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Effect of Baduanjin exercise on cognitive function in patients with post-stroke cognitive impairment: Study protocol for a randomized controlled trial

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Abstract

Introduction: Post-stroke cognitive impairment is one of the most common complications in stroke survivors, and over 65% of these patients suffer from cognitive impairment at 12 months following onset, which strongly affects the rehabilitation of their motor function and quality of life. Therefore, it is important to improve the cognitive ability of stroke survivors. As an important component of traditional Chinese Qigong exercises, characterized by the coordination of mind and body with a low exercise intensity, Baduanjin has the potential benefit of improving cognitive ability for stroke patients with cognitive impairment. The primary purpose of this study is to investigate the effectiveness and safety of Baduanjin training on the cognitive function of stroke survivors.

Method and analysis: This study is designed as a randomized, two-arm parallel controlled trial with allocation concealment and assessors blinding. A total of 48 participants will be recruited and randomly allocated into the Baduanjin exercise intervention or control group. Baduanjin intervention will last 24 weeks with a frequency of 3 days a week and 40 min a day. Global cognitive function and the specific domains of cognition (i.e., memory, processing speed, execution, attention

and visuospatial ability) will be measured at baseline, 8 weeks, 16 weeks, 24 weeks after intervention and 28 weeks after an additional 4-week follow-up period, while the motor function and quality of life will be measured at baseline, 24 weeks after intervention, and 28 weeks after an additional 4-week follow-up period.

Discussion: This protocol presents a rigorous design of a randomized parallel controlled trial that aims to evaluate the effectiveness of Baduanjin exercise on cognitive function, motor function and quality of life in stroke patients with cognitive impairment. A positive result will provide powerful evidence for Baduanjin exercise to improve cognitive function, motor function and quality of life in stroke survivors with cognitive impairment.

Ethics and dissemination: Ethics approval was obtained from the Ethics Committee of Fujian University of Traditional Chinese Medicine Subsidiary Rehabilitation Hospital (approval number: 2016KY-022-01). The findings will be disseminated through peer-reviewed publications and at scientific conferences.

Strengths and limitations of this study

- This protocol presents a rigorous design of a randomized parallel controlled trial that aims to evaluate the effectiveness of Baduanjin exercise on the cognitive function, motor function and quality of life in stroke patients with cognitive impairment.
- A broad measurement tool and multiple measurement time points will be used to judge the effects of Baduanjin exercise on cognitive ability in stroke patients.
- If the result we will reach is positive, that will provide a powerful evidence of Baduanjin exercise on improve cognitive function, motor function and quality of

life in stroke survivors with cognitive impairment.

- The efficacy of a 24-week Baduanjin exercise intervention in stroke patients with cognitive impairment remains to be determined.

Trial registration

ChiCTR-INR-16009364. Registration date: 10 October, 2016.

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Keywords

Baduanjin exercise, cognitive impairment after stroke, randomized controlled trial

Background

Stroke affects 15 million people annually and is a leading cause of death and disability worldwide [1]. In China, there are 6 million patients suffering from stroke, and this number increases at an annual rate of 9%. Stroke is associated with many long-term complications, such as motor dysfunction, language dysfunction and cognitive impairment. Post-stroke cognitive impairment is one of most common complications. Over 65% of stroke survivors suffer from cognitive impairment at 12 months following onset, and a third of them may transform to dementia [2], which greatly impacts the quality of life of stroke survivors [3]. As a consequence, it is significant to improve the cognitive function as soon as possible to promote functional

recovery and improve quality of life in stroke survivors [4].

Theoretically, pharmacological therapy for cognition function may lead to improved recovery. Current data also indicate that a number of drugs may have short-term benefits [5-7], but no drug treatment to date has shown convincing clinical evidence on preventing further cognitive decline or restoring cognitive function for stroke survivors [8]. Thus, increasing attention has been paid to non-drug treatments. Aerobic exercises have been widely recognized because of their obvious effect of improving cognitive ability in stroke survivors [9-11]. However, most stroke patients do not have sufficient compliance to achieve sufficient improvements in aerobic exercise protocols due to an important concern of safety. Therefore, future stoke studies involving aerobic exercise training should determine optimal protocols for individuals with physical limitations [12]. As a mind-body exercise with mild to moderate intensity, Baduanjin exercise is one of the most common forms of Qigong that has been practised in China for more than 1000 years [13]. Baduanjin exercise consists of eight separate and smooth movements and is easier to learn and practice with less limitation than other aerobic exercises [14]. Therefore, this exercise is more suitable for older adults, especially stroke patients. Increasing studies have demonstrated that regular practice of Baduanjin exercise was beneficial to improve the physical and psychological outcomes in older people, such as improving blood lipid metabolism and sleep quality, lowering blood pressure, reducing depression and anxiety, and improving physical flexibility [15-19]. Currently, several studies also show that regular Baduanjin exercise could slow normal age-related decline in the memory domain, and delay ageing of intelligence in older adults [20-21]. Consequently, we speculate that regular Baduanjin exercise could be beneficial for cognitive function in patients with

post-stroke cognitive dysfunction. The primary aim of this study is to conduct a randomized controlled trial to evaluate systematically the effect of Baduanjin exercise on the cognitive function in stroke patients with cognitive impairment.

Method/Design

This report describes a two-arm, randomized, parallel controlled trial with allocation concealment and assessor blinding. The primary purpose is to evaluate the effect of Baduanjin on cognitive functions, including global cognitive ability, and primary cognitive domains, such as memory, attention, and visuospatial ability, in stroke patients with cognitive impairment.

This study will be conducted at the Wufeng Community Centre in the Gulou District and the Cangxia Community Centre in the Taijiang District, Fuzhou City, Fujian, China, which are counterpart support communities of the Affiliated Rehabilitation Hospital of Fujian University of Traditional Chinese Medicine. A total of 48 eligible participants will be randomly allocated to either the intervention group (the Baduanjin exercise group) or the control group (the health education group) in a 1:1 ratio. The participants in the intervention group will accept Baduanjin exercise training intervention three times a week and the routine health education once every four weeks for 24 weeks, while those allocated to the control group will only receive the routine health education once every four weeks for 24 weeks. Primary and secondary outcomes will be measured at baseline, 8 weeks, 16 weeks and 24 weeks after intervention and at 28 weeks (after an additional 4-week follow-up period). A flow diagram of the study design is shown in Figure 1. The study protocol is reported according to Standard Protocol Items: Recommendations for Intervention Trials 2013 (SPIRIT). A SPIRIT Checklist and the schedule of enrolment, interventions and

assessments are provided in Additional file 1 and Figure 2.

Sample size

Sample size was calculated on the basis of the changes in global cognitive ability after 24 weeks of intervention between comparison groups with a significance level of 5% and a two-tailed critical region. The means and their standard deviations (mean±SD) of global cognitive ability in the control and aerobic exercise intervention group were 75.93±4.9 and 81.07±6.16, respectively, at post-intervention according to the published literature [22]. A sample size of 40 participants was calculated to ensure the same effect size with 80% power by Gpower 3.1.9.2 software. Considering a 20% attrition rate, a total of 48 participants is necessary, with 24 participants being assigned to each group.

Study population

The study population is stroke patients with a diagnosis of cognitive impairment living in Fuzhou City. The inclusion and exclusion criteria for the study sample are as follows.

Inclusion criteria

The eligible participants should meet all of the following criteria:

①Clinical diagnosis of stroke according to the fourth national academic conference on cerebrovascular diseases Diagnostic Criteria for All Kinds of Cerebrovascular Disease [23] and confirmed by computed tomography or magnetic resonance imaging;

②Have cognitive impairment diagnosed by Diagnostic and Statistical Manual Disorders (DSM-V);

First ever stroke over three months;

Aged between 45 and 75 years;

Be conscious, with stable vital signs;

Ability to walk at least 10 metres without external force and auxiliary equipment;

Written informed consent.

Exclusion criteria

Criteria for exclusion are the following:

Have been suffering from brain tumour, brain trauma, brain parasite disease, or other diseases that could cause cognitive impairment;

Severe language, vision, and/or auditory impairment or a neuropsychiatric disorder precluding cognitive examination;

Have been suffering from diseases related to cognitive impairment confirmed by anamnesis, doctors, or families or with a history of cognitive drug use before stroke;

Beck Depression Scale-II score >13;

Patients with alcohol or drug abuse;

Have been suffering from a severe medical condition, such as heart, liver, kidney, and endocrine diseases and haematopoietic system disease;

Participating in another clinical trial that would affect the evaluation results of this study.

Withdrawal or dropout criteria

Participants in neither the intervention nor control group will be terminated to continue this trial according to the following criteria:

① Unwilling to continue this trial;

② Suffering from the deterioration of stroke disease or other serious organic diseases during the study period;

③ Do not complete the training scheme for four weeks during the study period;

④ Those who reject to be measured or followed up;

⑤ Suffering from the serious adverse event related to the research.

Recruitment and screening

The recruitment of eligible participants will be conducted by posting up posters on the community publicity column, sending leaflets, and setting up a recruiting station at the Wufeng Community Centre in the Gulou District and the Cangxia Community Centre in the Taijiang District, Fuzhou City. The potentially eligible individuals will first complete a screening to determine their eligibility according to the inclusion and exclusion criteria. Eligible individuals will receive the information about this trial and have an informed discussion with two trained research assistants regarding the information provided. Those who are interested in this study will sign the written informed consent, and the baseline assessment will subsequently be arranged.

Randomization and allocation concealment

After baseline assessment, the eligible participants will be randomly assigned to either the intervention group or the control group with equal rate. The random allocation sequence will be generated using the PLAN procedure of the statistical software SAS v9.0 and be managed by an independent research assistant who is not involved in

recruitment, evaluation and intervention of the participants. The eligible participants will be informed of their allocation result by the independent research assistant via telephone.

Blinding

In this trial, it is impossible to blind the participants and exercise coaches because this trial investigates a non-pharmacological intervention, but two types of blind codes will be used to blind the outcome assessors and data statisticians. We will assign an independent research manager to be in charge of the random allocation sequence and the blind codes. The participants' allocation result (the intervention group or the control group) will be replaced using alphabet 'A' or 'B' in the first blind code, and the real meaning of 'A' or 'B' will be marked in the second blind code. When the data-base is locked, the independent research assistant will deliver the group code 'A' or 'B' of participants to the statistician, and the real meaning of group 'A' or 'B' will be declared after analysis of all data is completed.

Intervention

All participants will continue routine medical or rehabilitative treatment and maintain usual visits with their primary care physicians throughout the study if necessary. Meanwhile, all of the participants will also receive the same health education programme during the intervention period. The Baduanjin exercise will be applied to the participants in the intervention group, while participants in the control group will be informed to maintain their usual lifestyle.

The routine medical or rehabilitative treatment will be in accordance with the Chinese Medical Association's Guidelines for the Prevention and Treatment of

Cerebrovascular Disease in China (2010) [24]. The detailed treatment schedule will be conducted by their primary care physicians and recorded by the research assistants. The health education is conducted by the professional neurologists with a frequency of once a month and 40 minutes each time. The content of health education primarily involves the knowledge of the prevention and rehabilitation of stroke according to "Out of the Misunderstanding of Stroke Patients' Rehabilitation" (a bestseller book for health education after stroke from the Chinese Association of TCM) [25].

