Efficacy and safety of electroacupuncture through nerve stimulation in patients with anxiety disorders: A protocol for a randomized, assessor-blind, three-arm, parallel-group clinical trial

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Abstract

Background: Anxiety disorders are among the most common mental health disorders, affecting a significant portion of the population. However, conventional treatments, such as pharmacotherapy and psychotherapy, often have limited effectiveness and may lead to undesirable side effects. Consequently, there is a growing demand for new alternative treatments for anxiety disorders. Recent studies suggest that electroacupuncture (EA) may demonstrate therapeutic effects in managing anxiety by mediating nerve stimulation.

Objective: This study is designed to assess the efficacy and safety of EA in treating anxiety disorders through nerve stimulation. Specifically, it will involve stimulating the median nerve at the PC6 acupoint (Neiguan) and the vagus nerve at the TF4 acupoint (Shenmen of ear acupuncture).

Methods: This study is a randomized, assessor-blind, three-arm, parallel-group clinical trial comprising the PC6 EA group, TF4 EA group, and a control group. Participants will include patients diagnosed with social anxiety disorder, panic disorder, agoraphobia, and generalized anxiety disorder. Eligible participants will be randomly assigned to one of the three groups, with each group containing 20 individuals. The EA groups will receive treatments at the designated acupoints twice weekly for eight weeks, totaling 16 sessions. The control group will receive usual care without any treatment interventions through the end of the study period. The primary outcome is the comparison of Hamilton Anxiety Rating Scale scores between the treatment groups and the control group. Secondary outcomes include scores on the Hamilton Anxiety Rating Scale, Beck Anxiety Inventory, Beck Depression Inventory-II, Patient Health Questionnaire-15, World Health Organization Quality of Life Assessment Instrument abbreviated version, Penn State Worry Questionnaire, Panic Disorder Severity Scale, and Liebowitz Social Anxiety Scale. Safety evaluation variables include the frequency of adverse events, vital signs, and suicide risk assessment. Exploratory variables include the Emotional Reactivity Test, Empathy Quotient, and Heart Rate Variability.

Results: The first participant was enrolled on December 15, 2022. As of October 2024, a total of 60 participants have been fully registered, and the intervention is currently in progress. We expect the completion of this trial to occur within the year 2025.

Conclusions: In this study, we will evaluate the safety and efficacy of electroacupuncture for anxiety disorders. By elucidating the therapeutic mechanisms of EA through nerve stimulation, this study will provide clinical evidences to support the development of potential intervention for patients with anxiety disorders. Clinical Trial: Trial registration number: KCT0008378 (Registered in Clinical Research Information Service of the Republic of Korea, https://cris.nih.go.kr/cris/search/detailSearch.do/24503)

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ABSTRACT

Background: Anxiety disorders are among the most common mental health disorders, affecting a significant portion of the population. However, conventional treatments, such as pharmacotherapy and psychotherapy, often have limited effectiveness and may lead to undesirable side effects. Consequently, there is a growing demand for new alternative treatments for anxiety disorders. Recent studies suggest that electroacupuncture (EA) may demonstrate therapeutic effects in managing anxiety by mediating nerve stimulation.

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Trial Registration: Trial registration number: KCT0008378 (Registered in Clinical Research Information Service of the Republic of Korea, https://cris.nih.go.kr/cris/search/detailSearch.do/24503)
Keywords: anxiety disorders; electroacupuncture; nerve stimulation; vagus nerve; median nerve;

Introduction

Anxiety disorders are defined as mental health conditions that are characterized by a set of symptoms, including excessive fear, anxiety, and related behavioral disturbances [1]. Anxiety disorders represent a significant proportion of mental health conditions, affecting an estimated 301 million people worldwide as of 2019 [2]. The prevalence of anxiety disorders is increasing due to factors such as an aging population, urbanization, and socioeconomic development [3]. These disorders not only result in substantial socioeconomic but also pose a threat to the ongoing growth and productivity of societies [4]. Therefore, the treatment and management of anxiety disorders are becoming increasingly important.

Treatment for anxiety disorders has been found to be effective with pharmacotherapy such as antidepressants and benzodiazepines [5], and psychotherapies like cognitive-behavioral therapy (CBT) and eye movement desensitization and reprocessing (EMDR) are also used [6, 7]. However, pharmacotherapy raises concerns due to side effects and resistance [8, 9], and is often met with negative perceptions by patients regarding psychiatric medications [10]. Additionally, although psychotherapy is generally effective, it is not always cost-effective nor consistently successful [11,12]. Thus, there is a need for treatments that are both cost-effective and associated with fewer adverse effects.

Recent studies suggest that acupuncture and electroacupuncture are effective treatments for anxiety disorders with fewer adverse effects compared to conventional pharmacotherapy [13]. Consequently, both acupuncture and electroacupuncture are being recommended as alternative methods for the chronic management and long-term treatment of anxiety disorders [14].

