Safety and Efficacy of Multisensory Stimulation Virtual Reality for Stroke Patients

Study Protocol

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Background

Stroke is one of the leading diseases threatening public health in China, characterized by high incidence, disability, mortality, and recurrence rates. Approximately 75% of stroke survivors are left with varying degrees of motor dysfunction, imposing a heavy psychological and economic burden on families and society [1,2]. In 2021, the GBD 2019 Stroke Collaborators reported in Lancet Neurology that stroke has become the third leading cause of disability worldwide [3]. Although acute treatments have improved with the widespread implementation of stroke units, thrombolysis, and mechanical thrombectomy, a significant number of patients (>75%) still experience severe impairments in multiple domains—including motor function, speech, and cognition，which drastically affect their quality of life, independence, and social participation [1]. Therefore, there is an urgent need to advance neurorehabilitation strategies. Currently, rehabilitation for post-stroke motor dysfunction predominantly relies on conventional exercise and physical therapies. While effective, these methods face challenges such as high costs, lengthy treatment cycles, variable therapist expertise, and poor patient adherence. Furthermore, optimal central nervous system recovery requires patients to develop functional motor patterns through coupled sensory, motor, and cognitive feedback. Thus, exploring precise and high-quality rehabilitation strategies is of great clinical significance.

In recent years, emerging technologies like telerehabilitation, exoskeleton robots, and brain-computer interfaces have been increasingly applied to stroke rehabilitation. Among them, virtual reality (VR) offers unique advantages. By breaking the scenario-constraints of conventional therapy, VR provides multi-sensory stimulation and dynamic environments characterized by interaction, immersion, and imagination (the "3I" features) [4,5]. Recognized by Nature for its distinct potential in rehabilitation [5,6], VR has been widely used and proven effective in promoting limb motor recovery. However, its widespread clinical application is often hindered by unclear mechanisms, unstandardized protocols, and sometimes the "misuse" or superficial application of the technology. Some studies report that while both VR and conventional therapies improve upper limb motor function, there is no significant difference between them [7,8]. A multicenter, single-blind, randomized controlled trial also showed that VR, as an add-on to

conventional therapy, yielded no significant additional benefits for subacute stroke patients [9]. Furthermore, a meta-analysis of 72 studies indicated that current VR trials generally have small sample sizes, and using VR is not necessarily more beneficial than conventional methods, though it may serve as a useful adjunct to increase overall therapy time [10]. Consequently, the true efficacy and necessity of VR in stroke rehabilitation remain controversial.

Beyond motor deficits, cognitive impairment is a common post-stroke sequela linked to neural damage in functional areas such as the cortical limbic system and frontal white matter [11,12]. VR uniquely addresses this by providing interactive, multi-modal sensory stimuli (visual, auditory, and haptic) that foster real-world-like brain and behavioral responses [13]. In a fully immersive VR system, physical movements are dynamically coupled with the virtual environment, enhancing the patient's sense of presence and providing the cognitive-motor integration essential for neurological recovery.

In summary, while the clinical efficacy of VR in treating post-stroke motor dysfunction remains debated, exploring the neural remodeling mechanisms of multi-sensory VR stimulation is an urgent challenge. As there is a lack of rigorously designed randomized controlled trials in this area, this study aims to provide high-quality evidence for the effectiveness of multi-sensory VR in improving post-stroke motor function and to further elucidate its underlying neural mechanisms.

Objectives and Hypotheses

Primary Research Objective

The primary objective of this study is to compare the effects of multi-sensory virtual reality (VR)-enhanced treadmill training versus treadmill training alone on the improvement of lower limb motor function, balance, and gait in stroke patients, and to explore the underlying neuroplasticity mechanisms using functional near-infrared spectroscopy (fNIRS).

Scientific Hypotheses and Expected Outcomes

It is hypothesized that multi-sensory VR intervention will be superior to conventional treadmill training in improving lower limb motor function in stroke patients. By integrating multi-dimensional quantitative assessments, including clinical scales, three-dimensional gait analysis, and fNIRS, which aims to further elucidate the internal mechanisms by which VR

promotes neural remodeling. Ultimately, the findings will provide high-quality, evidence-based support for the clinical implementation of VR technology in post-stroke motor rehabilitation.

