Trials

STUDY PROTOCOL

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Comparing the effects of Swiss-ball training and virtual reality training on balance, mobility, and cortical activation in individuals with chronic stroke: study protocol for a multi-center randomized controlled trial

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Abstract

Background Balance and mobility deficits are major concerns in stroke rehabilitation. Virtual reality (VR) training and Swiss-ball training are commonly used approaches to improve balance and mobility. However, no study has compared the efficacy of VR training, Swiss-ball training, and their combination in improving balance and mobility function or investigated cortical activation and connectivity in individuals with stroke.

Methods A prospective, single-blinded, parallel-armed, multi-center randomized controlled trial with factorial design will be conducted. Seventy-six participants aged 30–80 years with stroke will be recruited. Participants will be allocated to one of the four groups: (A) the VR training + Swiss-ball training + conventional physical therapy group; (B) the Swiss-ball training + conventional physical therapy group; (C) the VR training + conventional physical therapy group; or (D) the conventional physical therapy group. All participants will receive 50 min of training per day, 5 times per week, for a total of 4 weeks. The primary outcomes will be balance and mobility measures. Secondary outcomes will include the 10-min walk test, dynamic gait index, and cortical activation. Outcomes will be measured on three occasions: at baseline, after the training, and at the 4-week follow-up.

Discussion This trial will provide evidence to determine whether there are differences in clinical outcomes and cortical activation following two different types of exercise programs and their combination, and to elucidate the recovery mechanisms of balance and mobility function in individuals with stroke.

Trial registration Chinese Clinical Trial Registry reference: www.chictr.org.cn (No. ChiCTR2400082135). Registered on May 24, 2024.

Keywords Stroke, Balance, Mobility, Cortical activation, Study protocol, Clinical trial, RCT

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Introduction

Background and rationale {6a}

Balance and mobility deficits are always major concerns in stroke rehabilitation [1]. The common balance- and mobility-related problems observed in individuals with stroke are slower gait speed, abnormal posture, poorer walking adaptability (e.g., obstacle avoidance), and greater susceptibility to falls [2]. Impaired balance and mobility function after stroke inevitably lead to restrictions in active participation in daily activities, thereby triggering a vicious cycle of social isolation and compromised quality of life [3].

A range of rehabilitation approaches have been used to improve balance and mobility in individuals with stroke [4]. Among them, virtual reality (VR) and Swiss-ball training are commonly used methods [5, 6]. Mounting evidence has shown that VR training combined with conventional physiotherapy could improve balance and mobility in individuals with stroke, especially in the chronic stage [7–11]. On the other hand, the liable surface of a Swiss ball poses more challenges for dynamic balance, coordination, and trunk control [12, 13]. Compared to regular physiotherapy, core stability exercises on both stable and unstable support surfaces are similarly useful in increasing patients' trunk control, strength, standing weight-bearing symmetry, and balancing confidence [14]. A systematic review and meta-analysis also showed that Swiss-ball exercise can enhance trunk control and balance function for individuals with stroke in acute and sub-acute stages [15].

Balance is maintained through the complex integration and coordination of multiple body systems, including the vestibular, visual, auditory, and motor systems, whereas little is known about the function and connection of neural structures during balance and mobility rehabilitation [16]. The activation of higher cortical processes in regulating balance and mobility is still poorly understood [17]. A few studies have shown positive correlations between neural plasticity changes and balance function recovery induced by VR training, which are mainly attributed to improved interhemispheric balance [18]. However, whether VR training could increase cortical activation and/or enhance cortical connectivity was not identified in these studies. Furthermore, no study has investigated the cortical activation induced by Swiss-ball training. Considering the compromised quality of life induced by balance and mobility deficits and the threat imposed by falls on individuals with stroke, identifying changes in cortical activity and connectivity during balance and mobility rehabilitation could provide a foundation for deciphering the mechanisms of interventions, thus contributing to the ongoing innovation of rehabilitation approaches [19, 20].

To the best of our knowledge, no study has compared the efficacy of VR training, Swiss-ball training, and their combination in improving balance and mobility function or investigated cortical activation and connectivity in individuals with stroke. Moreover, as proposed by previous studies, VR training and Swiss-ball training improve balance and mobility function may be due to different mechanisms [21–23], but whether the combination of these two training approaches could increase the cortical activation and connectivity in individuals with stroke, thus augment the recovery of balance and mobility function is still unknown.

Objectives {7}

Therefore, the research question of this study is as follows: what effects do Swiss-ball training, VR training, and their combination have on balance, mobility, and cortical activation in individuals with stroke? We hypothesized that (1) Swiss-ball training and VR training will result in different improvements in balance and mobility function and different changes in cortical activation in individuals with stroke and (2) combined training will have greater changes in cortical activation, thus leading to greater improvements in balance and mobility function than training alone in individuals with stroke. The aims of this study are thus to (1) investigate the effects of Swiss-ball training, VR training, and their combination on mobility, balance, and cortical activation in individuals with stroke and (2) provide evidence for elucidating the recovery mechanisms of balance and mobility function in individuals with stroke.

