Study Protocol

Combining acupuncture and acupressure for dementia elderly: an assessor-blinded, randomized controlled trial

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Introduction

Dementia in the local community and impacts

Dementia is a syndrome describing a decline in memory and many other cognitive domains, and is associated with many neurodegenerative diseases, such as Alzheimer's disease (AD), vascular disease (for vascular dementia), etc.[1] Mild cognitive impairment (MCI) is an intermediate state between normal cognitive aging and dementia, with a slight decline in memory and cognitive abilities compared to their counterparts. MCI is regarded as an intermediate state between normal cognitive aging and dementia, and the rates of conversion from MCI to dementia ranged from 6.0% to 44.8%, as reported in previous studies.[2]

According to the World Health Organization (WHO), dementia is one of the major causes of disability and dependency in elderly people.[3] The WHO reported that 2.1 billion people could live to the age of over 60 by 2050, and the number of people with dementia could rise to 139 million in 2050, compared to 55 million in 2019.[4] In Hong Kong, about 1.2 million people currently live to the age of over 65, and about one-tenth of them are suffering from dementia.[5] It is expected that almost one in three of our population will be aged 65 or above by 2041.[5] Many elderly people with dementia live in nursing homes and elderly daycare centers. It poses a significant burden on caregivers, families, and the public healthcare system.

Until now, no interventions have been proven to totally cure dementia, and current drug therapies can only postpone its progression.[6] For AD dementia, the Food and Drug Administration has approved several categories of medications, such as acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists.[1,6] For MCI and other dementia etiologies, pharmacological treatments are limited. The treatment of dementia should achieve different goals, not only slowing down cognitive deterioration but also improving patients' quality of life.

Patients with dementia not only have a wide range of cognitive impairments, including progressive memory loss, increasing difficulty in communication and language, concentration and attention, reasoning and judgment, but also develop a variety of frailty-related symptoms, mainly including physical and psychological frailty, such as musculoskeletal deterioration, neurological disorders, sleep, emotional, and even psychotic symptoms.[7-8] Medical comorbidities in the elderly may limit their tolerance of medication. Management of dementia is sophisticated and has become a huge burden in future public healthcare systems.

The overall purpose of the management of dementia in the elderly is to reduce dementia- and frailty-caused adverse outcomes that increase disability, dependency, hospitalization, and long-term care admission. However, there is a dearth of effective interventions improving the quality of life of elderly with dementia. The development of holistic management strategies that not only prevent and slow down cognitive deterioration, but also reduce various other symptoms is therefore highly desired.

Acupuncture and acupressure for dementia and elderly frailty-related symptoms

Acupuncture has been widely used in local clinical practice. Numerous studies have shown the benefits of acupuncture in reducing cognitive deterioration in patients with cognitive impairment and dementia and in animal models. Acupuncture is also effective in improving physical disability, rigidity, gait, and postural balance in aging adults with stroke and Parkinson's disease.[9-10] A large body of evidence further confirms the effectiveness of various acupuncture regimens in treating pain, fatigue, sleep disturbance, anxiety, and depression. On the other hand, it is well demonstrated that, as a convenient therapy, acupressure has particular benefits in alleviating sleep disturbance, anxiety, depression, and agitation in elderly people with dementia.[11-15] Acupressure also has positive effects on the recovery of motor function and the daily activities of stroke patients.[16] These studies suggest that the elderly with dementia could benefit from acupuncture and acupressure.

Our related studies

We have developed a novel acupuncture mode called comprehensive acupuncture therapy (CAT). CAT was built up from "dense cranial electroacupuncture stimulation (DCEAS)",[17] which consists of dense frontal acupoints with additional electrical stimulation, together with manual stimulation of multiple body acupoints selected based on previous clinical trials, the experience of acupuncture experts, and traditional Chinese Medicine (TCM) theory on the elderly's constitutions.[18] The efficacy of CAT has been well proven in our previous studies.[17,19-21] Most recently, we have completed three clinical trials that evaluated the efficacy of acupuncture treatment for vascular dementia;[22] stroke-caused cognitive deterioration;[19] and chemotherapy-induced cognitive impairment.[20] All these trials have consistently revealed that acupuncture is effective in alleviating cognitive impairment. Furthermore, our several studies have confirmed the efficacy of acupuncture in improving major depression;[17,23] insomnia and anxiety;[24-25] poststroke depression and movement disability.[19,21]

Acupressure is a form of massage therapy involving the application of pressure to acupoints or specific body surfaces. We have developed a caregiver-performed acupressure protocol called 'Comfy Acupressure for the Elderly (CAE)' and a demonstration video is accessible at https://www.youtube.com/watch?v=pAqNIZPKmnM.[26] CAE protocol was initially developed based on traditional Chinese Medicine theory and practice, with the aim of improving the quality of life and preventing aging and age-related conditions in the elderly. We have also shown the effectiveness of caregiver-performed acupressure on the general quality of life in frail older people,[26] and self-administered acupressure for insomnia disorder.[27]

These studies have led us to hypothesize that (1) CAT and CAE monotherapy could reduce cognitive impairment and related comorbid symptoms in aged people with dementia; and (2) CAT and CAE as a holistic intervention could produce additive effects than routine care in improving cognitive impairment, frailty-related disability and dependency, as well as comorbid symptoms in elderly people with dementia.