Trial Design and Statistical Methods

Overall Framework and Timepoints

This study is a single center randomized single blind controlled trial. A total of 40 stroke patients will be enrolled and randomly assigned to either the multi-sensory virtual reality enhanced treadmill training group or the treadmill training group in a 1 to 1 ratio. The entire trial includes a baseline period and a 4-week intervention period and a 3 month follow up period. Based on conventional rehabilitation both groups will receive their respective treadmill interventions with a frequency of 7 sessions per week for 4 consecutive weeks. Assessments will be conducted at four key time points including baseline on Day 0 and mid intervention at Week 2 and post intervention at Week 4 and long term follow up at Week 12. The evaluation system focuses on lower limb motor function and neural remodeling mechanisms. The primary outcome measure is the Fugl-Meyer Assessment Lower Limb scale. Secondary outcomes include three-dimensional gait analysis and the Berg Balance Scale and the Activities of Daily Living scale and the Mini Mental State Examination and the Montreal Cognitive Assessment and functional near infrared spectroscopy. Adverse events such as falls and dizziness will be recorded throughout the study to evaluate clinical safety.

Study Type

This study is a single center randomized single blind controlled trial.

Sample Size and Statistical Framework

Sample Size Calculation

$$n = \frac{(Z_\alpha + Z_\beta)^2 * 2\sigma^2}{\delta^2}$$

The sample size for this study was estimated using PASS 15.0 software before the start of the trial. Based on parameters from previous research we set the significance level at 0.1 and the power at 0.8 and the allowable error at 6.5 and the standard deviation at 8.0 for the calculation. The results

indicated that 20 patients are required for each group and the total sample size is 40.

Statistical Methods

All data analysis will be performed using SPSS 27.0 statistical software. The Kolmogorov Smirnov test will be used to evaluate the normal distribution of data before description. Continuous variables with a normal distribution will be expressed as mean and standard deviation while non normal data will be presented as median and interquartile range. Categorical variables will be described using frequencies and percentages. In the analysis of efficacy and safety before and after treatment we will use independent or paired t tests for normally distributed data and Mann Whitney U tests for non-normal data. Comparisons of categorical variables such as adverse events will be conducted using the Chi square test or Fisher's exact test. Correlation analysis will use Pearson or Spearman tests depending on the data distribution. For key observation indicators during the follow up period a linear mixed model will be used for repeated measures analysis to test group differences as well as time and interaction effects. To control for potential heterogeneity caused by age the study will also perform stratified analysis by age group. A P value of less than 0.05 will be considered statistically significant for all tests.

Procedures and Clinical Pathway

Study Design

This study is a prospective single center randomized parallel controlled clinical trial. The entire research period is divided into a baseline screening and assessment phase as well as a 4 week clinical intervention period and a 3 month long term follow up period. Following enrollment both groups will receive their established rehabilitation interventions 7 times per week for 4 consecutive weeks. To scientifically quantify the intervention efficacy and the disease recovery process the study avoids high frequency and fragmented visit schedules and instead establishes four precise clinical assessment time points including baseline on Day 0 and mid intervention at Week 2 and post intervention at Week 4 and long term follow up at Week 12.

Clinical Visits and Assessment Sequence

Screening Period at V0

Initial screening of subjects will be completed before the trial officially begins. Researchers must verify whether stroke patients diagnosed via neuroimaging meet all inclusion and exclusion criteria and collect detailed medical histories and complete basic physical examinations and obtain written informed consent signed by the patients.

Randomization and Baseline Assessment at V1

Patients meeting the screening criteria will be randomly assigned to either the intervention group or the control group and comprehensive collection of baseline core data will be performed on Day 0. The assessment focuses strictly on the core endpoint of this study which primarily involves the lower limb Fugl-Meyer Assessment score. Secondary evaluations performed simultaneously include three-dimensional gait detection and the Berg Balance Scale and the Activities of Daily Living scale and the Mini Mental State Examination and the Montreal Cognitive Assessment. Furthermore, brain function detection using fNIRS based on real world walking paradigms will also be completed.

