



Aura Intervention for Temporal Lobe Epilepsy: A Prospective, Randomized, Controlled Clinical Trial Protocol

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ABSTRACT

AIM: To determine the feasibility and efficacy of aura intervention in preventing the recurrence of temporal lobe epilepsy (TLE) by observing the changes in the seizure frequency and quality of life (QOL) scale score.

MATERIAL and METHODS: A total of 160 patients will be selected from a pre-established database and randomly divided into the experimental group and the control group. The proposed study is divided into four stages and requires approximately one and a half years for completion. The primary outcome measure is the change in seizure frequency, and the secondary one is the quality of life.

RESULTS: We expect that our subjects show a lasting, stable, and clinically relevant reduction in seizure frequency and improvement in the quality of life, suggesting that aura intervention may be one more feasible way to treat patients with auras, specifically those who experience refractory epilepsy.

CONCLUSION: The ability to perceive auras is the premise of our trial. We mainly study TLE as it relatively has more incidence of auras and a higher cure possibility compared to other types of epilepsy. Although we currently address our problems in a small group of subjects, we believe that the studied aura intervention can easily be applied to millions of patients with epilepsy worldwide if this intervention is considered effective.

KEYWORDS: Temporal lobe epilepsy, Seizure, Aura, Intervention

ABBREVIATIONS: AEDs: Antiepileptic drugs, DBS: Deep brain stimulation, ANT: Anterior nucleus of thalamus, ILAE: International league against epilepsy, NAc: Nucleus accumbens, QOL: Quality of life, TLE: Temporal lobe epilepsy

INTRODUCTION

Temporal lobe epilepsy (TLE) is the most common type of focal epilepsy and sometimes show resistance to medication. Available data indicate that more than 30% of epileptic patients are refractory to antiepileptic drugs (AEDs), and the application of AEDs is still a controversial issue (3,20,23). Temporal lobectomy is an accepted and

advocated approach for medically refractory TLE, but it has certain risks and complications. In addition, deep brain stimulation (DBS) has also helped some patients with intractable epilepsy. Anterior nucleus of thalamus (ANT) is the most well-established target for DBS and recent studies suggest that DBS of the nucleus accumbens may also reduce the seizure frequency in patients with drug-resistant epilepsy (8,24). However, there still remains a certain recurrence rate

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after invasive treatment. Nowadays, several researchers focus on noninvasive therapies, hypothesizing that these are better solutions compared to invasive therapies for patients with TLE.

Previous studies have emphasized the importance of the aura in the clinical diagnosis of TLE. Aura is a subjective ictal phenomenon that essentially comprises all of the patient's sensations, possibly prior to the observable seizure (16). In Gowers' study, more than 50% of their patients precede an aura. According to clinical manifestations, we can mainly classify auras into these following categories: automatism, special sensory symptoms, psychic symptoms, and autonomic symptoms (Table I). The most common aura is abdominal origin (10). As the initial symptoms of epileptic seizures, several types of auras have value in localization or lateralization (1). The symptoms of auras are closely associated with the function of the cortical areas where it originated. Autonomic auras, specifically gastrointestinal discomfort, are suggestive of TLE.

According to the International League Against Epilepsy (ILAE), "It may be that, as in simple partial seizures, the aura is the whole seizure. When consciousness is subsequently lost, the aura is in fact the signal symptom of a complex partial seizure." This guideline suggests that aura is associated with seizures and can be observed as the initial seizure. Between the warning symptom and an observable seizure, there is usually a time window, during which (and generally also during the warning symptom) patients remain able to act (9,10). Interestingly, some patients describe their personal experience, stating that they could reduce seizure frequency or even prevent seizure occurrence with certain cognitive, emotional, and behavioral strategies (2,11). In the first Hungarian multicenter epidemiologic study, approximately 20% of patients enrolled tried to inhibit the onset or mitigate the course of the seizure and approximately 10% considered their spontaneous activity performed in that direction to be successful. Aura intervention, such as a voluntary interruption of the evolution of the aura to the complex partial phase, may be beneficial to some patients (12). However, aura is not a necessary component of epilepsy originated from temporal lobe lesions (22). For patients who can detect the presence of auras, we aim to determine if aura intervention could help prevent the recurrence of epilepsy. Thus, we designed the following experiment to test this idea.

