Statistical Analysis Plan

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

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Abbreviations

Abbreviations: CAT, comprehensive acupuncture therapy; CAE, Comfy Acupressure for the Elderly; DSF, Digit Span Forward; DSR, Digit Span Reverse; MoCA, Montreal Cognitive Assessment; MBI, Modified Barthel Index; VAS, Visual Analogue Scale; GDS, Geriatric Depression Scale; ISI, Insomnia Severity Index.

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Introduction

This statistical analysis plan (SAP) describes the planned analyses to be performed on data collected in the clinical trial titled "Combining acupuncture and acupressure for dementia elderly: an assessor-blinded, randomized controlled trial". No statistical analyses will be performed until the final version of this SAP has been approved.

Study design

It 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.

Hypothesis and aims

The hypotheses of this trial are:
(a) acupuncture, acupressure, and their combination are feasible, safe, and could produce better management outcomes than routine care for the elderly with cognitive impairment or dementia; and
(b) combining acupressure and acupuncture as a holistic intervention could even produce additive and even synergistic effects over their monotherapies.

The aims of this study are:
(a) to determine whether the condition of cognitive impairment in the treatment group improves significantly when compared to the control;
(b) to determine whether other symptoms (e.g., functional independence, pain, depression, and sleep disorder) in the treatment group improve more than in the control group; and
(c) to investigate whether acupuncture or acupressure is safe for the elderly with cognitive impairment or dementia.

Patient population

Elderly patients with cognitive impairment or dementia are eligible for enrolment.

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 on the Global Deterioration Scale.[2]

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) have had surgery on the head or neck; or
(g) are currently receiving anti-coagulant treatment.

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.

Intervention

(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. Details of selected acupoints and treatment procedures can be found in the study protocol.
(c) CAE regimen: Subjects assigned to the CAE group will receive CAE in addition to routine care. CAE interventions will be conducted 3 times per week for 12 consecutive weeks. The detailed procedure for CAE is summarized in the study protocol.

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

Study outcomes

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.[3-4] Assessments will be conducted at baseline, week 6, and week 12.

Secondary outcomes

Assessments will be conducted at baseline, week 6, and week 12.
The secondary outcomes will include:
(a) the Digit span test for attentional function, short-term memory, and working memory, including the Digit Span Forward (DSF) and the Digit Span Reverse (DSR);[5]
(b) the Modified Barthel Index (MBI) for functional independence;[6-7]
(c) the Visual Analogue Scale (VAS) for pain;[8]
(d) the 15-item Geriatric Depression Scale (GDS-15) for depression;[9-10] and
(e) the Insomnia Severity Index (ISI) for insomnia.[11]

Safety outcomes

The severity of adverse events (AEs) will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria.[12] 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 date and time of onset, duration, severity, relationship to intervention, and action taken accordingly. The causality between treatment procedures and AEs will be assessed.

Sample size determination

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.[13] 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.[14] 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).

Data processing and analysis

General principles

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 all primary and secondary outcomes, two-tailed P-values will be reported in addition to confidence intervals. The nominal level of statistical significance (α) will be 5%. The analysis and reporting of the results will follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Analysis software

All analyses will be performed using R Studio version 4.0.0 or later.

Analysis Populations

All analyses will be carried out on the intention-to-treat (ITT) population, for which participants have been randomized, completed the baseline assessment regardless of protocol compliance.[15] The flow of patients throughout the trial will be shown using a CONSORT diagram (Figure 1).

Demographic characteristics and baseline comparisons

Baseline comparisons will be tabulated for the following variables (Proposed Table 1):

(a) Age
(b) Gender (Categories: male / female)
(c) Marital status (Categories: married or living with partner / single, separated, divorced, or widowed)
(d) Education level (Categories: uneducated / primary or below / lower secondary / upper secondary / university or above)
(e) Past occupation (Categories: managers and administrators / professional and associate professional / skilled and semi-skilled worker / unskilled worker / housework / others)
(f) Type of cognitive impairment (Categories: Alzheimer's disease / vascular dementia / others)
(g) Past medical history (Categories: cardiometabolic disease / malignant neoplasm / stroke / Parkinson's disease / psychotic disorder / affective disorder)
(h) Current medication (Categories: cholinesterase inhibitors / glutamate regulators / antidepressants / antipsychotics / hypnotics)

(i) Baseline MoCA score
(j) Baseline DSF and DSR scores
(k) Baseline MBI score
(l) Baseline VAS score
(m) Baseline GDS-15 score
(n) Baseline ISI score

Continuous variables will be presented using mean with standard deviation (SD). One-way analysis of variance (one-way ANOVA) will be used to detect differences in continuous baseline variables.