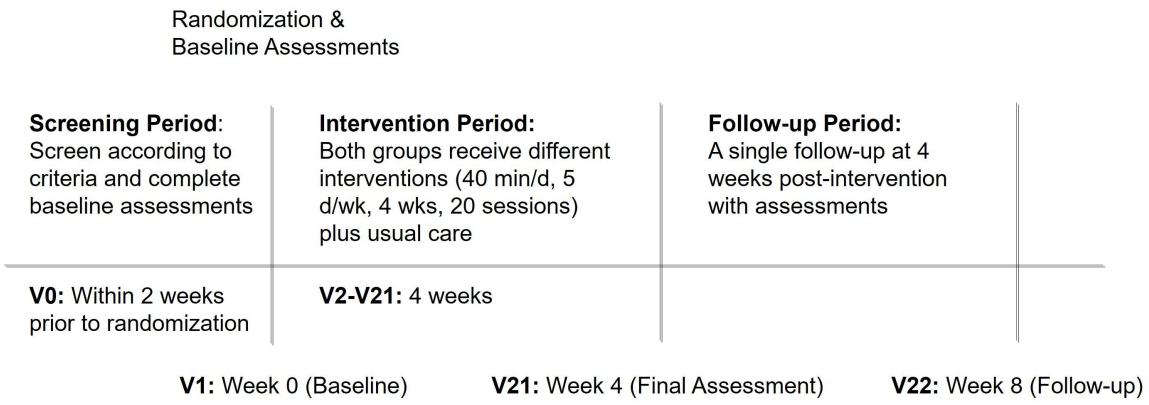
Intervention Period and Process Assessment at V2 to V21

Patients will officially enter a 4-week treadmill intervention phase with 7 sessions per week. During the intervention the research team will continuously monitor and record the frequency and severity of safety related adverse events such as falls and dizziness. At two key time points including mid intervention at Week 2 and post intervention at Week 4 professional rehabilitation therapists who are blinded to the group assignments will perform repeated assessments of all motor and cognitive and fNIRS brain function indicators identical to those at baseline.

Follow up Period at V22

A long-term observation phase will begin after the 4-week intervention is completed. The final follow up assessment will be conducted at Week 12 which is 3 months after the intervention. Evaluators will again collect all established indicators including FMA LE and BBS and three-dimensional gait analysis and ADL and MMSE and MoCA as well as fNIRS detection to scientifically evaluate the long-term functional improvement and brain remodeling effects brought by the intervention.

Study Flowchart



Randomization and Blinding Design

Randomization and Grouping

A total of 40 stroke patients will be included in this study and assigned into groups using a clear odd and even number randomization method. Each successfully enrolled patient will be randomly assigned an independent identification number between 1 and 40. This study follows a 1 to 1 allocation ratio and

the specific rule is that patients assigned an odd number will be directly allocated to the control group for treadmill training alone and patients assigned an even number will be allocated to the experimental group for multi-sensory VR enhanced treadmill training. The allocation concealment process will be strictly managed by a designated staff member to ensure the objectivity and fairness of the enrollment process.

Implementation of Blinding and Unblinding

Since the intervention methods used in the experimental and control groups make it impossible to blind the subjects and the practitioners this study adopts a single blind setting. To effectively reduce potential bias caused by subjective assessment a strict single blind evaluation design is implemented. Throughout the entire trial period all researchers responsible for collecting clinical data and assessing rehabilitation outcomes will remain completely unaware of the group assignments and the specific intervention protocols for the patients.

Assessment of Blinding Effectiveness

At the end of the final follow up visit evaluators will be required to make a forced choice regarding which group they believe the patient was assigned to. This procedure is used to assess the effectiveness of blinding for the evaluators. The guessing options for the evaluators include the experimental group or the control group or do not know. Based on the final results the single blind trial is considered successfully implemented if the proportion of do not know responses is high or if the proportions of experimental group and control group guesses are similar.

