Study protocol and Statistical Analysis Plan

Title:Effectiveness of nurse-led clinics training program on mild cognitive impairment

patients: a randomized controlled trial protocol

NCT number:2021029

Date of the document:2024-01-03

Study protocol

Abstract

Introduction: Globally, nurse-led clinics(NLCs) have been developed to serve and follow up on patients who have just been discharged from the hospital. NLCs cognitive training program as a potentially effective and promising treatment for MCI patients.

Methods: The study is a single-blind, randomized-controlled trial. Eligible patients need to be diagnosed as MCI. Participants will be randomized into either a NLCs training group or a home-based training group. Both groups will undergo total 72hour across 12 months. The outcome measures will be assessed at baseline, at the 6 months and 12 months during the intervention. The primary outcome is global cognitive function, assessed by the 30-item the Mini-Mental State Examination (MMSE), and the secondary outcomes include changes in other neuropsychological assessments and in result of resting electroencephalography (EEG) .

Results: The trial is currently ongoing, and it is anticipated that recruitment will be completed in June 2025.

Discussion: This trial will evaluate the efficacy and safety of NLCs cognitive training in patients with MCI, and further explore the potential mechanisms by analyzing teh results of neuropsychological assessments and EEG.

Trial registration:

Keywords: mild cognitive impairment, nurse-led clinics, computerized cognitive training, randomized controlled clinical trial

1 Introduction

Cognitive impairment that is a syndrome with persistent cognitive impairment occurs on a continuum from mild, moderate, to severe states, which is manifested as one or more impairments in cognitive domains.[1] There is a high prevalence of mild cognitive impairment (MCI) in China. Among adults aged 60 and above, there are about 38.77 million MCI patients with a prevalence rate as high as 15.5%.[2] In addition, among nervous system diseases, 22.8% patients with Parkinson's disease and 34%~65% patients with multiple sclerosis also have cognitive impairment.[3,4] The provision of social care and the hours of unpaid care by families for patients who are living with cognitive impairment currently costs amount to £15.7 (US $21.6) billion and £13.9 (US $19.2) billion a year respectively.[5] Given the magnitude of the problem in terms of individuals or family affected and the costs associated with cognitive impairment, the prevention and treatment of cognitive impairment is currently a public health priority at the center of the global action plan (2017–2025), requiring new solutions to support patients and families in managing disabilities related to the disease.[6]

In this context, the need to promptly intervene with cognitive training on residual capabilities is well known. Previous studies have shown computerized cognitive training (CCT) interventions could improve global cognitive function in patients with

MCI.[7] At the same time, cognitive training can significantly improve the overall cognitive function of patients regardless of short-term ($\leqslant$10 weeks), medium-term (10~20 weeks) or long-term ($\geqslant$ 20 weeks) intervention.[8] Furthermore, giving intensive training after the normal training dose maybe get preferable cognitive function improvement and effect maintenance.[9]

The increasing prevalence of MCI and importance of CCT have led to a growing demand for cognitive training services in an outpatient setting. It is likely to be a critical point of continuous, sufficient dose and high quality cognitive training in the effect of CCT.[10] Hence, remote guidance and detection by medical staff are important for patients to cognitive training to meet the individual needs.[11] Globally, nurse-led clinics(NLCs) have been developed to serve and follow up on patients who have just been discharged from the hospital. NLCs are defined as clinical practice facilities where nurses have their own formalized and structured standard to address healthcare needs of patients and their families.[12] The clinics are run by advanced practicing nurses (APNs) who can monitor and support MCI to persist in cognitive training for a long time after discharge. In each consultation, the APNs also equip their families with the knowledge and caregiving skills to deal independently with the numerous challenges faced by their loved ones, thereby reducing the feeling of caregiving burden. The novelty of nurse-led clinics in cognitive training, randomized controlled trials demonstrating the effectiveness of the solution is still scarce.

This trail is the first study to test the efficacy of nurse-led clinics cognitive training on MCI patients using a single-blind, randomized controlled trial design. We hypothesize that nurse-led clinics cognitive training can (a)decelerate or ameliorate cognitive decline, (b)ameliorate anxiety and depressive symptoms, (c)increase the quality of life for both patients and family members, (d)improve the ability of daily life, (e)reduce the incidence of agitation.

2 Methods

2.1 Study design

This single-center, single-blind trial. All participants will be recruited from Xuanwu Hospital, Capital Medical University, Beijing. This study will be reported in accordance with both the CONsolidated Standards of Reporting Trials (CONSORT) statement and the CONSORT statement for nonpharmacological interventions.

The participants will be randomized into either a NLCs training group or a home-based training group. Both groups will undergo 72, 1-hour sessions of NLCs training or 144, 30-minute sessions of home-based training across 12 months. The outcomes will be assessed at baseline, at 6-month and 12-month follow-up. The outcomes will include multiple neuropsychological assessments to examine the effect of NLCs training on cognitive functions, resting-state EEG to measure brain connectivity and neural activity.