Categorical variables will be presented by counts with percentages. Percentages will be calculated according to the number of patients for whom data are available. Categorical variables will be analyzed using the Chi-square test or Fisher's exact test.

Discontinuation will be summarized by counts with percentages. Chi-square test or Fisher's exact test will be used to detect differences between the four groups.

Primary outcome

A linear mixed-effect model will be applied to compare the primary outcome (changes in total MoCA score from baseline), 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. Pairwise comparisons will be further carried out to examine between-group differences. Two-tailed P-values will be reported in addition to confidence intervals (Proposed Tables 2 and 3).

Subgroup analysis will be further conducted to compare outcomes to detect whether these subgroup factors are associated with outcomes. The following subgroups include:
(a) Age (<85 years and ≥ 85 years);
(b) Gender (male and female); and
(c) severity of dementia (mild cognitive decline [Stage 3], moderate cognitive decline [Stage 4], moderately severe cognitive decline [Stage 5])

Secondary outcomes

A linear mixed-effect model will be applied to compare the secondary outcomes, including changes in scores of the Digit span test (DSF and DSR), 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. Pairwise comparisons will be further carried out to examine between-group differences. Two-tailed P-values will be reported in addition to confidence intervals (Proposed Tables 2 and 3).

Safety outcomes

AEs related to treatment will be tabulated by treatment group without statistical tests or confidence intervals (Proposed Table 4).

All AEs that occurred throughout the trial will be tabulated by treatment group and AE category (mild, moderate, severe, life-threatening, or death). Chi-square test or Fisher's exact test will be used to detect differences between the four groups (Proposed Table 5).

Details of serious AEs and death cases will be summarized and listed in a separate table.

Interim analysis

No interim outcome analyses were done prior to the completion of the study to avoid assessment bias.

Missing data

A linear mixed-effect model will be conducted for all analyses of primary and secondary outcomes without imputation of missing data.[16]

Proposed Tables

Table 1. Baseline characteristics

Characteristic	CAT (n=62)	CAE (n=62)	CAT+CAE (n=62)	Routine care (n=62)	Total (n=248)	*P* value
Age, years *	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX
Gender (Female) †	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Marital status †						XX
Married or living with partner	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Single, separated, divorced, or widowed	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Education level †						XX
Uneducated	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Primary or below	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Lower Secondary	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Upper Secondary	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
University or above	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Past occupation †						XX
Managers and administrators	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Professional and associate professional	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Skilled and semi-skilled worker	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Unskilled worker	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Housework	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Others / no information	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Type of cognitive impairment †						XX
Alzheimer's disease	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Vascular dementia	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Others ‡	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	
Past medical history †						
Cardiometabolic disease	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Malignant neoplasm	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Stroke	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Parkinson's disease	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Psychotic disorder	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Affective disorder	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Current medication †						
Cholinesterase inhibitors	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Glutamate regulators	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Antidepressants	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Antipsychotics	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Hypnotics	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
MoCA *	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX
DSF *	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX
DSR *	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX
MBI *	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX

Characteristic	CAT (n=62)	CAE (n=62)	CAT+CAE (n=62)	Routine care (n=62)	Total (n=248)	*P* value
VAS *	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX
GDS *	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX
ISI *	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX ± XX	XX

Abbreviations: CAT, comprehensive acupuncture therapy; CAE, Comfy Acupressure for the Elderly; DSF, Digit Span Forward; DSR, Digit Span Reverse; MoCA, Montreal Cognitive Assessment; MBI, Modified Barthel Index; VAS, Visual Analogue Scale; GDS, Geriatric Depression Scale; ISI, Insomnia Severity Index.

* Continuous data are expressed as mean ± SD and were examined using One-way ANOVA. Those which statistical differences $P<0.05$ reached the significance level are indicated in bold font.

† Categorical data are expressed as count (percentage) and were examined using Chi-square (χ^2) or Fisher Exact test. Those which statistical differences $P<0.05$ reached the significance level are indicated in bold font.

‡ Other types of cognitive impairment included mild cognitive impairment, Parkinson's disease dementia, mixed dementia, etc.

