



Original article

Effectiveness and safety of thread embedding acupuncture for drug-resistant epilepsy outpatient in Viet Nam: a two-arm parallel design, randomized, controlled clinical trial

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Abstract: *Introduction:* People with drug-resistant epilepsy (DRE) are at high risk of sudden unexpected deaths and lower quality of life. Experiments showed thread embedding acupuncture (TEA) has a seizure-reducing effect; however, data on DRE has been limited. This trial aimed to establish the efficacy and safety of TEA in people with DRE. *Method:* This was a two-arm, randomized controlled trial conducted on 30 DRE outpatients, which was fulfilled drug-resistant International League Against Epilepsy. The study was conducted at the Epilepsy clinic, Nguyen Tri Phuong Hospital, Ho Chi Minh City, from December 2020 to March 2022. All procedures for TEA and sham TEA (STEA) groups were identical. Seizure frequency diaries at the baseline and monthly follow-up visits by the participants. The Quality of Life in Epilepsy Inventory (QOLIE-31) scores at the baseline and 16 weeks; the National Hospital Seizure Severity Scale (NHS3) scores at the baseline, 8 weeks, and 16 weeks and the adverse events at monthly follow-up visits by a researcher. *Results:* A reduction in relative seizure frequency and the score change in QOLIE-31 and NHS3 in the TEA group were significantly different from the STEA group when analyzing each group separately ($p < 0.05$). However, when comparing two groups, no significant difference was found in the change in seizure freedom and QOLIE-31 ($p > 0.05$). Mild pain appeared in all participants after the intervention, but no serious adverse effects of TEA were observed. *Conclusion:* TEA is a safe technique to use in people with DRE. However, the effectiveness of TEA needs further study.

Keywords: drug-resistant epilepsy; thread embedding acupuncture; randomized clinical trial; quality of life; adverse effects.

1. INTRODUCTION

Epilepsy is a chronic neurological disease that affects individuals of all ages worldwide. In 2016, there were approximately 50 million people with active epilepsy globally, and about 74% of the patients were in rural areas in low-income countries. As stated in a population-based epidemiological study in a rural district in Viet Nam, the prevalence of active epilepsy was 4.4 per 1,000, similar to some Asian countries. Following International League

Against Epilepsy (ILAE), epilepsy is conceptually defined as "a disease characterized by an enduring predisposition to generate epileptic seizures," and an epileptic seizure is "a transient occurrence of signs and symptoms due to abnormal excessive or synchronous neuronal activity in the brain" [1]. Most people with epilepsy can be treated mainly by antiseizure drugs (ASMs). However, about 30% of the epileptic population continues to have seizures despite medication, even with new generation ASMs [2, 3]. In 2010,

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drug-resistant epilepsy (DRE) was defined by ILAE as a failure of adequate usage of two tolerated and appropriate ASM schedules either as monotherapy or in combination to totally control seizure [3]. Patients with DRE have increased risks of a sudden unexpected death, psychiatric comorbidities, psychosocial issues, and lower quality of life, so exploring more effective management is an essential clinical need. Some alternative treatments and medications among the DRE population include epilepsy surgery, neuromodulation, and a ketogenic diet. However, in a low-income country like Viet Nam, there are several difficulties, including funding issues, lack of expertise, and lack of facilities [4].

Acupoint embedding therapy (AET) is a kind of acupuncture treatment using a needle attached to an absorbable thread that has been used to manage various disorders, including epilepsy in Viet Nam. Depending on the type of absorbable thread used, two commonly used methods in Vietnam are catgut-embedding therapy and thread-embedding acupuncture (TEA) with polydioxanone (PDO) [5, 6]. Around the world, TEA has been widely used in Korea, China, and Taiwan for the treatment of internal disease, musculoskeletal disease, obesity, cosmetic surgery, neuropsychiatry, ...etc [7]. From previously published studies, the effects of TEA in controlling epileptic seizures might come from the release of neurotransmitters including gamma-butyric acid, endogenous opioid peptides, and serotonin [8]. To the best of our knowledge, no controlled trials of the efficacy and safety of TEA in treating DRE have yet been published. The objectives of the current study were to assess the effectiveness and safety of TEA on seizure frequency and the quality of life in people with DRE.