Hypothesis and aims to be tested

Our hypothesis is that for the elderly with cognitive impairment or dementia, acupuncture and acupressure are feasible, safe, and could produce better management outcomes than routine care. The aims of this study are: (1) to determine whether the conditions of cognitive impairment in the treatment groups improve significantly when compared to control; (2) to determine whether other symptoms (e.g., functional independence, pain, depression, and sleep disorder) in the treatment groups improve more than in control; and (3) to investigate whether acupuncture or acupressure is safe for the elderly with cognitive impairment or dementia.

Plan of Investigation

Design

This is an assessor-blinded, randomized controlled trial. A total of 248 eligible subjects will be recruited from local nursing and care homes. They will be randomly assigned to either an acupuncture group (named the "comprehensive acupuncture therapy [CAT]" group), an acupressure group (named the "Comfy Acupressure for the Elderly [CAE]" group), a combined acupuncture and acupressure group (named the CAT+CAE group), or a control group (named the routine care group), with 62 subjects per group. Subjects assigned to the CAT, CAE, and CAT+CAE groups will respectively receive 2 sessions of CAT, 3 sessions of CAE, and a combination of both per week for 12 weeks. The primary outcome is the baseline-to-endpoint change in score of the Montreal Cognitive Assessment

(MoCA). Secondary outcomes include various domains of MoCA, functional independence, psychological well-being, sleep quality, and level of pain. A generalized linear mixed-effect model will be used to compare outcomes over time among the four groups. This trial has been approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Ref No.: UW 19-821). The study protocol has been registered at ClinicalTrials.gov (NCT04305951) before enrolment. The trial will be conducted in compliance with the protocol, the ethical principles of the Declaration of Helsinki and its subsequent amendment. The study flow chart is shown in Figure 1.

Subjects

Inclusion criteria

Subjects will be eligible for this study if they: (a) are aged 65 years or above, (b) have a clinical diagnosis of any type of dementia or met the criteria of major and mild neurocognitive disorder based on the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5);[1] and (c) have mild to moderate dementia at a stage of 3 to 5 (Stage 3: mild cognitive decline; Stage 4: moderate cognitive decline/mild dementia; Stage 5: moderately severe cognitive decline/moderate dementia) on the Global Deterioration Scale.[28]

Exclusion criteria

Subjects will be excluded if they: (a) have the severity of dementia with a stage below 3 or above 5 on the Global Deterioration Scale; (b) have severe skin lesions on acupuncture and acupressure areas; (c) have a significant bleeding tendency; (d) have a heart pacemaker or implantable cardioverter defibrillator; (e) are currently receiving acupressure as a regular therapy; (f) had surgery on the head or neck; or (g) are currently receiving anti-coagulant treatment.

Estimation of sample size

Our recent study showed that CAT treatment for 8 weeks produced a 2.3±2.8 (SD) score greater improvement than control (minimum acupuncture stimulation, MAS) on MoCA in patients with poststroke cognitive impairment.[19] One similar trial has reported that acupuncture treatment alone for 3 months yielded a 1.9±4.1 greater improvement than nimodipine, a commonly used anti-hypertension drug, on MoCA in patients with poststroke cognitive impairment.[29] Based on these two trials, we expect that CAT could yield an average 2.1 [(2.3+1.9)/2 = 2.1] score greater improvement on MoCA than routine care, with an average standard deviation (SD) equal to a 1.7-fold of mean difference [(2.8/2.3 + 4.1/1.9)/2 = 1.7)], i.e., SD = 1.7 x 2.1 = 3.6. The following formula is then used to further calculate the sample size:

$$n = \frac{2}{(M/SD)^2} \times C_{p,power}$$

where n is the number of subjects required in each arm and M is the mean difference that is equal to 2.1. SD is the standard deviation that is 3.6. $C_{p,power}$ is equal to 7.9 when the two-tailed level of α and power (1-β) are set at 0.05 and 80%, respectively. It requires 62 subjects per arm, with an assumed dropout rate of 25%. We propose to recruit a total of 248 subjects (n = 62 per arm for 4 arms).

Methods

Screening

Screening will be conducted by general physicians, registered occupational therapists, social workers, and research assistants in nursing and care homes.

Randomization, central allocation and blindness

One independent research assistant will be in charge of randomization and central allocation as the central coordinator. After confirmation of patients' eligibility and completion of the baseline assessment, participants will be randomly assigned to CAT, CAE, CAT+CAE, or routine care groups in a ratio of 1:1:1:1. Random codes were produced in advance using simple, complete, non-sequential numbers, with a block of 4, 8 and 12, through a random allocation software at http://mahmoodsaghaei.tripod.com/Softwares/randalloc.html. Randomization information will be sealed in sequentially numbered opaque envelopes.

Central allocation will be conducted, i.e., site investigators who are responsible for subjects' eligibility will obtain the opaque envelope from the central coordinator for an eligible subject who will be allocated to one of the four groups. Each envelope will be opened by acupuncturists after the participant completes the baseline assessment. Clinical assessors and data analysts will be blind to patients' treatment.

Treatment procedure

(a) Routine care: All participants in the four groups will continue their current routine care and medications as usual. These routine cares will serve as covariates included in outcome analysis.

(b) CAT regimen: Subjects assigned to the CAT group will receive CAT treatment in addition to routine care. CAT will be conducted for 2 sessions per week for 12 consecutive weeks, a total of 24 treatment sessions. Registered Chinese medicine practitioners (CMPs) with a master's degree or above and with at least 5 years of acupuncture experience will be responsible for acupuncture treatment. A brief introduction to acupuncture procedures will be given by a CMP during the first visit. Details of selected acupoints are illustrated and summarized in Figure 2 and Table 1.