Table 2. Between-group comparison in outcomes versus CAU group

Outcomes	CAT vs. Routine care		CAE vs. Routine care		CAT+CAE vs. Routine care	
	Difference (95% CI)	*P* value‡	Difference (95% CI)	*P* value‡	Difference (95% CI)	*P* value‡
Primary outcome						
MoCA *						
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Secondary outcomes						
DSF *						
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
DSR *						
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
MBI *						
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
VAS †						
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
GDS †						
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
ISI †						
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX

Outcomes	CAT+CAE vs. CAT		CAT+CAE vs. CAE		CAT vs. CAE	
	Difference (95% CI)	*P* value‡	Difference (95% CI)	*P* value‡	Difference (95% CI)	*P* value‡
Primary outcome						
MoCA *						
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Secondary outcomes						
DSF *						
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
DSR *						
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
MBI *						
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
VAS †						
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
GDS †						
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
ISI †						
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX

Abbreviations: CAT, comprehensive acupuncture therapy; CAE, Comfy Acupressure for the Elderly; DSF, Digit Span Forward; DSR, Digit Span Reverse; GDS, Geriatric Depression Scale; ISI, Insomnia Severity Index; MBI, Modified Barthel Index; MoCA, Montreal Cognitive Assessment; VAS, Visual Analogue Scale.

* A greater positive value represents improvement in symptoms.
† A greater negative value represents improvement in symptoms.
‡ *P* value was calculated using a mixed-effects model with baseline adjustment to illustrate between-group differences. Those which statistical differences $p<0.05$ reached significance level are indicated in bold font.

Table 3. Intra-group comparison in outcomes

	Change from baseline							
	CAT (n=62)		CAE (n=62)		CAT+CAE (n=62)		Routine care (n=62)	
Outcomes	Mean (95%CI)	*P* value‡	Mean (95%CI)	*P* value‡	Mean (95%CI)	*P* value‡	Mean (95%CI)	*P* value‡
Primary outcome								
MoCA *								
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Secondary outcomes								
DSF *								
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
DSR *								
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
MBI *								
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
VAS †								
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
GDS †								
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
ISI †								
Week-6	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX
Week-12	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX	XX (XX, XX)	XX

Abbreviations: CAT, comprehensive acupuncture therapy; CAE, Comfy Acupressure for the Elderly; DSF, Digit Span Forward; DSR, Digit Span Reverse; GDS, Geriatric Depression Scale; ISI, Insomnia Severity Index; MBI, Modified Barthel Index; MoCA, Montreal Cognitive Assessment; VAS, Visual Analogue Scale.

* A greater positive value represents improvement in symptoms.

† A greater negative value represents improvement in symptoms.

‡ *P* value was calculated using a mixed-effects model with baseline adjustment to illustrate pre- and post-treatment within-group differences. Those which statistical differences $p<0.05$ reached significance level are indicated in bold font

Table 4. Adverse events related to treatment, n (%)*

Adverse event	CAT (n = 62)	CAE (n = 62)	CAT+CAE (n = 62)
Bleeding at the site of needling	XX (XX)	XX (XX)	XX (XX)
Hematoma around the site of needling	XX (XX)	XX (XX)	XX (XX)
Dizziness after treatment	XX (XX)	XX (XX)	XX (XX)
Headache after treatment	XX (XX)	XX (XX)	XX (XX)
Localized pain	XX (XX)	XX (XX)	XX (XX)
Needle phobia	XX (XX)	XX (XX)	XX (XX)

Abbreviations: CAT, comprehensive acupuncture therapy; CAE, Comfy Acupressure for the Elderly.
* Data was expressed as number of patients (%).

Table 5. Reported adverse events in different categories, n (%)*

Adverse Event Category	CAT (n=62)	CAE (n=62)	CAT+CAE (n=62)	Routine care (n=62)	P-value*
Any	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Mild	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Moderate	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Severe	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Life-threatening	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX
Death	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX

Abbreviations: CAT, comprehensive acupuncture therapy; CAE, Comfy Acupressure for the Elderly.
* Data was expressed as number of patients (%). Those which statistical differences $p<0.05$ reached significance level are indicated in bold font.