■ MATERIAL and METHODS

Written informed consent is obtained from all study subjects. Relevant materials have been submitted to the local ethics committees for review. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Subjects

Criteria

Subjects are selected from a pre-established database. This database collects diagnostic, and treatment information of epilepsy patients, such as primary sites, stage, medication and

surgery. Sex is not restricted in our trial. Eligible candidates should meet all of the following criteria: (a) age over 18, (b) ability to understand and follow instructions, (c) TLE consistent with the ILAE criteria, (d) average incidence of at least twice a month, (e) awareness of premonitory features, and (f) unchanged anticonvulsant ordination for at least one month prior to participation and no ongoing psychopharmacological treatment (6).

At the same time, patients are excluded in any of the following cases: (a) greatly fluctuating seizure frequency or a history of recurrent and persistent seizures, (b) taking more than two AEDs, (c) progressive epilepsy, and (d) other serious medical problems, such as cancer, brain tumors, stroke, serious heart disease (7) (Table II).

Sample Size

A study showed that approximately 30% of patients with epilepsy suggested a real effect of aura intervention (17). Assuming a similar proportion of successfully improved patients, we estimate that 59 patients for each group would achieve over 80% power to detect significant overall differences between the groups (two-sided, $\alpha=0.05$). Furthermore, assuming a 20% loss to follow-up, we need to recruit a minimum of 74 patients for each group. A total of 160 eligible patients are expected to be recruited in our study.

Randomization

We randomly select patients meeting the above criteria from a pre-established database. Considering the problem of noncompliance, we will extract 20% more than the estimated sample size. Randomization is performed in a 1:1 ratio with the use of a web-based system, with stratification according to sex and age (18–64 and ≥ 65 years old) (Figure 1). The grouping schemes are concealed in opaque and sealed envelopes.

Researchers should ensure that the envelopes are numbered in advance and opened sequentially only after the subject's name and other details are written on the appropriate envelope (21). Both the clinical team (medical and nursing staff) and the patients are blinded to the group allocation.

Study Design

We recruit patients with TLE from Nanfang Hospital, Southern Medical University. In the baseline examination, subjects are interviewed to obtain basic information and undergo physical examination. Subsequently, a 10-ml blood sample is drawn from the subjects. Moreover, they need to complete a scale that assesses their current QOL. In this four-stage clinical trial, seizure precipitants, such as emotional stress, sleep deprivation, and tiredness, should be avoided or controlled to the maximum extent during the whole experiment. Besides, patients' neuropsychiatric status should be evaluated by a psychiatrist and those with psychiatric disorder should have adequate treatment. The proposed study ideally requires approximately one and a half years for completion, from patient recruitment to trial implementation and subsequently to patient follow-up and data preservation and management.