Intervention group

Participants in the intervention group will receive a 24-week Baduanjin exercise training, except for the routine medical or rehabilitative treatment and health education. The Baduanjin exercise training will last for 24 weeks with a frequency of 3 days a week and 40 min a day. The training scheme of Baduanjin exercise originates from the 'Health Qigong Baduanjin Standard' enacted by the State Sports General Administration in 2003 [26]. The whole set of Baduanjin exercise consists of ten postures (including the preparation and ending posture) (Figure 3). The participants will be gathered together to train when there are more than five participants recruited in the same community. Qualified Baduanjin exercise coaches from the Fujian University of Traditional Chinese Medicine with more than 5 years of teaching experience will be employed to guide participants' training.

Control group

The participants in the control group will not receive any specific exercise training from the study scheme. These participants will be requested to maintain their original habit of lifestyle.

Follow-up

After the 24-week intervention period, all participants will enter an additional 4-week follow-up period. The participants will resume their original lifestyle during the follow-up period. Telephone follow-up or home visiting will be performed once a week by the research assistants. The information on participants' subjective feeling, medications and daily activity, as well as cognitive and motor function, will be recorded or evaluated.

Participant retention and adherence

The success of the intervention is strongly dependent on participants' active participation. To motivate participants' active participation, the staff will use several strategies to improve adherence to the intervention program: ① researchers will explain in detail the benefit of practising Baduanjin exercise after participants are randomly allocated into the intervention group; ②coaches will motivate participants' interest for the Baduanjin exercise training when they instruct participants practising the Baduanjin exercise; and ③the research assistants will remind participants to practice the Baduanjin exercise according to the study scheme by calling them on the phone. In addition, participant who complete the programme successfully will be rewarded with 100 RMB incentive money. Attendance of the Baduanjin exercise training will be recorded and assessed through records of the proportion of training days. Participants will be marked as absent when they do not attend the training session.

To improve participant retention, once a subject is randomized, the research assistants will make every reasonable effort to ensure the subjects stays for the entire study period. In detail, study assistants will ①maintain participants' interests by interview and phone calls; ②provide periodic communications via materials and talks to inform the participants of our acknowledgement of their support; and ③be as flexible as

possible with the study schedule in resolving time conflicts with participants' life.

Outcome Assessment

Primary outcome

Global cognitive function will be measured using the Montreal Cognitive Assessment scale (MoCA). The MoCA scale is a brief test to evaluate the global cognitive ability by testing attention, naming, visuospatial/executive function, memory, language, visual structure skills, abstraction, calculation, and orientation with a total score of 0-30 (a higher score equals better function). The Chinese vision of the MoCA (Beijing version) was revised and is widely used in China with good validity and reliability [27]. Primary outcome will be assessed at baseline, 8 weeks, 16 weeks and 24 weeks after intervention and at 28 weeks after a 4-week follow-up period by the neurologists at the Affiliated Rehabilitation Hospital of FJTCM, who will be blinded to the allocation results of participants.

Secondary outcomes

Secondary outcomes involving the specific cognitive domains (i.e., execution, memory, attention, processing speed and visuospatial skill), gait, motor ability, balance ability, activities of daily living and quality of life will be measured at baseline, 24 weeks of intervention and 28 weeks after a 4-week follow-up period by the blinded medical staff or research assistants.

- Executive ability will be assessed using the Trail Making Test (TMT). The TMT consists of two parts, TMT-A and TMT-B: TMT-A requires the participants to sequentially connect 25 encircled numbers on a sheet of paper, while TMT-B requires participants to draw a line alternating between numbers and letters in

ascending order between the number and the letter, and the TMT-B/TMT-A is considered as a valid index of executive ability [28].

- Memory will be measured using the Chinese vision of the Auditory Verbal Learning Test (AVLT) [29]. AVLT includes three subtests of immediate recall, short-term-delayed recall and long-term delayed recognition. In the immediate recall test, subject will be requested to repeat immediately a list of 15 unrelated words said by the assessor three times; after 15 minutes, subject will be asked to recall the 15 words, and the correct rate is the score of short-term-delayed recall. In the long-term delayed recognition test, a subject is given another list of 15 unrelated words and must recognize the original list of 15 words [30]. The Chinese version of the AVLT has been reported reliable with split-half reliability, internal consistency and structure validity [29].

- Attention will be measured using the Test of Attention Performance (TAP, V.2.3), which is based on computer-aided neuropsychological tests for assessing the attentional performance [31]. Four of this test's sub-tests, including alertness for reaction, general attention, Go/No Go and divided selective attention, will be chosen for this trial.

- Processing speed will be measured by the Digit Symbol Coding (DSC), which is a subtest of the Wechsler Adult Intelligence Scale-Revised China (WAIS-RC) with nine numbers from 1 to 9 and nine corresponding symbols [32]. A subject will be asked to draw each symbol under its corresponding number within a 90 s time limit, and the number of correct answers is its scores.

- Visuospatial ability will be assessed by the Clock Drawing Task (CDT), which is a vision-dependent task [33]. The participants will be asked to draw a clock reading a

specific time (generally 11:10). The correctness in clock drawing will be classified according to four categories [34].

- Gait stability and the interactions between cognitive tasks and gait will be measured by gait analysis [35]. Participants were instructed to walk in two assigned conditions: free walking as usual and walking as usual with executing a calculation task. The gait parameters in two conditions will be measured with the America Motion Analysis gait analysis system, and the numbers of completion and error rates in calculation tasks will be recorded.

- Motor Function will be evaluated using the Fugl-Meyer Assessment scale (FMA), which is known for its good validity and reliability in evaluating upper and lower limb function after stroke [36]. The FMA consists of 50 items based on a six-stage recovery process of Brunnstrom's hemiplegia classification, and 66 points of a possible 100 total score apply to the upper limbs, and the other 34 points are applied to the lower limbs [37].

- Balance Function will be measured by the Berg Balance Scale (BBS), which consists of a set of 14 tasks to quantitatively assess the static and dynamic balance abilities [38]. The BBS is not only one of the most important measurement scales to evaluate the balance function of patients after stroke but can also be used as the risk predictor of accidental fall in stroke patients [39].

- Activities of Daily Living（ADL） will be assessed using the Modified Barthel Index (MBI), which is a widely used standard scale for assessing functional disability in basic ADL. The MBI contains 10 projects with a total of 100 points, and the higher the score means the better the daily life self-care ability [40].

- Quality of life will be measured by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), which is currently the most commonly used in clinical evaluation of quality of life in the general population and patients. The SF-36 consists of 36 items to assess eight health concepts, and each of them is evaluated separately by the normalized scores from 0 to 100, with the higher score corresponding to better health status [41]. The Chinese SF-36 has been demonstrated to have high reliability and validity in the Chinese population [42].

Safety evaluation

Although no adverse events are reported currently regarding Baduanjin exercise, any unexpected adverse events during the intervention period will be reported to the research assistants, and causality in relation to the Baduanjin exercise training and the severity of adverse events will be evaluated. Serious adverse events will be reported to the ethics committee immediately.

Data management and monitoring

Data will be collected by the outcomes assessors using the print-based case report forms (p-CRFs), and the p-CRFs will later be inputted into the web-based case report forms (w-CRFs) in an electronic data capture system (EDC) by research assistants. The research assistants are also responsible for the integrity and accuracy of data when data are inputted into w-CRFs by means of checking on value ranges, or logical checks. The EDC system and web servers will be provided to the data management centre of FJTCM (http://210.34.74.191/srtp/users/loginlangth.action) and meet the available standards for security (the data management centre, which belongs to the Science and Technology Department of FJTCM, is in charge of the monitoring and auditing of all research data in FJTCM). Participants' data in w-CRFs will be stored in

the EDC system in a separate password-protected location. All documents will be retained securely for five years after completion of the study.

Statistical analysis

Statistical analysis will be performed using SPSS 22.0 (IBM, Chicago, IL, USA) software package by an independent statistician who is not involved in the outcome assessment, with a two-sided p value <0.05 being considered to be statistically significant. Continuous variables will be expressed using mean and its standard error for normal distributions or median and its interquartile range for non-normal distributions. Categorical variables will be described as frequencies or percentages.

Baseline characteristics between comparison groups will be compared using a t-test or Mann-Whitney U test for continuous variables and Pearsonχ^2 or Fisher's exact test for categorical variables.

The analysis of primary or secondary outcomes will be based on an intention to treat (ITT) principle, and the missing data will be imputed using a multiple imputation method. The group difference between intervention and control group at each time point (8-week, 16-week, and 24-week after intervention or 4-week follow-up period) will be analysed using Student's t-test or Mann-Whitney U-test. The linear mixed model with restricted maximum likelihood will be used to analyse the interaction effect of Group×Time.

Adverse events (AEs) will be analysed using a chi-square test or Fisher's exact test. If the formal statistical analyses between-groups cannot be performed due to the lack of power, AEs will be tabulated and summarized using descriptive statistics.

Ethics

This study protocol conformed to the Declaration of Helsinki. Ethics approval of this study protocol, and consent forms were obtained from the Ethics Committee of Fujian University of Traditional Chinese Medicine Subsidiary Rehabilitation Hospital (approval number: 2016KY-022-01). The study background and main objective as well as potential benefits and risks will be fully explained to the participants and their families. Before participating in the study, participants will sign the informed consent document prior to participation.

Dissemination

The study protocol has been registered and is available on the Chinese Clinical Trial Registry website (http://www.chictr.org.cn with the identifier number ChiCTR-INR-16009364). Study results will be first informed to each participant and later disseminated to researchers, healthcare providers, healthcare professionals and the general public through courses, presentations and the internet, regardless of the magnitude or direction of effect. The results will also be documented in a published peer reviewed academic journal.

Discussion

As one of the most common forms of Chinese traditional exercises, Baduanjin exercise consists of eight separate movements, each of which focuses on a different physical area of the body [13]. Compared with other aerobic exercises, Baduanjin exercise is not only easy to learn but also is less physical and cognitive demanding [43]. Therefore, Baduanjin has become a popular and safe community exercise to promote health in the community of the older population of China. Furthermore, different from other types of aerobic exercise, Baduanjin is also a mind-body exercise combined

with the holistic view and the theory of traditional Chinese medicine in that practitioners are required to reach coordination between mind and body [14]. Several studies have reported that regular Baduanjin training has a positive effect in slowing normal age-related memory decline [20-21]. Zhu HM et al. even reported that Baduanjin exercise can delay the cognitive impairment progression for the elderly diabetic patients with mild cognitive impairment [44]. Therefore, it is reasonable to assume that regular Baduanjin training could be beneficial to cognitive function in stroke patients. This proposed study aims to investigate the effect of Baduanjin exercise on cognitive function, as well as observing the effect on motor function and quality of life in the stroke patients with cognitive impairment. This study will employ rigorousness to control bias, such as randomization, parallel control, and blinding of the outcome assessors and statistician. To ensure participants master standard Baduanjin movements, we will also employ qualified physical exercise teachers to serve as the Baduanjin exercise coaches. However, a potential limitation of this study is that participants and coaches cannot be blinded because it is impossible to make them blinded in non-pharmacological trials [45]. Therefore, performance bias may be inevitable, but the exercise coaches will be not involved in the recruitment, outcome assessment, or data analysis of this study. Another challenge that we may encounter for the study is the difficulty in recruiting the eligible stroke patients. Those stroke patients or their families may worry about the exercise risk and prefer to stay in their home and maintain a fairly static life. In addition, a higher dropout rate may also be expected due to the above concerns. To address these problems, we will encourage participants to practice the Baduanjin training at their home after they master this exercise. We also accounted for the higher dropout rate in the sample size estimation to ensure the sufficient statistical power for the study.