This study aims to assess the efficacy and safety of electroacupuncture treatment for anxiety disorders, with a particular focus on treatments at acupoints PC6 (Neiguan) and TF4 (Shenmen of ear acupuncture), compared with a control group.

Methods

Study design

This study is designed as a randomized, three arm assessor-blinded, parallel-group clinical trial, will be conducted at the Daejeon Korean Medicine Hospital of Daejeon University, Republic of Korea. It aims to evaluate the efficacy and safety of two distinct electroacupuncture interventions in the treatment anxiety disorders, in comparison to usual care. The interventions specifically target to stimulate the median nerve via acupoint PC6 and the vagus nerve via acupoint TF4. The control group, constituting usual care, will not receive any treatment.

To ensure the rigor and validity of our findings, this study protocol (version 1.4, June 2023) adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.

Study procedure

During the initial screening visit, potential participants will receive a comprehensive explanation of the study's purpose, procedures, risks, and benefits and will be asked to provide written consent. Those who voluntarily consent and meet the inclusion and exclusion criteria—as determined through demographic information surveys, medical and medication history reviews, vital signs measurements (blood pressure, pulse, temperature), laboratory tests, pregnancy tests, the Structured Clinical Interview for DSM-5 (SCID-5), and the Columbia Suicide Severity Rating Scale (C-SSRS) assessments—may be enrolled in this study. The SCID-5 will be used to diagnose subtypes of

anxiety disorders, including social anxiety disorder, panic disorder, agoraphobia, generalized anxiety disorder, and other specified anxiety disorders. Participants who do not meet the diagnostic criteria for an anxiety disorder as per the SCID-5 will be excluded from the study. The C-SSRS will be used to assess the risk of suicide; participants scoring 4 or above, indicating a high risk of suicide, will also be excluded from study selection.

Following registration, subjects will be randomly assigned to one of three groups: the electroacupuncture-vagus nerve stimulation (EA-VNS) group, the electroacupuncture-median nerve stimulation (EA-MNS) group, or the usual care group. Participants in the treatment groups will undergo electroacupuncture sessions twice weekly for a total of 16 sessions over eight weeks. Conversely, the usual care group will not receive any interventions during this period.

The evaluation of the treatment group is scheduled to occur at the initial, eighth, and final visits. For the control group, assessments will be conducted in the first, fourth, and eighth weeks. During the initial and final assessments for the treatment group, and the first and eighth weeks for the control group, the following instruments will be administered: Hamilton Anxiety Rating Scale (HAM-A), Beck Anxiety Inventory (BAI), Beck Depression Inventory-II (BDI-II), Patient Health Questionnaire-15 (PHQ-15), World Health Organization Quality of Life Assessment Instrument abbreviated version (WHOQOL-BREF), Liebowitz Social Anxiety Scale-Self Report (LSAS-SR), The Panic Disorder Severity Scale (PDSS), and Penn State Worry Questionnaire (PSWQ). LSAS-SR will be conducted only for patients with social anxiety disorder, PDSS only for those with panic disorder or agoraphobia, and PSWQ only for those with generalized anxiety disorder. A mid-point evaluation using the HAM-A and BAI will be conducted during the eighth visit for the treatment group or in the fourth week for the control group. The detailed schedules are described in Table 1 and the study flow is presented in Figure 1.

Table 1. Timeline of trial

Period	Screening	Treatment				
Assessment		Baseline		Mid-term		Final
Week	Week -1	Week 0	Week 1~4	Week 4	Week 5~8	Week 8
Visit		Visit 1[a]	Visit 2~7[b,c]	Visit 8	Visit 9~15†‡	Visit 16
Consent	●					
Demographic information	●					
Medical history	●	●	◎	●	◎	●
Physical examination	●					
Vital signs	●	●	◎	●	◎	●

Body Weight & Height	●					●
Laboratory test[d]	●					
Pregnancy test[e]	●					
SCID-5	●					
C-SSRS	●					●
Inclusion/ Exclusion criteria	●					
Randomization		●				
Item	HAM-A, BAI		●		●	●
	PHQ-15, BDI-II		●			
	WHOQO L-BREF		●			●
	PSWQ, PDSS, LSAS-SR[f]		●			●
	EQ, PSS		●			●
Emotional Reactivity test			●			●
Check concomitant drugs			●	◎	●	◎	●
Check Adverse effects			●	◎	●	◎	●
EA-MNS, EA-VNS[g]			◎	◎	◎	◎	◎
HRV			●		●		●
Education of visit schedule	●	●	◎	●	◎		

