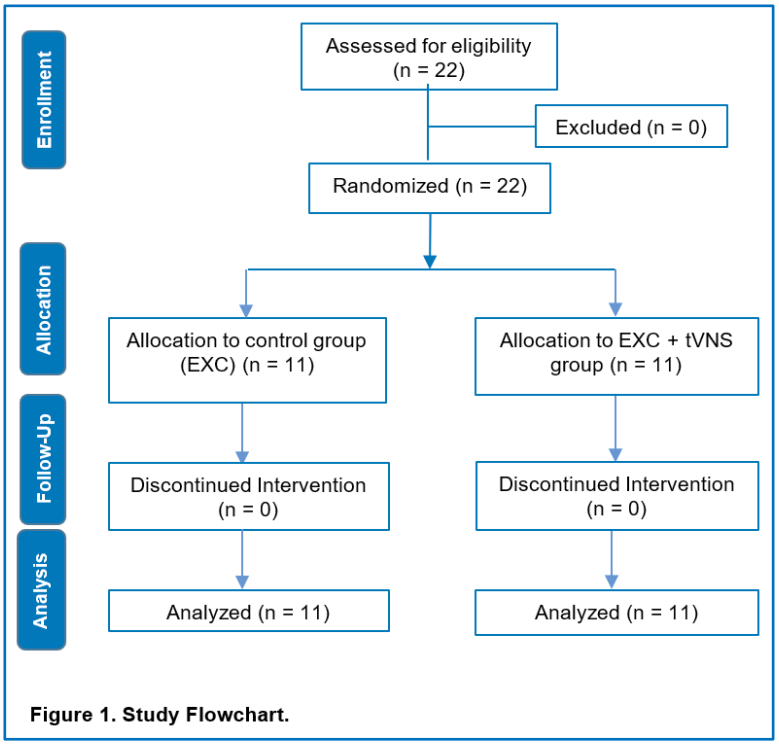

Figure 1. Study Flowchart.

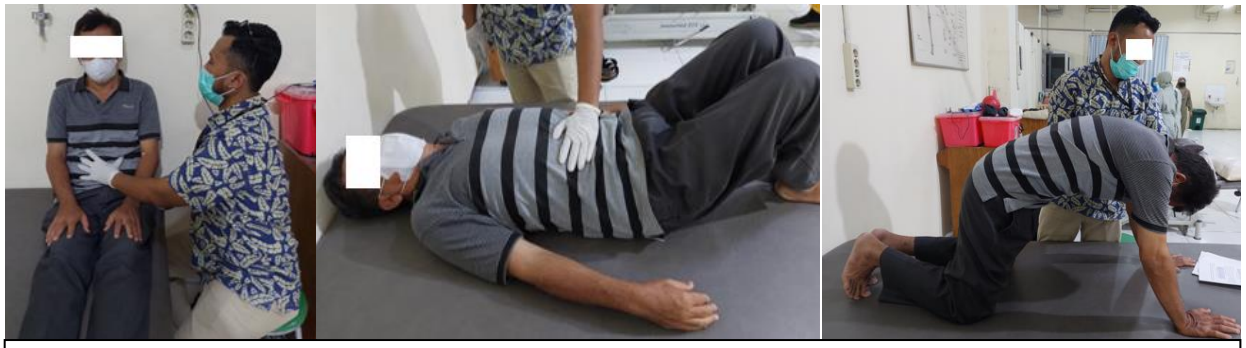

Figure 2: Participants doing exercise led by physiotherapist

showing signs of red flags, the NPRS pain score 4–7, and able to understand instructions. The exclusion criteria were a history of taking analgesics except for paracetamol and NSAIDs, the consumption of a new analgesic in the past 2 weeks, the use of other modalities in the last 1 week, history trauma or skin disorders, history of face pain, the use of metal implants including pacemakers, pregnancy, history of heart disease (e.g., dysrhythmia, arrhythmia, coronary heart disease), history of neurological disorders (including seizures or epilepsy), history of moderate-severe depression (Hamilton Depression Rating Scale ≥ 17), history of vasovagal syncope, history of metal allergy to skin, alcohol and drug dependence, and obesity grade II (BMI ≥ 30 kg/m^2). Twenty-two patients (17 male and 5 female) aged 42.2 ± 9.9 y old met the inclusion criteria. This study used non-probability consecutive sampling to recruit the sample in which all research subjects who met the inclusion criteria were included until the number of subjects was fulfilled.