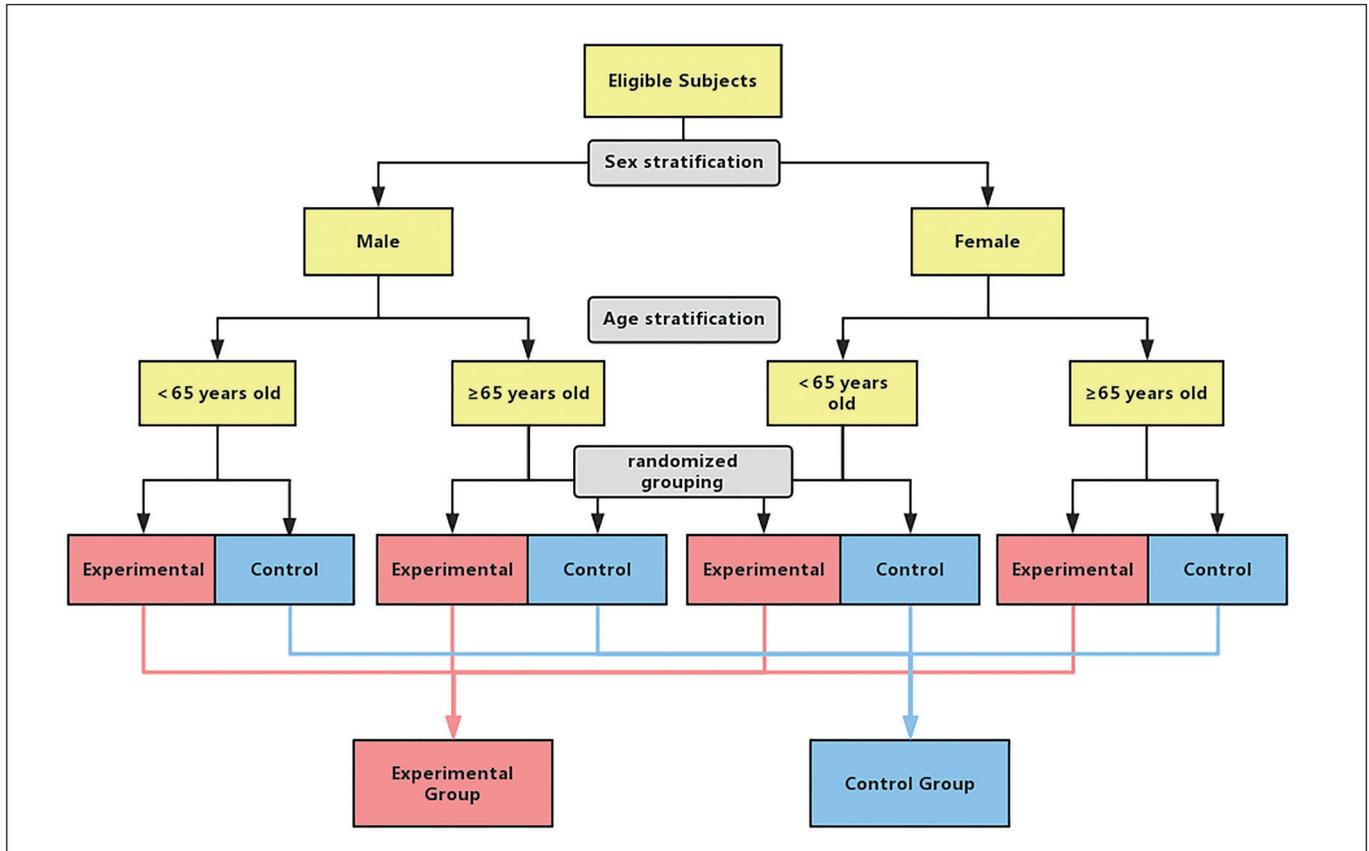


Figure 1: Experimental process and time allocation.

Observation period

Subjects are assessed for inclusion in this phase after an 8-week period of keeping the e-diary for seizure frequency in detail. Eligible subjects are those who record at least four seizures in an 8-week baseline seizure diary without 28-day seizure-free period (18). Ineligible subjects are suspended from the subsequent clinical trials to ensure the control of variables. In the following phases of the trial, based on the original treatment, the experimental group will receive training and aura intervention, and the control group is designed as the waiting group.

Training period

Clinical observation, self-report, narratives, and videos from their families all play an indispensable role in the selection of methods. Individualized interventions are mainly classified into three categories: emotional, cognitive, and behavioral interventions. Selection of spontaneous strategies for seizure control is specific to degree of awareness (11). We will perform standardized intervention training for the experimental group, with the purpose of enabling patients to make the most suitable self-repeating intervention quickly and accurately before each onset. Every time the aura is felt, patients need to prevent further progress under the direction, using the type of intervention previously identified.

Intervention period

During this period, the experimental group is expected to halt the progress with trained intervention on their own, while the control group continues to follow their original treatment plan. Researchers need to observe and record the e-diary kept by all patients every time the episodes come to an end. Regarding each epileptic seizure, if there is no further episode under the condition of aura intervention or spontaneous remission, the result is recorded as A1. Conversely, it is recorded as A0.

Follow-up period

We aim to determine if the intervention has a lasting effect on later seizures. Therefore, we plan to follow up patients from both groups 6 months after the end of the intervention period, specifically by a phone call every 2 weeks (Figure 2). Changes in seizure frequency in the observation, intervention, and post-intervention periods help assess the validity of intervention. At the end of the study, subjects are expected to complete the same questionnaire again as they do at baseline.

Statistical Analyses

We calculate the ratio of A1/A0 in data analysis. If $A1/A0 \geq 1$ (which means 50% or more seizures are successfully interrupted), the aura intervention is considered to be effective. We determine whether the intervention is effective in the short term by comparing the proportion of successfully improved

patients between the two groups. If the difference is greater than 15%, it indicates that the aura intervention is effective.

Additionally, a nested case-control design will be used in our study to analyze potential confounding factors, including tobacco smoking, alcohol consumption, duration and etiology of epilepsy, seizure frequency, current AED history, type of auras, and other variables. Subjects with $A1/A0 \geq 1$ are

identified as effective group, and for each, two matched controls are selected from among those considered as ineffective group with $A1/A0 < 1$. The effective group and the control group will be, respectively, divided into the exposed and non-exposed groups according to the presence of exposure. Exposure is defined prior to the observation period based on data collection at baseline. Finally, we calculate the value of the odds ratio for further analysis.