The acupuncture treatments will be conducted at the subjects' corresponding care homes. Each subject will receive a maximum of 26 needles per treatment session, adjusted by their tolerance, in a supine position. The following 14 body acupoints with only manual stimulation will be used: Shenmen (HT7, 神門), Hegu (LI4, 合谷), Waiguan (TH5, 外關), Zusanli (ST36, 足三里), Fenglong (ST40, 豐隆) and Sanyinjiao (SP6, 三陰交) on both sides, and Zhongwan (CV12, 中脘) and Guanyuan (CV4, 關元) in the midline. Meanwhile, electrical stimulation will be conducted on six pairs of frontal acupoints with positive (+) and negative (-) electrode cord connections as follows: Baihui (GV20, 百會) and Yintang (EX-HN3, 印堂), left Sishencong (EX-HN1, 四神聰) and Toulinqi (GB15, 頭臨泣), right Sishencong (EX-HN1, 四神聰) and Toulinqi (GB15, 頭臨泣), bilateral Shuaigu (GB8, 率谷), bilateral Taiyang (EX-HN5, 太陽), and bilateral Touwei (ST8, 頭維).

Disposable acupuncture needles with 0.25 mm in diameter and 25 or 40 mm in length (Agent: MOCM International Medical Instrument Limited; manufacturer: Wuxi Jiajian Medical Instrument Co., Ltd.) will be inserted at a depth of 10-30 mm perpendicularly or obliquely into acupoints. Manual manipulation will be carried out on all acupoints to evoke a needling sensation *de qi*. Electrical stimulation is additionally delivered on the 6 pairs of frontal acupoints. The output peak current and voltage of the machine (model: ITO ES-360) are 6 V and 48 mA, respectively, with a constant wave at a frequency of 2 Hz and a phase duration of 100 μs for 30 minutes. The stimulation intensity will be adjusted to a level at which patients feel most comfortable. The low frequency could produce broader neuromodulation compared to the higher frequency. The electrical stimulation will be adjusted according to the patients' tolerance. Each session of treatment will last for 30 minutes.

(c) CAE regimen: Subjects assigned to the CAE group will receive CAE in addition to routine care. The detailed procedure for CAE is summarized in Table 2. CAE interventions will be conducted 3 times per week for 12 consecutive weeks, a total of 36 treatment sessions. Trained research assistants or registered CMPs will be responsible for CAE treatment. CAE consists of 12 steps that take about 15 minutes to complete and mainly concentrate on the acupoints on the face, head, neck, and shoulder. All chosen acupoints are easily localized and conveniently operated by informal caregivers after proper

training. All techniques that demand professional training or involve potential risks (e.g., joint mobilization) are excluded.

(d) CAT+CAE: Subjects assigned to the CAT+CAE group will receive CAT+CAE in addition to routine care. The procedure is a combination of CAT+CAE as described above.

(e) Post-trial treatment of subjects in the routine care group: Those who are initially assigned to the routine care group will have a choice to receive CAT, CAE, or CAT+CAE treatment for 12 weeks after they complete the trial. The post-trial treatment will serve as compensation for their participation.

(f) Termination criteria and post-termination management: To ensure participants' safety, those who cannot tolerate acupuncture or acupressure or are hospitalized due to the aggravation of their condition will be discontinued from the study and given individual clinical treatment.

Control group

The group that receives routine care only will serve as the control group. For acupuncture, sham acupuncture techniques such as Streitberger needle may not be suitable for elderly subjects as they are associated with an increased risk of skin injury. Also, sham acupuncture has been proved not to be an inert method.[30] For acupressure, the CAE regimen involved multiple steps like pressing and kneading different body parts. Typical sham acupressure procedures, like using a non-acupoint or placebo acupressure device, are not applicable for the CAE treatment.[31]

Assessment

(a) Primary outcome**:** The primary outcome will be evaluated by the mean change of the Montreal Cognitive Assessment (MoCA) score between baseline and endpoint. The MoCA test assesses seven domains of cognitive function, including visuospatial, naming, attention, language, abstraction, recall, and orientation domains, for a total possible score of 30 points.[32-33] It has been well established for the detection of MCI, with sensitivity for detecting MCI of 90% compared to 18% for the Mini-Mental State Examination (MMSE),[32] and the evaluation of the severity of cognitive impairment. A score of 25 points or less is indicative of cognitive impairment, but the score needs to be adjusted for age and education.[32] We have applied MoCA in the two previous studies.[19-20]

(b) Secondary outcomes: The secondary outcomes will include the Digit span test for attentional function, short-term memory, and working memory, the Modified Barthel Index (MBI) for functional independence, the Visual Analogue Scale (VAS) for pain, the 15-item Geriatric Depression Scale (GDS-15) for depression, and the Insomnia Severity Index (ISI) for insomnia.