Trial design {8}

This study will be a prospective, single-blinded, parallel-armed, multi-center randomized controlled trial (RCT) with factorial design. Participants will be allocated to one of the four groups: (A) the VR + Swiss-ball training + conventional physical therapy group, (B) the Swiss-ball training + conventional physical therapy group, (C) the VR training + conventional physical therapy group, or (D) the conventional physical therapy group. Figure 1 shows the flow chart of the trial process. The checklist of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) is provided in Appendix I.

Methods: participants, interventions, and outcomes

Study setting {9}

The study setting will be in Kunming LIH Skycity Rehabilitation Hospital, The Second People's Hospital of Kunming, and Shanghai Yangzhi Rehabilitation Hospital.

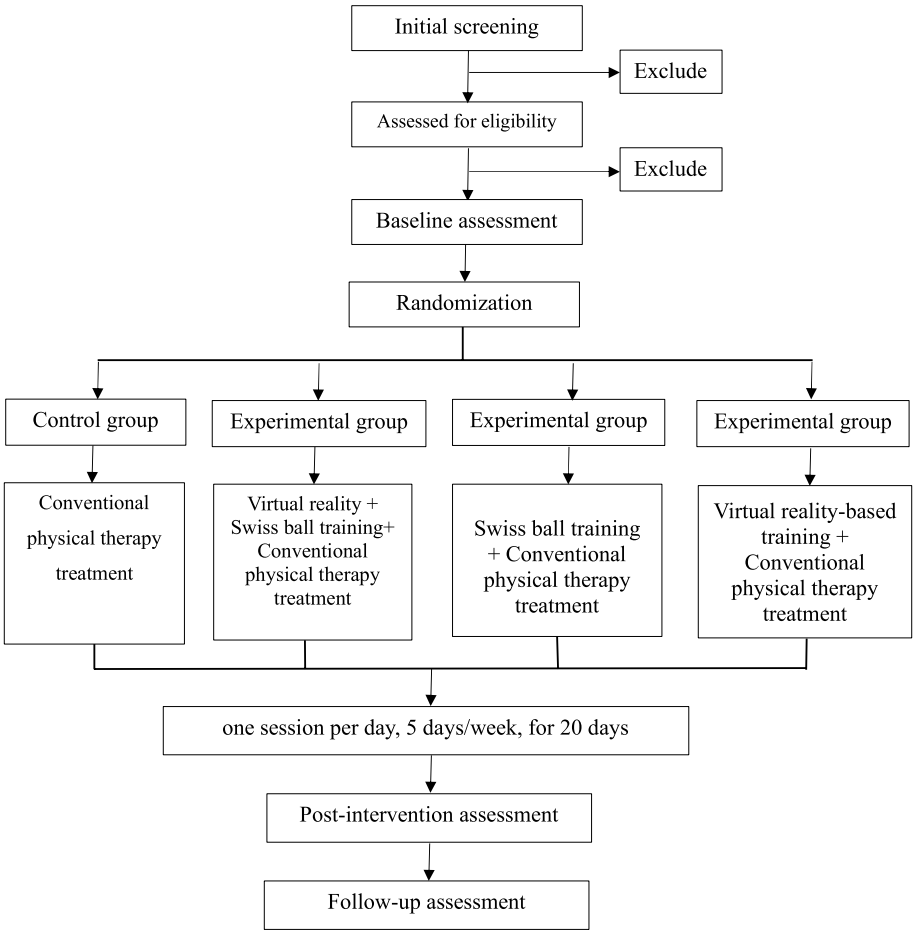

Fig. 1 Study flowchart of trial process

Eligibility criteria {10}

The inclusion criteria are as follows: (1) a confirmed diagnosis of stroke; (2) first onset and over 6 months; (3) aged between 30 and 80 years; (4) medically stable; (5) absence of cognitive impairment (Mini-Mental State Examination score > 23); (6) able to follow 3-step commands; and (7) independent walking at least 10 m. The exclusion criteria were as follows: (1) other neurological conditions (e.g., Parkinson's disease or multiple sclerosis); (2) other diseases that affect performance in walking and balance; and (3) pain during standing or walking.

Who will take informed consent? {26a}

Professional rehabilitation therapists will explain the trial to potential participants. If participants showed willingness to participate in the trial, then the therapist will obtain the participant's signature on the informed consent form.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

N/A. Additional consent provisions are not needed for collection and use of participant data and biological specimens in trial.

Interventions

Explanation for the choice of comparators {6b}

Although VR training and Swiss-ball training in conjunction with conventional physiotherapy have demonstrated efficacy in improving balance and mobility among stroke survivors, no study has compared the efficacy of VR training, Swiss-ball training, and their combined training directly in one trial. By the factorial design, the main effect (VR training and Swiss-ball training) and the interaction effect (combined training) on the therapeutic benefits and cortical activation can all be compared.

