Functional Anterior Temporal Lobectomy via Minicraniotomy as a Novel Surgical Therapy for Temporal Lobe Epilepsy: A Randomized, Controlled Trial

BACKGROUND: Anterior temporal lobectomy (ATL) is the most effective therapy for drug-resistant temporal lobe epilepsy (TLE). However, patients are reluctant to choose the surgery for the fear of risks after large frontotemporal craniotomy. Epileptologists also have cautious attitude towards referring patients with TLE for ATL due to surgical related trauma. As a new surgical approach, functional anterior temporal lobectomy (FATL) is a minimally invasive therapy for well addressing above concerns.

OBJECTIVE: To compare the surgical procedure, safety, and efficacy of FATL for TLE with ATL.

METHODS: This was a single-center, prospective, randomized controlled trial. A total of 120 patients aged between 18 and 60 years with drug-resistant TLE will be enrolled for at least 3 years. Patients will be randomly assigned to receive either FATL (n = 60) or ATL (n = 60). Primary outcomes include surgery duration, intraoperative blood loss, length of skin incision, size of bone flap, postoperative hospital stay, cosmetic appearance of the wound, and complications at the 1-year follow-up after surgery. Secondary outcomes are seizure outcomes, quality of life evaluated by the epilepsy-specific Quality of Life in Epilepsy Inventory-89, and neuropsychological outcomes.

EXPECTED OUTCOMES: We expect to find more favorable outcomes of FATL for TLE compared to ATL, while seizure outcomes following FATL are expected to be similar to ATL.

DISCUSSION: The surgical procedure, safety, and efficacy of FATL for TLE will be verified in this trial. FATL is a less-invasive approach. As a level 1 evidence, FATL could be strongly recommended to treat TLE.

SHORT TITLE: Functional anterior temporal lobectomy for TLE

KEY WORDS: Anterior temporal lobectomy, Functional anterior temporal lobectomy, Minicraniotomy, Randomized controlled trial, Temporal lobe epilepsy.

ABBREVIATIONS: ATL, anterior temporal lobectomy; eCRF, electronic case report forms; EEG, electroencephalogram; FLAIR, fluid-attenuated inversion recovery; FATL, functional anterior temporal lobectomy; ICF, informed consent form; IQ, intelligence quotient; MRI, magnetic resonance imaging; PET, positron emission computed tomography; TLE, temporal lobe epilepsy.

GENERAL INFORMATION

Title: Evaluate the Surgical Procedure, Safety, and Efficacy of Functional Anterior Temporal Lobectomy for Temporal Lobe Epilepsy Comparing with the Anterior Temporal Lobectomy.

Trial Abbreviation: Minimally invasive surgical epilepsy trial for TLE (MISET-TLE).

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Approved by the Ethical Committee of the First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China; number XJTU1AF2021LSK-194)

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RATIONALE AND BACKGROUND INFORMATION

Temporal lobe epilepsy (TLE) is a chronic neurological disease characterized by progressive seizures, following by a latency period of several years after various injuries including febrile seizures, infection, trauma, tumors, and vascular malformation.[1] Hippocampal sclerosis is the most common histopathological finding.[2] The macroscopic changes of TLE with hippocampal sclerosis are the diminished size, sclerosis, and reduced metabolism in mesial temporal structures (amygdala, hippocampus, and parahippocampal gyrus).[3] The microscopic changes include neuronal loss, gliosis, and axonal reorganization.[1] As TLE progresses, most of the patients become resistant to current antiepileptic drugs. Therefore, TLE is the most frequent subtype of refractory focal epilepsy in adults.