Digit Span is a measure of working and short-term memory, and is evaluated in two formats, Forward Digit Span and Reverse Digit Span, with a total possible score of 14 points, respectively. The Digit span test is a simple test to further evaluate subjects' attentional function, short-term memory, and working memory.[34]

MBI is a validated outcome measure to evaluate the functional status of patients. MBI consists of 10 items, i.e., feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation, and stair climbing, to score with a five-step scoring system.[35-36] MBI score ranges from 10 to 50, with a higher score indicating a higher level of independence. VAS is a simple instrument to measure subjective experience in pain. A horizontal line that represents the severity of symptoms from 0, no pain, to 10, very severe pain, is shown, and the patient should mark the point on the line that reflects the subject's perception of the current state.[37] Functional independence and pain are measured, as previous studies have confirmed the benefits of acupressure and acupuncture in improving disability and pain.[9,11]

The GDS-15 consists of 15 questions in which subjects are asked to respond by answering yes or no in reference to how they felt over the past week.[38-39] Of the 15 items, 5 items (question numbers 1, 5, 7, 11, 13) indicate depression when answered negatively, while the rest (question numbers 2, 3, 4, 6, 8, 9, 10, 12, 14, 15) indicate the presence of depression when answered positively. The GDS-15 score is interpreted as follows: normal (0-4), mild depression (5-8), moderate depression (9-11), and severe depression (12-15). GDS can be used in mild to moderately cognitively impaired older adults.[40] ISI is a

validated 7-item scale to assess the severity of insomnia.[41] The total score ranges from 0 to 28, with scores of 0-7 indicating no clinically significant insomnia, 8-14 indicating subthreshold insomnia, 15-21 indicating moderate insomnia, and 22-28 indicating severe insomnia. Depressive and sleep symptoms are investigated because elderly people with cognitive impairment often have comorbid emotional and sleep disorders. The benefits of acupuncture and acupressure for depression and insomnia have been confirmed in our previous studies.[17,21,24]

(c) Adverse events: The severity of adverse events (AEs) will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria.[42] AEs will be systematically recorded, in which AEs that first appear in the study or worsen relative to the pre-study status will be recorded at each visit, including the date and time of onset, duration, severity, relationship to intervention, and action taken accordingly. All possible events will be independently evaluated by staff who do not assess treatment outcomes. The causality between treatment procedures and AEs will be assessed.

Fatal or life-threatening unexpected AEs will be reported to the regulatory bodies as soon as possible but no later than 7 calendar days after first knowledge by the principal investigator (PI) that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. This report would include an assessment of the importance and implications of the findings, including relevant previous experience with the same or similar medicinal products. For other serious, unexpected AEs that are not fatal or life-threatening, they will be reported as soon as possible but no later than 15 calendar days after first knowledge by the PI or that the case meets the minimum criteria for expedited reporting. For non-serious AEs and serious AEs that are expected, they will be reported in a brief summary at the conclusion of the trial.

(d) Assessment schedule: Clinical assessment will be conducted at baseline, week 6, and week 12 (Table 3). For AEs, participants in active treatment groups will be asked whether they have experienced any AEs on each treatment and assessment session. Participants in the control group will be recorded for all AEs on a regular basis (baseline, 6, and 12 weeks).

Data Management

(a) Maintenance of consistency and fidelity**:** The study will last about 3 years and be carried out at multiple sites. There will also be many different professional investigators involved in the study. To ensure consistency and fidelity of intervention and assessment across sites and throughout a study period, training workshops will be conducted pre-trial and once per year thereafter. All investigators and caregivers will receive training. A training manual will be prepared for CAT and CAE procedures and clinical assessment instruments.

For intervention training, the PI and a senior CMP will instruct and demonstrate CAT and CAE. Trainees will practice CAT and CAE with each other. Investigators and caregivers who will perform CAT and CAE must obtain satisfactory training outcomes, which will be rated by the PI and a senior CMP.

For clinical assessment training, an investigator who has extensive experience in clinical assessment will instruct clinical instruments. An elderly person with dementia will be invited to be evaluated for MoCA by investigators who will be responsible for clinical assessment. An inter-rater reliability coefficient (k value) of >0.80 must be achieved after the completion of each training workshop.

To further ensure consistency and fidelity, the following additional measures will be taken: (1) all assessors will be deployed to each site via central allocation; (2) all assessments from baseline throughout the endpoint for each individual will be performed, if possible, by the same assessor who is blind to participants' interventions; and (3) all interventions of each patient will be conducted by the same investigator or caregiver, if possible.

(b) Safety assurance and ethical consideration: A Case Record Form (CRF) will be used to record each participant's treatment. Emergency contact numbers (the investigator's mobile number and a designated center staff member's mobile number) will be provided in the informed consent for

caregivers to report and seek advice in case of any AE. Paper copies of CRFs are stored in locked cabinets. Data will be entered using the double-entry strategy on password-protected computers.

The study will be carried out in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendment, and ICH-GCP. This trial has been approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Ref No.: UW 19-821). The study protocol has been previously registered at ClinicalTrials.gov (NCT04305951) before enrolment. A full explanation of the study goal, procedures, and potential side effects and risks will be presented to each patient recruited. All participants are required to provide written consent. For those who cannot fully understand the study due to cognitive impairment, consent will be obtained from their guardians. Informed consent and other documents provided to patients will be written in both English and Chinese. This study is conducted on Chinese patients. Patients would not receive remuneration, but treatments and assessments directly associated with the clinical trial will be provided at no cost. The issue of confidentiality is a major ethical issue, and will be solved by recording the data in a manner that does not allow the participants to be identified (i.e., using a non-recognizable code for each patient). A review of medical records that have already been recorded as part of clinical care. Therefore, this poses no physical risks.