Intervention description {11a}

The training protocol for the four groups was developed based on the research intervention description of the TIDieR template [24]; the details are provided in Table 1. The individuals in each group will receive their respective training (five 50-min sessions per week) for 4 weeks. Each training session will be supervised by one instructor with experienced physical therapy background, with an instructor-to-participant ratio of 1:1. All training sessions will take place in an exercise room in the hospital. The training sessions for the four groups are conducted at different times of the day so that participants will not be exposed to observe other treatments. During the exercise, the participants will be monitored and supervised with adequate care to avoid falls or fall-related injuries.

(1) Conventional physical therapy group

The conventional physical therapy group served as an active control group, enabling us to determine whether the observed changes in the Swiss-ball training, VR training, or combined training group are a function of maturation or repeated testing. Conventional physical therapy includes passive movements, stretching, resistance exercises, and gait training (Supplementary Table 1, Appendix II).

(2) VR training + conventional physical therapy group

The iMove Integrated Function Training System (Dihe Medical Company Ltd., Beijing, China) combines intensive training activities with intuitive software games to provide real-time feedback (Fig. 2). Three VR-assisted lower limb balance, gait, and mobility training games, including rolling the ball, falling the ball, running, and jumping (Supplementary Fig. 1, Appendix II), are available for patients (Supplementary Table 2, Appendix II). Since VR training will only take 20 min, the rest of the training time will be completed by conventional physical therapy.

(3) Swiss-ball training + conventional physical therapy group

Swiss-ball training includes supine, sitting, standing, trunk rotations, core stability enhancing, balance, and coordination exercises (Supplementary Fig. 2, Appendix II), along with progression modification for each exercise (Supplemental Table 3, Appendix II). The Swiss-ball exercise will perform 5 repetitions/set, 3 sets/session, for 20 min, with intermittent rest. Since Swiss-ball training will take only 20 min to complete, the rest of the training time will be completed by conventional therapy.

(4) VR training + Swiss-ball training + conventional physical therapy training group

This group will receive 20 min of VR training and 20 min of Swiss-ball training; the rest of the training time will be completed by conventional therapy.

Criteria for discontinuing or modifying allocated interventions {11b}

Although the trial is very safe in itself, if participants show the irreversible exercise-related adverse events during trial, such as nausea, dizziness, disorientation, postural instability, or fatigue, the trial will be stopped to the participant.

Strategies to improve adherence to interventions {11c}

We will take the following measures to achieve the best training adherence:

1. During the 20 days of training, a strict training plan will be made for each subject on a weekly basis, and the training schedule will be adjusted according to the actual conditions of the participant.
2. Close attention will be given to the feedback and fitness of the participants during training.
3. The intervention effect on subjects during training will be evaluated daily.
4. Patients' decision to withdraw from the study will be supported.

Relevant concomitant care permitted or prohibited during the trial {11d}

N/A. There are no restrictions regarding concomitant care during the trial.

Provisions for post-trial care {30}

N/A. Ancillary and post-trial care provisions are deemed irrelevant to the present study design. Furthermore, compensation for trial participation is not anticipated as the trial does not pose harm to participants.

Outcomes {12}

Except for the demographic data, all the outcomes will be measured on three occasions, i.e., before, after the training, and at the 4-week follow-up (Table 2).

Primary outcomes

Berg balance scale (BBS) The BBS is a 14-item scale that quantifies balance and fall risk based on direct observation. The items are graded on a scale of 0 to 4, with a score of 0 reflecting inability to finish the assignment and a score of 4 representing completion of independent