In summary, this report describes the first randomized controlled trial to evaluate systematically the rehabilitative effect of Baduanjin exercise on cognitive ability and motor function in stroke patients. This study will determine if Baduanjin training is likely to be effective in improving cognitive function, including global cognitive function and specific cognitive domains, in stroke patients with cognitive impairment. This study will also investigate if Baduanjin training can improve the motor function and quality of life for stroke patients with cognitive impairment and determine if this exercise is acceptable to them. If this trial is successfully conducted and demonstrates a significant result, that intervention would provide an effective rehabilitation approach for stroke patients and adequate supporting evidence for the application of regular Baduanjin exercise in patients with post-stroke cognitive impairment. Conversely, if this exercise training is not effective, the study will identify the factors that contributed to the negative outcome.

Trial status

This trial is currently in the recruitment phase.

Abbreviations

SD: Standard deviation; DSM-V: Diagnostic and statistical manual disoeders,5th edition; SAS 9.0: Statistical analysis system; TCM: Traditional Chinese medicine; MoCA: Montreal cognitive assessment scale; FJTCM: Fujian University of Traditional Chinese Medicine; TMT: Trail Making Test; AVLT: Auditory verbal

learning test; TAP: Test of attention performance; DSC: Digit symbol coding; WAIS-RC: Wechsler adult intelligence scale-revised China; CDT: Clock drawing task; FMA: Fugl-Meyer assessment scale; BBS: Berg balance scale; BI: Barthel index; ADL: Activities of daily living; SF-36: Item short-form health survey; CRF: Case report form; EDC: Electronic data capture system; SPSS 22.0: Statistic package for social science 22.0; ITT: Intention to treat.

Declarations

Authors' contributions

CLD and ZGH conceived and designed of the study protocol and contributed to drafting the manuscript. ZYH and XZY wrote the manuscript and participated in the coordination and implementation of the study. ZGH revised the study protocol and wrote several sections of the manuscript. YBZ and TJ helped develop the study measures and data collection. All authors contributed to drafting the manuscript and have read and approved the final version of the manuscript.

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Availability of data and materials

This is not applicable because this is a paper of a study protocol.

Consent for publication

Not applicable.

Competing interests

None declared.

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Additional files:

Additional file 1: SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents.

Additional figure 1: Study design.

Additional figure 2: Schedule of enrolment, interventions, and assessments.

Additional figure 3: Ten postures of Baduanjin.

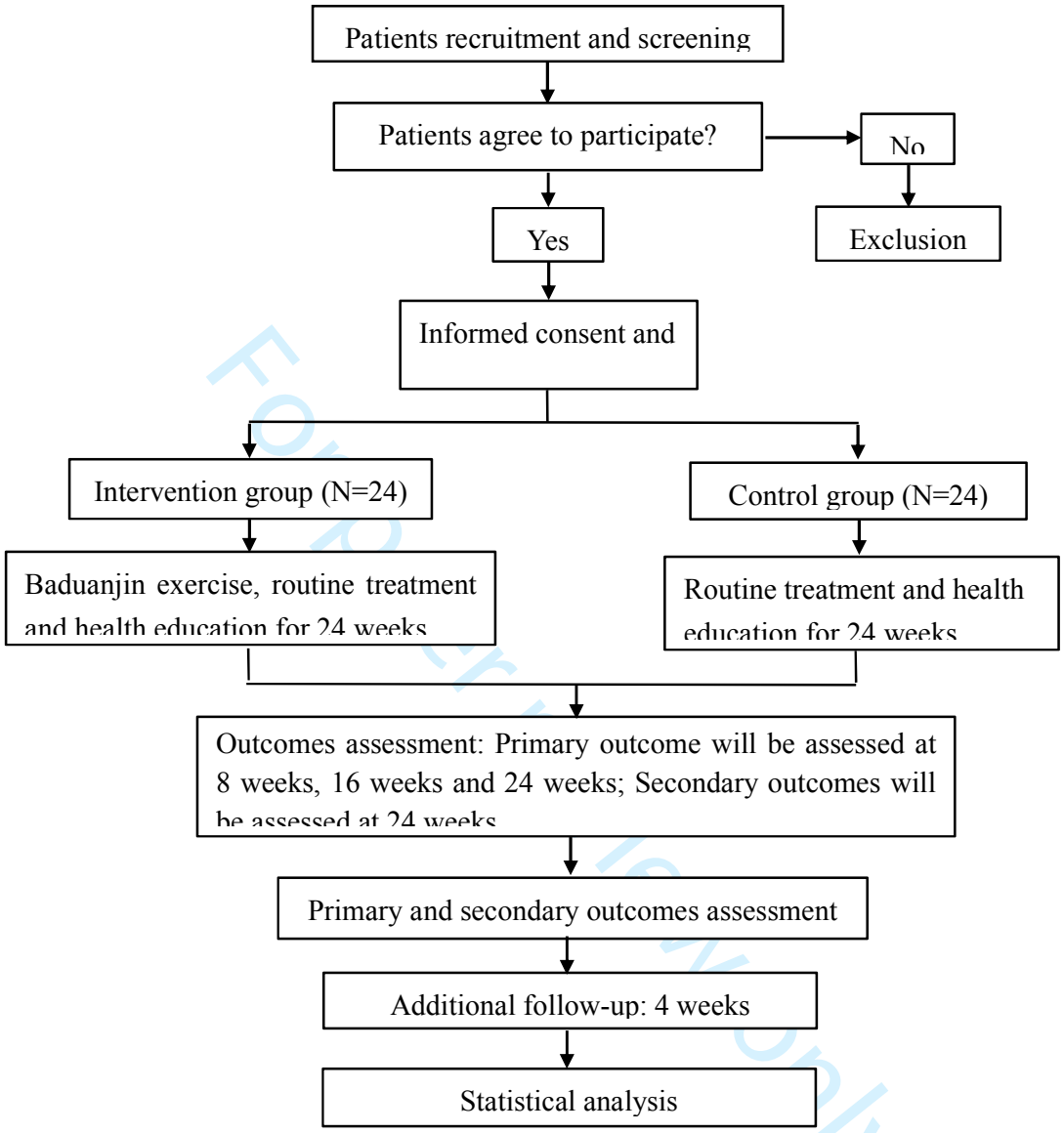

Figure 1 Flow diagram of study design

STUDY PERIOD						
	Enrolment	Allocation	Intervention			Follow-up
TIMEPOINT*	$-t_1$	0	t_1	t_2	t_3	t_4
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
ALLOCATION		X				
INTERVENTIONS:						
Intervention group (Baduanjin exercise training+health education)			←	—	→	
Control group (Health education)			←	—	→	
ASSESSMENTS:						
Basic characteristics	X					
Global cognitive function	X		X	X	X	X
Executive ability	X		X	X	X	X
Memory	X		X	X	X	X
Attention	X		X	X	X	X
Processing speed	X		X	X	X	X
Visuospatial ability	X		X	X	X	X
Gait stability	X				X	X
Motor Function	X				X	X
Balance Function	X				X	X
Activities of Daily Living	X				X	X
Quality of Life	X				X	X
Adverse events			X	X	X	

<Figure Legend>

* $-t_1$= -2-(-1) weeks, 0= Baseline, t_1 = Week 8, t_2 = Week 16, t_3 = End of treatment Week 24, t_4 = Follow Up Week 28.

Figure 2: Schedule of enrolment, interventions, and assessments

A: Preparation posture

B: Prop up the sky by two hands to regulate

C: Draw a bow on both sides like shooting a

D: Raise single arm up to regulate spleen (Pi)

E: Look back to treat five strains and seven

E: Look back to treat five strains and seven

G: Pull toes with both hands to reinforce the

H: Clench one's fist and glare to increase

I: Rise and fall on tiptoe seven times to

J: Ending posture

Figure 2: Ten postures of Baduanjin

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&21
	5b	Name and contact information for the trial sponsor	21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	11
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12&16
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16-17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17-18

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9&16
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16-18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16&18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Available in the informed consent materials
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available in Chinese vesion
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effect of Baduanjin exercise on cognitive function in patients with post-stroke cognitive impairment: Study protocol for a randomized controlled trial

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Effect of Baduanjin exercise on cognitive function in patients with post-stroke cognitive impairment: Study protocol for a randomized controlled trial

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Abstract

INTRODUCTION: Post-stroke cognitive impairment is one of the most common complications in stroke survivors, and over 65% of these patients suffer from cognitive impairment at 12 months following onset, which strongly affects the rehabilitation of their motor function and quality of life. Therefore, it is important to improve the cognitive ability of stroke survivors. As an important component of traditional Chinese Qigong exercises, characterized by the coordination of mind and body with a low exercise intensity, Baduanjin has the potential benefit of improving cognitive ability for stroke patients with cognitive impairment. The primary purpose of this study is to investigate the effectiveness and safety of Baduanjin training on the cognitive function of stroke survivors.

METHOD AND ANALYSIS: This study is designed as a randomized, two-arm parallel controlled trial with allocation concealment and assessors blinding. A total of 48 participants will be recruited and randomly allocated into the Baduanjin exercise intervention or control group. Baduanjin intervention will last 24 weeks with a frequency of 3 days a week and 40 min a day. Global cognitive function and the

specific domains of cognition (i.e., memory, processing speed, execution, attention and visuospatial ability) will be measured at baseline, 8 weeks, 16 weeks, 24 weeks after intervention and 28 weeks after an additional 4-week follow-up period, while the motor function and quality of life will be measured at baseline, 24 weeks after intervention, and 28 weeks after an additional 4-week follow-up period.

ETHICS AND DISSEMINATION: Ethics approval was obtained from the Ethics Committee of Fujian University of Traditional Chinese Medicine Subsidiary Rehabilitation Hospital (approval number: 2016KY-022-01). The findings will be disseminated through peer-reviewed publications and at scientific conferences.

TRIAL REGISTRATION NUMBER: ChiCTR-INR-16009364; Pre-results.

Registration date: 10 October, 2016.

KEYWORDS

Baduanjin exercise, cognitive impairment after stroke, randomized controlled trial

Strengths and limitations of this study

- This protocol presents a rigorous design of a randomized parallel controlled trial that aims to evaluate the effectiveness of Baduanjin exercise on the cognitive function, motor function and quality of life in stroke patients with cognitive impairment.
- A broad measurement tool and multiple measurement time points will be used to judge the effects of Baduanjin exercise on cognitive ability in stroke patients.

- If the result we will reach is positive, that will provide a powerful evidence of Baduanjin exercise on improve cognitive function, motor function and quality of life in stroke survivors with cognitive impairment.
- The efficacy of a 24-week Baduanjin exercise intervention in stroke patients with cognitive impairment remains to be determined.

Introduction

Stroke affects 15 million people annually and is a leading cause of death and disability worldwide [1]. In China, there are 6 million patients suffering from stroke, and this number increases at an annual rate of 9%. Stroke is associated with many long-term complications, such as motor dysfunction, language dysfunction and cognitive impairment. Post-stroke cognitive impairment is one of most common complications. Approximately 65% of stroke survivors suffer from some extent to cognitive impairment at five years post-stroke, and up to a quarter of those stroke survivors with cognitive impairment are more likely to transition to dementia [2], which is associated with increased disability and a poor quality of life [3]. As a consequence, it is significant to improve the cognitive function as soon as possible to promote functional recovery and improve quality of life in stroke survivors [4].