Figure 3: Participants receiving tVNS on the left ear (cymba conchae and conchae)

Ethical committee approval was obtained from The Ethical Committee in Health Research, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (No. 0411/KEPK/IV/2022). Written verbal informed consents were obtained from all participants.

Table 2 summarizes the general characteristics of the participants. This was a truly experimental, pre and post-test randomized control trial. The subjects were randomized using sample randomization using a lottery method to the intervention group (exercise therapy and tVNS, n = 11) and the control group (exercise therapy, n = 11). After two weeks, all participants completed therapy without any drop-out. The data collection was taken before and 24 h after 2 weeks of intervention. The study flow chart is given in Figure 1.

2.1. Exercise Therapy

Both groups received exercise therapy according to the LBP exercise principles, e.g., kinesthetic awareness, mobility/flexibility, and muscle performance,[15] and based on the American College of Sports Medicine (ACSM) Guidelines,[16] as explained in Table 2. Exercises were done two days a week for two weeks, led by a physiotherapist (Figure 2).

2.2. Transcutaneous Auricular Vagus Nerve Stimulation (tVNS)

The intervention group (EXC + tVNS) received additional tVNS therapy, which was administered transcutaneously via ABVN using a transcutaneous electrical nerve stimulation (TENS) Myomed 632® device with special electrodes placed on the skin of the left ears (cymba conchae and conchae) (Figure 3). The frequency of stimulation was 25 Hz, the pulse width was 250 μs, the intensity as the patient's tolerance, and the duration was 20 min.[17,18] It was given five times a week for two weeks based on the previous study protocol. The participants were checked and monitored for complaints and vital signs before, during, immediately after, and 30 min after stimulation (Figure 3).

Table 1: **Baseline characteristics of the participants**

Variable	EXC + tVNS group (n = 11) Means ± SD	P-value (Normality)	EXC group (n = 11) Means ± SD	P-value (Normality)	P-value (Homogeneity)
Age (y)	40.55 ± 10.73	0.936	43.82 ± 9.23	0.687	0.657
Sex	M = 8 (72.7%) F = 3 (27.3%)		M = 9 (81.8%) F = 2 (18.2%		0.336
Body Height (cm)	164.64 ± 8.64	0.975	166.64 ± 9.27	0.437	0.670
Body Weight (kg)	67.09 ± 11.97	0.878	67.91 ± 14.80	0.666	0.161
BMI (kg/m^2)	24.92 ± 3.59	0.929	24.85 ± 3.63	0.885	0.652
NPRS	5.45 ± 1.13	0.242	5.82 ± 1.08	0.246	0.615
HDRS	4.45 ± 3.86	0.368	4.45 ± 3.67	0.309	0.935
RMDQ	9.45 ± 4.44	0.885	10.55 ± 5.05	0.814	0.629

BMI, Body Mass Index. NPRS, Numerical Pain Rating Scale. RMDQ, Roland Morris Disability Questionnaire. Significant if P < 0.05

2.3. Roland Morris Disability Questionnaire (RMDQ)

Assessment of functional status with questionnaires is important for research and clinical purpose. The most widely used instruments to measure disability is the Oswestry Disability Index (ODI), the Roland Morris Disability Questionnaire (RMDQ), and the Quebec Back Pain Disability Scale (QDS).[19] The RMDQ is a self-administered disability measure consisting of 24 yes/no statements that relate specifically to physical functioning to assess disability in patients with CLBP.[20] This questionnaire is a commonly used measure and performs well as a measure of physical functioning in CLBP.[21] The higher numbers on a 24-point scale indicate the higher levels of disability.[20]

2.4. Statistical Analysis

IBM SPSS Statistics 25 is utilized for statistical analysis and calculations. To compare the RMDQ before and after treatment in each group (control and treatment), a paired t-test was carried out if the datas were distributed normally, or the Wilcoxon signed rank test was performed if the datas were not distributed normally. To compare the post-test scores and the difference in scores between the intervention and control groups, an independent sample t-test was applied if the datas were distributed normally, or the Mann-Whitney test was performed if the datas were not distributed normally. To compare the pre and post-test of each RMDQ item we used non-parametric test (Wilcoxon signed rank test). The P-value was considered significant when $P < 0.05$. The calculation of the effect size (Cohen's d) was applied to compare the efficiency of reducing the RMDQ between the intervention and control groups.

