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Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine

Informed Consent Form

A multicenter randomized controlled trial on the efficacy and safety of cervical lymph vessel/node-venous anastomosis combined with donepezil versus donepezil alone in the treatment of Alzheimer's disease

Introduction

We sincerely invite you to take part in this clinical study entitled "A multicenter randomized controlled trial on the efficacy and safety of cervical lymph vessel/node-venous anastomosis combined with donepezil versus donepezil alone in the treatment of Alzheimer's disease." This study is being conducted under the responsibility of Yixin Zhang, MD, and has been reviewed and approved by the Ethics Committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine.

Please read this informed consent form carefully and make a prudent decision about whether to participate in this study. Participation is entirely voluntary. As a research participant, you must provide written informed consent before entering this clinical study. When your study doctor or study staff discusses this informed consent form with you, you may ask him or her to explain anything you do not understand. We encourage you to discuss this study fully with your family members and friends before making a decision. You have the right to refuse participation or withdraw at any time without penalty and without losing any rights to which you are otherwise entitled. If you are currently participating in another study, please inform your study doctor or study staff.

Research Background

Alzheimer's disease is the most common cause of dementia. It seriously affects patients' daily life and behavioral function and causes a high social burden and heavy family burden. At present, most non-pharmacological and pharmacological treatments for Alzheimer's disease focus on improving cognitive function and psychiatric symptoms. These are symptomatic treatments and cannot delay disease progression. Our team proposes to use the extracranial supermicrosurgical technique of deep cervical lymphatic vessel/node-venous anastomosis to promote cerebral lymphatic reflux, thereby improving the deposition of pathological proteins such as Aβ and Tau in brain tissue and ultimately improving brain function in patients with Alzheimer's disease. Based on preliminary results of our prior single-center single-arm study, this surgical intervention showed positive effects on cognitive function and psychiatric symptoms. Therefore, we will further conduct this multicenter randomized controlled trial.

This study uses random assignment. All participants will be randomly assigned to two groups, and each participant has the same probability of entering either group. Random assignment will be generated by a computer system, and neither researchers nor participants can determine or influence the assignment in advance. Eligible participants will be assigned to one of two groups: one group will receive deep cervical lymphatic vessel/node-venous anastomosis combined with oral donepezil; the other group, as the control group, will receive oral donepezil alone. The surgical procedure includes exposing the external jugular vein, internal jugular vein, surrounding lymphatic vessels, and lymph nodes in the neck, and anastomosing the lymphatic vessel/node tissue complex to veins to improve cerebral lymphatic reflux pathways. It should be noted that this study is intended to scientifically evaluate the efficacy and safety of the surgical treatment combined with drug therapy compared with drug therapy alone, and the surgery itself is an investigational therapeutic measure.

Purpose of the Study

The purpose of this study is to investigate the efficacy and safety of supermicrosurgical deep cervical lymphatic vessel/node-venous anastomosis combined with oral donepezil, compared with oral donepezil alone, in patients with Alzheimer's disease accompanied by moderate dementia.

Study Procedures

If you agree to participate and meet the eligibility criteria, you will be enrolled in the study. This is a multicenter randomized controlled trial and will enroll 216 research participants.

Inclusion Criteria

(1) The patient or guardian signs the informed consent form;

(2) Age 50-80 years (≥50 years, ≤80 years), male or female;

(3) The first diagnosis is Alzheimer's disease with dementia;

(4) MMSE score ≤24;

(5) Positive β-amyloid protein PET imaging findings;

(6) HAMD score ≤17;

(7) Hachinski score ≤7;

(8) No AD-related drug treatment has been received within the past 1 month;

(9) ASA grade 1-3 (≥ grade 1, ≤ grade 3);

(10) CDR-SB score of 9.5-15.5.