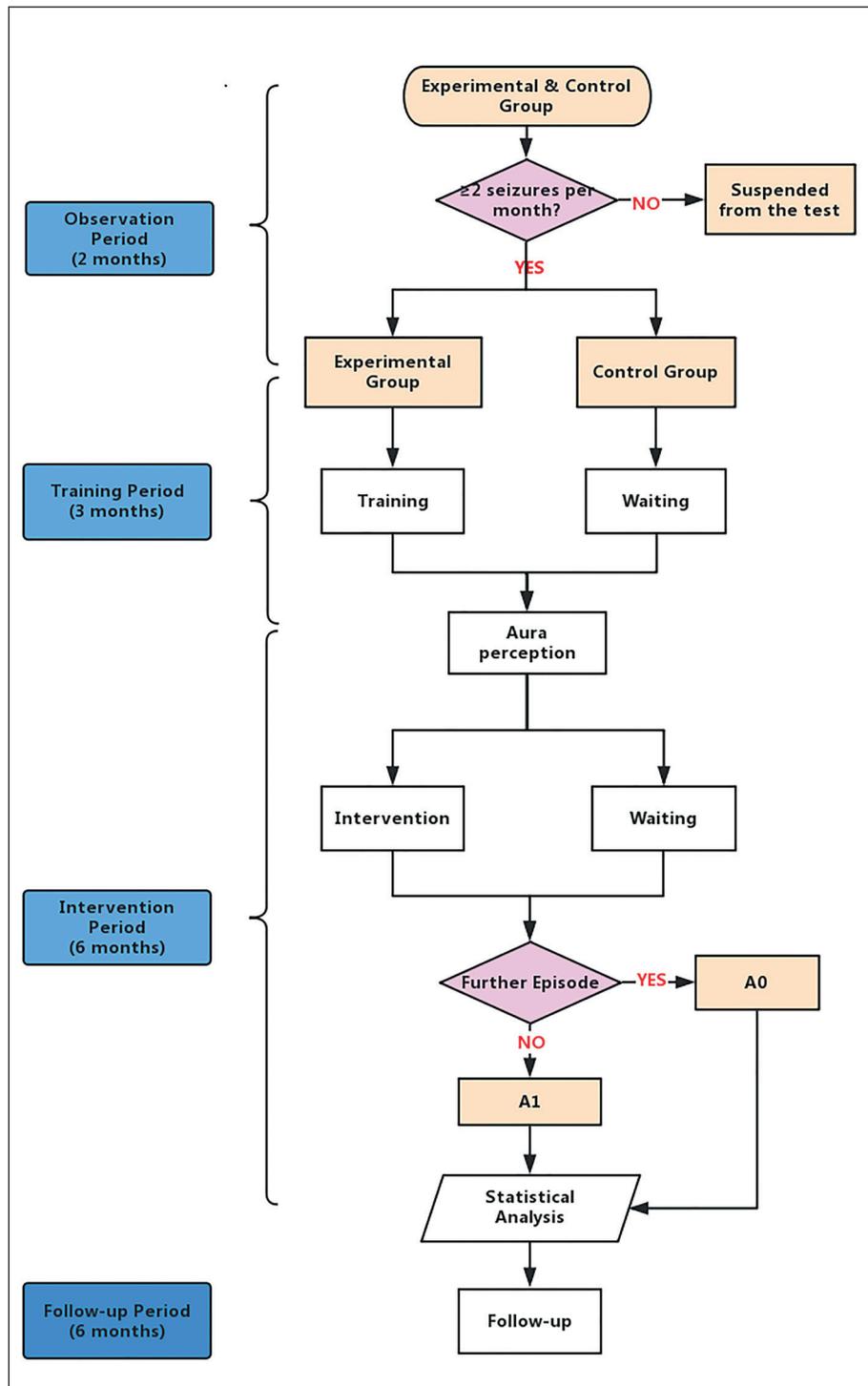


Figure 2: Stratified randomization.

■ OUTCOME MEASURES

Primary outcome measure

The primary outcome measure is the change in seizure frequency, specifically the frequency of grand mal seizures. The baseline is obtained by averaging the seizure count over the 2-month observation period. At the end of the trial, we compare the seizure frequency, respectively, calculated in the last 2 months of the intervention and follow-up periods with the baseline frequency. Outcomes will be categorized as follows: seizure-free (decreased by 100%), improved (decreased by $\geq 50\%$), minimal change (decreased by $< 50\%$), and worsened (increased seizures), or “insufficient documentation” for subjects who do not provide adequate documentation for this step of analysis (for example, less than 8 weeks of consecutive documentation each at the beginning and at the end of the intervention) (17).