2. MATERIALS AND METHOD

2.1. Study design and participants

This study was a randomized, controlled, assessor-blinded clinical trial with a two-arm parallel design. Participants were recruited from the Epilepsy Clinic at the Department of Neurology, Nguyen Tri Phuong Hospital in Ho Chi Minh City, Viet Nam. Data collection was from December 20, 2020, to March 21, 2022.

We calculated the expected minimum sample size of 27 DRE patients per group with the formula:

$$n_1 \geq \frac{[Z_{1-\frac{\alpha}{2}}\sqrt{(r+1)p(1-p)} + Z_{1-\beta}\sqrt{rp_1(1-p_1) + p_2(1-p_2)}]^2}{r(p_2 - p_1)^2}$$

With:

$$p = \frac{p_1 + rp_2}{1+r}$$

In which:

$$\alpha = 0,05 \rightarrow Z_{1-\alpha/2} = 1,96.$$

$$\beta = 0,2 \rightarrow Z_{1-\beta} = 0,84.$$

p_1 : the percentage of patients achieving seizure control in the control group. From the research results of the author Chen et al [2], the seizure-free control rate with 2 ASMs is 11,6% $\rightarrow p_1 = 0,12$.

p_2 : The percentage of patients achieving seizure control in the intervention group, expected to be as effective as ASMs monotherapy through Chen's study [2] is 45,7% $\rightarrow p_2 = 0,46$.

$r = 1$.

n_1 : Minimum sample size for the control group

n_2 : Minimum sample size for the intervention group.

Unfortunately, due to the COVID-19 pandemic, only 30 patients were recruited for both groups. The inclusion criteria were: (1) adults aged from 18 to 60 years old, (2) being defined as DRE according to ILAE criteria and having one or more seizures per three later months. We excluded DRE individuals who (1) underwent epilepsy surgery; (2) had certain conditions that were inappropriate for TEA due to skin disorders (swollen, hot, and red at acupuncture points), or hemostatic disorders (international normalized ratio > 2.0 or current use of anticoagulant); (3) were pregnant; (4) had other diseases that might affect the outcomes, including body exhaustion, severe gastroenteropathy, cardiovascular disorders, diabetes mellitus, renopathy, hepatopathy, thyroidopathy, or progressive neurological signs due to acute disorders such as acute stroke, brain tumors; (5) TEA within six months; (6) current psychiatric diseases including depression, schizophrenia, or anxiety; and (7) alcoholism (more than 3 cups a day) [9].

2.2. Randomization and blinding

Randomization was conducted to avoid bias and to blind the subjects and researchers. The randomness was organized at a 1: 1 ratio by lottery: (1) the treatment group with odd numbers and (2) the control group with even numbers. Statistician (T.D.P.) who was not involved in the recruitment and clinical assessment randomly assigned the participants to each group with the same probability. The independent statistician kept the generated randomization table; the file was collected from disclosure.

In this trial, blinding the practitioner (D.V.N.) was impossible due to the characteristics of the intervention. V.-D.N. is a traditional medicine doctor who performed TEA and STEA procedures; two processes were completely similar in terms of tools (needle); the only difference was that one with thread (TEA group) and one without thread (STEA group). However, it was impossible to identify which patients were undergoing TEA or STEA because after removing the needle, there was no trace of difference between TEA and STEA. However, it was designed to be assessor-blinded to control bias as much as possible. The clinical assessment was performed by a researcher who did not conduct the intervention and randomization (A.T.M.L.). A.T.M.L. is a Western medicine neurologist who did not participate in the TEA and STEA procedure and the randomization; A.T.M.L. was the neurologist who performed the clinical neurological assessment to fill out the clinical information (seizure information) and the evaluation questionnaire (the NHS3) in the case report form (CRF). There was no randomization information exchange and intervention type between the two doctors (D.V.N. and A.T.M.L.).