Intervention Protocols and Parameters

Experimental Group

Patients randomly assigned to the experimental group will receive multi-sensory stimulation virtual reality combined with treadmill training in addition to conventional rehabilitation therapy which includes physical therapy and motor function training. The intervention frequency is 7 sessions per week for 4 consecutive weeks. This immersive VR system utilizes a circular projection screen to provide 12 types of virtual visual scenes and is equipped with stereo speakers and real time odor playback devices to achieve synchronized visual and auditory and olfactory stimulation. During training the VR environment undergoes real time dynamic adjustments based on the movement of the treadmill. When terrain fluctuations appear in the virtual scene the

treadmill generates corresponding inclinations to provide balance related sensory feedback for the patient. Patients can also interact with the virtual environment through buttons on both sides of the treadmill or camera-based motion capture gestures based on their individual abilities. Professional rehabilitation therapists will individually adjust core parameters such as virtual scenes and ambient music as well as treadmill speed and assistance levels and resistance and inclination according to the actual rehabilitation needs of each patient.

Control Group

Patients randomly assigned to the control group will also receive conventional rehabilitation therapy but will only undergo treadmill training alone without any virtual reality environmental stimulation. The intervention frequency remains strictly consistent with the experimental group at 7 sessions per week for 4 consecutive weeks. To ensure effective matching and comparability of training intensity between the two groups rehabilitation therapists will customize a treadmill training plan based on the current physical condition of each patient. During each training session therapists will timely adjust key parameters such as treadmill speed and assistance levels and resistance and inclination to ensure the entire rehabilitation program fully meets the specific treatment needs and physiological tolerance of the patient.

Baseline Data Acquisition

During the study baseline period on Day 0 researchers will systematically collect and record various basic information and core assessment data of the subjects. The collection will first include demographic characteristics such as age and sex as well as disease related data such as the date of stroke diagnosis and previous medical history and comorbidities. Regarding efficacy evaluation indicators the research will strictly focus on the multi-dimensional system established in this protocol. Baseline data for motor and balance functions will be quantitatively collected through the Fugl-Meyer Assessment Lower Limb scale and the Berg Balance Scale as well as an objective three-dimensional gait analysis system. Cognitive status and activities of daily living will be assessed using the Mini Mental State Examination and the Montreal Cognitive Assessment and the Activities of Daily Living scale. Furthermore, functional near infrared spectroscopy detection based on real world walking paradigms will be completed during the baseline phase to obtain initial cortical blood oxygen changes and functional connectivity benchmark data. All information will be accurately entered into the Case Report Forms to serve as the core control standard for evaluating subsequent intervention efficacy.

Treatment Compliance Monitoring

To evaluate compliance with the research treatment any reasons for non-compliance should also

be recorded in detail.

Concomitant Medication and Therapy

All medications and other treatments including dosages and dates used for other comorbidities during the trial period must be recorded in the Case Report Forms. The relevant information must be documented on the concomitant treatment page of the Case Report Forms.

Clinical Outcome Measures

The clinical outcome evaluation system of this study has been strictly streamlined to ensure precise quantification of rehabilitation efficacy and neural mechanisms. The primary outcome measure is clearly defined as the Fugl-Meyer Assessment Lower Limb scale and it is used for the core assessment of lower limb motor function recovery. Secondary outcome measures focus on comprehensive functional performance and cranial nerve remodeling including motor biomechanics and balance control evaluated via three-dimensional gait analysis and the Berg Balance Scale. Additional measures include independence in daily living measured by the Activities of Daily Living scale and cognitive status reflected by the Mini Mental State Examination combined with the Montreal Cognitive Assessment as well as cortical blood oxygen changes and functional connectivity during specific walking tasks measured by functional near infrared spectroscopy. Furthermore, safety evaluation indicators primarily monitor the frequency and severity of adverse events such as falls and dizziness during the intervention to ensure the overall clinical safety of the subjects.

Evaluation Methods

All clinical scales and three-dimensional gait analysis as well as functional near infrared spectroscopy brain function tests in this study will be completed at the Department of Rehabilitation Medicine of the First Affiliated Hospital of Chongqing Medical University. To minimize subjective assessment bias all scale measurements and objective tests will be strictly performed by rehabilitation therapists who have received standardized professional training and the evaluators remain completely blinded to the specific intervention protocols and group assignments of the patients. Regarding the assessment schedule the collection of all aforementioned indicators is strictly standardized to be completed at four key time points including baseline on Day 0 and mid intervention at Week 2 and post intervention at Week 4 and

three months after the intervention at Week 12.