Epilepsy surgery has proven to be very efficient for TLE and superior to medical therapy in two randomized controlled trials.[4,5] Patients undergoing surgical therapy have a high seizure-free rate, ranging from 60% to 80 %, while the rate is less than 5% with medical treatment.[6] Since surgical therapy of temporal lobe epilepsy and the technique of temporal lobectomy were firstly reported by Penfield in 1950s,[7,8] anterior temporal lobectomy (ATL) is the most frequently used approach for TLE.[9] For patients with TLE, Engel suggested that referral to ATL should be strongly considered.[10] The decision analysis showed that ATL increased life expectancy and quality-adjusted life expectancy in patients with TLE compared with medical management.[11] Although complication rates after ATL have decreased dramatically over time,[12] complications remain an unavoidable consequence of this large frontotemporal craniotomy. ATL creates a large cavity due to temporal lobe resection, causing potential risks such as subdural collections, cerebrospinal fluid leakage, and brain shifts. Scar wound and muscular atrophy after frontotemporal craniotomy result in poor cosmetic appearance, hindering the usage of ATL. With advances in minimally invasive surgery, ATL has been modified to different surgical approaches for TLE.[13,14] As a standard procedure, ATL still has excellent results compared with other approaches.[14]

However, ATL for TLE is underutilized worldwide by far. A nationwide survey in Sweden showed annual number of epilepsy surgery declined between 1991 and 2007 at a rate of 2.5 per year, suggesting neurologists have a cautious attitude towards epilepsy surgery.[15] Similarly, the numbers for all surgical procedures except vagus nerve stimulation had decreased from

2000 to 2011 in United Kingdom.[16] As well, the annual rate of ATL for TLE declined by >65% between 2006 and 2010.[17] Reasons for the decline in ATL for TLE are unclear and speculative. One of the important factors may be that ATL is performed by large frontotemporal craniotomy, causing potential complications (e.g. poor cosmetic appearance, infection, neurological deficits, etc.). Fear of the risks after large craniotomy makes patients reluctant to choose ATL and epileptologists inactive to refer patients with TLE to surgical center.

For addressing the above concerns, we modify the surgical approach. Functional anterior temporal lobectomy (FATL) via minicraniotomy is established as an alternative. To date, this open surgery for TLE has not been reported. The surgical procedure, safety, and efficacy of FATL must be verified. Therefore, we present a protocol for the MISET-TLE trial. This is the first study to evaluate the clinical outcomes of FATL as a novel surgical approach for TLE.

STUDY GOALS AND OBJECTIVES

Hypothesis

As a minimally invasive procedure, the overall hypothesis is that patients with TLE will benefit from FATL, with seizure control and neuropsychological outcomes no less than standard ATL whereas complications and cosmetic appearance superior to ATL. Therefore, the goal of this study was to measure the surgical technique, safety, and efficacy of FATL compared to ATL at the department of neurosurgery in our hospital.

Primary Objective

- Minimally invasive outcomes: surgery duration, intraoperative blood loss, length of skin incision, bone flap size, and postoperative hospital stay.
- Complications and cosmetic appearance of the wound at the 1-year follow-up after epilepsy surgery.

Secondary Objectives

- Seizure outcomes were categorized according to the Engel and International League Against Epilepsy (ILAE) classifications.[18] The actuarial seizure outcomes over time were evaluated using the Kaplan–Meier analysis.

- Quality of life is evaluated by the epilepsy-specific Quality of Life in Epilepsy Inventory-89 (QOLIE-89; range of scores, 0 to 100, with higher scores indicating better quality of life).[19]
- Neuropsychological outcomes were assessed according to the consensus reported by Brissart.[20]

STUDY DESIGN

MISET-TLE is a single-center, prospective, single-blinded, double-arm, randomized controlled trial. A total of 120 patients are planned to be recruited (60 patients per group). The anticipated completion date will be in July 2024. SPIRIT checklist is used when writing our report.[21]

Inclusion/Exclusion Criteria

Inclusion Criteria

- male or female aged between 18 and 60 years.
- drug-resistant TLE, with remaining seizures after two or more tolerated and appropriately chosen antiepileptic drugs for at least 1 year.
- monthly or more frequent seizures during the preceding year prior to the trial.
- full-scale intelligence quotient (IQ) more than 70, able to understand and complete the trial.
- signed informed consent.
- good compliance, at least 12-month follow-up after surgery.