(c) Record retention: The PI, research team, and ethical review authority are responsible for overseeing this study to get access to, use, and retain subjects' personal data for the purposes of clinical study, and the relevant regulatory bodies can get access to subjects' personal data for the purposes of checking and verifying the integrity of study data and assessing compliance with the study protocol and relevant requirements. All collected data will be secured in compliance with the Hong Kong Personal Data (Privacy) Ordinance (CAP 486). The collected personal information and study data will be kept for 3 years after the completion of the study.

Data processing and analysis

One biostatistician who is blinded to interventions will be responsible for statistical analysis. The analysis will be carried out on the intention-to-treat (ITT) population, for which participants have been randomized.[43] A linear mixed-effect model will be applied to compare the primary outcome (changes in total MoCA score from baseline) and secondary outcomes (changes in scores of the Digit span test, MBI, VAS, GDS and ISI), with time (baseline, week 6, and week 12) and group (CAT, CAE, CAT+CAE, and routine care) as categorical fixed factors and random intercepts within a scaled identity covariance matrix. Gender, age, baseline MoCA score, and baseline medication will serve as covariates. Subgroup analysis will be further conducted to compare outcomes by gender, age, and severity of dementia to detect whether these factors are associated with the outcomes. Pairwise comparisons will be further carried out to examine between-group differences. One-way analysis of variance (one-way ANOVA) will be used to detect differences in continuous baseline variables. Categorical baseline variables, including discontinuation and incidence of AEs, will be analyzed using the Chi-square test or Fisher's exact test. Statistical significance was defined as a two-tailed $P < 0.05$. The analysis will be conducted using R Studio software.

Termination criteria

(a) Premature termination or suspension of study: The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study: (1) new information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study; (2) a significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

(b) Premature termination or suspension of investigational sites: A study site may be terminated prematurely or suspended if the site (including the investigator) is found to be in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or

is otherwise permitted by the contractual agreement.

(c) Procedures for premature termination or suspension: In the event that the PI, an institutional review board (IRB) / research ethics committee (REC) or a regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the PI; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

(d) Criteria for discontinuation or withdrawal of a subject: (1) pretreatment event or AE: the subject has experienced a pretreatment event or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the pretreatment event or AE; (2) major protocol deviation: the discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health; (3) lost to follow-up: the subject does not return to the site, and attempts to contact the subject are unsuccessful; (4) withdrawal of consent: the subject wishes to withdraw from the study; (5) study termination: the PI, IRB, REC, or regulatory agency terminates the study.

(e) Procedures for discontinuation or withdrawal of a subject: The investigator may terminate a subject's study participation at any time during the study when the subject meets the study termination criteria. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination would be recorded. Subjects who discontinue the study during the treatment period will visit the site as soon as possible for clinical assessment, if applicable. To ensure participants' safety, those discontinued because of severe side effects or hospitalizations due to any reason will be given individual clinical treatment. Discontinued or withdrawn subjects will not be replaced.

Anticipated results and potential pitfalls

Our several previous studies have confirmed the effectiveness of CAT and CAE monotherapy in elderly patients. This provides a direct and solid basis to ensure the success of the proposed study. We therefore expect that CAT and CAE could produce better outcomes than routine care in improving cognitive deterioration, functional dependence, psychological, sleep, and pain symptoms. Furthermore, related collaborative networks, protocols, and the research team have been well established. It is very unlikely that impassable obstacles will be encountered in the proposed studies. Despite this, the completion of the recruitment in a timely manner may be a potential issue. If the recruitment cannot reach the goal within the designed timeframe at the end of the first year, additional study sites will be sought.

Publication policy

The results of this study are going to be published in peer-reviewed journals, with the abstract available online at the clinical trial register. Subjects enjoy rights of the protection of the confidentiality of their personal data.

Impact on People's Health and Health Services as well as Plan to Disseminate Research Findings to End Users

If the proposed study could achieve positive results, it would demonstrate that CAT and CAE therapy could be effective in improving the quality of life for the elderly with dementia. We will then

establish a collaborative network consisting of acupuncturists, nurses, physiotherapists, and other caregivers and hold serial training workshops to introduce such treatment strategies to community caregivers and family members. Through these training workshops, CAT and CAE could become standard interventions for the elderly with dementia. We hope the elderly with dementia can obtain benefits from this study and reduce caregivers' family and public health care system burdens.

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Figure 1. Study flow chart. t, timepoint; CAT, comprehensive acupuncture therapy; CAE, Comfy Acupressure for the Elderly