2.3. Interventions

The study included three periods: a baseline of 12 weeks, an intervention of 12 weeks, and a follow-up of the outcome data after four weeks. After the baseline period, the participants were randomly assigned to TEA or STEA through restricted randomization.

All patients were treated as outpatients and received treatment every four weeks; each patient will receive four times TEA or STEA. Each treatment lasted about 30 minutes. A Traditional Medicine (TM) doctor with ten years of experience in TEA practice (D.V.N.) performed both TEA and STEA treatments. All procedures will be performed according to the Clean Needle Technique. The methodology was based on the Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement [10].

2.4. Thread embedding acupuncture procedure

2.4.1. Thread embedding acupuncture (TEA)

The acupoints were selected based on the Vietnamese Ministry of Health guideline [6] and based on preceding studies on acupuncture for patients with epilepsy [11-13]. The six TEA points used were GV20, BL15, BL18, ST40, GV14, and GB34. Appendix 1 shows the detailed information on TEA treatment. Among TEA group, the participants would receive a total of 4 TEA treatments every four weeks.

Mono-shaped TEA with a needle (31G-30 mm) and polydioxanone thread (7-0 USP size, 30 mm) (JBP V line; Feel-tech Co., Ltd, JBP Korea, Republic of Korea) were used in this study.

Patients were placed in a prone position. The TM doctor inserted 10 disposable sterile needles and immediately withdrew them without stimulation, and manual manipulation for Deqi would not be allowed. Before and after the treatment, practitioners sterilized the skin at the acupuncture point region with 70% alcohol-saturated cotton pads. On the day of TEA treatment, movement or stimulation of acupuncture sites was not allowed to prevent the thread from protruding.

2.4.2. Sham Thread-embedding acupuncture (STEA)

The procedures of the Sham TEA, including acupoints and size of TEA, were similar to that of the TEA group. However, we used the thread-removed TEA in the Sham TEA group, and we performed the aseptic removal procedure of thread with secret conditions for patient blindness.

2.4.3. Co-interventions

ASMs were maintained at the fixed dose prescribed by the neurologists for both study groups for the duration of the study.

2.5. Outcome measures

The primary outcome was (1) the mean change in seizure frequency; and (2) the quality-of-life assessment. The mean change in seizure frequency was calculated by the median number of seizures per month divided by the median number of seizures per month during baseline. The participants recorded seizure frequency using seizure diaries collected at the baseline and monthly follow-up visits. The seizure diary was completed by patients and confirmed by caregivers

because there were focal seizures in which patients still were aware during the episodes. The quality of life (QOL) assessment was recorded by The Quality of Life in Epilepsy Inventory (QOLIE-31). The QOLIE-31 was collected at the first visit for the baseline and the last visit after 16 weeks. This questionnaire included seven subscales with health concepts: emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life. The Vietnamese QOLIE-31 was translated and validated. The QOLIE-31 score was calculated with higher converted scores always reflecting better quality of life. The manual guided the calculation of the total and subscale scores [14].

The secondary outcomes included (1) satisfactory seizure control was the proportion of participants with $\geq 50\%$ reduction in seizure frequency at 16 weeks relative to baseline, including seizure freedom (no seizure recorded); (2) the National Hospital Seizure Severity Scale (NHS3) scores [15] were used to assess seizure severity at the baseline, eight weeks, and 16 weeks; and (3) epileptiform discharges (ED) were recorded by Electroencephalograph (EEG) at the baseline, and 16 weeks. Epileptiform discharges are generalized, or focal spikes and sharps followed by slow waves, from 20 - 200 milliseconds. Trained neurologists interpreted the EDs during a 20-minute standard EEG.