Theoretically, pharmacological therapy for cognition function may lead to improved recovery. Current data also indicate that a number of drugs may have short-term benefits [5-7], but no drug treatment to date has shown convincing clinical

evidence on preventing further cognitive decline or restoring cognitive function for stroke survivors [8]. Thus, increasing attention has been paid to non-drug treatments. Aerobic exercises have been widely recognized because of their obvious effect of improving cognitive ability in stroke survivors [9-11]. However, most stroke patients do not have sufficient compliance to achieve sufficient improvements in aerobic exercise protocols due to an important concern of safety. Therefore, future stoke studies involving aerobic exercise training should determine optimal protocols for individuals with physical limitations [12]. As a mind-body exercise with mild to moderate intensity, Baduanjin exercise is one of the most common forms of Qigong that has been practised in China for more than 1000 years [13]. Baduanjin exercise consists of eight separate and smooth movements and is easier to learn and practice with less limitation than other aerobic exercises [14]. Therefore, this exercise is more suitable for older adults, especially stroke patients. Increasing studies have demonstrated that regular practice of Baduanjin exercise was beneficial to improve the physical and psychological outcomes in older people, such as improving blood lipid metabolism and sleep quality, lowering blood pressure, reducing depression and anxiety, and improving physical flexibility [15-19]. Currently, several studies also show that regular Baduanjin exercise could slow normal age-related decline in the memory domain, and delay ageing of intelligence in older adults [20-21]. Consequently, the primary aim of this study is to conduct a randomized controlled trial to evaluate systematically the effect of Baduanjin exercise on the cognitive function in stroke patients with cognitive impairment.

Method/Design

This report describes a two-arm, randomized, parallel controlled trial with allocation

concealment and assessor blinding. The primary purpose is to evaluate the effect of Baduanjin on cognitive functions, including global cognitive ability, and primary cognitive domains, such as memory, attention, and visuospatial ability, in stroke patients with cognitive impairment.

This study will be conducted at the Wufeng Community Centre in the Gulou District and the Cangxia Community Centre in the Taijiang District, Fuzhou City, Fujian, China, which are counterpart support communities of the Affiliated Rehabilitation Hospital of Fujian University of Traditional Chinese Medicine. A total of 48 eligible participants will be randomly allocated to either the intervention group (the Baduanjin exercise group) or the control group (the health education group) in a 1:1 ratio. The participants in the intervention group will accept Baduanjin exercise training intervention three times a week and the routine health education once every four weeks for 24 weeks, while those allocated to the control group will only receive the routine health education once every four weeks for 24 weeks. Primary and secondary outcomes will be measured at baseline, 8 weeks, 16 weeks and 24 weeks after intervention and at 28 weeks (after an additional 4-week follow-up period). A flow diagram of the study design is shown in Figure 1. The study protocol is reported according to Standard Protocol Items: Recommendations for Intervention Trials 2013 (SPIRIT). A SPIRIT Checklist and the schedule of enrolment, interventions and assessments are provided in Additional file 1 and Figure 2.

Figure 1: Study design.

Additional file 1: SPIRIT 2013 Checklist.

Figure 2: Schedule of enrolment, interventions, and assessments.

Patient and Public Involvement

This trial is currently in the recruitment phase. No patients and or public has involved in the trial.

Sample size

Sample size was calculated on the basis of the changes in global cognitive ability after 24 weeks of intervention between comparison groups with a significance level of 5% and a two-tailed critical region. The means and their standard deviations (mean±SD) of global cognitive ability in the control and aerobic exercise intervention group were 75.93±4.9 and 81.07±6.16, respectively, at post-intervention according to the published literature [22]. A sample size of 40 participants was calculated to ensure the same effect size with 80% power by Gpower 3.1.9.2 software. Considering a 20% attrition rate, a total of 48 participants is necessary, with 24 participants being assigned to each group.

Study population

The study population is stroke patients with a diagnosis of cognitive impairment living in Fuzhou City. The inclusion and exclusion criteria for the study sample are as follows.

Inclusion criteria

The eligible participants should meet all of the following criteria:

①Clinical diagnosis of stroke according to the fourth national academic conference on cerebrovascular diseases Diagnostic Criteria for All Kinds of Cerebrovascular Disease [23] and confirmed by computed tomography or magnetic resonance imaging;

□Have cognitive impairment diagnosed by Diagnostic and Statistical Manual Disorders (DSM-V);

□First ever stroke over three months;

□Aged between 45 and 75 years;

□Be conscious, with stable vital signs;

□Ability to walk at least 10 metres without external force and auxiliary equipment;

□Written informed consent.

Exclusion criteria

Criteria for exclusion are the following:

□Have been suffering from brain tumour, brain trauma, brain parasite disease, or other diseases that could cause cognitive impairment;

□Severe language, vision, and/or auditory impairment or a neuropsychiatric disorder precluding cognitive examination;

□Have been suffering from diseases related to cognitive impairment confirmed by anamnesis, doctors, or families or with a history of cognitive drug use before stroke;

□Beck Depression Scale-II score >13;

□Patients with alcohol or drug abuse;

□Have been suffering from a severe medical condition, such as heart, liver, kidney, and endocrine diseases and haematopoietic system disease;

□Participating in another clinical trial that would affect the evaluation results of this study.

Withdrawal or dropout criteria

Participants in neither the intervention nor control group will be terminated to continue this trial according to the following criteria:

① Unwilling to continue this trial;

② Suffering from the deterioration of stroke disease or other serious organic diseases during the study period;

③ Do not complete the training scheme for four weeks during the study period;

④ Those who reject to be measured or followed up;

⑤ Suffering from the serious adverse event related to the research.

Recruitment and screening

The recruitment of eligible participants will be conducted by posting up posters on the community publicity column, sending leaflets, and setting up a recruiting station at the Wufeng Community Centre in the Gulou District and the Cangxia Community Centre in the Taijiang District, Fuzhou City. The potentially eligible individuals will first complete a screening to determine their eligibility according to the inclusion and exclusion criteria. Eligible individuals will receive the information about this trial and have an informed discussion with two trained research assistants regarding the information provided. Those who are interested in this study will sign the written informed consent, and the baseline assessment will subsequently be arranged.

Randomization and allocation concealment

After baseline assessment, the eligible participants will be randomly assigned to either the intervention group or the control group with equal rate. The random allocation sequence will be generated using the PLAN procedure of the statistical software SAS

v9.0 and be managed by an independent research assistant who is not involved in recruitment, evaluation and intervention of the participants. The eligible participants will be informed of their allocation result by the independent research assistant via telephone.

Blinding

In this trial, it is impossible to blind the participants and exercise coaches because this trial investigates a non-pharmacological intervention, but two types of blind codes will be used to blind the outcome assessors and data statisticians. We will assign an independent research manager to be in charge of the random allocation sequence and the blind codes. The participants' allocation result (the intervention group or the control group) will be replaced using alphabet 'A' or 'B' in the first blind code, and the real meaning of 'A' or 'B' will be marked in the second blind code. When the data-base is locked, the independent research assistant will deliver the group code 'A' or 'B' of participants to the statistician, and the real meaning of group 'A' or 'B' will be declared after analysis of all data is completed.

Intervention

All participants will continue routine medical or rehabilitative treatment and maintain usual visits with their primary care physicians throughout the study if necessary. Meanwhile, all of the participants will also receive the same health education programme during the intervention period. The Baduanjin exercise will be applied to the participants in the intervention group, while participants in the control group will be informed to maintain their usual lifestyle.

The routine medical or rehabilitative treatment will be in accordance with the Chinese

Medical Association's Guidelines for the Prevention and Treatment of Cerebrovascular Disease in China (2010) [24]. The detailed treatment schedule will be conducted by their primary care physicians and recorded by the research assistants. The health education is conducted by the professional neurologists with a frequency of once a month and 40 minutes each time. The content of health education primarily involves the knowledge of the prevention and rehabilitation of stroke according to "Out of the Misunderstanding of Stroke Patients' Rehabilitation" (a bestseller book for health education after stroke from the Chinese Association of TCM) [25].

Intervention group

Participants in the intervention group will receive a 24-week Baduanjin exercise training, at the same time, they also receive routine medical or rehabilitative treatment and health education. The Baduanjin exercise training will last for 24 weeks with a frequency of 3 days a week and 40 min a day. The training scheme of Baduanjin exercise originates from the 'Health Qigong Baduanjin Standard' enacted by the State Sports General Administration in 2003 [26]. The whole set of Baduanjin exercise consists of ten postures (including the preparation and ending posture) (Figure 3). The participants will be gathered together to train when there are more than five participants recruited in the same community. Qualified Baduanjin exercise coaches from the Fujian University of Traditional Chinese Medicine with more than 5 years of teaching experience will be employed to guide participants' training.

Figure 3: Ten postures of Baduanjin.

Control group

The participants in the control group will not receive any specific exercise training

from the study scheme. These participants will be requested to maintain their original habit of lifestyle.

In order to exclude bias from the exceed activity of participants, all participants in both intervention and control group will be required to record an activity log in the intervention period, in which the duration and intensity of their activity in a whole day will be classified into three sections including the duration of low-intensity, moderate-intensity, or high-intensity activities.

Follow-up

After the 24-week intervention period, all participants will enter an additional 4-week follow-up period. The participants will resume their original lifestyle during the follow-up period. Telephone follow-up or home visiting will be performed once a week by the research assistants. The information on participants' subjective feeling, medications and daily activities will be recorded. The primary and secondary outcomes will be evaluated at end of follow-up period.

Participant retention and adherence

The success of the intervention is strongly dependent on participants' active participation. To motivate participants' active participation, the staff will use several strategies to improve adherence to the intervention program: ① researchers will explain in detail the benefit of practising Baduanjin exercise after participants are randomly allocated into the intervention group; ②coaches will motivate participants' interest for the Baduanjin exercise training when they instruct participants practising the Baduanjin exercise; and ③the research assistants will remind participants to practice the Baduanjin exercise according to the study scheme by the WeChat group. In addition, participant who complete the programme successfully will be rewarded

with 100 RMB incentive money no matter which group they belongs to. Attendance of the Baduanjin exercise training will be recorded and assessed through records of the proportion of training days. Participants will be marked as absent when they do not attend the training session.

To improve participant retention, once a subject is randomized, the research assistants will make every reasonable effort to ensure the subjects stays for the entire study period. In detail, study assistants will □maintain participants' interests by interview and phone calls; □provide periodic communications via materials and talks to inform the participants of our acknowledgement of their support; and □be as flexible as possible with the study schedule in resolving time conflicts with participants' life.

Outcome Assessment

Primary outcome

Global cognitive function will be measured using the Montreal Cognitive Assessment scale (MoCA). The MoCA scale is a brief test to evaluate the global cognitive ability by testing attention, naming, visuospatial/executive function, memory, language, visual structure skills, abstraction, calculation, and orientation with a total score of 0-30 (a higher score equals better function). The Chinese vision of the MoCA (Beijing version) was revised and is widely used in China with good validity and reliability [27]. Primary outcome will be assessed at baseline, 8 weeks, 16 weeks and 24 weeks after intervention and at 28 weeks after a 4-week follow-up period by the neurologists at the Affiliated Rehabilitation Hospital of FJTCM, who will be blinded to the allocation results of participants.

Secondary outcomes

Secondary outcomes involving the specific cognitive domains (i.e., execution,

memory, attention, processing speed and visuospatial skill), gait, motor ability, balance ability, activities of daily living and quality of life. Executive ability, memory, attention, Processing speed and visuospatial ability will be measured at baseline, 8 weeks, 16 weeks and 24 weeks after intervention and at 28 weeks after a 4-week follow-up period. Gait stability, motor Function, balance function, activities of daily living and quality of life will be assessed at baseline, 24 weeks of intervention and 28 weeks after a 4-week follow-up period. All outcome assessments will be measured by the blinded medical staff.