Table 1 The training protocol for each group base on the TIDieR template

Item	Virtual reality + Swiss ball + conventional physical therapy training group	Swiss-ball training + conventional therapy group	Virtual reality training + conventional therapy group	Conventional therapy group
1. Brief name	VRT + SBT + CPT	SBT + CPT	VRT + CPT	CPT
2. Why	1. VRT can enhance neural motor pathway cortical recombination, synaptic function, and neuroplasticity. Repetitive movement is essential for acquiring motor skills, but successful feedback and pleasant experiences are needed for further mastery 2. SBT activate/stimulate a comatose patient by stimulating the reticular formation's afferent and efferent channels to and from the brain. Motivate a patient by stimulating limbic systems. Increase awareness, proprioception, balance, and coordination (through cerebellar, sensorimotor, and vestibular stimulation) 3. CPT enhances muscle performance by restoring or maintaining strength, power, endurance, balance, quality of life, and tissue remodeling	1. SBT activate/stimulate a comatose patient by stimulating the reticular formation's afferent and efferent channels to and from the brain. Motivate a patient by stimulating limbic systems. Increase awareness, proprioception, balance, and coordination (through cerebellar, sensorimotor, and vestibular stimulation) 2. CPT enhances muscle performance by restoring or maintaining strength, power, endurance, balance, quality of life, and tissue remodeling	1. VRT can enhance neural motor pathway cortical recombination, synaptic function, and neuroplasticity. Repetitive movement is essential for acquiring motor skills, but successful feedback and pleasant experiences are needed for further mastery 2. CPT enhances muscle performance by restoring or maintaining strength, power, endurance, balance, quality of life, and tissue remodeling	1. CPT enhances muscle performance by restoring or maintaining strength, power, endurance, balance, quality of life, and tissue remodeling
3. What materials	iMove Integrated Function Training System, and the model is iMove-Standard. The display size is 42-inch touch display, and the power supply is AC 220 V, 50 Hz, 700 VA. The operating environment for this is 5–50°, less than or equal to 85% non-condensing humidity, and greater than or equal to 100 Pa. The device consists of a display, a trolley, and a sensor. Three VR-assisted lower limb balance, gait, and mobility training games will be available for patients to choose from (roll the ball, falls ball, run and jump) Swiss ball CPT includes passive movements, stretching, resistance exercises, and gait training	1. Swiss ball 2. CPT includes passive movements, stretching, resistance exercises, and gait training	1. iMove Integrated Function Training System, and the model is iMove-Standard. The display size is 42-inch touch display, and the power supply is AC 220 V, 50 Hz, 700 VA. The operating environment for this is 5–50°, less than or equal to 85% non-condensing humidity, and greater than or equal to 100 Pa. The device consists of a display, a trolley, and a sensor. Three VR-assisted lower limb balance, gait, and mobility training games will be available for patients to choose from (roll the ball, falls ball, run and jump) 2. CPT includes passive movements, stretching, resistance exercises, and gait training	1. CPT includes passive movements, stretching, resistance exercises, and gait training

Table 1 (continued)

Item	Virtual reality + Swiss ball + conventional physical therapy training group	Swiss-ball training + conventional therapy group	Virtual reality training + conventional therapy group	Conventional therapy group
4. Procedures	This training group will receive 50-min session per day for 20 days (5 days/week) 1. VRT group will receive three specifically designed games for enhancing the balance, gait, and mobility for 20 min 2. SB training will take 20 min to complete training exercises; the rest of the training time will be made up by the conventional therapy. Swiss ball exercise training will perform with 5 repetitions, 3 sets of exercises with intermittent rest between each segment, for 20 min	This group will receive 50-min therapy in one session/day, 5 days/week, for 20 days. SBT group will take 20 min to complete; the rest of the training time will be made up by the conventional therapy. SB exercise training will perform with 5 repetitions, 3 sets of exercises with intermittent rest between each segment, for 20-min session	This training group will receive 50-min session per day for 20 days (5 days/week) VRT group will receive three specifically designed games for enhancing the balance, gait, and mobility for 20 min. The rest of the training time will be made up by the conventional therapy	This training group will receive 50-min session per day for 20 days (5 days/week) CPT group will receive passive movements, stretching, resistance exercises, and gait training (50 min)
5. Who provided	The intervention measures of the groups in this study were carried out by rehabilitation trained professional therapists. Intervention measures were developed by experimental researchers			
6. How	Interventions in this study will be conducted in one-on-one training sessions daily			
7. Where	The intervention will be carried out in the inpatient ward of the Department of Neurology Rehabilitation in LIH Skycity Hospital affiliated with Kunming Medical University			
8. When and how much	During 20 days of rehabilitation training, all groups will receive training lasting 50 min/day and 5 days/week for 20 days. The intensity was adjusted immediately according to the function of patients' lower limbs			
9. Tailoring	The intervention of the four groups can be tailored to the function of the patients. Before training, therapists will do a basic and quick evaluation of patients' lower limb function to determine the personalized intervention intensity that is best for them. It can also be tailored to the desires of the patients			
11. How well	Evaluators overseeing intervention results will be blinded to the group allocation process and randomization results to ensure the objectivity and impartiality of the evaluation results			