The researcher (A.T.M.L.) assessed the adverse events (AEs) at each visit based on vital signs, medical history, and neurological examinations. Commonly reported AEs in previous TEA studies include swelling, ecchymosis, a feeling of tightness, pain, infection, dimpling, thread extrusion, and foreign body reaction [16, 17]. We recorded all identified AEs in the case report form without referencing their association with interventions. If there were severe AEs (SAEs), the participants would temporarily stop this clinical trial.

2.6. Statistical analysis

Data were processed by Epidata 3.1 and analyzed by Stata 15.0. Quantitative variables were presented as median (interquartile range) because of skewed distributions; qualitative variables were presented as frequencies. For comparison of baseline patient characteristics, we used Mann-Whitney U-test for comparisons of medians and Fisher's exact test for comparisons of proportions. The median difference in score changes from baseline to 16 weeks were compared between the TEA group and STEA group using Mann-Whitney U-test. Additionally, score changes for the QOLIE-31 dimensions and NHS Severity Scale were assessed for the two groups separately, using Wilcoxon signed rank-sum test. We chose a 5% significance level.

3. RESULTS

3.1. Characteristics of participants

All 40 participants were screened for eligibility. Of these, ten met the exclusion criteria or withdrew consent (Figure 1).

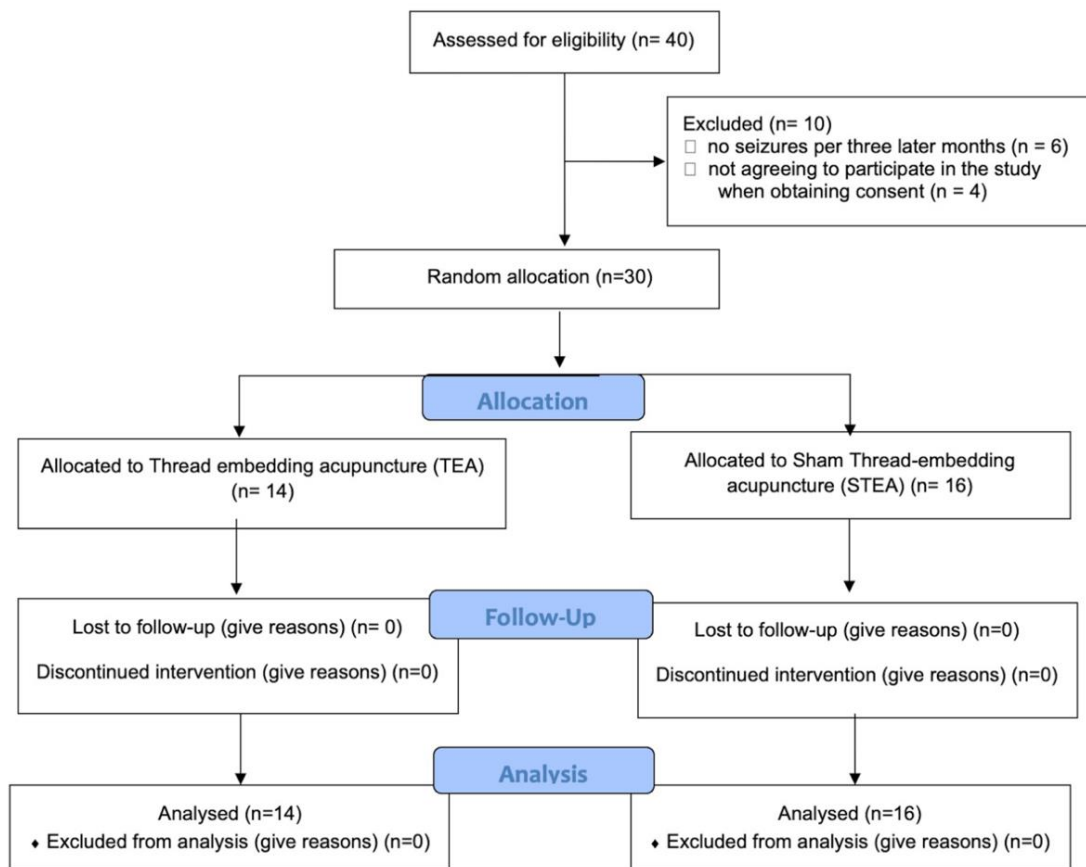


Figure 1. Study flow chart

Table 1. Characteristics at baseline of subjects among TEA and STEA groups

	TEA (n = 14)	STEA (n = 16)	p-value*
Male/Female	4/10	4/12	0.825
Age, median (IQR)	28.5 (23.5 – 36.5)	29.0 (22.0 – 33.0)	1.000
Age at onset, median (IQR)	13.0 (9.0 – 30.0)	18.0 (11.0 – 28.0)	0.851
Age at diagnosis, median (IQR)	13.5 (9.5 – 30.0)	20 (12.0 – 28.0)	0.632
Current number of AEDs, median (IQR)	2.0 (2.0 – 3.0)	2.0 (2.0 – 3.0)	0.923