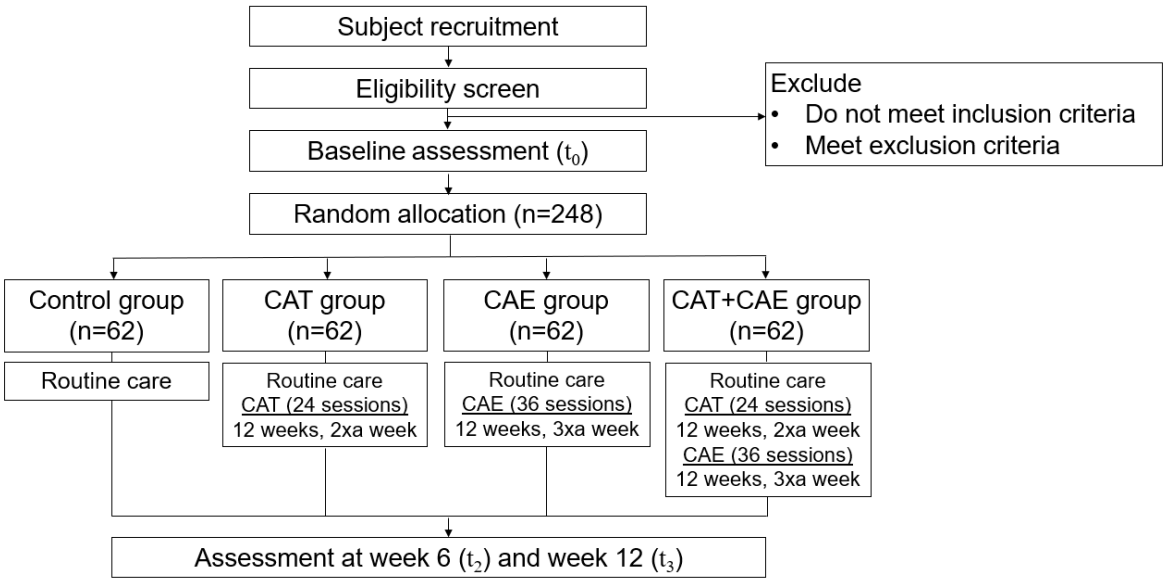

Figure 2. Illustration of selected acupoints in the trial

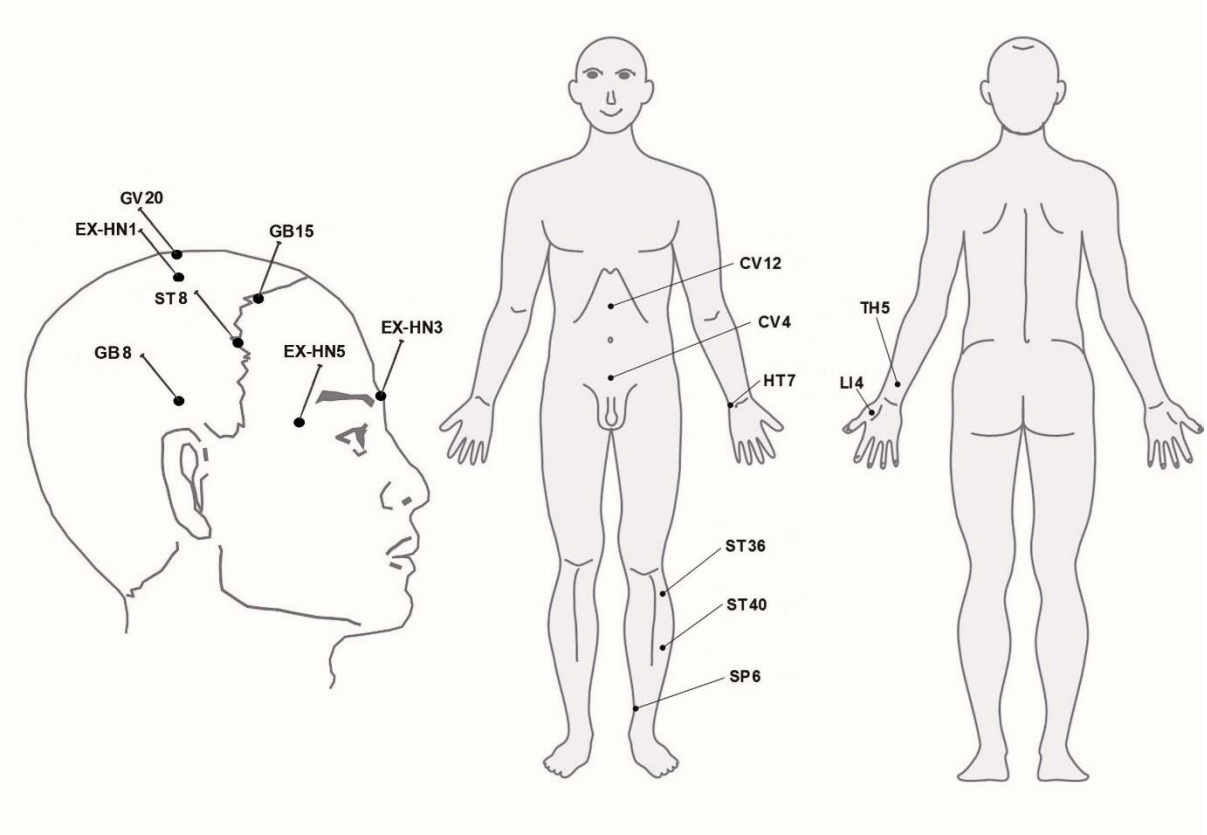

Table 1. Location, traditional Chinese medicine (TCM)-based therapeutic effects and manipulation of the selected acupoints in the trial