SCID-5: Structured Clinical Interview for DSM-5, C-SSRS: Columbia Suicide Severity Rating Scale, HAM-A: Hamilton Anxiety Rating Scale, BAI: Beck Anxiety Inventory, PHQ-15: Patient Health Questionnaire-15, BDI-II:Beck Depression Inventory-II, WHOQOL-BREF: World Health Organization Quality of Life Assessment Instrument abbreviated version, PSWQ: Penn State Worry Questionnaire, PDSS: The Panic Disorder Severity Scale, LSAS-SR: Lievowitz Social Anxiety Scale-Self Report, EQ: Empathy Quotient, PSS: Perceived Stress Scale, EA-MNS: Eleactroacupuncture treatment for PC6 (Neiguan), EA-VNS: Electroacupuncture treatment for TF4 (Shenmen of ear acupuncture), HRV: Heart Rate Variability

[a]Visit 1 is scheduled to occur within 10 days of screening.

[b]Visits 2~7 are implemented 4 times within 2 weeks + 2 days from visit 1. Similarly, visits 9~ 15 are implemented 4 times within 2 weeks + 2 days after visit 8. Electroacupuncture treatments are typically scheduled twice a week, but once to three visits per week are permitted.

[c]Only the experimental group follows this schedule.

[d]Lab test items are as follows: complete blood cell count (red blood cell, white blood cell, hemoglobin, hematocrit, platelet, erythrocyte sedimentation rate, white blood cell differential count), blood chemistry test (aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, hemoglobin A1c), thyroid function test (triiodothyronine, free thyroxine, thyroid stimulating hormone), pregnancy test (urine human chorionic gonadotropin, applicable only to fertile women).

[e]A pregnancy test is only performed for fertile women who have had a menstrual period within the last year.

[f]PSWQ: for generalized anxiety disorder and other anxiety disorders. PDSS: for panic disorder and agoraphobia, LSAS-SR: for social anxiety disorder.

[g]Electroacupuncture treatment will be conducted according to each group.

Study populations

Inclusion criteria

1) Aged 19 to 70 years.
2) Diagnosed with an anxiety disorder including social anxiety disorder, panic disorder, agoraphobia, generalized anxiety disorder, other specified anxiety disorders, and unspecified anxiety disorder as assessed through the Structured Clinical Interview for DSM-5 (SCID-5).
3) Voluntarily decided to participate in this study and signed the written consent form.
4) Able to complete electroacupuncture-neural stimulation treatments over 8 weeks.

Exclusion criteria

1) At high risk of suicide as assessed by the Columbia-Suicide Severity Rating Scale with a score of 4 or more.
2) With a history of schizophrenia or bipolar disorder.
3) Diagnosed with separation anxiety disorder, selective mutism, substance-induced anxiety disorder, anxiety disorder due to medication, or anxiety disorder due to other medical conditions.
4) Received acupuncture treatment within last 4 weeks.
5) With a history of alcohol or other substance use disorders within the last 8 weeks.
6) With a history of cerebrovascular disease, brain tumor, or traumatic brain injury.
7) With a history of neurological or systemic disease that may affect central nervous system.
8) In medical conditions requiring inpatient treatment.
9) Usage of a pacemaker.
10) With contraindications to acupuncture treatment (e.g., acupuncture-associated vasovagal response or tissue damage due to acupuncture).
11) Taken medication or participated in another clinical trial within the last month.
12) Pregnant or lactating women, or those not using medically acceptable methods of

contraception during the study period.

13) Deemed inappropriate for enrollment due to other reasons as determined by the investigators.

Interventions

In this study, electroacupuncture treatments will be administered by qualified Korean medical doctors with at least one year of clinical experience. Subjects assigned to the electroacupuncture treatment groups will receive treatments twice a week, with a total of 16 sessions over an 8-week period. Each session will last 20 minutes. For EA-MNS group, the needle will be inserted at PC6, while for EA-VNS group, the needle will be inserted at TF4.

The needles will be stimulated using an electroacupuncture stimulator (model STN-110, Streatek Co., Ltd., Anyang, Korea). For the electroacupuncture-median nerve stimulating group, needles will be inserted at PC6 and at a non-acupoint approximately 0.5 cm proximal to PC6 on the right arm. Subsequently, the hook-shaped or magnetic output terminal of the electroacupuncture stimulator will be attached to administer electrical stimulation. The electrical stimulation for EA-MNS will be conducted at 12 Hz for 20 minutes. For the electroacupuncture-vagus nerve stimulating group, needles will be inserted at TF4 and at a non-acupoint surrounding 0.7 to 1.0 cm away from TF4 on the right ear. The method of attaching the electroacupuncture stimulator is the same as for the EA-MNS group. The electrical stimulation for EA-VNS will be conducted at 100 Hz for 20 minutes. In both groups, the intensity of the electrical stimulation (in mA) will be set to a level that the subject reports as a 4 to 5 on a scale from 0 to 10. The Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) for acupuncture treatment is described in Table 2.