Seizure type**			
Focal seizures	9/14	10/16	0.919
Focal seizures to bilateral tonic-clonic	8/14	7/16	1.000
Number of seizures per month, median (IQR)	3.0 (2.5 – 4.0)	3.0 (3.0 – 4.0)	1.000

* Mann-Whitney U-test for comparisons of medians, Fisher’s exact test for comparisons of proportions ** Seizure type was based on Fisher et al. (2017), Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia, 58: 522-530.

Table 2. QOLIE-31 scores at baseline and after 16 weeks of study

QOLIE-31 scores	Baseline			After 16 weeks			p-value ^b	
	TEA (n = 14)	STEA (n = 16)	p-value ^a	TEA (n = 14)	STEA (n = 16)	p-value ^a	TEA	STEA
Seizure worry	45.0 (28.7 – 53.8)	43.8 (28.7 – 53.0)	0.723	58.7 (50.0 – 71.8)	54.5 (51.0 – 65.3)	0.755	0.007	0.001
Overall quality of life	53.8 (47.5 – 67.5)	53.8 (45.0 – 67.5)	0.983	66.3 (55.0 – 67.5)	61.3 (50.0 – 67.5)	0.207	0.005	0.084
Emotional well-being	48.0 (44.0 – 64.0)	54.0 (48.0 – 64.0)	0.883	70.0 (62.0 – 76.0)	62.0 (56.0 – 68.0)	0.133	0.001	0.026
Energy/fatigue	50.0 (47.5 – 62.5)	52.5 (50.0 – 60.0)	0.933	70.0 (55.0 – 75.0)	57.5 (50.0 – 65.0)	0.085	0.005	0.046
Cognitive functioning	56.7 (48.0 – 75.3)	56.7 (48.0 – 77.3)	0.884	73.3 (63.3 – 81.3)	64.7 (54.7 – 77.3)	0.227	0.002	0.026
Medication effects	33.3 (8.3 – 56.9)	32.0 (0.0 – 66.7)	0.950	55.6 (20.8 – 72.2)	38.9 (22.2 – 66.7)	0.466	0.009	0.084
Social functioning	36.0 (24.5 – 51.0)	34.5 (22.0 – 57.0)	0.950	59.5 (36.0 – 76.0)	46.5 (37.0 – 57.0)	0.441	0.003	0.026
Overall score	48.8 (42.5 – 57.7)	44.4 (41.7 – 59.1)	0.803	65.0 (53.9 – 72.2)	57.2 (45.5 – 63.9)	0.135	0.001	0.001

a Mann-Whitney U-test for comparisons of medians between TEA and STEA group
 b Wilcoxon signed rank-sum test for comparisons of median changes from baseline to 16 weeks in TEA group and STEA group

The characteristics at baseline of subjects were not significantly different between the TEA and STEA groups (Table 1).