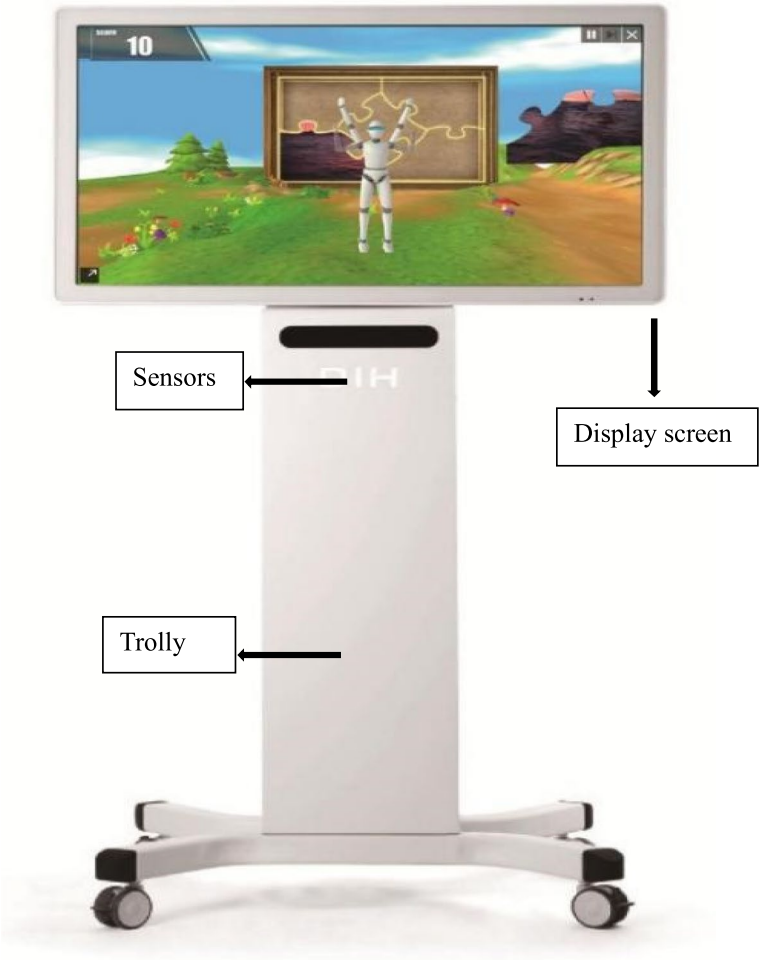

Fig. 2 iMove integrated function-training system

Table 2 Outcome domains and measurement instruments

Outcome domain	Measurement instrument		T0	T1	T2
Primary outcomes					
Balance function	Berg balance scale	BBS	×	×	×
Mobility function	Timed up-and-go test	TUG	×	×	×
Secondary outcomes					
Gait parameters	10-m walking test	10MWT	×	×	×
Mobility function	Dynamic gait index	DGI	×	×	×
Cortical activation	Functional near-infrared spectroscopy	fNIRS	×	×	×

T0 baseline, *T1* post-intervention, *T2* at 4-week follow-up

tasks. A total score of 56 potential points is calculated. Balance impairment, acceptable, and good are represented by scores of 0 to 20, 21 to 40, and 41 to 56, respectively. The BBS has shown excellent inter-rater and intra-rater reliability (ICC = 0.90) and concurrent validity (correlation with Postural Assessment Scale for Stroke Patients: Pearson's $r = 0.92–0.95$) in individuals with stroke [25, 26].

Timed up-and-go (TUG) test The participants will sit in the chair with their arms comfortably resting on their laps or at their sides (not on the armrests) and hips

positioned back in the seat. The test starts when the assessor says "Go," and the stopwatch starts. The participants will then stand up from their chair, walk 3 m at their fastest speed, turn around, return to their chair, and sit down. The score is the time taken to complete the test. The TUG has shown excellent test–retest reliability (ICC = 0.89) and concurrent validity (correlation with Community Balance and Mobility Scale: Spearman's $\rho = 0.75$) in individuals with stroke [27, 28].

Secondary outcomes

10-m walking test A computerized system (GB Gait Analysis System, NJ, China) will be used to collect data on gait parameters (speed, step length, and cadence). Participants will walk along a 14-m walkway at a comfortable speed, and only the middle 10 m of the walkway will be recorded. Excellent test–retest reliability (ICC = 0.89) has been shown in the 10-m walking test [27].

Dynamic gait index (DGI) In this eight-item assessment, various walking tasks (stable state walking, changing speeds, walking with both horizontal and vertical head rotations, walking while stepping over and around obstacles, turning while walking, and stair ascending) are included. The scores are assigned on a 4-point scale: 3 = no gait dysfunction, 2 = minor impairment, 1 = moderate impairment, and 0 = severe impairment, with a potential score ranging from 0 to 24 points. Excellent test–retest and inter-rater reliability (ICC = 0.96, 0.96, respectively) and concurrent validity (correlation with the BBS, the time of walking test, and the TUG, Pearson's $r = 0.68–0.83$) have been demonstrated [29].

Functional near-infrared spectroscopy (fNIRS) evaluation task paradigm A multichannel fNIRS system (ETG4100, FUJIFILM Corporation, Japan) will be used to track variations in the concentrations of deoxygenated hemoglobin (HbR) and oxygenated hemoglobin (HbO) in the frontal, parietal, occipital, and temporal regions of the brain. The fNIRS signals will be preprocessed using HomER2 toolbox in Matlab 2014a (The MathWorks Inc.) [30]. The raw signals will be firstly converted to optical density changes and the spline interpolation algorithm will be applied to correct motion artifacts during data acquisition. Then, a bandpass filter between 0.01 and 0.2 Hz will be applied to remove physiological noises and drifts. Finally, the optical density will be converted to ΔHbO on the basis of the modified Beer-Lambert law. We will cut a temporal window from − 5 to 30 s relative to the onset of blocks ($t = 0$ s) for averaging [31, 32].