- Executive ability will be assessed using the Trail Making Test (TMT). The TMT consists of two parts, TMT-A and TMT-B: TMT-A requires the participants to sequentially connect 25 encircled numbers on a sheet of paper, while TMT-B requires participants to draw a line alternating between numbers and letters in ascending order between the number and the letter, and the TMT-B/TMT-A is considered as a valid index of executive ability [28].

- Memory will be measured using the Chinese vision of the Auditory Verbal Learning Test (AVLT) [29]. AVLT includes three subtests of immediate recall, short-term-delayed recall and long-term delayed recognition. In the immediate recall test, subject will be requested to repeat immediately a list of 15 unrelated words said by the assessor three times; after 15 minutes, subject will be asked to recall the 15 words, and the correct rate is the score of short-term-delayed recall. In the long-term delayed recognition test, a subject is given another list of 15 unrelated words and must recognize the original list of 15 words [30]. The Chinese version of the AVLT has been reported reliable with split-half reliability, internal consistency and structure validity [29].

- Attention will be measured using the Test of Attention Performance (TAP, V.2.3), which is based on computer-aided neuropsychological tests for assessing the attentional performance [31]. Four of this test's sub-tests, including alertness for reaction, general attention, Go/No Go and divided selective attention, will be chosen for this trial.

- Processing speed will be measured by the Digit Symbol Coding (DSC), which is a subtest of the Wechsler Adult Intelligence Scale-Revised China (WAIS-RC) with nine numbers from 1 to 9 and nine corresponding symbols [32]. A subject will be asked to draw each symbol under its corresponding number within a 90 s time limit, and the number of correct answers is its scores.

- Visuospatial ability will be assessed by the Clock Drawing Task (CDT), which is a vision-dependent task [33]. The participants will be asked to draw a clock reading a specific time (generally 11:10). The correctness in clock drawing will be classified according to four categories [34].

- Gait stability and the interactions between cognitive tasks and gait will be measured by gait analysis [35]. Participants were instructed to walk in two assigned conditions: free walking as usual and walking as usual with executing a calculation task. The gait parameters in two conditions will be measured with the America Motion Analysis gait analysis system, and the numbers of completion and error rates in calculation tasks will be recorded. Those gait parameters mainly comprise of step length (cm), stride length (cm), forward velocity (cm/s), cadence (steps/min), total support time (%), swing time (%), double support time (%), single support time (%) and step width (cm). All these parameters include the affected and unaffected side.

- Motor Function will be evaluated using the Fugl-Meyer Assessment scale (FMA), which is known for its good validity and reliability in evaluating upper and lower limb function after stroke [36]. The FMA consists of 50 items based on a six-stage recovery process of Brunnstrom's hemiplegia classification, and 66 points of a possible 100 total score apply to the upper limbs, and the other 34 points are applied to the lower limbs [37].

- Balance Function will be measured by the Berg Balance Scale (BBS), which consists of a set of 14 tasks to quantitatively assess the static and dynamic balance abilities [38]. The BBS is not only one of the most important measurement scales to evaluate the balance function of patients after stroke but can also be used as the risk predictor of accidental fall in stroke patients [39].

- Activities of Daily Living（ADL） will be assessed using the Modified Barthel Index (MBI), which is a widely used standard scale for assessing functional disability in basic ADL. The MBI contains 10 projects with a total of 100 points, and the higher the score means the better the daily life self-care ability [40].

- Quality of life will be measured by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), which is currently the most commonly used in clinical evaluation of quality of life in the general population and patients. The SF-36 consists of 36 items to assess eight health concepts, and each of them is evaluated separately by the normalized scores from 0 to 100, with the higher score corresponding to better health status [41]. The Chinese SF-36 has been demonstrated to have high reliability and validity in the Chinese population [42].

Safety evaluation

Although no adverse events are reported currently regarding Baduanjin exercise, any unexpected adverse events during the intervention period will be reported to the research assistants, and causality in relation to the Baduanjin exercise training and the severity of adverse events will be evaluated. Serious adverse events will be reported to the ethics committee immediately.

Data management and monitoring

Data will be collected by the outcomes assessors using the print-based case report forms (p-CRFs), and the p-CRFs will later be inputted into the web-based case report forms (w-CRFs) in an electronic data capture system (EDC) by research assistants. The research assistants are also responsible for the integrity and accuracy of data when data are inputted into w-CRFs by means of checking on value ranges, or logical checks. The EDC system and web servers will be provided to the data management centre of FJTCM (http://210.34.74.191/srtp/users/loginlangth.action) and meet the available standards for security (the data management centre, which belongs to the Science and Technology Department of FJTCM, is in charge of the monitoring and auditing of all research data in FJTCM). Participants' data in w-CRFs will be stored in the EDC system in a separate password-protected location. All documents will be retained securely for five years after completion of the study.

Statistical analysis

Statistical analysis will be performed using SPSS 22.0 (IBM, Chicago, IL, USA) software package by an independent statistician who is not involved in the outcome assessment, with a two-sided p value <0.05 being considered to be statistically significant. Continuous variables will be expressed using mean and its standard error for normal distributions or median and its interquartile range for non-normal

distributions. Categorical variables will be described as frequencies or percentages.

Baseline characteristics between comparison groups will be compared using a t-test or Mann-Whitney U test for continuous variables and Pearsonχ^2 or Fisher's exact test for categorical variables.

The analysis of primary or secondary outcomes will be based on an intention to treat (ITT) principle, and the missing data will be imputed using a multiple imputation method. The group difference between intervention and control group at each time point (8-week, 16-week, and 24-week after intervention or 4-week follow-up period) will be analysed using Student's t-test or Mann-Whitney U-test. Linear models or linear regression will be applied to adjust analysis if incomparability of baseline characteristics between groups appears. The linear mixed model with restricted maximum likelihood will be used to analyse the interaction effect of Group×Time.

Adverse events (AEs) will be analysed using a chi-square test or Fisher's exact test. If the formal statistical analyses between-groups cannot be performed due to the lack of power, AEs will be tabulated and summarized using descriptive statistics.

Ethics

This study protocol conformed to the Declaration of Helsinki. Ethics approval of this study protocol, and consent forms were obtained from the Ethics Committee of Fujian University of Traditional Chinese Medicine Subsidiary Rehabilitation Hospital (approval number: 2016KY-022-01). The study background and main objective as well as potential benefits and risks will be fully explained to the participants and their families. Before participating in the study, participants will sign the informed consent document prior to participation.

Dissemination

The study protocol has been registered and is available on the Chinese Clinical Trial Registry website (http://www.chictr.org.cn with the identifier number ChiCTR-INR-16009364). Study results will be first informed to each participant and later disseminated to researchers, healthcare providers, healthcare professionals and the general public through courses, presentations and the internet, regardless of the magnitude or direction of effect. The results will also be documented in a published peer reviewed academic journal.

Discussion

As one of the most common forms of Chinese traditional exercises, Baduanjin exercise consists of eight separate movements, each of which focuses on a different physical area of the body [13]. Compared with other aerobic exercises, Baduanjin exercise is not only easy to learn but also is less physical and cognitive demanding [43]. Therefore, Baduanjin has become a popular and safe community exercise to promote health in the community of the older population of China. Furthermore, different from other types of aerobic exercise, Baduanjin is also a mind-body exercise combined with the holistic view and the theory of traditional Chinese medicine in that practitioners are required to reach coordination between mind and body [14]. Several studies have reported that regular Baduanjin training has a positive effect in slowing normal age-related memory decline [20-21]. Zhu HM et al. even reported that Baduanjin exercise can delay the cognitive impairment progression for the elderly diabetic patients with mild cognitive impairment [44]. Therefore, it is reasonable to assume that regular Baduanjin training could be beneficial to cognitive function in stroke patients. This proposed study aims to investigate the effect of Baduanjin exercise on cognitive

function, as well as observing the effect on motor function and quality of life in the stroke patients with cognitive impairment. This study will employ rigorousness to control bias, such as randomization, parallel control, and blinding of the outcome assessors and statistician. To ensure participants master standard Baduanjin movements, we will also employ qualified physical exercise teachers to serve as the Baduanjin exercise coaches. However, a potential limitation of this study is that participants and coaches cannot be blinded because it is impossible to make them blinded in non-pharmacological trials [45]. Therefore, performance bias may be inevitable, but the exercise coaches will be not involved in the recruitment, outcome assessment, or data analysis of this study. Another challenge that we may encounter for the study is the difficulty in recruiting the eligible stroke patients. Those stroke patients or their families may worry about the exercise risk and prefer to stay in their home and maintain a fairly static life. In addition, a higher dropout rate may also be expected due to the above concerns. To address these problems, we will encourage participants to practice the Baduanjin training at their home after they master this exercise. We also accounted for the higher dropout rate in the sample size estimation to ensure the sufficient statistical power for the study.

In summary, this report describes the first randomized controlled trial to evaluate systematically the rehabilitative effect of Baduanjin exercise on cognitive ability and motor function in stroke patients. This study will determine if Baduanjin training is likely to be effective in improving cognitive function, including global cognitive function and specific cognitive domains, in stroke patients with cognitive impairment. This study will also investigate if Baduanjin training can improve the motor function and quality of life for stroke patients with cognitive impairment and determine if this

exercise is acceptable to them. If this trial is successfully conducted and demonstrates a significant result, that intervention would provide an effective rehabilitation approach for stroke patients and adequate supporting evidence for the application of regular Baduanjin exercise in patients with post-stroke cognitive impairment. Conversely, if this exercise training is not effective, the study will identify the factors that contributed to the negative outcome.

Trial status

This trial is currently in the recruitment phase.

Abbreviations

SD: Standard deviation; DSM-V: Diagnostic and statistical manual disoeders,5th edition; SAS 9.0: Statistical analysis system; TCM: Traditional Chinese medicine; MoCA: Montreal cognitive assessment scale; FJTCM: Fujian University of Traditional Chinese Medicine; TMT: Trail Making Test; AVLT: Auditory verbal learning test; TAP: Test of attention performance; DSC: Digit symbol coding; WAIS-RC: Wechsler adult intelligence scale-revised China; CDT: Clock drawing task; FMA: Fugl-Meyer assessment scale; BBS: Berg balance scale; BI: Barthel index; ADL: Activities of daily living; SF-36: Item short-form health survey; CRF: Case report form; EDC: Electronic data capture system; SPSS 22.0: Statistic package for social science 22.0; ITT: Intention to treat.

Declarations

Authors' contributions

CLD and ZGH conceived and designed of the study protocol and contributed to drafting the manuscript. ZYH and XZY wrote the manuscript and participated in the coordination and implementation of the study. ZGH revised the study protocol and wrote several sections of the manuscript. YBZ and TJ helped develop the study measures and data collection. All authors contributed to drafting the manuscript and have read and approved the final version of the manuscript.

Funding

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Availability of data and materials

This is not applicable because this is a paper of a study protocol.

Consent for publication

Not applicable.

Competing interests

None declared.

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Additional files:

Additional file 1: SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents.

Additional figure 1: Study design.

Additional figure 2: Schedule of enrolment, interventions, and assessments.

Additional figure 3: Ten postures of Baduanjin.