3.2. Primary outcome

Seizure frequency

Figure 2 shows a declined trend in relative seizure frequency, i.e., the median number of seizures per month

divided by the average median number of seizures per month during baseline, in both groups during this study ($p < 0.05$, Wilcoxon signed rank-sum test).

Five participants in TEA achieved satisfactory seizure control, including one who was seizure-free, compared with one STEA patient. The seizure freedom rate and satisfactory seizure control rate after 16 weeks of study were not significantly different between the TEA group and the STEA group ($p > 0.05$, Fisher's exact test).

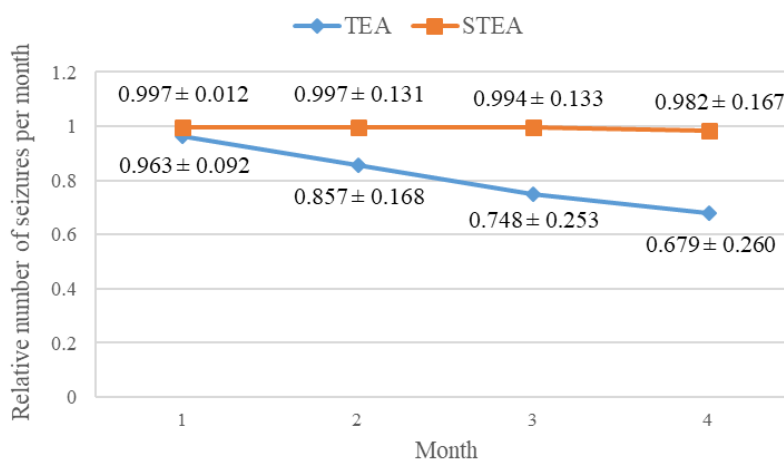


Figure 2. Relative changes in the number of seizures per month (\pm SD, standard deviation)

QOLIE-31 scores

At baseline and the end of the study period of 16 weeks, no significant difference in any of the QOLIE-31 subscales and total scores was found between the TEA group and the STEA one ($p > 0.05$, Mann-Whitney U-test). When analysing two groups separately, significant changes from baseline to the end of the study period were seen in any of the QOLIE-31 scales except for overall quality-of-life and medication-effect subscales in the STEA group ($p < 0.05$, Wilcoxon signed rank-sum test) (Table 2).

3.3. Secondary outcome

Seizure Severity

No significant difference was found between the two groups in score changes on NHS Severity Scale from baseline to eight weeks. However, score changes in the NHS Severity Scale from baseline to 16 weeks as well as from eight weeks to 16 weeks in the TEA group significantly differed from those in the STEA group ($p < 0.05$, Mann-Whitney U-test) (Table 3).

Table 3. Median changes in seizure severity from baseline to 16 weeks, after 16 weeks of study

Seizure Severity	From baseline to 8 weeks			From baseline to 16 weeks			From 8 weeks to 16 weeks		
	TEA (n = 14)	STEA (n = 16)	p-value	TEA (n = 14)	STEA (n = 16)	p-value	TEA (n = 14)	STEA (n = 16)	p-value
NHS3	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.604	-2.0 (-3.0 – -1.0)	0.0 (-1.0 – 0.0)	<0.001	-2.0 (-2.5 – -1.0)	0.0 (0.0 – 0.0)	<0.001

NHS3: National Hospital Seizure Severity Scale

Epileptiform discharges

No significant difference in the epileptiform discharges could be demonstrated between two EEG measurements at 16 weeks and the baseline

3.4. Safety assessment

Mild pain appeared in all participants after the intervention but resolved within 15 minutes of follow-up. Two cases in the TEA group recorded ecchymosis; edema occurred up to a week after the treatment. However, other SAEs were not seen in both groups.