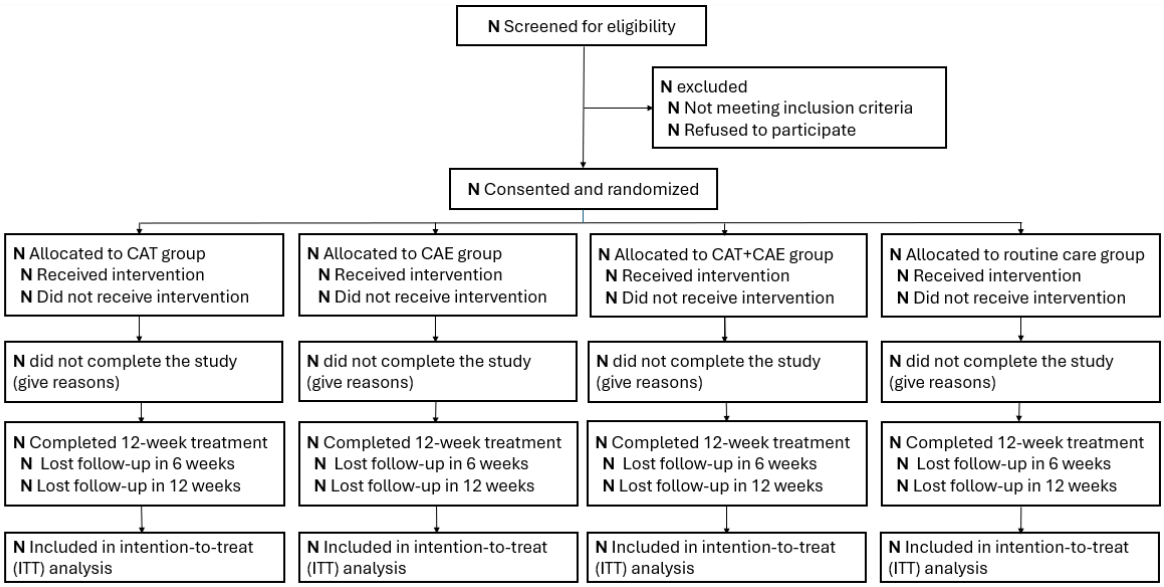

Figure 1. CONSORT Flowchart

References

1. American Psychiatric Pub. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub; 2013.
2. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry. 1982;139(9):1136-9. doi: 10.1176/ajp.139.9.1136
3. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x
4. Yeung PY, Wong LL, Chan CC, Leung JL, Yung CY. A validation study of the Hong Kong version of Montreal Cognitive Assessment (HK-MoCA) in Chinese older adults in Hong Kong. Hong Kong Med J. 2014;20(6):504-10
5. Jones G, Macken B. Questioning short-term memory and its measurement: Why digit span measures long-term associative learning. Cognition. 2015;144:1-13. doi: 10.1016/j.cognition.2015.07.009
6. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. J Clin Epidemiol. 1989;42(8):703-9. doi: 10.1016/0895-4356(89)90065-6
7. Leung SO, Chan CC, Shah S. Development of a Chinese version of the Modified Barthel Index-- validity and reliability. Clin Rehabil. 2007;21(10):912-22. doi: 10.1177/0269215507077286
8. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health. 1990;13(4):227-36. doi: 10.1002/nur.4770130405
9. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982;17(1):37-49. doi: 10.1016/0022-3956(82)90033-4
10. Chiu HF, Lee HC, Wing YK, Kwong PK, Leung CM, Chung DW. Reliability, validity and structure of the Chinese Geriatric Depression Scale in a Hong Kong context: a preliminary report. Singapore Med J. 1994;35(5):477-80.
11. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep. 2011;34(5):601-8. doi: 10.1111/j.1532-5415.1992.tb01988.x
12. Shah S. Common terminology criteria for adverse events. USA: National Cancer Institute; 2022; 784:785.
13. Zhang ZJ, Zhao H, Jin GX, Man SC, Wang YS, Wang Y, et al. Assessor- and participant-blinded, randomized controlled trial of dense cranial electroacupuncture stimulation plus body acupuncture for neuropsychiatric sequelae of stroke. Psychiatry Clin Neurosci. 2020;74(3):183-90. doi: 10.1111/pcn.12959
14. Wang S, Yang H, Zhang J, Zhang B, Liu T, Gan L, Zheng J. Efficacy and safety assessment of acupuncture and nimodipine to treat mild cognitive impairment after cerebral infarction: a randomized controlled trial. BMC Complement Altern Med. 2016;16:361. doi: 10.1186/s12906-016-1337-0
15. Gupta SK. Intention-to-treat concept: A review. Perspect Clin Res. 2011;2(3):109-12. doi: 10.4103/2229-3485.83221
16. Twisk J, de Boer M, de Vente W, Heymans M. Multiple imputation of missing values

was not necessary before performing a longitudinal mixed-model analysis. J Clin Epidemiol. 2013 Sep;66(9):1022-8. doi: 10.1016/j.jclinepi.2013.03.017