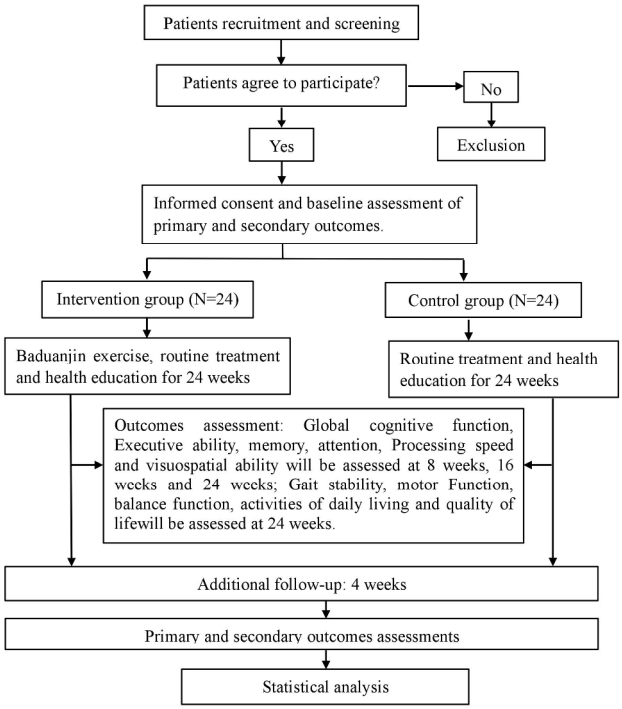

Figure 1 Flow diagram of study design

210x297mm (300 x 300 DPI)

STUDY PERIOD						
	Enrolment	Allocation	Intervention			Follow-up
TIMEPOINT*	$-t_1$	0	t_1	t_2	t_3	t_4
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
ALLOCATION		X				
INTERVENTIONS:						
Intervention group (Baduanjin exercise training+health education)			←	—	→	
Control group (Health education)			←	—	→	
ASSESSMENTS:						
Basic characteristics	X					
Global cognitive function	X		X	X	X	X
Executive ability	X		X	X	X	X
Memory	X		X	X	X	X
Attention	X		X	X	X	X
Processing speed	X		X	X	X	X
Visuospatial ability	X		X	X	X	X
Gait stability	X				X	X
Motor Function	X				X	X
Balance Function	X				X	X
Activities of Daily Living	X				X	X
Quality of Life	X				X	X
Adverse events			X	X	X	

<Figure Legend>
* $-t_1$= -2-(-1) weeks, 0= Baseline, t_1 = Week 8, t_2 = Week 16, t_3 = End of treatment Week 24, t_4 = Follow Up Week 28.

Figure 2: Schedule of enrolment, interventions, and assessments

215x279mm (300 x 300 DPI)

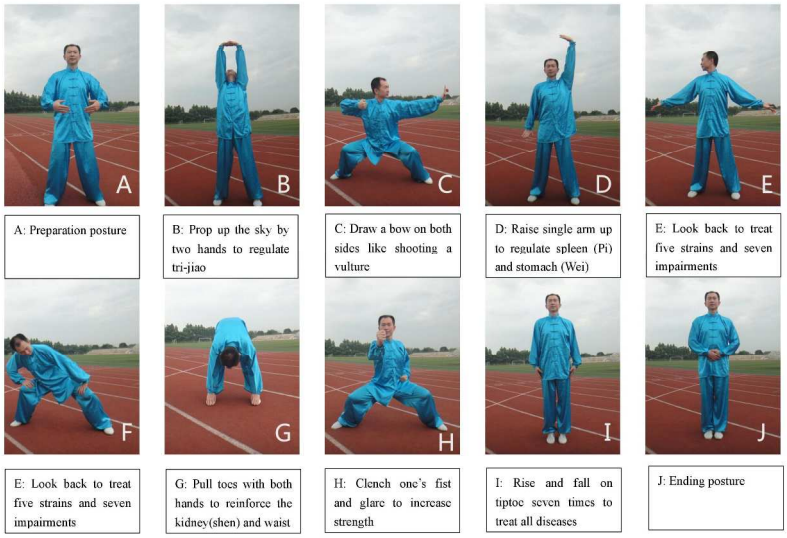

Figure 3: Ten postures of Baduanjin

297x210mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&21
	5b	Name and contact information for the trial sponsor	21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	11
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12&16
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16-17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17-18

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9&16
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16-18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16&18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Available in the informed consent materials
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available in Chinese vesion
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Effect of Baduanjin exercise on cognitive function in patients with post-stroke cognitive impairment: Study protocol for a randomized controlled trial

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Effect of Baduanjin exercise on cognitive function in patients with post-stroke cognitive impairment: Study protocol for a randomized controlled trial

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Abstract

INTRODUCTION: Post-stroke cognitive impairment is one of the most common complications in stroke survivors, and over 65% of these patients suffer from cognitive impairment at 12 months following onset, which strongly affects the rehabilitation of their motor function and quality of life. Therefore, it is important to improve the cognitive ability of stroke survivors. As an important component of traditional Chinese Qigong exercises, characterized by the coordination of mind and body with a low exercise intensity, Baduanjin has the potential benefit of improving cognitive ability for stroke patients with cognitive impairment. The primary purpose of this study is to investigate the effectiveness and safety of Baduanjin training on the cognitive function of stroke survivors.

METHOD AND ANALYSIS: This study is designed as a randomized, two-arm parallel controlled trial with allocation concealment and assessors blinding. A total of 48 participants will be recruited and randomly allocated into the Baduanjin exercise intervention or control group. Baduanjin intervention will last 24 weeks with a

frequency of 3 days a week and 40 min a day. Global cognitive function and the specific domains of cognition (i.e., memory, processing speed, execution, attention and visuospatial ability) will be measured at baseline, 8-, 16-, 24-week after intervention and after an additional 4-week follow-up period, while the motor function and quality of life will be measured at baseline, 24-week after intervention, and after an additional 4-week follow-up period.

ETHICS AND DISSEMINATION: Ethics approval was obtained from the Ethics Committee of Fujian University of Traditional Chinese Medicine Subsidiary Rehabilitation Hospital (approval number: 2016KY-022-01). The findings will be disseminated through peer-reviewed publications and at scientific conferences.

TRIAL REGISTRATION NUMBER: ChiCTR-INR-16009364; Pre-results.

Registration date: 10 October, 2016.

KEYWORDS

Baduanjin exercise, cognitive impairment after stroke, randomized controlled trial

Strengths and limitations of this study

- This protocol presents a rigorous design of a randomized parallel controlled trial that aims to evaluate the effectiveness of Baduanjin exercise on the cognitive function, motor function and quality of life in stroke patients with cognitive impairment.
- A broad measurement tool and multiple measurement time points will be used to

judge the effects of Baduanjin exercise on cognitive ability in stroke patients.

- If the result we will reach is positive, that will provide a powerful evidence of Baduanjin exercise on improve cognitive function, motor function and quality of life in stroke survivors with cognitive impairment.
- The efficacy of a 24-week Baduanjin exercise intervention in stroke patients with cognitive impairment remains to be determined.

Introduction

Stroke affects 15 million people annually and is a leading cause of death and disability worldwide [1]. In China, there are 6 million patients suffering from stroke, and this number increases at an annual rate of 9%. Stroke is associated with many long-term complications, such as motor dysfunction, language dysfunction and cognitive impairment. Post-stroke cognitive impairment is one of most common complications. Approximately 65% of stroke survivors suffer from some extent to cognitive impairment at five years post-stroke, and up to a quarter of those stroke survivors with cognitive impairment are more likely to transition to dementia [2], which is associated with increased disability and a poor quality of life [3]. As a consequence, it is significant to improve the cognitive function as soon as possible to promote functional recovery and improve quality of life in stroke survivors [4].

Theoretically, pharmacological therapy for cognition function may lead to

improved recovery. Current data also indicate that a number of drugs may have short-term benefits [5-7], but no drug treatment to date has shown convincing clinical evidence on preventing further cognitive decline or restoring cognitive function for stroke survivors [8]. Thus, increasing attention has been paid to non-drug treatments. Aerobic exercises have been widely recognized because of their obvious effect of improving cognitive ability in stroke survivors [9-11]. However, most stroke patients do not have sufficient compliance to achieve sufficient improvements in aerobic exercise protocols due to an important concern of safety. Therefore, future stoke studies involving aerobic exercise training should determine optimal protocols for individuals with physical limitations [12]. As a mind-body aerobic exercise with mild to moderate intensity, Baduanjin exercise has an emphasis on a combination of symmetrical physical postures, meditative mind, and breathing techniques in a harmonious manner, and is one of the most common forms of Qigong that has been practised in China for more than 1000 years [13]. Compared to complex and lengthy exercise form such as Tai Chi, Baduanjin exercise only consists of eight separate and smooth movements which is less physically and cognitively demanding, and is easier to learn and practice with less limitation[13-14]. Therefore, this exercise is more suitable for older adults, especially stroke patients. Increasing studies have demonstrated that regular practice of Baduanjin exercise was beneficial to improve the physical and psychological outcomes in older people, such as improving blood lipid metabolism and sleep quality, lowering blood pressure, reducing depression and anxiety, and improving physical flexibility [15-19]. Currently, several studies also show that regular Baduanjin exercise could slow normal age-related decline in the memory domain, and delay ageing of intelligence in older adults [20-21]. Consequently, the primary aim of this study is to conduct a randomized controlled trial to evaluate systematically the effect of

Baduanjin exercise on the cognitive function in stroke patients with cognitive impairment.

Method/Design

This report describes a two-arm, randomized, parallel controlled trial with allocation concealment and assessor blinding. The primary purpose is to evaluate the effect of Baduanjin on cognitive functions, including global cognitive ability, and primary cognitive domains, such as memory, attention, and visuospatial ability, in stroke patients with cognitive impairment.

This study will be conducted at the Wufeng Community Centre in the Gulou District and the Cangxia Community Centre in the Taijiang District, Fuzhou City, Fujian, China, which are counterpart support communities of the Affiliated Rehabilitation Hospital of Fujian University of Traditional Chinese Medicine. A total of 48 eligible participants will be randomly allocated to either the intervention group (the Baduanjin exercise group) or the control group (the health education group) in a 1:1 ratio. The participants in the intervention group will accept Baduanjin exercise training intervention three times a week and the routine health education once every four weeks for 24 weeks, while those allocated to the control group will only receive the routine health education once every four weeks for 24 weeks. Primary and secondary outcomes will be measured at baseline, 8-, 16- and 24-week after intervention and after an additional 4-week follow-up period. A flow diagram of the study design is shown in Figure 1. The study protocol is reported according to Standard Protocol Items: Recommendations for Intervention Trials 2013 (SPIRIT). A SPIRIT Checklist and the schedule of enrolment, interventions and assessments are provided in Additional file 1 and Figure 2.

Figure 1: Study design.

Additional file 1: SPIRIT 2013 Checklist.

Figure 2: Schedule of enrolment, interventions, and assessments.

Patient and Public Involvement

This trial is currently in the recruitment phase. No patients and or public has involved in the trial.

Sample size

Sample size was calculated on the basis of the changes in global cognitive ability after 24 weeks of intervention between comparison groups with a significance level of 5% and a two-tailed critical region. The means and their standard deviations (mean±SD) of global cognitive ability in the control and aerobic exercise intervention group were 75.93±4.9 and 81.07±6.16, respectively, at post-intervention according to the published literature [22]. A sample size of 40 participants was calculated to ensure the same effect size with 80% power by Gpower 3.1.9.2 software. Considering a 20% attrition rate, a total of 48 participants is necessary, with 24 participants being assigned to each group.

Study population

The study population is stroke patients with a diagnosis of cognitive impairment living in Fuzhou City. The inclusion and exclusion criteria for the study sample are as follows.