Task paradigm

[Task-1] Participants static standing on the stable surface with eyes open and the arms closed to the body.
[Task-2] Participants static standing on the foam with eyes closed, and arms closed to the body.
[Task-3] Participants stepping on the foam, with eyes open and arms closed to the body.

The participants will perform the three tasks. Each task will last for 60 s (perform for 30 s and rest for 30 s) and repeat three times. During the tasks and rest periods, each participant will be required to stand on the stable platform and look forward with their eyes open. Figure 3 shows how the participants' feet will be positioned steadily on the platform for each task [33].

Participant timeline {13}
Timeline for participants' enrolment, interventions, and assessments is shown in Table 3.

Sample size {14}
The sample size was estimated using GPower 3.1 software (Heinrich-Heine-Universitas, Dusseldorf, Germany). Previous studies demonstrated a significant interaction on the balance scores between the VR or Swiss-ball training group and the conventional therapy group, yielding various effect size [7, 9]. In general, a new intervention should produce a similar change or beyond; subsequently, the effect size should be at least moderate to high. However, a conservative approach was adopted for our sample size estimation, due to considering the comparison of two distinct treatment factors: VR training and Swiss-ball training, and their combined application, alongside a relative short 4-week intervention period, we thus assumed a small effect size for the primary outcome (Berg balance scale, $f = 0.2$). With a level at 0.05, a statistical power of 0.8, and a 4 × 3 repeated-measures ANOVA (group factor: 4; time factor: 3, pre-, post-, and follow-up) will be used, 64 participants in total were generated. Considering an attrition rate of 15%, a total of 76 participants will be required for this study, i.e., 19 in each group.

Recruitment {15}
The participants will be recruited from the inpatients of Kunming LIH Skycity Rehabilitation Hospital, The Second People's Hospital of Kunming, and Shanghai Yangzhi Rehabilitation Hospital. The study team will screen and assess the eligibility of the participants first. All patients

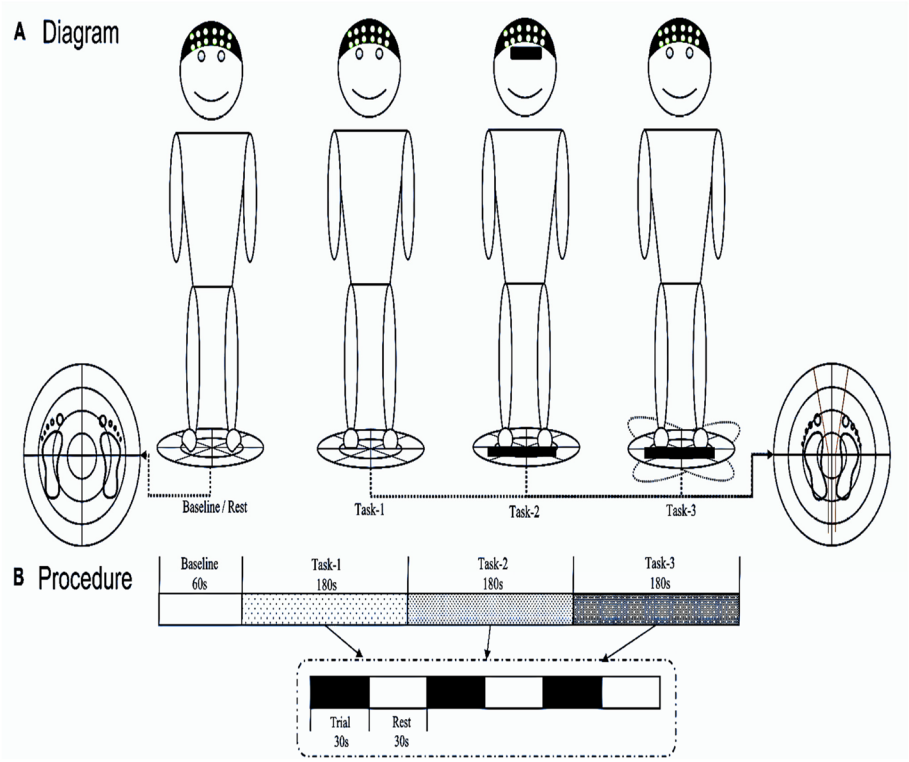

Fig. 3 Functional near-infrared spectroscopy (fNIRS) evaluation task paradigm. **A** Diagram of three upright tasks paradigm. **B** fNIRS testing procedure

will be informed about the research progress and their partial results throughout the follow-up period. In addition, the researchers will maintain constant contact with the physicians responsible for each patient. Physicians and patients will receive a final report on the results at the end of the study.

Assignment of interventions: allocation

Sequence generation {16a}

The random allocation sequence will be generated by an online generator (www.randomization.com).

Concealment mechanism {16b}

The allocation sequence will be kept in a sealed, opaque envelope.

Implementation {16c}

The principal investigator will assign participants to the respective intervention groups.