Safety Evaluation and Adverse Events

The safety evaluation of this study primarily focuses on the occurrence of adverse events during the intervention and the core indicators include the frequency of events such as falls and dizziness during the intervention process. If a subject experiences a serious adverse event such as a severe fall leading to functional impairment or intense dizziness or severe vomiting the research team will immediately terminate the participation of that patient to ensure medical safety. All adverse events must be recorded in detail and the overall incidence rate of adverse events will be objectively calculated by dividing the total number of adverse events by the total number of subjects. Furthermore, the sponsor will be responsible for the medical follow up costs of the subjects if any serious adverse events directly related to this clinical trial occur.

Safety Considerations and Benefits

Potential Risks and Mitigation

This clinical trial is relatively safe overall however there is still a potential risk of adverse events such as falls and dizziness during the virtual reality combined with treadmill intervention. During the screening phase before enrollment the research team has strictly excluded patients at high risk of such adverse events. If mild discomfort occurs during the intervention the principal investigator and the team will make timely clinical assessments and provide appropriate treatment based on the actual condition of the subject. It must be emphasized that if a serious adverse event occurs such as a severe fall leading to impaired motor function or heavy vertigo or even projectile vomiting the researchers will immediately terminate the participation of that patient to ensure medical safety.

Discomfort and Technical Safety

During conventional rehabilitation interventions subjects may experience a certain degree of physical fatigue or mild dizziness. Very few patients withdraw from studies due to these common discomforts. If a subject experiences discomfort during training professional rehabilitation therapists will individually adjust parameters such as treadmill speed and assistance levels and resistance and inclination based on the current physical state of the patient to effectively alleviate symptoms and ensure safety. Additionally, the imaging assessment method used in this study such

as functional near infrared spectroscopy is a completely non-invasive detection method and will not cause any harm to the human body under routine operation.

Direct and Indirect Benefits

Subjects participating in this trial will receive all comprehensive clinical assessments and objective tests prescribed in the protocol free of charge under the full follow up and professional management of the research team. Through standardized multi-sensory intervention, the lower limb motor function and gait performance of the subjects are expected to achieve positive improvements. Furthermore, if any serious adverse event directly related to the research occurs during the trial the sponsor will provide full coverage and bear the subsequent medical follow up costs. The participation of subjects will also provide solid data support for elucidating the neuroplasticity mechanisms of virtual reality technology in promoting stroke recovery and further promote more precise and efficient clinical rehabilitation practices in the future.

Participant Selection and Ethics

Identification of Study Population

This trial will recruit 40 patients with confirmed stroke at the Department of Rehabilitation Medicine of the First Affiliated Hospital of Chongqing Medical University. The diagnosis of the research subjects must be clearly confirmed as a first episode stroke through clinical evaluation and neuroimaging.

Inclusion and Exclusion Criteria

Inclusion Criteria

1）Diagnosis of first stroke confirmed by neuroimaging such as CT or MRI.

2）Age between 18 and 85 years.

3）Lower limb Fugl-Meyer Assessment (FMA-LE) score of less than 34.

4）Ability to complete walking with minimal assistance.

5）Mini Mental State Examination (MMSE) score between 20 and 30 and the ability to understand and follow instructions during the trial.

6）Patients who voluntarily sign the informed consent form.

Exclusion Criteria

1）Presence of severe visual or hearing impairment.

2）Women who are pregnant or breastfeeding.

3）Presence of unrepaired cranial defects or metal implants in the body following brain surgery.

4）Presence of other diseases affecting lower limb motor function such as osteoarthritis or recent lower limb fractures.

5）Previous history of severe mental illness or other neurological diseases or acute cardiopulmonary insufficiency or multi organ failure or brain tumors or epilepsy.

Safety Monitoring and Protection

During the clinical intervention the research team will closely monitor and properly record potential adverse events such as falls and dizziness. If a patient experiences a serious adverse event such as a severe fall leading to impaired motor function or heavy vertigo or even projectile vomiting the researchers will immediately terminate the participation of that patient to effectively ensure the life and health and medical safety of the subjects.

Study Completion and Termination

The research is considered officially completed when the last subject in the trial finishes the established follow up assessment. Throughout the trial the principal investigator has the right to terminate the study at any time based on clinical safety considerations especially when assessments find that continuing the intervention may harm the legal rights and physical or mental health of the subjects.