Inclusion criteria

The eligible participants should meet all of the following criteria:

Clinical diagnosis of stroke according to the fourth national academic conference on cerebrovascular diseases Diagnostic Criteria for All Kinds of Cerebrovascular Disease [23] and confirmed by computed tomography or magnetic resonance imaging;

Have cognitive impairment diagnosed by Diagnostic and Statistical Manual Disorders (DSM-V);

First ever stroke over three months;

Aged between 45 and 75 years;

Be conscious, with stable vital signs;

Ability to walk at least 10 metres without external force and auxiliary equipment;

Written informed consent.

Exclusion criteria

Criteria for exclusion are the following:

Have been suffering from brain tumour, brain trauma, brain parasite disease, or other diseases that could cause cognitive impairment;

Severe language, vision, and/or auditory impairment or a neuropsychiatric disorder precluding cognitive examination;

Have been suffering from diseases related to cognitive impairment confirmed by anamnesis, doctors, or families or with a history of cognitive drug use before stroke;

Beck Depression Scale-II score >13;

Patients with alcohol or drug abuse;

Have been suffering from a severe medical condition, such as heart, liver, kidney,

and endocrine diseases and haematopoietic system disease;

Participating in another clinical trial that would affect the evaluation results of this study.

Withdrawal or dropout criteria

Participants in neither the intervention nor control group will be terminated to continue this trial according to the following criteria:

① Unwilling to continue this trial;

② Suffering from the deterioration of stroke disease or other serious organic diseases during the study period;

③ Do not complete the training scheme for four weeks during the study period;

④ Those who reject to be measured or followed up;

⑤ Suffering from the serious adverse event related to the research.

Recruitment and screening

The recruitment of eligible participants will be conducted by posting up posters on the community publicity column, sending leaflets, and setting up a recruiting station at the Wufeng Community Centre in the Gulou District and the Cangxia Community Centre in the Taijiang District, Fuzhou City. The potentially eligible individuals will first complete a screening to determine their eligibility according to the inclusion and exclusion criteria. Eligible individuals will receive the information about this trial and have an informed discussion with two trained research assistants regarding the information provided. Those who are interested in this study will sign the written informed consent, and the baseline assessment will subsequently be arranged.

Randomization and allocation concealment

After baseline assessment, the eligible participants will be randomly assigned to either the intervention group or the control group with equal rate. The random allocation sequence will be generated using the PLAN procedure of the statistical software SAS v9.0 and be managed by an independent research assistant who is not involved in recruitment, evaluation and intervention of the participants. The eligible participants will be informed of their allocation result by the independent research assistant via telephone.

Blinding

In this trial, it is impossible to blind the participants and exercise coaches because this trial investigates a non-pharmacological intervention, but two types of blind codes will be used to blind the outcome assessors and data statisticians. We will assign an independent research manager to be in charge of the random allocation sequence and the blind codes. The participants' allocation result (the intervention group or the control group) will be replaced using alphabet 'A' or 'B' in the first blind code, and the real meaning of 'A' or 'B' will be marked in the second blind code. When the data-base is locked, the independent research assistant will deliver the group code 'A' or 'B' of participants to the statistician, and the real meaning of group 'A' or 'B' will be declared after analysis of all data is completed.

Intervention

All participants will continue routine medical or rehabilitative treatment and maintain usual visits with their primary care physicians throughout the study if necessary. Meanwhile, all of the participants will also receive the same health education programme during the intervention period. The Baduanjin exercise will be applied to

the participants in the intervention group, while participants in the control group will be informed to maintain their usual lifestyle.

The routine medical or rehabilitative treatment will be in accordance with the Chinese Medical Association's Guidelines for the Prevention and Treatment of Cerebrovascular Disease in China (2010) [24]. The detailed treatment schedule will be conducted by their primary care physicians and recorded by the research assistants. The health education is conducted by the professional neurologists with a frequency of once a month and 40 minutes each time. The content of health education primarily involves the knowledge of the prevention and rehabilitation of stroke according to "Out of the Misunderstanding of Stroke Patients' Rehabilitation" (a bestseller book for health education after stroke from the Chinese Association of TCM) [25].

Intervention group

Participants in the intervention group will receive a 24-week Baduanjin exercise training, at the same time, they also receive routine medical or rehabilitative treatment and health education. The Baduanjin exercise training will last for 24 weeks with a frequency of 3 days a week and 40 min a day. The training scheme of Baduanjin exercise originates from the 'Health Qigong Baduanjin Standard' enacted by the State Sports General Administration in 2003 [26]. The whole set of Baduanjin exercise consists of ten postures (including the preparation and ending posture) (Figure 3). The participants will be gathered together to train when there are more than five participants recruited in the same community. Qualified Baduanjin exercise coaches from the Fujian University of Traditional Chinese Medicine with more than 5 years of teaching experience will be employed to guide participants' training.

Figure 3: Ten postures of Baduanjin.

Control group

The participants in the control group will not receive any specific exercise training from the study scheme. These participants will be requested to maintain their original habit of lifestyle.

In order to exclude bias from the exceed activity of participants, all participants in both intervention and control group will be required to record an activity log in the intervention period, in which the duration and intensity of their activity in a whole day will be classified into three sections including the duration of low-intensity, moderate-intensity, or high-intensity activities.

Follow-up

After the 24-week intervention period, all participants will enter an additional 4-week follow-up period. The participants will resume their original lifestyle during the follow-up period. Telephone follow-up or home visiting will be performed once a week by the research assistants. The information on participants' subjective feeling, medications and daily activities will be recorded. The primary and secondary outcomes will be evaluated at end of follow-up period.

Participant retention and adherence

The success of the intervention is strongly dependent on participants' active participation. To motivate participants' active participation, the staff will use several strategies to improve adherence to the intervention program: ① researchers will explain in detail the benefit of practising Baduanjin exercise after participants are randomly allocated into the intervention group; ②coaches will motivate participants' interest for the Baduanjin exercise training when they instruct participants practising the Baduanjin exercise; and ③the research assistants will remind participants to

practice the Baduanjin exercise according to the study scheme by the WeChat group. In addition, participant who complete the programme successfully will be rewarded with 100 RMB incentive money no matter which group they belongs to. Attendance of the Baduanjin exercise training will be recorded and assessed through records of the proportion of training days. Participants will be marked as absent when they do not attend the training session.

To improve participant retention, once a subject is randomized, the research assistants will make every reasonable effort to ensure the subjects stays for the entire study period. In detail, study assistants will □maintain participants' interests by interview and phone calls; □provide periodic communications via materials and talks to inform the participants of our acknowledgement of their support; and □be as flexible as possible with the study schedule in resolving time conflicts with participants' life.

Outcome Assessment

Primary outcome

Global cognitive function will be measured using the Montreal Cognitive Assessment scale (MoCA). The MoCA scale is a brief test to evaluate the global cognitive ability by testing attention, naming, visuospatial/executive function, memory, language, visual structure skills, abstraction, calculation, and orientation with a total score of 0-30 (a higher score equals better function). The Chinese vision of the MoCA (Beijing version) was revised and is widely used in China with good validity and reliability [27]. Primary outcome will be assessed at baseline, 8 weeks, 16 weeks and 24 weeks after intervention and after an additional 4-week follow-up period by the neurologists at the Affiliated Rehabilitation Hospital of FJTCM, who will be blinded to the allocation results of participants.

Secondary outcomes

Secondary outcomes involving the specific cognitive domains (i.e., execution, memory, attention, processing speed and visuospatial skill), gait, motor ability, balance ability, activities of daily living and quality of life. Executive ability, memory, attention, Processing speed and visuospatial ability will be measured at baseline, 8 weeks, 16 weeks and 24 weeks after intervention and after an additional 4-week follow-up period. Gait stability, motor Function, balance function, activities of daily living and quality of life will be assessed at baseline, 24 weeks of intervention and after an additional 4-week follow-up period. All outcome assessments will be measured by the blinded medical staff.

- Executive ability will be assessed using the Trail Making Test (TMT). The TMT consists of two parts, TMT-A and TMT-B: TMT-A requires the participants to sequentially connect 25 encircled numbers on a sheet of paper, while TMT-B requires participants to draw a line alternating between numbers and letters in ascending order between the number and the letter, and the TMT-B/TMT-A is considered as a valid index of executive ability [28].

- Memory will be measured using the Chinese vision of the Auditory Verbal Learning Test (AVLT) [29]. AVLT includes three subtests of immediate recall, short-term-delayed recall and long-term delayed recognition. In the immediate recall test, subject will be requested to repeat immediately a list of 15 unrelated words said by the assessor three times; after 15 minutes, subject will be asked to recall the 15 words, and the correct rate is the score of short-term-delayed recall. In the long-term delayed recognition test, a subject is given another list of 15 unrelated words and must recognize the original list of 15 words [30]. The Chinese version of the AVLT has been reported reliable with split-half reliability, internal consistency

and structure validity [29].

- Attention will be measured using the Test of Attention Performance (TAP, V.2.3), which is based on computer-aided neuropsychological tests for assessing the attentional performance [31]. Four of this test's sub-tests, including alertness for reaction, general attention, Go/No Go and divided selective attention, will be chosen for this trial.

- Processing speed will be measured by the Digit Symbol Coding (DSC), which is a subtest of the Wechsler Adult Intelligence Scale-Revised China (WAIS-RC) with nine numbers from 1 to 9 and nine corresponding symbols [32]. A subject will be asked to draw each symbol under its corresponding number within a 90 s time limit, and the number of correct answers is its scores.

- Visuospatial ability will be assessed by the Clock Drawing Task (CDT), which is a vision-dependent task [33]. The participants will be asked to draw a clock reading a specific time (generally 11:10). The correctness in clock drawing will be classified according to four categories [34].

- Gait stability and the interactions between cognitive tasks and gait will be measured by gait analysis [35]. Participants were instructed to walk in two assigned conditions: free walking as usual and walking as usual with executing a calculation task. The gait parameters in two conditions will be measured with the America Motion Analysis gait analysis system, and the numbers of completion and error rates in calculation tasks will be recorded. Those gait parameters mainly comprise of step length (cm), stride length (cm), forward velocity (cm/s), cadence (steps/min), total support time (%), swing time (%), double support time (%), single support time (%) and step width (cm). All these parameters include the

affected and unaffected side.

- Motor function will be evaluated using the Fugl-Meyer Assessment scale (FMA), which is known for its good validity and reliability in evaluating upper and lower limb function after stroke [36]. The FMA consists of 50 items based on a six-stage recovery process of Brunnstrom's hemiplegia classification, and 66 points of a possible 100 total score apply to the upper limbs, and the other 34 points are applied to the lower limbs [37].

- Balance function will be measured by the Berg Balance Scale (BBS), which consists of a set of 14 tasks to quantitatively assess the static and dynamic balance abilities [38]. The BBS is not only one of the most important measurement scales to evaluate the balance function of patients after stroke but can also be used as the risk predictor of accidental fall in stroke patients [39].

- Activities of Daily Living（ADL） will be assessed using the Modified Barthel Index (MBI), which is a widely used standard scale for assessing functional disability in basic ADL. The MBI contains 10 projects with a total of 100 points, and the higher the score means the better the daily life self-care ability [40].

- Quality of life will be measured by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), which is currently the most commonly used in clinical evaluation of quality of life in the general population and patients. The SF-36 consists of 36 items to assess eight health concepts, and each of them is evaluated separately by the normalized scores from 0 to 100, with the higher score corresponding to better health status [41]. The Chinese SF-36 has been demonstrated to have high reliability and validity in the Chinese population [42].

Safety evaluation

Although no adverse events are reported currently regarding Baduanjin exercise, any unexpected adverse events during the intervention period will be reported to the research assistants, and causality in relation to the Baduanjin exercise training and the severity of adverse events will be evaluated. Serious adverse events will be reported to the ethics committee immediately.