Acupoint	Location	TCM-based therapeutic effects	Manipulation	Number of needles insertion
GV20 (Baihui, 百會)	At the vertex of the scalp, 7 *cun* directly above the midpoint of the posterior hairline.	Tonifies *Yang*, opens the orifices and rejuvenates the mind, relieves headache and dizziness, is widely used for senile dementia, insomnia, and mental disorders.	Transverse insertion, 0.5-0.8 *cun*, forwards or backwards.	1, unilateral
EX-HN3 (Yintang, 印堂)	At the midway of the medial ends of the eyebrows	Calms the mind and reduces anxiety, is widely used for headache, dizziness, forgetfulness, agitation, and insomnia.	Transverse insertion, 0.3-0.5 *cun*, downwards.	1, unilateral
EX-HN1 (Sishencong, 四神聰)	Four points in all, at the vertex of the scalp, 1 *cun* respectively anterior, posterior, and lateral to GV20 (Baihui).	Calms the mind, restores consciousness and opens the orifices, and suppresses sympathetic activity, is widely used for insomnia, epilepsy and mental disorders.	Transverse insertion, 0.5-0.8 *cun*.	2, left and right
GB15 (Toulinqi, 頭臨泣)	One the forehead, 0.5 *cun* within the anterior headline, midway between GV24 (Shenting) and ST8 (Touwei).	Reduces headache and dizziness, opens the orifices, rebalances mood, and suppresses convulsion and nervousness.	Transverse insertion, 0.5-0.8 *cun*, backwards.	2, bilateral
ST8 (Touwei, 頭維)	At the corner of the head, 0.5 *cun* directly above the hairline, 4.5 *cun* lateral to the midline of the head.	Dispels wind, relieves pain and improves eyesight, is commonly used for headache, dizziness, and eye diseases.	Transverse insertion, 0.5-1 *cun*, backwards subcutaneously.	2, bilateral
GB8 (Shuaigu, 率谷)	On the temple, 1.5 *cun* directly above the apex of the car.	Dispels head cloudiness, opens the orifices, relieves pain and agitation, is commonly used for migraine and vertigo.	Subcutaneous insertion, 0.5-0.8 *cun*.	2, bilateral
EX-HN5 (Taiyang, 太陽)	At the temple, in the depression about 1 *cun* posterior to the midpoint between the lateral of the eyebrow and the outer canthus.	Alleviates headache, dizziness, insomnia, and eye diseases.	Oblique insertion, 0.3-0.5 *cun* inferiorly.	2, bilateral
CV12 (Zhongwan, 中脘)	On the anterior midline of the abdomen, 4 *cun* above the umbilicus.	Strengths the spleen, reduces indigestion and diuresis, improves stomach movement, particularly benefits stress-related digestive disorders, e.g., stomachache, heartburn, and diarrhea. Modulates the limbic-medial prefrontal network related to emotional and cognitive function.	Perpendicular insertion, 0.5-1.2 *cun*.	1, unilateral

CV4 (Guanyuan, 關元)	On the anterior midline of the abdomen, 3 *cun* below the umbilicus.	Tonifies *Qi* and *Yang*, strengthens the foundation of the body, benefits constipation, urine retention, frequent nocturia and indigestion. Modulates the limbic-medial prefrontal network related to emotional and cognitive function.	Perpendicular insertion, 0.5-1.2 *cun*.	1, unilateral
HT7 (Shenmen, 神門)	At the wrist joint, on the radial side of the tendon of flexor carpi ulnaris, along the most distal transverse crease of the wrist.	Calms the mind and tranquilizes the spirit, is commonly used for a variety of psychogenic conditions, including insomnia and neurosis.	Perpendicular insertion, 0.3-0.5 *cun*.	2, bilateral
TH5 (Waiguan, 外關)	2 *cun* above the transverse crease on the back of the wrist, in the depression between the ulnar and radius.	Expels Wind and clears heat, tonifies *Qi* and *Yang*, and activates meridians, is widely used for febrile disease, headache, dizziness, and psychogenic pain.	Perpendicular insertion, 0.5-1 *cun*.	2, bilateral
LI4 (Hegu, 合谷)	Over the dorsum of the hand, between first and second metacarpal bones, at the level of the midpoint of the second metacarpal bone on the radial side.	Expels Wind and releases the exterior, relieves pain and strengthens immunity, is used for febrile disease, stroke sequela, psychogenic tension and pain. Commonly used acupoint for anesthesia.	Perpendicular insertion, 0.5-1 *cun*.	2, bilateral
ST36 (Zusanli, 足三里)	3 *cun* below the depression in the lateral patellar ligament, 1 fingerbreadth lateral to the anterior crest of the tibia.	Harmonizes and strengthens the spleen and the stomach, reinforces healthy and original *Qi*, calms the spirit and activates meridians, is commonly used for gastrointestinal discomfort, stress and fatigue. Evokes a robust response in the limbic-paralimbic-neocortical network involved in autonomic, pain, mood, and cognitive function.	Perpendicular insertion, 1-1.5 *cun*.	2, bilateral
SP6 (Sanyinjiao, 三陰交)	3 *cun* superior to the prominence of the medial malleolus, posterior to the medial crest of the tibia.	Tonifies *Yin* and improves vitality and immunity, clams the mood by nourishing the three foot meridians, including the spleen, kidney and liver, is widely used for endocrine and immune system disorders, e.g., insomnia, fatigue and pain.	Perpendicular insertion, 1-1.5 *cun*.	2, bilateral
ST40 (Fenglong, 豐隆)	8 *cun* below the depression in the lateral patellar ligament, 2 fingerbreadth lateral to the anterior crest of the tibia.	Harmonizes and strengthens the spleen and the stomach, relieves phlegm, calms the mind and opens the orifices, is widely used for dizziness, epilepsy and mental disorders.	Perpendicular insertion, 0.5-1 *cun*.	2, bilateral

Table 2. Detailed treatment procedures of “Comfy Acupressure for the Elderly (CAE)”