Table 2. Standards for reporting interventions in clinical trials of acupuncture checklist

STRICTA list			EA-MNS group	EA-VNS Group
1) Acupuncture rationale	a)	Style of acupuncture	Meridian of Traditional Korean Medicine	Meridian of Traditional Korean Medicine
	a)	Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with reference where appropriate	Based on previous studies show that stimulation of median nerve or PC6 acupoint is effective for anxiety symptoms [14, 15].	Based on previous studies show that stimulation of the vagus nerve or TF4 acupoint is effective for anxiety symptoms [14, 16].
	b)	Extent to which treatment was varied	N/A	
2) Needling details	a)	Names (or location if no standard name) of points used	PC6 (Neiguan) on the right arm A non-acupoint about 0.5 cm towards the body from PC6 on the same arm	TF4 (Shenmen of ear acupuncture, located at the bifurcation of the cruca of antihelix) on the right arm A non-acupoint surrounding 0.7 to 1.0cm away from TF4 on the same ear
	b)	Number of needle insertions	2	

			per subject per session		
		c)	Depth of insertions, based on a specified unit measurement, or on a particular tissue level	N/A	
		d)	Response sought	Stimulus intensity set to 4-5 on a 0-10 scale, as reported by the subject	
		e)	Needle stimulation	Electrical At a frequency of 12Hz	Electrical At a frequency of 100Hz
		f)	Needle retention time	20 min	
		g)	Needle type	0.20 mm * 15mm, Dongbang medical, stainless steel	
3)	**Treatment regimen**	a)	Number of treatment sessions	16	
		b)	Frequency and duration of treatment sessions	Twice a week for 8 weeks (16 times in total)	
4)	**Co-intervention**	a)	Details of other interventions administered to the acupuncture group	N/A	
5)	**Practitioner background**	a)	Description of participating acupuncturists	Korean Medicine Doctor with over 1 year of clinical experience	
		b)	Years in acupuncture practice		
		c)	Qualification or professional affilation		

Criteria for concomitant drugs

Permissible drugs

Drugs that have been taken consistently at a stable dose for at least four weeks prior to study participation and are not expected to interfere with the interpretation of the clinical trial results may be permitted at the discretion of the researcher. Additionally, drugs intended for the transient treatment of other conditions can be co-administered after consultation with the researcher. Comprehensive details of all concomitant drugs—including the name of the drug, purpose of administration, dosage, and duration—will be documented in the case report form.

Prohibited drugs

During the trial period, the administration of drugs that may influence anxiety symptoms is prohibited, including systemic steroids, antipsychotics, antidepressants, benzodiazepines, and sleeping pills. However, if antidepressants, benzodiazepines, and sleeping pills have been

administered at a stable dose for at least two weeks prior to screening, their continuous use may be permitted.

Efficacy variables

Primary outcome

The primary outcome will be assessed by analyzing changes in the Hamilton Anxiety Rating Scale (HAM-A) scores from baseline to week 8 in two separate comparisons:

- Between the EA-MNS group and the Usual Care group.
- Between EA-VNS group and the Usual Care group.

Research Hypothesis

- Hypothesis 1 [H0 : μ1 = μ2, H1 : μ1 ≠ μ2]
  - μ1 : Changes in HAM-A score from baseline to week 8 in the EA-MNS group
  - μ2 : Changes in HAM-A score from baseline to week 8 in the Usual Care group
- Hypothesis 2 [H0 : μ3 = μ2, H1 : μ3 ≠ μ2]
  - μ2 : Changes in HAM-A score from baseline to week 8 in the Usual Care group
  - μ3 : Changes in HAM-A score from baseline to week 8 in the EA-VNS group

Secondary outcomes

The secondary outcomes will be assessed as follows:

- Changes in HAM-A scores from baseline to week 8 between the EA-MNS group and the EA-VNS group.
- Evaluation of rates of loss of diagnosis and complete remission of anxiety disorder, as measured by HAM-A scores, from baseline to week 8 between the EA-MNS group and the Usual Care group.
- Evaluation of rates of loss of diagnosis and complete remission of anxiety disorder, as measured by HAM-A scores, from baseline to week 8 between the EA-VNS group and the Usual Care group.
- Evaluation of rates of loss of diagnosis and complete remission of anxiety disorder, as measured by HAM-A scores, from baseline to week 8 between the EA-MNS group and the EA-VNS group.
- Changes in BAI, BDI-II, PHQ-15, WHOQOL-BREF, PSWQ, PDSS, and LSAS-SR scores from baseline to week 8 between the EA-MNS group and the Usual Care group.
- Changes in BAI, BDI-II, PHQ-15, WHOQOL-BREF, PSWQ, PDSS, and LSAS-SR scores from baseline to week 8 between the EA-VNS group and the Usual Care group.
- Changes in BAI, BDI-II, PHQ-15, WHOQOL-BREF, PSWQ, PDSS, and LSAS-SR scores from baseline to week 8 between the EA-MNS group and the EA-VNS group.