4. DISCUSSION

In this study, the seizure frequency and the score changes in QOLIE-31 and NHS Severity Scale from before of first intervention (baseline) to the end of the study of 16 weeks in the TEA group were significantly different from those in the STEA group when analyzing each group separately. From the viewpoint of traditional Chinese medicine, epilepsy is described as a disorder of disturbance of emotion and Qi. The main pathological factor of epilepsy is the retention of turbid phlegm, “no phlegm, no epilepsy” [18, 19], which results in an imbalance of Yin and Yang and dysfunction of Zang-fu (in Ancient Chinese philosophy, qi, yin, yang are abstract concepts of the energy or essence vital to homeostasis and zang-fu are used to describe the organ systems) [8, 20]. Thus, by stimulating numerous acupoints of the conception and governor vessels and twelve meridians (e.g., Heart channel, Liver channel), the disrupted flow of Qi can be adapted, and the imbalance between Yin and Yang can be restored; therefore, epilepsy is alleviated. The formula for acupoints used in epilepsy research is diverse [8]. Of the six acupoints used in this study, GV20 (to regulate liver yang, benefit the heart and calm the spirit) and GV14 (to expel pathogens and firm the yang) are the two points of the governor vessels that are widely used in acupuncture formulas for epilepsy and refractory epilepsy treatment [20]; BL15 (Back-Shu acupoints of Heart to

treat heart pain and unbind the chest), BL18 (Back-Shu acupoints of Liver to expel liver wind, regulate and smoothen the qi flow and resolve depression) and GB34 (Hui meeting of the sinew; to resolve damp-heat, remove obstructions from the channel, relax the tendons and subdue rebellious Qi), ST40 (to expel phlegm and dampness) [8, 19].

Furthermore, many techniques to stimulate acupoints have been studied in treating epilepsy, such as electroacupuncture, ear acupuncture, and AET [21]. Not only may AET have a short-term effect on dredging meridians, but it also exerts long-term acupoint stimulation [5]. Catgut is a natural absorbable thread, mainly used in AET. Acupoint catgut-embedding has been used in treating epilepsy in many previous studies. Mechanisms of the effectiveness of acupoint catgut-embedding in epilepsy have been synthesized in earlier studies, including changes in nerve potentials, changes in membrane ion channels, reduction of neural circuits in seizure, induction of immune inflammation response, the release of active substances such as serotonin and arachidonic acid; reduction apoptosis number of neurons in the hippocampus by inhibiting P53 protein and increasing bcl-2 protein expression [8, 18, 22]. However, PDO, a synthetic monofilament polymer made from polyester or polydioxanone polymer, is used as an alternative tool for catgut thread because PDO thread maintains similar effectiveness and optimizes adverse effects in AET [5].

DRE is a challenging issue in epilepsy treatment. The pathogenesis of DRE is complex and associated with neuroinflammatory, autoimmune, and neurodegenerative processes [23]. To our best knowledge, we are unaware of previous controlled studies reported using TEA that used PDO thread for DRE with a prospective design similar to our research. In this study, the PDO thread may have maintained similar efficacy to the catgut thread for epilepsy and exerted some effect on DRE control through the decrease of seizure frequency and the score change in QOLIE-31 and NHS Severity Scale from before of first intervention (baseline) to the end of the study of 16 weeks in the TEA group were significantly different from that in

the STEA group when analyzed each group separately. PDO is a safe and well-tolerated bioresorbable polymer with no considerable adverse effects on immune functions and a tendency to induce anti-inflammatory responses with long-term exposure in vivo [24]. However, when comparing the TEA and STEA groups, there was no significant difference in the change in seizure freedom, QOLIE-31, and NHS scores. Besides, the change in EEG has not been recorded, possibly because the follow-up time is not long enough to cause a change in EEG. The adverse effects of TEA in this study were similar to those of previous TEA studies, demonstrating that TEA is a safe technique to use in patients with DRE.