Exclusion Criteria

(1) Presence of contraindications to MRI, ICG angiography, or PET scan;

(2) Presence of contraindications to lumbar puncture;

(3) Severe heart disease or unstable hemodynamic status;

(4) Severe lung disease, including severe obstructive, restrictive, or mixed ventilatory dysfunction, or acute inflammation within 3 months;

(5) Hepatic insufficiency, AST or ALT >3 times the upper limit of normal;

(6) Renal insufficiency, GFR <60 mL/min or need for blood purification treatment;

(7) MRI indicates active or acute intracranial lesions, including intracranial infection, space-occupying lesions, major hemorrhage, and ≥4 lobar microbleeds, etc.;

(8) History of cerebral hemorrhage or cerebral infarction with severe residual neurological dysfunction;

(9) Blood diseases, bleeding/coagulation disorders, coagulation dysfunction;

(10) Abnormal thyroid function;

(11) Moderate or severe stenosis of intracranial or cervical vessels with severe residual neurological dysfunction;

(12) Severe hypertension not effectively controlled, systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg;

(13) The disease requires systemic use of steroids;

(14) Drug addiction (including alcohol, narcotics, and alcohol dependence);

(15) Severe infectious diseases, including HIV positivity, severe infection, etc.;

(16) Severe psychiatric disease or potential suicide risk;

(17) Within 3 years after radical surgery for malignant tumor;

(18) Participation in other interventional clinical trials within the past three months;

(19) In the physician's judgment, poor compliance, inability to complete, or unwillingness to cooperate with regular postoperative follow-up;

(20) Other circumstances that the physician considers unsuitable for this clinical trial;

(21) Anti-Aβ monoclonal antibody treatment has been received within half a year;

(22) Previous neck surgery.

The study process includes four stages: screening, baseline collection, treatment, and post-treatment follow-up.

Screening stage: If you are willing to participate, after obtaining written signed consent from you or your legal representative, the doctor will collect your basic information and clinical data, including medical history, medication history, surgical history, allergy history, tumor history, previous participation in clinical research, and relevant previous medical examination results. The study doctor will determine whether you meet the eligibility criteria and whether there are any conditions unsuitable for participation based on interview, physical examination, and necessary auxiliary examinations.

Screening-related examinations may include: (1) interview, physical examination, and general assessment, including age verification, vital signs, neurological interview and examination, mental status, and compliance assessment; (2) neuropsychological and functional scales, including MMSE, CDR-SB, BADL, IADL, HAMD, and Hachinski; (3) blood tests including routine blood tests, C-reactive protein, coagulation, liver function, renal function, electrolytes, fasting glucose, myocardial injury markers, BNP, thyroid function, tumor markers, HIV, syphilis, and hepatitis-related tests; (4) cardiopulmonary and other auxiliary tests including electrocardiogram, echocardiography, pulmonary function, chest CT, and cervical ultrasound; (5) neuroimaging examinations including enhanced brain MRI and SWI, cerebral CTA, and beta-amyloid PET (Aβ-PET). If screening shows that you do not meet the criteria or are not suitable for participation, you will not enter subsequent study procedures, and the study doctor will explain the reason to you or your family.

Baseline collection stage: If you pass screening and enter the study, the study doctor will further complete and organize your baseline data before formal treatment begins. Baseline data are an important reference for subsequent assessment of treatment effects, safety, and related research indicators. To ensure data completeness, even if certain tests were performed during screening, any result that needs to be kept and analyzed as pretreatment baseline data will be clearly recorded in the baseline collection stage.

Baseline collection mainly includes: (1) basic information, history, medication, vital signs, physical examination, and adverse event/concomitant medication records; (2) gross photographs and videos; (3) neuropsychological, activities of daily living, and behavioral scales including MMSE, MoCA, CDR-SB, BADL, IADL, AES, and NPI; (4) imaging examinations including Aβ-PET, Tau-PET, enhanced brain MRI and SWI, glymphatic MRI research sequences, and cervical ultrasound; (5) blood and CSF sample collection and testing. Blood and CSF testing includes Aβ-42, Aβ-40, Aβ-42/Aβ-40, P-tau181, pTau217, GFAP, NfL and other AD-related pathological proteins and neural injury biomarkers, and may also include IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNF-α, IFN-γ, IFN-α and other inflammatory markers, as well as APOE polymorphism testing. These examinations are used to record your pretreatment disease state and biological characteristics and for later efficacy, safety, and mechanistic analyses.