Assignment of interventions: blinding

Who will be blinded {17a}

The allocation will be blinded to the outcome assessors and the data analyst. Participants will be instructed not to disclose the allocation to the outcome assessors.

Procedure for unblinding if needed {17b}

N/A. Emergency unblinding to our trial is not applicable because it is impossible to blind the participants and rehabilitation trainers in our trial.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Before the start of the study, to ensure the quality of the research, we will train the recruiting doctors, physical therapists, and assessors, check the relevant equipments, and take the following steps:

1. The recruiting doctors fully understand the experimental process.
2. The therapists will be trained on how to conduct the training program and how to deal with potential adverse events during the training.
3. The assessors will be trained on how to appropriately collect and process outcome indicators.
4. The VR equipment and gait analyzer (data analysis equipment) will be debugged to achieve the optimal running state of the equipment.

Table 3 Timeline for participants' enrolment, interventions, and assessments

	STUDY PERIOD						
	Enrolment	**Allocation**	**Post-allocation**				**Follow-up**
TIMEPOINT	$-t_1$	**0**	t_1	t_2	t_3	t_4	t_8
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
A: VR+ Swiss ball + conventional physical therapy			♦—	—	—	—♦	
B: VR + conventional physical therapy			♦—	—	—	—♦	
C: Swiss ball + conventional physical therapy			♦—	—	—	—♦	
D: Conventional physical therapy			♦—	—	—	—♦	
ASSESSMENTS:							
Berg Balance Scale, Time up and go test, 10-minute walk test, Dynamic gate index, Functional Near-infrared Spectroscopy		X				X	X
Speed, Step length, Cadence		X				X	X

Plans to promote participant retention and complete follow-up {18b}

The follow-up assessment will be performed at 4 weeks after the completion of the training program. The participants will be phoned and invited to the hospital to perform the assessment.

Data management {19}

The safety supervision committee of involved hospitals will oversee this project and evaluate the experimental design, scientific rigor, participant safety, adherence to medical ethics, and data management. Strict measures will be implemented to safeguard the privacy rights of each participant. Initial data and outcome indicators will be securely stored in a highly protected database, and anonymization procedures will be rigorously followed to ensure the safety and confidentiality of all participants.

Confidentiality {27}

Personal information concerning potential and enrolled participants will be collected and maintained in strict adherence to confidentiality protocols throughout all phases of the trial. Before commencement, informed consent will be obtained from each participant, outlining the purpose, procedures, and risks involved in the study. During the trial, all collected data will be anonymized and securely stored, accessible only to authorized personnel involved in data analysis and trial oversight. Following the conclusion of the trial, all personal information will be maintained under strict safeguarding protocols. Any residual identifiable data, including specific protocol codes, will be securely archived for the mandated retention period by institutional and regulatory directives governing confidentiality and data protection.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

N/A. Biological specimens are not relevant to our trial.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Data entry will be performed by two independent researchers so that the accuracy of the input data can be cross-checked. The Statistical Package for Social Sciences (SPSS) version 26 will be used to conduct the data analysis. Intention-to-treat analysis will be performed. The normality of the data will be checked using the Shapiro–Wilk test. To compare the baseline characteristics of the four groups, one-way ANOVA (or its nonparametric equivalent: Kruskal–Wallis test) or Chi-square tests will be used, depending on whether the criteria for parametric statistics are fulfilled. Those relevant variables that show important between-group differences will be entered as covariates for subsequent analysis. To compare the treatment effects of the 4 intervention approaches, multivariate 4×3 ANOVA or ANCOVA with repeated measures (mixed design; repeated factor: time; between-subject factor: group) will be used to determine the time effect and treatment$\times$time interaction effect for each outcome variable of interest. The Greenhouse–Geisser correction will be applied if the assumption of sphericity is violated. If significant results are found, post hoc multiple comparisons of group effects and contrast analyses of time effects will be performed. Bonferroni adjustment will be performed in post hoc analysis to account for the increased risk of type I errors associated with multiple comparisons. If the criteria for parametric statistics are not fulfilled, the Mann–Whitney test and Wilcoxon test will be used.

Interim analyses {21b}

The interim analysis will be conducted when half of the sample size is completed, to observe the trend of outcomes and double-check the trial process.

Methods for additional analyses (e.g., subgroup analyses) {20b}

N/A. No additional analyses beyond the primary and secondary outcomes will be conducted for the study.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Intention-to-treat analysis (ITT) approach will be used for data analysis. If data are missing, the last observation carried forward method will be adopted.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The current study data and statistical code are accessible upon reasonable request from the corresponding author. Additionally, the complete protocol can be obtained from the same correspondence.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The Safety Supervision Committee of the coordinating hospital will be in charge of overseeing this project. This committee assumes primary responsibility for evaluating the experimental design, scientific rigor, and procedural integrity throughout the study. Moreover, it ensures the safety of participants, adherence to medical ethics, and proper management and processing of collected data [34]. The Trial Steering Committee convenes to assess

the availability of suitable study participants and oversees critical stages such as trial initiation. Additional meetings are planned at appropriate intervals corresponding to data collection points. Each committee provides comprehensive support for the trial, encompassing pre-, post-, and follow-up assessments to facilitate robust data collection and analysis.