Safety variables

The safety evaluation variables in this study will include the frequency of adverse events, vital signs, and suicide risk assessment. All adverse events that occur during the clinical trial will be assessed for their severity and the causal relationship with the intervention, and their frequency will be used as an evaluation variable. If clinically significant adverse events are observed, changes in vital signs will be assessed compared to pre-intervention values. The C-SSRS will be used to evaluate the risk of suicide in participants, and a score of 4 or higher will be considered indicative of a suicide risk.

Exploratory variables

The exploratory variables in this study will include the Emotional Reactivity Test, Empathy Quotient (EQ), Perceived Stress Scale (PSS), and Heart Rate Variability (HRV). The Emotional Reactivity Test, EQ, and PSS will be assessed at baseline and at week 8, while HRV will be assessed at baseline, week 4, and week 8.

The Emotional Reactivity Test is a behavioral assessment that measures an individual's responses to both positive and negative emotional stimuli. This test is designed to assess the phenomenon of emotional contagion by observing changes in facial expressions in response to emotional stimuli. It is based on experimental models from past research on emotion processing [17,18]. Subjects are shown video clips that comprise four emotional contexts (joy, sadness, fear/anxiety and neutral) and their facial expressions are recorded while they watched the emotional stimulus clips. Following the recording phase, subjects will report the degree of their emotional state in response to the emotional stimuli on a scale 0-9 using E-Prime® software (Psychology Software Tools, Inc., Sharpsburg, PA, USA). Facial expressions will be analyzed using iMotion software (iMotions A/S, Copenhagen, Denmark).

The electrocardiogram (ECG) signal will be recorded using electrodes placed on the subject's chest. Heart rate and R-R intervals will be extracted form the ECG data using an in-house script developed in MATLAB (2016b, The MathWorks, Inc., Natick, MA). The time-domain HRV metrics will include RRmean (the mean R-R interval), SDNN (the standard deviation of R-R interval, and RMSSD (the root mean squares of successive differences). The frequency-domain HRV metrics that will be calculated include the low-frequency power (LF: 0.04~0.15 Hz), high-frequency power (HF: 0.15-0.4 Hz) and the normalized LF and HF power following standard recommendations [19].

Sample size

Considering the absence of prior clinical trials proving the therapeutic effect of electroacupuncture in anxiety disorders compared to a control group, this study references preliminary life science research that recommends enrolling 15 subjects per group [20]. Therefore, to accommodate potential variances and ensure statistical robustness, we plan to enroll 15 subjects per group, for a total of 45 subjects. Anticipating a dropout rate of approximately 25%, this study has calculated the need for 20 subjects per group, for a total of 60 subjects.

Randomization, allocation

In this study, participants will be randomly assigned to one of three groups: the EA-VNS group, the EA-MNS group, or the usual care group. Stratified block randomization will be employed, using SAS® software (Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA), to ensure an unbiased and equal allocation (1:1:1 ratio) across the groups. The stratification criteria will include the specific type of anxiety disorder diagnosed in each participant, such as panic disorder, agoraphobia, generalized anxiety disorder, social anxiety disorder, and other specified anxiety disorders. This method ensures proportional representation of each anxiety disorder subtype within each study arm, thereby controlling for variability in treatment response based on the type of anxiety disorder. The randomization list in this study will be held by an independent statistician and will not be disclosed to ensure confidentially. The randomized codes will be placed in opaque, sealed envelopes and stored in a locked cabinet. Randomization envelopes will be opened in the order of participant enrollment to assign each group. The opened envelopes will be stored separately, and the date, time of opening, and the opener's signature will be recorded on the envelopes.

Blinding

Given the nature of the interventions, it is not feasible to blind participants in this study. However, to preserve the integrity of the study outcomes, assessor blinding will be strictly maintained. Researchers responsible for evaluating the efficacy and safety outcomes will not participate in the administration of interventions or in the randomization process.

Data management

All clinical trial-related information, including case report forms, consent forms, and supporting documentation, will be recorded, processed, and preserved to facilitate proper reporting,

interpretation, and verification. Records containing participants' personal information will be strictly confidential. In all documents associated with the clinical trial, including case report forms, participants will be identified only by their identification codes and initials, not by their names.

Monitoring

Monitoring will be conducted to ensure that the clinical trial is executed in accordance with the approved protocol and applicable regulations. This process includes verifying compliance with the protocol, ensuring accurate and appropriate data collection, reviewing consent and re-consent forms, and verifying the proper collection and reporting of adverse events.