3. Results

The study sample comprised 22 participants, 11 participants in the control group (EXC) and 11 participants in the intervention group (EXC + tVNS). All variables showed approximately normal distribution, including age, sex, body weight, height, BMI, NPRS, HDRS, and RMDQ. There were no significant differences between any variables between the control and intervention groups ($P > 0.05$).

The RMDQ scores between the intervention and control groups before and after therapy are described in Table 3. The baseline and post-test scores in the intervention group were 9.45 ± 4.44 and 2.18 ± 2.71 respectively. There was a significant reduction in RMDQ scores before and after therapy in the intervention group ($P = 0.000$).

The baseline and post-test scores in the control group were 10.55 ± 5.05 and 2.36 ± 2.06 respectively. There was a significantly reduces in RMDQ scores before and after therapy in the control group ($P = 0.001$).

The therapeutic effect size was calculated using Cohen's d for both groups. The intervention's effect size was 1.98 and the control's effect size was 2.12. This result indicates that both groups had a large influence on the reduction of the RMDQ score. There were no differences in RMDQ scores between the intervention and control group after therapy ($P = 0.861$). The delta RMDQ scores (Δ RMDQ) in the intervention group and control group were 7.27 ± 4.36 vs. 8.18 ± 5.42 ($P = 0.669$) respectively. There was no significant difference in Δ RMDQ scores between the intervention and control groups.

Table 2: Exercise therapy protocol

Exercise	Position	Frequency (times/wk)	Repetition (times)	Time (sec)	Set	Procedure
Breathing exercise with diaphragmatic breathing	Semi-Fowler sitting	2	4	8	1	Relaxed and comfortable position. Shoulder shrug and relaxation positions. The therapist's hand is placed on rectus abdominal muscle. Inhale slowly through the nose. Shoulder and upper chest relaxed, abdomen slightly raised. Exhale slowly through the mouth
Posture Correction (Kinesthetic awareness)	Standing position	2	4	15	1	Stand up straight with center of gravity fell just anterior atlanto-occipital. Gravity line passes through cervical and lumbar vertebra, hip joint, anterior knee joint, and anterior ankle joint.
Abdominal drawing-in (Muscle performance)	Supine position with knee flexion. Soles of feet touch the floor	2	8	8	2	Neutral spine position. Breath-in and breath-out. Gently pull the navel toward the spine and hold.
Cat and camel (Muscle performance)	Quadruped position	2	8	8	2	Inhale with arching through the spine as a camel hump. Exhale with sink the back down towards the floor and head up.
Pelvic tilt (Mobility/flexibility)	Supine position with knee flexion. Soles of feet touch the floor	2	4	15	1	Press the lower back so it's flat on the floor. This movement is combined with contracting the abdominal and gluteus muscles.
Single knee to chest (Mobility/flexibility)	Supine position with knee flexion. Soles of feet touch the floor	2	4	15	1	Pull one of knee up to touch the chest as far as possible. At the same time, lift the head and shoulders off the floor
Double knee to chest (Mobility/flexibility)	Supine position with knee flexion. Soles of feet touch the floor	2	4	15	1	Pull both of knee up to touch the chest as far as possible. At the same time, lift the head and shoulders off the floor

4. Discussion

This is one of the few studies to report that exercise therapy with or without stimulation of the vagus nerve (tVNS) reduces disability status in CLBP patients. Thefindings of this study found no significant difference was found between control and intervention groups. The tVNS had no superior effects when added to the exercise

Table 3: RMDQ scores of both groups (Baseline, Post-test, and Effect size)

Group	Baseline	Post-test	P-value	Effect Size (Cohens'd)
EXC + tVNS group	9.45 ± 4.44	2.18 ± 2.71	0.000	1.98
EXC group	10.55 ± 5.05	2.36 ± 2.06	0.001	2.12

Values are presented as mean ± standard deviation. Significant if P < 0.05

therapy.