Treatment stage: If you meet the eligibility criteria, you will be randomly assigned by central randomization with stratified block randomization to one of the two groups below.

If assigned to the intervention group, you will receive cervical lymphatic vessel/node-venous anastomosis combined with oral donepezil. The surgery will be performed under general anesthesia. Using refined microsurgical techniques, lymphatic vessels/nodes in specific cervical areas will be anastomosed to veins to improve lymphatic reflux. During surgery, pathological lymph nodes may be collected as appropriate and a very small amount of lymphatic fluid may be collected. Starting on postoperative day 1, you will take donepezil orally once daily. The starting dose is 5 mg; after 6 weeks, if tolerated, the dose will be adjusted to 10 mg. If intolerance occurs, 5 mg will be maintained, and another attempt to increase to 10 mg will be made after 6 weeks. The total duration of medication is 18 months. If the higher dose is consistently not tolerated, the 5 mg dose may be maintained throughout.

If assigned to the control group, you will not undergo surgery and will receive oral donepezil alone. The method of administration, dose adjustment, and treatment duration are the same as those in the intervention group: once daily oral administration starting from 5 mg, increasing to 10 mg after 6 weeks if tolerated; if not tolerated, remaining at 5 mg and attempting escalation again after 6 weeks. Total treatment duration is 18 months. If the higher dose is consistently not tolerated, the 5 mg dose may be maintained throughout.

Regardless of your group, we will closely monitor your health status and promptly manage any discomfort or adverse drug reactions that may occur.

Post-treatment follow-up stage: Study follow-up will continue until 18 months after the start of intervention. If necessary, follow-up may be extended. You will return for re-examination at 1 week, 1 month, 3 months, 6 months, 12 months, and 18 months after intervention, including neuropsychological assessments, PET scans, MRI scans, cervical ultrasound, blood tests, and CSF tests. The schedules are as follows.

Visit Schedule for the Combined Intervention Group

Item	Preoperative	Immediately postoperative	1 week post-op ±1 day	1 month post-op ±7 days	3 months post-op ±14 days	6 months post-op ±14 days	12 months post-op ±14 days	18 months post-op ±14 days
Signed informed consent	√							
Gross photographs/videos	√		√	√	√	√	√	√
Adverse events	√	√	√	√	√	√	√	√
CDR	√		√	√	√	√	√	√
Neuropsychological scales (MMSE, MoCA, AES, NPI, BADL, IADL)	√		√	√	√	√	√	√
HAMD, Hachinski	√							
PET	√					√	√	√
MRI plain	√		√	√	√	√	√	√
MRI contrast-enhanced	√					√	√	√
Cervical ultrasound	√			√	√	√	√	√
CSF	√		√			√	√	√
Blood	√		√	√	√	√	√	√
Lymph nodes/lymphatic fluid		√ (intraoperative)						

Indices for CSF and blood tests include Aβ-42, Aβ-40, Aβ-42/Aβ-40, P-tau181, GFAP, NfL, pTau217, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNFα, IFN-γ, and IFN-α. Note: At each follow-up visit, approximately 8-9 mL of blood and 6 mL of CSF will be collected. During surgery, 1-2 angular, level II, and level III cervical lymph nodes are planned to be collected, and 0.5-3 mL of lymphatic fluid from each side may be drawn.