Statistical methods

Definition of analysis set

The analysis sets for evaluating data obtained in this clinical trial are defined as follows: The Full Analysis Set (FAS) is in accordance with to the Intent-To-Treat (ITT) principle, encompassing all subjects who met the inclusion and exclusion criteria, were randomly assigned, and for whom baseline measurements and at least one post-baseline primary outcome was obtained. The Per Protocol Set (PPS) includes subjects from the FAS who have adhered to at least 75% of the total intervention and do not meet any discontinuation or dropout criteria. The Safety Analysis Set (SAS) comprises all subjects who have undergone at least one safety assessment following random assignment.

All data, including efficacy outcomes, will be analyzed using the FAS, with the PPS serving as a secondary analysis group for additional analyses. Safety variables will be analyzed using the SAS. Continuous data will be presented as means and confidence intervals, while categorical data will be presented as frequencies and percentages (%). If necessary, initial characteristics of subjects measured at screening or baseline may be categorized for subgroup analysis.

Unless specifically stated otherwise, all statistical analyses in this study's results will be conducted as two-sided tests, with a significance level set at 5%. However, for the analysis of the primary outcome, the significance level will be set at 2.5%. Statistical analyses will be performed using SAS® software (version 9.4 or higher, SAS Institute Inc., Cary, NC, USA).

Statistical methods for analyzing efficacy outcomes

Primary outcomes

The primary outcome analysis will employ a Mixed-effect model repeated measure (MMRM) approach, including each treatment group and visit timepoint as fixed factors, with subjects as random factors, and accounting for interactions between groups and visit timepoints. Variables that show statistically significant differences in demographic or sociological characteristics, or other factors potentially influencing anxiety disorders, will be incorporated as fixed factors. Results will be presented with means, 97.5% confidence intervals, and p-values. Additionally, if significant baseline differences exist between groups, an Analysis of Covariance (ANCOVA), adjusted for baseline values as a covariate, will be conducted.

Secondary outcomes

The analysis of secondary outcome variables will adhere to the same methodology employed for the primary outcomes. Changes in continuous variables from baseline to week 8 in BDI-II, BAI, PHQ-15, WHOQOL-BREF, PSWQ, PDSS, and LSAS-SR will be assessed using the same analytical approach, with a significance level set at 5%. To evaluate the differences in measurements before and after the intervention within each group, the Student’s Paired t-test or Wilcoxon signed rank test will be employed for both primary and secondary outcomes. Additionally, to examine the trend changes over time between the EA-MNS and EA-VNS groups, Repeated Measures Analysis of Variance (ANOVA) will be conducted. This analysis will include testing the interaction between the groups

and visits to ascertain how differences evolve over time. If the interaction is found to be significant, post-hoc tests will be implemented to identify significant differences between the groups at specific time points based on baseline measurements. Furthermore, the binary variables such as loss of diagnosis and complete remission of anxiety disorder as assessed by HAM-A will be compared between groups using logistic regression, which will provide odds ratios and 95% confidence intervals.

Statistical methods for safety outcomes

The safety analysis will encompass the severity of adverse events, their causal relationship with the intervention, the incidence rate of adverse events by group, the rate of adverse events leading to dropout, and the incidence rate of serious adverse events. The proportion of participants who dropped out due to treatment failure or adverse events will be reported for each group, along with 95% confidence intervals. Additionally, the Chi-square test or Fisher exact test may be employed to compare observed frequencies against expected frequencies. Also, the number of cases assessed as having a high risk of suicide during the study period will be presented by group, and statistical testing may be conducted if necessary.

Statistical methods to handle missing data

When using the MMRM for variable analysis, no separate imputation for missing values will be conducted. Conversely, in cases where ANCOVA is employed, missing values will be imputed using the Multiple Imputation method.

Statistical analysis of demographic and baseline characteristics

In this study, descriptive statistics for demographic and pre-treatment characteristics will be presented for each group. Continuous variables will be analyzed using either ANOVA or the Kruskal-Wallis test, depending on the data distribution. Categorical variables will be analyzed using the Chi-square test or Fisher’s exact test; Fisher’s exact test will be applied when more than 25% of cells in a contingency table have an expected frequency of less than five. If necessary, significant differences in baseline characteristics between groups will be adjusted for by incorporating these characteristics as covariates in the efficacy variable analysis.

Ethical consideration

The study protocol, consent forms, participants information sheets, and all other documentation provided to the participants have received approval from the Institutional Review Board of Daejeon University Daejeon Medical Center (DJDSKH-22-BM-19). This clinical trial has been registered with the Clinical Information Services (CRIS) as of April 21, 2023 (identifier: KCT0008378). All participants will be thoroughly informed about the details of the clinical trial. The consent of participants will be obtained in accordance with the ethical principles and standards based on the Declaration of Helsinki.