Exclusion Criteria

- tumor in the temporal lobe.
- extratemporal epilepsy and temporal plus epilepsy.
- drug-responsive epilepsy, seizure freedom with current drugs in the past year.
- pseudoseizures.
- seizures arising from the bilateral temporal lobes.
- significant comorbidities including progressive neurological disorders, active psychosis, and drug abuse.
- a full-scale IQ lower than 70, inability to complete tests.

- previous epilepsy surgery.
- poor compliance and inadequate follow-up.

METHODOLOGY

Screening and Enrollment

Pre-screening will be conducted for known or referred patients with TLE who may be eligible for the trial. All potential subjects will undergo a detailed screening visit at our center. Presurgical evaluations include seizure semiology, electroencephalography, imageology, and neuropsychology. Long-term video scalp electroencephalogram (EEG) with bilateral sphenoid electrodes in the standard 10–20 system will be used to monitor each patient for more than 24 hours. The 3-Tesla magnetic resonance imaging (MRI) epilepsy protocol includes three-dimensional (axial, coronal, and sagittal) scanning of T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences with a slice thickness of 1 mm without an intervening gap. If epileptiform discharges arising from bilateral temporal lobes in scalp EEG, MRI, and EEG are inconsistent, intracranial EEG was performed for the lateralization of the epileptic focus. Positron emission computed tomography (PET) will be performed to evaluate the metabolism of the temporal lobe, especially in patients with negative MRI findings. Then, MRI and PET will be processed and merged using 3D slicer software (ver. 4.7).

Each patient case will be discussed by a multidisciplinary epilepsy team consisting of neurologists, neurosurgeons, neuroradiologists, and nuclear medicine specialists to confirm eligible patients. In addition, the assessments of neuropsychologists and psychiatrists will be taken into consideration before the trial to evaluate coexisting psychiatric conditions. Above evaluations will serve as baseline results. Flow chart of the study is showed in Figure 1. Recruitment advertisement of trial is issued on the Internet and introduced to regional epilepsy centers and associations in Northwest China, for securing the number of eligible subjects.

Randomization and Blinding

Patients will be assigned with computer-generated random numbers by an independent statistician. Randomization is stratified by sex, with separate permuted blocks for each sex. Allocations are concealed until participants' eligibility and identities are confirmed. Allocations are also sequentially numbered in a 1:1 ratio to either receive FATL (experimental group) or

ATL (control group). Assessors evaluating the outcomes will be blinded to treatment throughout the study. Blinding is maintained by having patients wear large hats during reviews to obscure skin incision and providing patients strict instructions not to reveal their treatment arm.

Surgical Intervention

FATL

Patients will be placed in the supine position with their head contralaterally rotated by 30°. The 3D model of the incision and bone flap will be printed prior to the surgery using the slicer software based on the MRI data. A slightly curve incision with a length of approximately 6 cm in the temporal region beginning from the zygomatic arch will be marked (Figure 2A). A temporal craniotomy via a small bone window with a diameter of about 3 cm will be performed (Figure 2B and C). From the temporal pole approximately 4-5 cm posteriorly, the temporal horn is opened by dissecting the middle temporal gyrus. The head of the temporal horn will be exposed. The amygdala will be resected. Then, the parahippocampal gyrus and the hippocampus will be resected en bloc. Temporal lobotomy is easy because of the large view following the removal of the mesial structures (Figure 2D and E). The lateral posterior temporal lobotomy was no more than 5 cm from the temporal pole. Finally, the temporal stem was divided to isolate the superior temporal gyrus.