Visit Schedule for the Medication-Only Group

Item	Before medication	Treatment start day	1 week after treatment ±1 day	1 month after treatment ±7 days	3 months after treatment ±14 days	6 months after treatment ±14 days	12 months after treatment ±14 days	18 months after treatment ±14 days
Signed informed consent	√							
Gross photographs/videos	√		√	√	√	√	√	√
Adverse events	√	√	√	√	√	√	√	√
CDR	√		√	√	√	√	√	√
Neuropsychological scales (MMSE, MoCA, AES, NPI, BADL, IADL)	√		√	√	√	√	√	√
HAMD, Hachinski	√							
PET	√					√	√	√
MRI plain	√		√	√	√	√	√	√
MRI contrast-enhanced	√					√	√	√
Cervical ultrasound	√							
CSF	√		√			√	√	√
Blood	√		√	√	√	√	√	√

Indices for CSF and blood tests include Aβ-42, Aβ-40, Aβ-42/Aβ-40, P-tau181, GFAP, NfL, pTau217, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNFα, IFN-γ, and IFN-α. Note: At each follow-up visit, approximately 8-9 mL of blood and 6 mL of CSF will be collected.

This study is expected to last 3 years. For you personally, participation in this study will last approximately 570 days.

All biological samples collected in this study will be stored in accordance with unified standards after completion of initial processing. Samples will be stored using anonymous codes in a -80°C ultra-low temperature freezer or liquid nitrogen tank. The storage environment is equipped with temperature monitoring and emergency systems to ensure stable sample quality. After completion of the testing items specified in this study protocol, any remaining samples will be properly preserved according to standard operating procedures. These samples will be strictly limited to subsequent scientific research use by this research group, and we undertake never to disclose sample information or use it for any unauthorized purpose.

Possible Benefits and Risks

This study may help delay the progression of your Alzheimer's disease, but the effect cannot be guaranteed. We hope that the information obtained through your participation may benefit you or patients with similar conditions in the future.

All treatments involve certain risks. Although extracranial supermicrosurgical deep cervical lymphatic vessel/node-venous anastomosis is a minimally invasive surgery and an effective method to improve cerebral lymphatic reflux, mild adverse reactions of conventional surgery may still occur during treatment or after surgery, including but not limited to postoperative infection, postoperative bleeding, and minor local vascular or nerve injury causing exudation, hematoma, seroma or edema, pain, and sensory or motor abnormalities.

Oral donepezil may also cause drug-related adverse reactions. Common reactions include nausea, vomiting, diarrhea, loss of appetite, muscle cramps, fatigue, dizziness, insomnia, etc. A small number of patients may develop bradycardia; therefore, heart rate should be closely monitored during medication. Most reactions are mild to moderate, but medication should still be used under medical guidance and with timely communication.

PET scans involve a small amount of radioactive tracer exposure; MRI examinations may cause claustrophobic discomfort, and contrast-enhanced MRI or ICG angiography may cause allergic reactions, nausea, rash, and similar reactions. The study doctor will evaluate contraindications before examinations and provide necessary monitoring during examinations.

In addition, this study requires repeated CSF collection by lumbar puncture. This is an invasive examination and will be performed by experienced physicians. Although serious complications are rare, risks may include post-puncture headache, low back pain, redness and swelling at the puncture site, bleeding, or infection.

Any treatment may cause unforeseen adverse reactions. If, during participation, the patient sustains surgery-related injury or experiences a serious adverse reaction recognized after expert consultation, the hospital will actively coordinate free management to eliminate these injuries or serious adverse reactions. If they cannot be completely eliminated, the hospital will provide appropriate compensation. If any discomfort or adverse reaction occurs, please contact the study doctor in time, and the study doctor will provide active diagnosis and treatment. Injury related to clinical surgical treatment will be handled according to our hospital's policies for surgical risk and complication management and relevant laws and regulations.