Secondary outcome measure

The secondary outcome measure is the QOL. The Quality of Life in Epilepsy Inventory (QOLIE-31) scale is administered to all the patients both at the baseline and at the end of the follow-up period. We use t-tests to compare the differences

in total and subscale scores. The paired-samples t-test is applied to detect significant differences between before and after the experiment in each group. For group comparison, we preliminarily determine whether there is baseline difference in each subscale between the two groups using the first completed scale. If not, independent-samples t-test will be used to detect significant difference between groups using the second scale.

■ DISCUSSION

Epilepsy is a major nervous system disease that can significantly interfere with an individual's normal life. At present, we mainly use drugs and surgery for treatment. Unfortunately, more than 30% of epileptic patients have inadequate seizure control with AEDs (14), which contributes to the increase of behavioral and psychological interventions. Behavioral and psychological interventions are less costly, non-invasive, and have few serious side effects, which are conducive to patient participation (15). Studies show that over 50% of patients with TLE have symptoms of aura, such as unpleasant smell (4), transitory blindness (9), musical hallucinations (5), or bizarre unusual dreams. Among patients with auras, approximately

Table I: Type of Auras

Type of Auras	Systems Involved
Automatism	—
Special sensory auras	visual, auditory, olfactory, gustatory, vertiginous, somato-sensory
Psychic auras	dysmnestic, cognitive, affective, illusions, structure hallucination
Autonomic auras	epigastric, cardiovascular, genito-urinary

Table II: Inclusion and Exclusion Criteria

Inclusion criteria

Age over 18 years old

Temporal lobe epilepsy consistent with ILAE criteria supported by either EEG or MRI data

Average seizure frequency of at least twice per month

Awareness of premonitory features

Ability to understand and follow instructions

Unchanged anticonvulsant ordination for at least 1 month prior to participation

No ongoing psycho-pharmacological treatment

Exclusion criteria

Widely fluctuating seizure frequency or history of recurrent status epilepticus

Taking with more than two anticonvulsant medications

Serious other medical problems such as brain tumors, cancer, stroke, significant heart disease

Psychiatric disorders such as schizophrenia or major depression

Progressive epilepsy

20% have motivation to take action to interrupt epileptic seizures, and 10% of the patients were successfully able to prevent epileptic seizures. When aura is perceived to occur, patients can spontaneously intervene in their own way to stop the episode from developing further. In this study, we aim to determine whether aura intervention is feasible in controlling TLE.

We have designed a four-stage controlled trial, and we expect to observe a lasting, stable, and evident reduction in seizure frequency and an increase in QOLIE-31 scale scores. If this is the case, the result will indicate that aura intervention may be of substantial help to patients who can predict epileptic seizures. If patients are able to perceive auras and have time to take action in the phase where full epileptic function does not yet exist, there is a significant chance of inhibiting the seizure.

However, we have met several challenges in this trial design, such as the selection of individualized intervention, length of training period, and threshold setting for measuring effectiveness. Clinical observation, self-report, narratives, and video recordings from their families contribute to the selection of methods. An optimum length of the training period is essential since an excessively short training period is not conducive to developing stable intervention behavior, whereas an extended period of training may magnify the difference in seizure counts. Therefore, regarding the training duration and the threshold setting, we have analyzed a significant amount of previous research data and refer to useful parameters to select the best setting.

Furthermore, it is worth mentioning that patients' motivation and compliance with intervention have an impact on the outcome of intervention (7). If physical conditions permit, a significant motivation and compliance help achieve seizure freedom. Additionally, patients participating in this study are highly selected with frequent and typical seizures. Thus, they are not generally representative of patients with epilepsy, which may limit the application of aura intervention to some extent.

CONCLUSION

In summary, aura intervention has significant potential in the treatment of epilepsy. Although it may lead to superior epilepsy control, it has received less attention compared with medical and surgical interventions. For adults with refractory epileptic seizures, aura intervention may be a good choice to enhance their QOL. With optimized design and personalized treatment, patients might be able to interrupt all predictable seizures and even become seizure-free. Although significant challenges in conducting randomized clinical trials are observed, much remains to be studied. Moreover, we firmly believe that aura intervention is considered potentially beneficial in controlling TLE in the future.

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AUTHORSHIP CONTRIBUTION

Study conception and design: JW

Data collection: XL, HZ, XZ

Analysis and interpretation of results: JW, XL, HZ

Draft manuscript preparation: JW, XL, HZ

Critical revision of the article: JD, YP, XZ, KY, SQ, HL

Other (study supervision, fundings, materials, etc...): JW

All authors (JW, HZ, XL, JD, YP, XZ, KY, SQ, HL) reviewed the results and approved the final version of the manuscript.

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