Step	Operating location	Procedure
Opening Tianmen (開天門)	From the center of the eyebrow to the forehead	Apply massage oil to the center of the subject’s forehead, then use the pad of the index and middle fingers of both hands, or the middle finger alone, to synchronously push straight upward from the midpoint between the subject’s eyebrows (EX-HN3, Yintang) to the hairline (GV24, Shenting). Repeat 15 times.
Pushing Kangong (分推坎宮)	From the inside to the outside of the eyebrows	Apply massage oil to the subject’s eyebrow, then use the pad of the index and middle fingers of both hands, or the middle finger alone, to synchronously push from the medial end of both eyebrows (BL2, Cuanzhu) to the depression on the supraorbital margin, at the lateral end of the eyebrows (SJ23, Sizhukong). Repeat 15 times.
Pressing and Kneading Taiyang (按揉太陽)	Acupoint EX-HN5 (Taiyang)	Using the pad of the middle finger of both hands, press and knead the acupoint EX-HN5 (Taiyang), in synchronized circular motion. Knead deeply to move the subcutaneous layer of the skin, instead of just rubbing the surface. Repeat 15 times.
Kneading Face (揉抹面部)	7 facial acupoints: GB14, (Yangbai), EX-HN5 (Taiyang), SI18 (Quanliao), LI20 (Yingxiang), ST6 (Jiache), ST4 (Dicang) and CV24 (Chengjiang)	Using the pads of the index, middle, and ring fingers of both hands, or the middle finger alone, to synchronously massage the subject’s face in circular motion, following the sequence below: forehead, temporal area, orbital area, zygomatic area, cheek area, nasal area, lower jaw. Focus on the following acupoints: GB14, (Yangbai), EX-HN5 (Taiyang), SI18 (Quanliao), LI20 (Yingxiang), ST6 (Jiache), ST4 (Dicang), and CV24 (Chengjiang) by repeating the circular kneading action on each acupoint. Repeat the action 3 times.
Grasping Wu Jing (拿五經)	The head area that Du meridian, Bladder meridian, and Gallbladder meridian circulate	Place a thin towel on the subject's head, then place one hand on top of the towel, with the pad of the middle finger on the Du meridian, index and ring fingers on the Bladder meridian, and thumb and little finger on the Gallbladder meridian. Move and synchronize all 5 fingers to lift and press on the treatment area. Move the hand up and down the meridians and sideways to cover the subject's entire head. Repeat for 3 minutes, spending 1 minute on the top, 1 minute on the sides, and 1 minute on the back of the skull.
Pressing and Kneading Fengchi (按揉風池)	Acupoint GB20 (Fengchi)	Place a thin towel on the subject's head, then use both thumbs or the thumb and index/middle finger of one hand to synchronously press and knead the acupoint GB20 (Fengchi) on both sides of the neck. Repeat 5 times.
Pressing and kneading the neck (按揉頸項部)	Neck	Place a thin towel on the subject’s neck area and use the thumb and index/middle finger of one hand to lift and massage both sides of the neck. Ensure that the action is rhythmic and synchronized. Repeat for 3 minutes, spending 1 minute on the upper, 1 minute on middle, and 1 minute on the lower part of the neck.
Pressing and Kneading Jianjing (按揉肩井)	Acupoint GB21 (Jianjing)	Place a thin towel on the subject's shoulder, then use both hands to massage the shoulder muscle with mellow force. Ensure that the action is rhythmic and synchronized. Repeat for 3 minutes.
Pressing and Kneading	Acupoint SI11 (Tianzong)	Use the thumbs or middle fingers of both hands to synchronously massage the acupoint SI11 (Tianzong) on both sides of the back. Repeated 5 times.

Tianzong (按揉天宗)		
Pushing Qiaogong (推橋弓)	Anterior cervical sternocleidomastoid muscle	Apply massage oil to the subject's sternocleidomastoid muscles in the front neck area, then use the pads of the index and middle fingers, or the middle finger alone, move swiftly downwards from the back of the ear, along the sternocleidomastoid muscle. The movement should be light and cause no discomfort to the subject. Repeat 50 times on each side.
Grasping Jianjing (拿肩井)	Acupoint GB21 (Jianjing)	Place a thin towel on the subject's shoulder, then use the thumbs and index/middle fingers of both hands to lift and grasp the shoulder muscle of both shoulders with appropriate force. Repeat 5 times.
Grasping Hegu (拿合谷)	Acupoint LI4 (Hegu)	Use the thumb and index/middle fingers of one hand to lift and grasp the acupoint LI4 (Hegu) of both hands of the subject with appropriate force. Repeat 5 times.

Table 3. Standard protocol items: recommendations for intervention trials (SPIRIT) schedule of enrollment, interventions, and assessment.

		Study Period			
	Enrolment	Allocation	Post-allocation		
Timepoint	$-t_1$	t_0	t_1 Start	t_2 6-week	t_3 12-week
Enrolment					
Eligibility screen	X				
Informed consent	X				
Demographics	X				
Allocation		X			
Interventions					
Intervention: CAT			◄	———	——— ►
Intervention: CAE			◄	———	——— ►
Control: routine care			◄	———	——— ►
Assessments					
MoCA		X		X	X
Digit Span		X		X	X
MBI		X		X	X
VAS		X		X	X
GDS		X		X	X
ISI		X		X	X

Abbreviations: t, timepoint; CAT, comprehensive acupuncture therapy; CAE, Comfy Acupressure for the Elderly; MoCA, Montreal Cognitive Assessment; MBI, Modified Bathel Index; VAS, Visual Analogue Scale; GDS, Geriatric Depression Scale; ISI, Insomnia Severity Index.