Data management and monitoring

Data will be collected by the outcomes assessors using the print-based case report forms (p-CRFs), and the p-CRFs will later be inputted into the web-based case report forms (w-CRFs) in an electronic data capture system (EDC) by research assistants. The research assistants are also responsible for the integrity and accuracy of data when data are inputted into w-CRFs by means of checking on value ranges, or logical checks. The EDC system and web servers will be provided to the data management centre of FJTCM (http://210.34.74.191/srtp/users/loginlangth.action) and meet the available standards for security (the data management centre, which belongs to the Science and Technology Department of FJTCM, is in charge of the monitoring and auditing of all research data in FJTCM). Participants' data in w-CRFs will be stored in the EDC system in a separate password-protected location. All documents will be retained securely for five years after completion of the study.

Statistical analysis

Statistical analysis will be performed using SPSS 22.0 (IBM, Chicago, IL, USA) software package by an independent statistician who is not involved in the outcome assessment, with a two-sided p value <0.05 being considered to be statistically

significant. Continuous variables will be expressed using mean and its standard error for normal distributions or median and its interquartile range for non-normal distributions. Categorical variables will be described as frequencies or percentages.

Baseline characteristics between comparison groups will be compared using a t-test or Mann-Whitney U test for continuous variables and Pearsonχ^2 or Fisher's exact test for categorical variables.

The analysis of primary or secondary outcomes will be based on an intention to treat (ITT) principle, and the missing data will be imputed using a multiple imputation method. The group difference between intervention and control group at each time point (8-week, 16-week, and 24-week after intervention or 4-week follow-up period) will be analysed using Student's t-test or Mann-Whitney U-test. Linear models or linear regression will be applied to adjust analysis if incomparability of baseline characteristics between groups appears. The linear mixed model with restricted maximum likelihood will be used to analyse the interaction effect of Group×Time.

Adverse events (AEs) will be analysed using a chi-square test or Fisher's exact test. If the formal statistical analyses between-groups cannot be performed due to the lack of power, AEs will be tabulated and summarized using descriptive statistics.

Ethics

This study protocol conformed to the Declaration of Helsinki. Ethics approval of this study protocol, and consent forms were obtained from the Ethics Committee of Fujian University of Traditional Chinese Medicine Subsidiary Rehabilitation Hospital (approval number: 2016KY-022-01). The study background and main objective as well as potential benefits and risks will be fully explained to the participants and their

families. Before participating in the study, participants will sign the informed consent document prior to participation.

Dissemination

The study protocol has been registered and is available on the Chinese Clinical Trial Registry website (http://www.chictr.org.cn with the identifier number ChiCTR-INR-16009364). Study results will be first informed to each participant and later disseminated to researchers, healthcare providers, healthcare professionals and the general public through courses, presentations and the internet, regardless of the magnitude or direction of effect. The results will also be documented in a published peer reviewed academic journal.

Discussion

As one of the most common forms of Chinese traditional exercises, Baduanjin exercise consists of eight separate movements, each of which focuses on a different physical area of the body [13]. Compared with other aerobic exercises, Baduanjin exercise is not only easy to learn but also is less physical and cognitive demanding [43]. Therefore, Baduanjin has become a popular and safe community exercise to promote health in the community of the older population of China. Furthermore, different from other types of aerobic exercise, Baduanjin is also a mind-body exercise combined with the holistic view and the theory of traditional Chinese medicine in that practitioners are required to reach coordination between mind and body [14]. Several studies have reported that regular Baduanjin training has a positive effect in slowing normal age-related memory decline [20-21]. Zhu et al. even reported that Baduanjin exercise can delay the cognitive impairment progression for the elderly diabetic

patients with mild cognitive impairment [44]. Therefore, it is reasonable to assume that regular Baduanjin training could be beneficial to cognitive function in stroke patients. This proposed study aims to investigate the effect of Baduanjin exercise on cognitive function, as well as observing the effect on motor function and quality of life in the stroke patients with cognitive impairment. This study will employ rigorousness to control bias, such as randomization, parallel control, and blinding of the outcome assessors and statistician. To ensure participants master standard Baduanjin movements, we will also employ qualified physical exercise teachers to serve as the Baduanjin exercise coaches. However, a potential limitation of this study is that participants and coaches cannot be blinded because it is impossible to make them blinded in non-pharmacological trials [45]. Therefore, performance bias may be inevitable, but the exercise coaches will be not involved in the recruitment, outcome assessment, or data analysis of this study. Another challenge that we may encounter for the study is the difficulty in recruiting the eligible stroke patients. Those stroke patients or their families may worry about the exercise risk and prefer to stay in their home and maintain a fairly static life. In addition, a higher dropout rate may also be expected due to the above concerns. To address these problems, we will encourage participants to practice the Baduanjin training at their home after they master this exercise. We also accounted for the higher dropout rate in the sample size estimation to ensure the sufficient statistical power for the study.

In summary, this report describes the first randomized controlled trial to evaluate systematically the rehabilitative effect of Baduanjin exercise on cognitive ability and motor function in stroke patients. This study will determine if Baduanjin training is likely to be effective in improving cognitive function, including global cognitive

function and specific cognitive domains, in stroke patients with cognitive impairment. This study will also investigate if Baduanjin training can improve the motor function and quality of life for stroke patients with cognitive impairment and determine if this exercise is acceptable to them. If this trial is successfully conducted and demonstrates a significant result, that intervention would provide an effective rehabilitation approach for stroke patients and adequate supporting evidence for the application of regular Baduanjin exercise in patients with post-stroke cognitive impairment. Conversely, if this exercise training is not effective, the study will identify the factors that contributed to the negative outcome.

Trial status

This trial is currently in the recruitment phase.

Abbreviations

SD: Standard deviation; DSM-V: Diagnostic and statistical manual disoeders,5th edition; SAS 9.0: Statistical analysis system; TCM: Traditional Chinese medicine; MoCA: Montreal cognitive assessment scale; FJTCM: Fujian University of Traditional Chinese Medicine; TMT: Trail Making Test; AVLT: Auditory verbal learning test; TAP: Test of attention performance; DSC: Digit symbol coding; WAIS-RC: Wechsler adult intelligence scale-revised China; CDT: Clock drawing task; FMA: Fugl-Meyer assessment scale; BBS: Berg balance scale; BI: Barthel index; ADL: Activities of daily living; SF-36: Item short-form health survey; CRF: Case

report form; EDC: Electronic data capture system; SPSS 22.0: Statistic package for social science 22.0; ITT: Intention to treat.

Declarations

ZGH and ZYH contributed equally to this paper.

Contributor ship statement

CLD(Correspondence) and ZGH conceived and designed of the study protocol and contributed to drafting the manuscript. ZYH and XZY wrote the manuscript and participated in the coordination and implementation of the study. ZGH revised the study protocol and wrote several sections of the manuscript. YBZ and TJ helped develop the study measures and data collection. All authors contributed to drafting the manuscript and have read and approved the final version of the manuscript.

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Availability of data and materials

This is not applicable because this is a paper of a study protocol.

Consent for publication

Not applicable.

Competing interests

None declared.

Reference:

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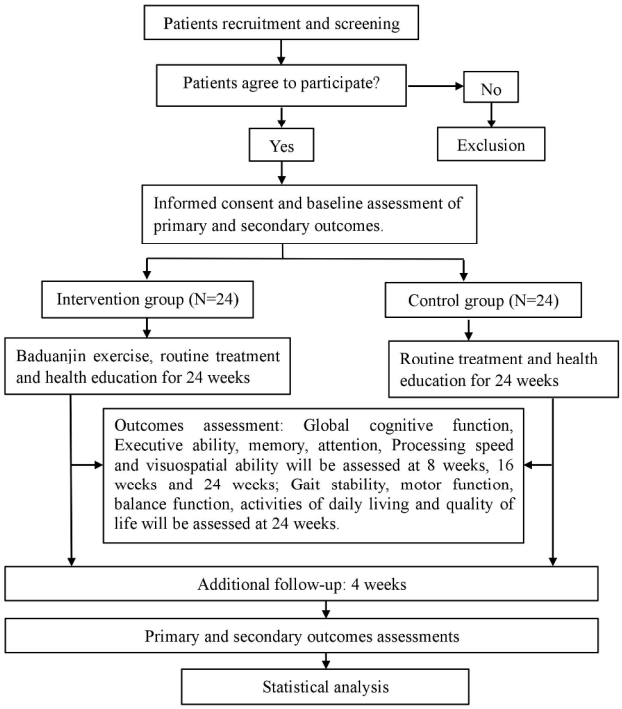

Figure 1 Flow diagram of study design

210x297mm (300 x 300 DPI)

STUDY PERIOD						
	Enrolment	Allocation	Intervention			Follow-up
TIMEPOINT*	$-t_1$	0	t_1	t_2	t_3	t_4
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
ALLOCATION		X				
INTERVENTIONS:						
Intervention group (Baduanjin exercise training+health education)			←	—	→	
Control group (Health education)			←	—	→	
ASSESSMENTS:						
Basic characteristics	X					
Global cognitive function	X		X	X	X	X
Executive ability	X		X	X	X	X
Memory	X		X	X	X	X
Attention	X		X	X	X	X
Processing speed	X		X	X	X	X
Visuospatial ability	X		X	X	X	X
Gait stability	X				X	X
Motor Function	X				X	X
Balance Function	X				X	X
Activities of Daily Living	X				X	X
Quality of Life	X				X	X
Adverse events			X	X	X	

<Figure Legend>
* $-t_1$= -2-(-1) weeks, 0= Baseline, t_1 = Week 8, t_2 = Week 16, t_3 = End of treatment Week 24, t_4 = Follow Up Week 28.

Figure 2: Schedule of enrolment, interventions, and assessments

215x279mm (300 x 300 DPI)

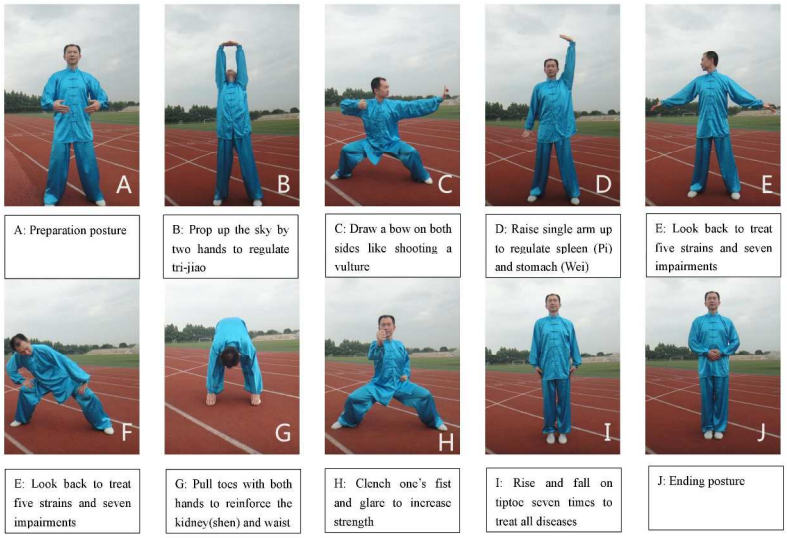

Figure 3: Ten postures of Baduanjin

297x210mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&21
	5b	Name and contact information for the trial sponsor	21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	11
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12&16
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16-17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17-18

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9&16
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16-18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16&18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Available in the informed consent materials
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available in Chinese vesion
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.