Informed Consent Procedures

The informed consent process of this study will be implemented by the research team from the Department of Rehabilitation Medicine at the First Affiliated Hospital of Chongqing Medical University. Researchers will provide patients and their families with a detailed and easy to understand explanation of the research protocol and procedures regarding multi-sensory virtual reality for improving motor function after stroke. The information provided clearly includes that the study intends to recruit 40 patients with confirmed stroke. After signing the informed consent form patients will undergo a strict check of inclusion and exclusion criteria and those who meet the criteria will be randomly assigned to groups. These participants will receive core assessments of motor function and balance and gait and cognitive function as well as fNIRS brain function at

the intervention and follow up nodes. The research team will give patients and their families sufficient time for consideration and once voluntary participation is confirmed the subject or their legal representative will sign and date the informed consent form. This trial does not include subjects who lack the capacity for civil conduct. If a subject or their legal representative is illiterate the informed consent process must be completed with the participation of an independent witness who will also sign and confirm the document. The informed consent form will be prepared in duplicate and after being signed by the investigator one copy will be kept by the subject or their legal representative and the other will be archived by the research team. The entire process of obtaining informed consent will be standardized and recorded in the medical records of the patient. If there are important protocol updates involving the trial in the future, they must be approved by the Ethics Committee before being fully explained to the patients again to obtain their renewed consent.

Financing and Compensation

The intervention period of this study is clear and relatively safe and adverse events occur very rarely. During the participation in this study the project team will provide all clinical scale assessments and objective instrument tests as well as corresponding rehabilitation interventions related to the trial free of charge. If a subject experiences a serious adverse event directly related to participating in this clinical trial the sponsor will be responsible for bearing the full cost of medical follow up and treatment to effectively protect the rights and economic interests of the subject.

Data Management and Quality Assurance

Data Acquisition and Entry Standards

Under the premise of obtaining full informed consent from the subjects the original data will be directly collected by professional researchers who have received unified training through paper forms or assessment instruments. To effectively avoid human bias that may occur during the digitalization of clinical data all original information will be entered into an electronic database in parallel by two independent researchers using a double entry method. If inconsistencies are found when comparing the information entered by the two people the research team will carefully check the original paper or instrument records to thoroughly investigate and correct errors to ensure the

accuracy of the final clinical data.

Quality Control and Traceability

Researchers responsible for data management will conduct a comprehensive and centralized check on the authenticity and completeness and accuracy of all collected data strictly according to the requirements of the study protocol. The core content of the quality control audit covers whether the actual enrolled cases strictly meet the inclusion and exclusion criteria stipulated in the protocol and whether the baseline and subsequent follow up assessments were completed on time within the strict time windows as well as whether adjustments to intervention parameters and all adverse events occurring during the study were recorded truthfully and in detail. Furthermore, all modifications involving data must strictly comply with traceability standards. If there is a need to correct the paper version of the Case Report Form it is strictly forbidden to smear or cover the original data. The original error must be crossed out with a single line and the correct data must be clearly marked beside it along with the signature of the person making the change and the date and the reason for the modification. The corresponding electronic database system will also fully enable the operation traceability function to completely record the status before and after every data change and the information of the operator to comprehensively guarantee the credibility and scientific rigor of the trial data.

Privacy and Confidentiality

After signing the informed consent form the research team will immediately assign a unique and independent code to each subject which will serve as their sole identification code throughout the entire study period and in the clinical research database. All collected original medical data will be strictly stored under this code and only authorized researchers can link the research data to the subject themselves through a confidential identification code list. Throughout the entire process of collection and transmission and processing and storage of patient data this study will strictly comply with relevant data protection laws and regulations to maximize the protection of personal privacy of the patients. In any final report or publicly published academic article related to this trial the research team will absolutely not use or disclose any sensitive information that could identify the personal identity of the subjects.

Dissemination and Publication

The final results of this study are planned to be shared through public reports at professional scientific and academic conferences or published in peer reviewed academic journals for extensive scientific exchange and sharing. When conducting any form of research result presentation or oral statement or article publication the research team will strictly implement confidentiality principles and will never involve or disclose any personal identity information or privacy protection content of the subjects. Meanwhile after the entire trial is completed, we will also provide timely feedback on the overall progress of the research and the final beneficial results to all subjects who participated in this trial.

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