ATL

Patients will be placed in the supine position with their head contralaterally rotated by 30°. A large frontotemporal craniotomy will be performed. A question mark-shaped incision with a length of 20-25 cm in the frontotemporal region beginning from the zygomatic arch will be marked (Figure 2F). The size of the bone flap is approximately 5 × 7 cm for exposure of the lateral temporal lobe (Figure 2G and H). ATL consists of a standard protocol including en bloc resection of the anterior 5 cm of the lateral temporal lobe, followed by the removal of mesial structures including the amygdala, parahippocampal gyrus, and the hippocampus (Figure 2I and J).

DISCUSSION

Currently, there is still no consensus on the optimal surgical approach for TLE,[14] and surgical approaches are often based on the neurosurgeon's experience and preference. The surgical goal for TLE is to perform a more extensive resection under the premise of minimal functional deficits to achieve maximum seizure control.[22] ATL involves removing 4–6 cm of the anterior temporal lobe, including the amygdala and hippocampus.[4] With the advances and understanding of microsurgical neuroanatomy and surgical techniques, minimally invasive surgery is a trend for less-invasive procedures, fewer complications, and better neuropsychological outcomes.

FATL is more likely to be accepted by patients compared with ATL. As a new surgical approach, FATL has several advantages. Firstly, amygdalohippocampectomy provides greater view for facilitating the temporal lobotomy, and guaranteeing the complete disconnection and isolation of the temporal lobe. Secondly, temporal lobotomy, disconnecting the lateral temporal cortex, avoids potential complications related to larger cavity volume after parenchymal defect in ATL. Thirdly, faster recovery is obtained due to a reduction in surgery duration, blood loss, complications, and hospital stay after this minimally invasive surgery. Finally, better cosmetic appearance of the wound is obtained because of minicraniotomy. Scar wound and muscular atrophy are common in patients with ATL by large frontotemporal craniotomy. We hypothesize that FATL is a less-invasive, safe and effective therapy for TLE. In this trial, we will compare the clinical outcomes of FATL for TLE with ATL.

TRIAL STATUS

Patient recruitment began in September 2021. This study is expected to be completed by July 2024. Final data analyses will be performed, and final reports will be published over the following year.

SAFETY CONSIDERATIONS

Complications, such as any deviation from the normal postoperative course, are defined by the criteria and definitions for ATL-associated complications reported by Brotis.[23] These include surgical-site infection, hemorrhage, neurological deficits, cerebrospinal fluid leak, subdural fluid collection, hydrocephalus, and medical complications (less likely, e.g., deep vein thrombosis, urinary tract infection, acute kidney/lung disorders, respiratory distress or failure,

etc.). The severity of a complication is graded as minor if it resolves within 3 months, and major if it lasts longer than 3 months and affects the activities of daily living.[24]

FOLLOW-UP

After surgery, patients continue to take antiepileptic drugs, and changes are made by clinicians as necessary to manage seizures. Study scheme and follow up are showed in Figure 3. Patients will be followed up for at least one year. Patients are seen in the outpatient clinic at 1 month after surgery, then every 3 months for 1 year, and subsequently at yearly intervals. Patients will be required to write detailed descriptions of all seizure events in their monthly seizure diaries. EEG and neuropsychological scales will be examined at each follow-up. MRI will be performed 3 months after surgery to evaluate the extent of resection. Antiepileptic drugs will be tapered and discontinued in the period of 3–6 months if patients remain seizure-free at 1 year after surgery. Antiepileptic drugs will be administered again when patients experience seizure recurrence.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Final data capture and storage will be performed via electronic case report forms (eCRF) using an electronic database that is fully compliant with privacy regulations. In addition to eCRFs, data will be retained along with relevant supporting documentation, such as scans, progress notes, nursing notes, blood work, and pathology reports. All records and documents pertaining to the study will be retained by all the participating study trial sites for at least 10 years from the completion of the study, and will be available for inspection by the research ethics board, quality assurance, and other regulatory bodies. Hard copy study files (consent forms, questionnaires, and coordinator source notes from participant research charts) will be kept secured with the Department of Neurosurgery. All computerized files will be password-protected.