There were some limitations in this study. Firstly, the sample size was small, which may reduce the power of the research and increase the margin of error. Secondly, there might have information bias during recording the seizure diaries due to unconsciousness of participants. Thirdly, without individualized procedures following the Traditional Chinese Medicine syndrome, all participants underwent the process the same way, which might impact the results. Next, randomization using even and odd lottery can limit randomization and blind. In the present study, we followed up for 16 weeks (from the time of first intervention to the end of the study) in selected DRE patients who had seizures within the past 12 weeks. However, in the clinical practice of DRE treatment, the follow-up period was usually one year. Accordingly, further studies with a more extended follow-up period (one year or more) are needed to evaluate the results.

Conclusion

We demonstrated the first prospective clinical trial to assess the efficacy and safety of the TEA treatment for DRE using objective and quantitative measurements. The findings of this study can be applied as a basis for further research with modified procedures or studies, and TEA can be indicated in combination with the control of DRE in the context of a low-income country such as Vietnam, which has not yet been able to popularize epilepsy surgery, neuromodulation, and ketogenic diets.

LIST OF ABBREVIATIONS

AET: Acupoint embedding therapy

AEs: Adverse events

ASMs: Antiseizure drugs

DRE: Drug-resistant epilepsy

EEG: Electroencephalograph

ED: Epileptiform discharge

ILAE: International League Against Epilepsy

NHS3: National Hospital Seizure Severity Scale

PDO: Polydioxanone

QOL: Quality of life

QOLIE-31: Quality of Life in Epilepsy Inventory

SAEs: Severe AEs

STEA: Sham TEA

STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture

TEA: Thread embedding acupuncture

ETHICAL STATEMENT

The protocol was based on the Declaration of Helsinki and the Viet Nam Clinical Practice Guidelines and approved by the ethical board of University of Medicine and Pharmacy at Ho Chi Minh City (617/HĐĐĐ-DHYD) and registered with ClinicalTrials.gov with identifier number NCT04673071.

The participants signed the written Informed Consent Form, following a detailed explanation. Personal information will be kept anonymous. Each participant will be assigned a unique study number. This number will help distinguish their data from the rest of the study population. Only research team staff authorized by the lead investigator could access this personal information.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.


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AUTHORS' CONTRIBUTION

D.V.N and A.T.M.L were the principal investigators and designed the study. A.T.M.L collected the medical data. D.V.N did the interventions. D.V.N did the literature search and wrote the initial draft of the manuscript. T.D.P did the statistical data analysis. A.T.M.L contributed medical data interpretation. All listed authors contributed to the revision of the manuscript.

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Appendix 1. The acupuncture points used in this study.

Acupuncture point	Location	Procedure
Baihui (GV20)	The midpoint of the connecting line between the auricular apices	3 cm deep oblique insertion toward nose
Xin Shu (BL15)	In the upper back region, at the same level as the inferior border of the spinous process of the fifth thoracic vertebra (T5), 1.5 B-cun lateral to the posterior median line	3 cm deep perpendicular insertion and both sides
Gan Shu (BL18)	In the upper back region, at the same level as the inferior border of the spinous process of the ninth thoracic vertebra (T9), 1.5 B-cun lateral to the posterior median line	3 cm deep perpendicular insertion and both sides
Fenglong (ST40)	On the anterolateral aspect of the leg, lateral border of the tibialis anterior muscle, 8 B-cun superior to the prominence of the lateral malleolus	3 cm deep perpendicular insertion and both sides
Dazhui (GV14)	In the posterior region of the neck, in the depression inferior to the spinous process of the seventh cervical vertebra (C7), on the posterior median line	3 cm deep perpendicular insertion
Yanglingquan (GB34)	On the fibular aspect of the leg, in the depression anterior and distal to the head of the fibula	3 cm deep perpendicular insertion and both sides