Patient public involvement and public involvement group

The trial entails active patient engagement facilitated by continuous communication between the coordinating trial group and potential participants within a hospital setting. This strategy aims to ensure comprehensive patient understanding and informed decision-making. Evidenced by heightened patient interest in participation, the emphasis on transparent communication underscores its pivotal role. Such an approach enhances comprehension of informed consent processes and fosters participant engagement in clinical research, bolstering transparency and fostering trust within the healthcare community.

Composition of the data monitoring committee, its role and reporting structure {21a}

Data entry will be performed by two independent researchers so that the accuracy of the input data can be cross-checked.

Adverse event reporting and harms {22}

VR is an emerging technology, and related products have been gradually developed in recent years [35]. To date, no relevant adverse events have been reported. Our research team will meticulously adhere to the pertinent regulations set forth by the medical ethics committee to uphold the paramount safety and ethical safeguarding of study participants. Adverse events (e.g., falls, pain, and dizziness) that occur during the study period, whether related to the study intervention, will be registered [36]. In addition, we will take the following measures to achieve the best training environment:

1. During the 20 days of training, a strict training plan will be made for each subject on a weekly basis, and the training schedule will be adjusted according to the actual conditions of the participant.
2. Close attention will be given to the feedback and fitness of the participants during training.
3. The intervention effect on subjects during training will be evaluated daily.
4. Patients' decision to withdraw from the study will be supported.

This study strictly complied with the clinical operation and internationally recognized legal requirements. Any adverse events will be reported directly to the ethics committee immediately, and the training regimen will be adjusted accordingly after each adverse event. There is no anticipated harm or compensation for trial participation.

Frequency and plans for auditing trial conduct {23}

The Project Management Group will convene regularly to assess trial progress and adherence to protocol, with meetings monthly scheduled. Additionally, the Trial Steering Group and Ethics Committee play critical roles in ongoing monitoring and review. These bodies are responsible for overseeing trial conduct, safeguarding participant welfare, and maintaining data integrity throughout the trial period. This structured approach ensures proactive monitoring and adherence to established ethical and regulatory standards throughout the trial.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Prompt communication with the funding body would be ensured through structured notifications. Subsequently, the principal investigator (PI) will inform the coordinating centers and ensure timely dissemination of the revised protocol. The PI will receive a copy of the updated protocol for inclusion in the Investigator Site File. We will meticulously document deviations from the established protocol by completing a breach report form. The clinical trial registry will diligently apply the corresponding updates to ensure a precise reflection of the modified procedures. This rigorous approach is crucial for maintaining transparency and accuracy in clinical trial management, aligning with regulatory standards, and safeguarding the integrity of the research process.

Dissemination plans {31a}

Dissemination plans include specific strategies for communicating trial results to healthcare professionals and the public. Pertinent findings will be disseminated through various channels such as conference presentations, peer-reviewed journal publications, and relevant medical forums. This ensures that key outcomes and insights from the trial reach stakeholders in the healthcare community and the wider public audience. Regular updates and summaries will be provided to ensure transparency and accessibility of the research findings, aligning with ethical standards and promoting informed decision-making in healthcare practice.

Discussion

This trial will provide evidence to show whether there is a difference in clinical outcomes and cortical activation following two different types of exercise programs and/or their combination in individuals with stroke. Specifically, this study will either prove or disprove the hypothesis that combined both Swiss-ball and VR training will have greater changes in cortical activation, thus leading to greater improvements in balance and mobility function than one type of training alone in individuals with stroke. The findings of this study will help inform exercise program recommendations and decipher the cortical mechanisms of balance and mobility rehabilitation for individuals with stroke.

Trial status

The protocol TRLS-D-24–00370 [EMID: a81956afa9d2b251] was submitted on 2024–3-26. The recruitment of this trial has begun on 2024–4-1 and it will be complete on 2025–3-1.

Abbreviations

VR	Virtual reality
BBS	Berg balance scale
TUG	Timed up-and-go
fNIRS	Functional near-infrared spectroscopy
DGI	Dynamic gait index
10MWT	10-M walking test

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions {31b}

Alisha Noreen, Lijuan Ao, and Lei Yang are involved in the conception and design of the research. Ethics approval was obtained from Jiani Lu. Lei Yang and Alisha Noreen drafted the manuscript. All the authors edited and revised the manuscript. All the authors read and approved the final version of the manuscript.

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Declarations

Ethics approval and consent to participate {24}

The ethics committee of Kunming Medical University approved the experiment. Ethical approval number KMMU2024MEC094. Informed consent to participate will be obtained from all participants.

Consent for publication {32}

All the authors read the manuscript and approved the publication.

Competing interests {28}

All the authors have no competing interests.

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