Statistical Considerations

Based on the mean surgery duration in our center (3.4 h in the ATL group vs. 3.0 h in the FATL group), we needed to enroll 50 patients per group in order to detect a statistical difference with 90 percent power at a two-sided significance level of 0.05. Anticipating up to a 20% attrition rate, there are 120 patients recruited.

Categorical data are presented as frequencies. Continuous data are expressed as mean ± standard deviation. Means are compared using the Student's t-test and proportions with the Chi-squared test; however, the Fisher exact test is used instead when cell sample sizes in the contingency table are small. Analyses are performed using SPSS version 22.0 (IBM, Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

QUALITY ASSURANCE

The research ethics board of our hospital will monitor the progress of the clinical trial for its safety and unexpected adverse effects, and related recommendations will be directed to the principal investigator. All adverse events will be reported within 24 hours of knowledge to the ethics board for evaluation.

EXPECTED OUTCOMES OF THE STUDY

This study aimed to clarify the safety and efficacy of FATL in TLE. We expect that patients with TLE underdoing FATL will have similar seizure-free rates, lower rates of complications, and better neuropsychological outcomes than those with ATL. This randomized controlled trial will provide level I evidence of the superiority of FATL for TLE, compared to ATL.

DURATION OF THE PROJECT

This trial will enroll 40 subjects per year over a 3-yr period. The follow-up duration of each individual patient will be at least 1 year. The estimated date of completion of the primary outcome measures will be July 2024; the estimated study completion date will be July 2025. The complete study duration is estimated to be 4 or 5 years.

PROJECT MANAGEMENT

The principal investigator of the study (Hua Zhang) will oversee the trial and enroll each patient, assisted by trial manager Yong Liu and Hao Wu. Surgery is performed by Hua Zhang. The data coordinating center are overseen by senior manager Qiang Meng. Perioperative management is performed by Dr. Changwang Du and Kuo Li. Outcomes are assessed by Huanfa Li, Shan Dong, and Xiaofang Liu. The data and safety of the trial will be monitored by the Institutional Review Board at our hospital.

ETHICS

Regulation

The study will be performed in accordance with the World Medical Association Declaration of Helsinki (2019). The MISET-TLE protocol was approved by the Ethical Committee of the First Affiliated Hospital of Xi'an Jiaotong University in Xi'an, China; (XJTU1AF2021LSK-194).

Informed Consent

Patients should not be persuaded, coerced or unduly influenced to participate in the trial. Patients should be given sufficient time (at least one day) and opportunity to understand the trial, ask questions. All questions should be answered to the patients' satisfaction. Patient-informed consent must be obtained prior to any study activities. The Informed Consent Form (ICF) should be signed by the patient or proxy. If the patient is unable to read and understand the ICF, a proxy should be present during the entire informed consent discussion. This proxy should also sign the ICF, stating that informed consent was freely given by the patient. The patient should receive one of the two signed copies of the ICF. In addition, the patient consented to publication of his/her image.

Disclosures

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Figure Legend

FIGURE 1. Flow chart of the study protocol. TLE- temporal lobe epilepsy; FATL- functional temporal lobectomy; ATL- anterior temporal lobectomy.

FIGURE 2. Functional temporal lobectomy and anterior temporal lobectomy for temporal lobe epilepsy. A-E: functional temporal lobectomy. Yellow line represents the trajectory of temporal lobe disconnection in the functional temporal lobectomy. F-J: anterior temporal lobectomy. Red line represents the extent of temporal lobe resection in the anterior temporal lobectomy. FATL- functional temporal lobectomy; ATL- anterior temporal lobectomy.

FIGURE 3. Study scheme and follow up after surgery. FATL- functional temporal lobectomy; ATL- anterior temporal lobectomy.