The study conducted by Monticone et al. (2012) on 179 CLBP patients who attended rehabilitation for 8 weeks showed that RMDQ has a moderate correlation to pain intensity which is measured by NPRS.[22] Recent systematic reviews found that exercise therapy reduced pain-related disability in adults with chronic non-specific LBP.[23] Moreover, the previous studies have shown the clinical effectiveness of tVNS on musculoskeletal pain in systemic lupus erythematosus (SLE) patients and hand osteoarthritis, respectively.[24,25] There are not many studies on the effect of combined exercise therapy and tVNS on pain and quality of life. A previous study found that combining exercise therapy and tVNS with 30 min of stimulation, pulse duration <500 ms, frequency 10 Hz and intensity as patient tolerance can decrease pain and improve quality of life in fibromyalgia patients, but there was no significant difference when compared to exercise alone.[18] This result is in accordance with our study in CLBP that showed tVNS had no additional effects over exercise therapy in patients with CLBP.

Exerciseherapy has been the most effective management for disability status in patients with CLBP. It has a positive effect on intensity of pain, improved function, and reduced sick leave. However, it is still unclear if one type of exercise is superior to others (the amount, frequency, and ideal length of exercise) to treat back pain.[10] Physical exercise, especially back muscle strengthening, is clinically recommended to help reduce pain.[27] The following components of physical function such as kinesthetic awareness, mobility/flexibility, and muscle performance are used in all intervention programs for spinal problems. Kinesthetic awareness can develop an awareness of safe spinal positions and spinal movements in all spine position (supine, prone, side-lying, sitting, and standing). It creates awareness regarding which postures make the symptoms better or worse, and identifying the neutral spinal position or position in helping patients manage their symptoms. Mobility/flexibility include stretching and flexibility exercise used to increase the mobility of restricting tissues. Muscle performance involves strength, power, endurance, and stability. Activation of deep segmental muscles as well as the superficial/global multi-segmental muscles of the neck and trunk are fundamental techniques for developing spinal stability. Besides flexibility and strengthening exercise, the exercise protocol also includes breathing exercise. Breathing exercise with diaphragmatic breathing has the benefit to increase ventilation, relaxation, relieving stress, teaching the patient how to deal with pain, improving functional capacity for exercise, daily activities and work and improving the strength of the diaphragm muscles.[15,28]

Participants in the EXC and EXC + tVNS groups complete exercise protocol for CLBP (diaphragmatic breathing, posture correction, abdominal drawing-in, cat and camel, pelvic tilt, and single-double knee to chest) 2 times/week for 2 weeks. This protocol were designed to meet the American College of Sports Medicine guidelines.[16] Overall, the reduction of disability status observed in this study could be because of the appropriate exercise program. The results of this study provide evidence related to the effects of starting early exercise therapy in CLBP patients. Previous studies examining the effects of exercise therapy on CLBP generally assessed the effects of exercise therapy after prolonged exercise. Waseem et al., compared the work-out effect of the core muscle and routine physical therapy exercise for the treatment of CLBP. A significant reduction in disability was observed in both groups after 6 weeks of treatment ($P < 0.05$).[29] Additionally, the research conducted by Saner et al., that involved 106 patients with CLBP demonstrates that after nine to twelve weeks of exercise (30 min/day, 2 times/week), there was an improvement of patient-specific functional scale (PSFS) and reduced RMDQ score ($P < 0.001$).[30] Exercise therapy promotes a range of positive health changes, such as reduction in chronic low-grade inflammations, both systemic and local, and decreasing risk of developing obesity.[31,32] Regular exercise may be considered a form of non-pharmacological treatment for obesity, LBP, and other chronic diseases.[33]

Clinical studies have shown that tVNS may contribute to modulating pain through a neural pathway via the nucleus tractus solitarius (NTS) and the area postrema. Visceral information is sent to areas of the forebrain (hypothalamus, amygdala, and cortex).[34] Transcutaneous auricular vagus nerve stimulation also increases activity in the locus coeruleus and the raphe nuclei and moderates the downstream release of norepinephrine and serotonin.[12] The vagus nerve has an anti-inflammatory role via the HPA axis activation through vagal afferent fibers and an anti-inflammatory role through a cholinergic anti-inflammatory pathway.[34,35] The tVNS also has a mechanism which can contribute to the regulation of mood and anxiety through stimulation in the limbic system.[12] This mechanism is needed as a psychological approach in patients with chronic pain.[10]