If the investigator obtains information that may affect your willingness to continue participation, you or your legal representative will be informed in a timely manner. For reasons related to health or safety, the physician has the right to terminate your continued participation at any time, including if you are found not to meet inclusion criteria, fail to undergo treatment and follow-up as required, another treatment is considered more appropriate, other safety factors arise, or the study is terminated early. Any treatment may also be ineffective, and disease may continue to progress because of treatment failure, concomitant disease, or other reasons.

Research Costs and Related Compensation

Because many examinations are involved before and after intervention and the related costs are relatively high, to reduce the financial burden caused by participation, after enrollment, costs directly related to the protocol will be covered by the research project team. These include research-related neuropsychological scale assessments, PET scans, MRI examinations, cervical ultrasound examinations, AD-related blood sample collection and testing, and CSF sample collection and testing.

If you are randomized to the combined intervention group, the research-related deep cervical lymphatic vessel/node-venous anastomosis surgery cost, anesthesia cost, and donepezil medication cost will be covered by the project team. If you are randomized to the control group, the research-related donepezil medication cost will also be covered by the project team.

For transportation costs incurred by your participation in protocol-specified regular follow-up visits, the hospital will provide unified reimbursement after you complete all follow-up visits, based on actual transportation receipts. The reimbursement cap for each trip to the hospital is RMB 500. After the study is completed, the hospital will also provide a

unified subsidy of RMB 500 for each CSF examination you actually undergo. Appropriate clinical trial insurance will be provided for you.

Alternative Treatment Options

If you choose not to participate in or withdraw from this study, you still fully retain the right to receive other non-surgical treatment options under the professional advice of your attending physician. Whether you participate will not affect your physician's objective medical evaluation of your condition or decisions regarding related treatment plans.

Your Rights and Obligations

Participation in this study is entirely voluntary. You may withdraw unconditionally at any time, and this will not affect your relationship with medical staff or your future diagnosis and treatment. All of your information will be kept strictly confidential, and only relevant personnel will be allowed to review your medical records to verify the accuracy of collected information and ensure that the study proceeds properly. Electronically transmitted information will be renamed to ensure confidentiality. Computer information will be password-protected. Throughout the trial, we will strictly protect your image privacy and de-identify any photographs and/or videos. When study results are reported at medical meetings or published in scientific journals, no personally identifiable information about you will be disclosed. If you decide to participate, you will sign an informed consent form and keep one copy.

During the study, you are obligated to provide truthful information about your medical history and current physical condition; inform the study doctor of any discomfort during the study; avoid restricted medications and foods; tell the study doctor whether you have recently participated in or are currently participating in other studies; comply with follow-up requirements; and cooperate seriously with the study doctor throughout the study.

After reading this information and discussing it with your doctor, if you have questions or concerns, please contact: Research staff: Ke Li; Telephone number: 18964547316; Address: Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. If you have questions about your rights, please contact the Medical Ethics Committee directly: 021-63057795.

Signature Page for the Research Participant's Informed Consent Form

I have fully understood the nature, purpose, methods, duration, and possible risks and benefits of this clinical study. My questions to the study doctor have been answered to my satisfaction. After full consideration, I voluntarily agree to participate in this study and am willing to cooperate closely with the study doctor throughout the treatment and observation process required by the study protocol.

1. I may consult the physician at any time for more related information.

2. I may withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

3. I agree that relevant regulatory authorities, the ethics committee, and representatives of the investigators may review my study records when necessary.

4. I have received a copy of the informed consent form signed and dated jointly by myself and the study doctor.

5. I decide to participate in this study and am willing to strictly follow the study protocol requirements and cooperate with the doctor throughout the study.

Research participant (signature):	_____	Legal representative (signature):	_____
Telephone number:	_____	Relationship to participant:	_____
Date:	_____/____/____	Reason for proxy signature:	_____
		Telephone number and date:	_____

I have accurately explained this document to the research participant. He/She has accurately read this informed consent form, and I certify that the participant has had the opportunity to ask questions. I certify that his/her consent is voluntary.

Study doctor (signature):	_____	Telephone number:	_____	Date of signature:	_____