Study protocol modifications

Any modifications to the study protocol require prior approval from the Institutional Review Board (IRB). This clinical trial will adhere to the approved protocol unless deviations are necessary to eliminate immediate risks to participants.

Adverse events

In this clinical trial, adverse events are defined as any harmful or unintended signs, symptoms, or diseases occurring in participants. It should be noted that not all such events necessarily have a causal relationship with the intervention. Serious adverse events include: death or life-threatening situations, hospitalization or prolongation of existing hospitalization, permanent or significant

disability or impairment, congenital anomalies or defects in a fetus, or other medically significant conditions such as drug dependency or abuse. However, not all adverse events are regarded as serious.

From the start of the intervention, any adverse events will be documented in detail, including the date of onset and resolution, the severity and outcome, the actions taken in relation to the intervention and the causal relationship with the intervention, any other suspected treatments or medications, and whether treatment for the adverse event was administered. During the study period, any serious adverse events must be reported by the research team to the principal investigator within 24 hours. The principal investigator is required to report all serious adverse events to the Institutional Review Board (IRB) in accordance with clinical trial regulations.

Dropout

In this study, dropout refers to the termination of participation before completing all phases of the study. Researchers can stop treatment and observation and withdraw the subject, or subjects can voluntarily withdraw at any time. A subject may be considered dropped out under the following circumstances:

1) If it is discovered after screening that the participant does not meet the inclusion/exclusion criteria.
2) If a systemic disease not identified during pre-treatment examinations is discovered.
3) If the subject experiences a serious adverse event and the researcher determines that continued participation is inappropriate.
4) If an adverse event is severe enough that the researcher deems continued participation to be inappropriate.
5) If symptoms worsen and the researcher determines that other treatment is necessary.
6) If the subject withdraws consent or requests to stop participation.
7) If the subject does not visit or cannot be followed up.
8) If the researcher determines that continuation of the clinical trial is inappropriate for any other reasons.

Discontinuation

In the following cases, this study can be discontinued early after consultation with the sponsoring organization.

1) If an unexpected and unacceptable risk is identified in a subject.
2) If moderate or severe adverse events considered related to the intervention occur in more than 25% of the subjects.
3) If not all subjects are enrolled by the end of the recruitment period.

Termination

This clinical trial will officially terminate once the target number of participants has been enrolled and data completeness and integrity have been confirmed.

Results

The first participant was enrolled on December 15, 2022. As of October 2024, a total of 60 participants have been fully registered, and the intervention is currently in progress. We expect the completion of this trial to occur within the year 2025.

Discussion

Some studies have reported that patients with anxiety disorders exhibit increased activity in the motor areas and motor networks of the brain [21,22]. This finding suggests that modulation of cerebral motor area functions could potentially regulate anxiety symptoms. In this study, the

frequency of median nerve is set at 12 Hz, based on previous studies suggesting that 12 Hz median nerve stimulation modulates the function of the brain's motor areas and improving symptoms. In this study, the frequency of median nerve stimulation is set at 12 Hz, based on a previous study. Studies [23,24] demonstrated that 12 Hz median nerve stimulation is effective in modulating the function of the brain's motor areas and improving symptoms. Similarly, the frequency of vagus nerve stimulation is set at 100 Hz to maximize the brain functions based on a previous study that found 100 Hz stimulation to be effective in increasing activity in the primary sensory cortex, pre-motor cortex, insular cortex, brainstem, and cerebellum [25].

Futhermore, we will utilize heart rate variability (HRV) to elucidate physiological mechanisms of EA in treating anxiety, particularly focusing on the regulation of autonomic nervous system. HRV analysis can offer a non-invasive and objective assessment of the autonomic nervous system's response to EA, potentially evaluating the underlying mechanisms.

Conclusion

The purpose of this clinical trial is to evaluate the efficacy and safety of electroacupuncture-neurostimulation in the treatment of anxiety disorders compared to a control group. We expect that electroacupuncture, through the stimulation of the median and vagus nerves, could become a novel therapeutic option for anxiety disorders.

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Conflicts of interest

The authors declare that they have no competing interests.