Both groups showed positive effects on the reduction of the RMDQ scores ($P = 0.000$ and $P = 0.001$). However, there was no significant difference in the RMDQ scores before and after treatment. There are several studies that show a positive effect of tVNS on pain. There was a significant reduction in NPRS score after 1 week of stimulation ($P < 0.001$), after 2 weeks of stimulation ($P < 0.001$), and after 3 weeks of stimulation ($P < 0.001$).[26]

A study was conducted by Courties et al. about the effect of tVNS on hand osteoarthritis. Eighteen patients who fulfilled the American College of Rheumatology (ACR) criteria of hand osteoarthritis received tVNS located in cymba conchae, 1 h/day at 25 Hz, intensity increased gradually with patient tolerance, and pulse width 50 μs for 4 weeks. There was a significant reduction of visual analog scale (VAS) in 16 of 18 patients ($P = 0.001$).[26] Barbanti et al., investigated the administration of non-invasive VNS (nVNS) as acute therapy on high frequency and chronic migraine. Fifty patients were instructed to use nVNS independently if there was a migraine attack 3 times in two weeks. The stimulation was 2 times 120 sec with 3 min interval in the cervical branch vagus nerve after 20 min onset of pain. VAS scores reduced 56% after 1 h of stimulation and 64.6% after 2 h of stimulation.[36] Different study results were shown by Laqua et al. Fifteen of 21 participants showed an increased pain threshold during stimulation ($P < 0.01$), while 6 participants showed a decreased pain threshold during stimulation ($P < 0.05$). Although the results are contradictory, it supports that tVNS can provide an analgesic effect that is highly dependent on individual sensitivity to stimulation parameters.[37]

When using the calculation following Cohen's D, the effect size of the intervention group (EXC + tVNS) was similar (1.98) to the control group (2.12). Due to the large effect of exercise therapy in this study, it is eventually difficult to distinguish the effect of the addition of the tVNS to exercise therapy. Hence, it is necessary to study the effect of the tVNS without exercise therapy compared to exercise therapy alone. Based on some literature, the best location for tVNS stimulation is not clearly defined. In the present study, the stimulation locations were concha and cymba concha, with a frequency of 25 Hz. Some of the best-suspected locations are concha, cymba concha, and tragus. A brain imaging study indicated that 25 Hz tVNS of the cymba concha and inner tragus resulted in greater activation in the nucleus tractus solitarius (NTS) and locus coeruleus (LC) compared to the control site (ear lobe). The other research demonstrated that stimulating cymba concha resulted in stronger activation in both NTS and LC than stimulating control sites.[38]

tVNS might be associated with some side effects such as skin rashes at the site of stimulation, headache, sore throat, coughing, hoarseness, and decrease in heart rate until fainting. In the present study, none of our patients developed any side effects. This may be because the frequency of the stimulation was recommended by the food and drug administration (FDA).

5. Limitation

Here are some limitations to the current study. First, both group had had exercise therapy, so the effects of the tVNS alone could not be assessed. Second, the follow-up was also relatively short (one day after treatment), making it impossible to compare the long-term benefits of tVNS, in addition, to exercise therapy alone in this study. Based on a tVNS review, it is still unclear which site and what frequency is best for the tVNS stimulation in pain cases. This study also did not categorize each participant's activity level in the group, which could be a distracting factor because activity can influence low back pain.

6. Conclusion

Addition of 2-weeks tVNS to exercise therapy did not show superior effect on disability improvement compare to exercise alone in chronic low back pain. Transcutaneous auricular vagus nerve stimulation can be used as additional treatment for chronic low back pain. Consideration of patient selection and care should be taken as mentioned in our study.

7. Future Scope

This is the first study in Indonesia to demonstrate that exercise therapy with or without stimulation of the vagus nerve (tVNS) reduces disability status in chronic low back pain. Future studies are necessary to confirm the effect of tVNS alone compared to exercise therapy on CLBP patients. Studies with long-term follow-up, with stimulation modifications at various locations, frequencies, and durations, and recruiting subjects based on activity level are also needed to further explore the beneficial effect of tVNS.

8. Data availability

The numerical data generated in this trial is available with the authors.

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10. Conflicts of interest

All authors have no conflict of interest to declare

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