Abbreviations

ANOVA: Analysis of variance, ANCOAVA: Analysis of Covariance, BAI: Beck Anxiety Index, BDI-II: Beck Depression Inventory-II, C-SSRS: Columbia Suicide Severity Rating Scale, DSM-5: Diagnostic and Statistical Manual of Mental Disorders-5, EA-MNS: Electroacupuncture-Median nerve stimulation, EA-VNS: Electroacupuncture-Vagus nerve stimulation, EQ: Empathy Quotient, FAS: Full Analysis Set, LSAS-SR: Liebowitz Social Anxiety Scale-Self Report, MMRM: Mixed-effect Model Repeated Measure, PDSS: The Panic Disorder Severity Scale, PHQ-15: Patient Health Questionnaire-15, PPS: Per Protocol Set, PSS: Perceived stress scale, PSWQ: Penn State Worry Questionnaire, SCID-5: Structured Clinical Interview for DSM-5, SAS: Safety Analysis Set, WHOQOL-BREF: WHO Quality of Life Assessment Instrument abbreviated version

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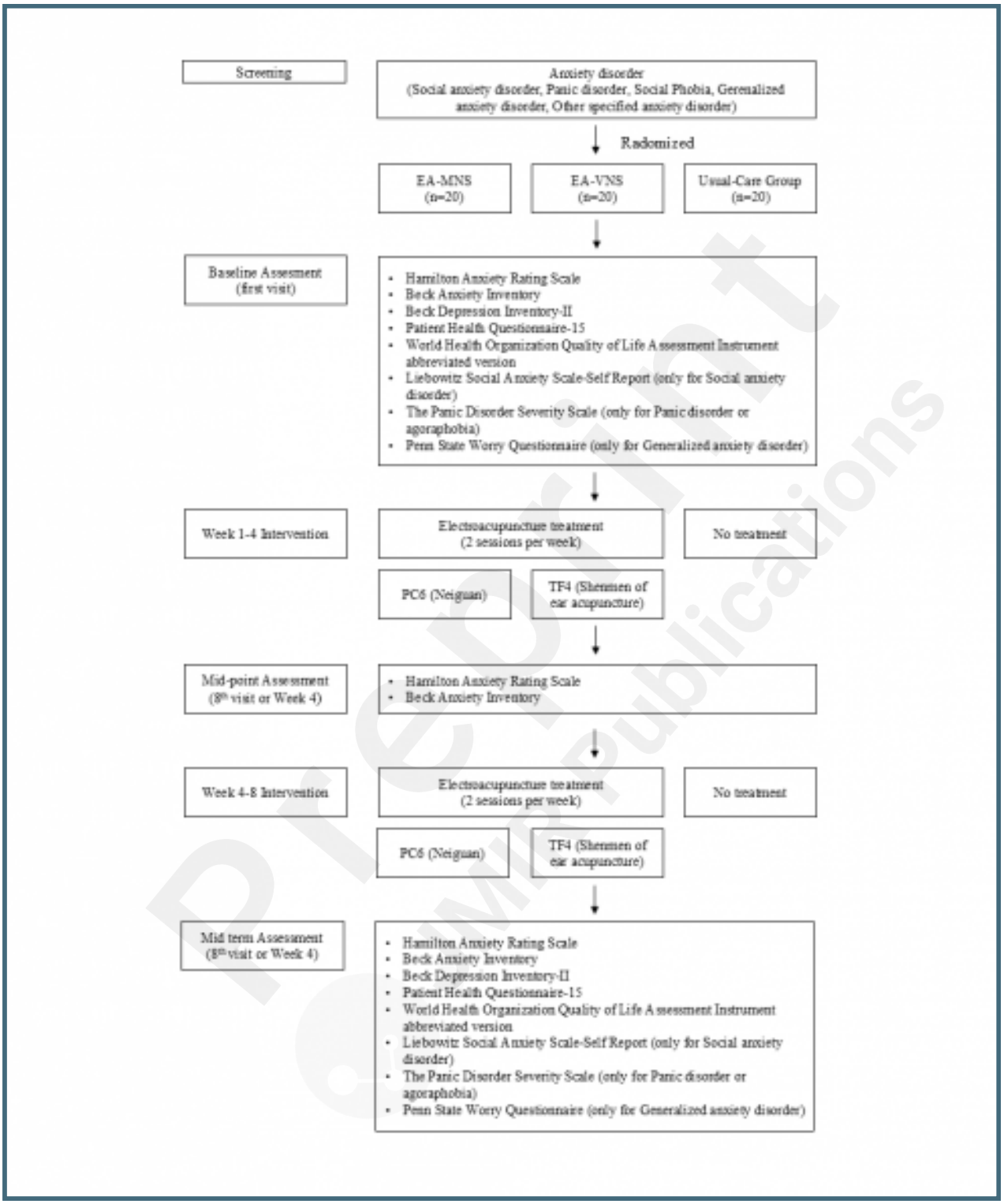
Supplementary Files

Untitled.
URL: http://asset.jmir.pub/assets/06e002e9c71a3a6485109c8635f52c73.docx

Figures

Flowchart of study procedure.



Multimedia Appendixes

WHO trial registration data set.
URL: http://asset.jmir.pub/assets/382ab82b8bc7763f0b4732253bdbf5d7.pdf

CONSORT (or other) checklists

Spirit Checklist.
URL: http://asset.jmir.pub/assets/8cc7971623d5b557ae1e62364a46577a.pdf