2.2 Participants

Patients with MCI will be recruited according to the following inclusion and exclusion criteria.

2.2.1 Inclusion criteria

1. Subjects with informed consent;
2. Literate Han Chinese, above the age of 18;
3. At least 6 years of education;
4. Neither normal nor demented according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, with a Clinical Dementia Rating(CDR) ≥0.5 on at least one domain and a global score ≤0.5; a Mini-Menta State Examination score ≥20 (primary school), or ≥24 (junior school or above).[13]
5. having normal vision and hearing with/without corrective devices.

2.2.2 Exclusion criteria

1. Severe aphasia, physical disabilities, or any other factor that might preclude completion of neuropsychological testing.
2. Clinically significant gastrointestinal, renal, hepatic, respiratory, infectious, endocrine, or cardiovascular system disease; cancer; alcoholism; drug addiction.
3. Illnesses affecting mobility or are unable to accept assessments or interventions that are required in this study.

Randomization

Participants will be randomly allocated to either the intervention group or the control group in a ratio of 1:1. After participants have given their informed consent, randomization will be performed by an independent statistician who is blinded to the patient interventions using IBM SPSS Statistics Software following the sequence: Data/select cases/random sample of cases/exact 1 case of the 2 total cases. Afterwards, the sealed randomization codes and intervention number are sent out to each center.

Blinding

Radiologists, statisticians, and neuropsychologists who measure the outcomes will be blinded to the randomization status. Blinding will also be maintained for data management, outcome assessment, and data analysis. Participants and therapists cannot be blinded to the intervention they receive or provide.

Intervention

CCT that is a multi-domain adaptive training program is used in this trial. Training paradigms include processing speed, attention, long-term memory, working memory, flexibility, calculation, and problem solving. To enable adaptive training, each task was designed with several difficulty levels. At the beginning, assignment tasks from these domains will be similar across participants. On each training day, five tasks (2 min per task, each three times, in total 30 min per day) will be assigned. Within each task, high accuracy (>80 %) is required to upgrade. The training is thus also adaptive at participant level, with a similar setup but personalized progress across

participants.

Cognitive training in NLCs, CCT was given twice a week during 1-6 months and once a week during 7-12 month in nursing clinic. There is 60 minutes at a time. All the patients were capable of performing the training under the guidance of APNs. At the same time, according to the caregivers' feedback, APNs will give them the desired care guidance.

Cognitive training in home, CCT was given four times a week during 1-6 months and twice a week during 7-12 month in nursing clinic. There is 30 minutes at a time. Nurses teach patients to acquire and carry out CCT at home during hospitalization. Nurses set the daily reminder function at 9:00am through training system. The data results of each training will be automatically stored in the personal information database in the cloud. And, a training report will be generated, including training difficulty, training results and training time. Nurses can examine patients' training through the cloud.

Cognitive training in tradition, the Home Cognitive Training Manual for Alzheimer's Disease compiled by our research team was distributed. And, the patients and their families were given detailed health education on the definition, clinical manifestations, drug and non-drug treatment, home nursing, the significance of cognitive training and the methods of cognitive training. Meanwhile, we established connection with patients for later follow-up.

2.5 Outcome measures

2.5.1 Neuropsychological assessments

The intervention will be assessed by *the Mini-Mental State Examination (MMSE)* and *the Montreal Cognitive Assessment (MoCA)*, in which scores range from 0 to 30, with higher scores representing better general cognitive performance.[14,15]

The World Health Organization-University of California-Los Angeles Auditory Verbal Learning Test (WHO-UCLA AVLT) which scores range from 0 to 45 will be used to assess memory function, with a higher value representing a better outcome.[16]

The Boston Naming Test (BNT) will be used to assess language performance, specifically visual naming ability.[17]

Instrumental activities of daily living(IADL) and *barthel index* is defined as being whether able to complete activity ability.[18,19]

Hamilton Anxiety rating scale(HARS), *the geriatric depression scale(GDS), the Cohen–Mansfield Agitation Inventory (CMAI)* and *neuropsychiatric Inventory(NPI)* will be used to measure neuropsychiatric symptoms.[20-23]

Zarit caregiver burden interview (ZBI) will be used to assess the burden of caregivers.[24]

2.5.2 Resting EEG

EEG was acquired using a 32-conductor Ag-AgCl electrode cap and amplifier (BioSemi, Amsterdam, Netherlands) with a 2048-Hz sampling rate. To reduce interference during signal acquisition, we ensured that the electrode resistance was<5 kΩ. During data collection, the participants were seated in a comfortable chair,

relaxed, refrained from speech or voluntary movements, and kept their eyes closed. The eyes-closed state was recorded for 5 min, and the data were stored on a computer for offline analysis.

2.5.3 Primary outcome

The primary outcome measure is the score change in MMSE from baseline to the end of the intervention.

2.5.4 Secondary outcome

The secondary outcomes for neuropsychological assessments include the score change from baseline to the 6-month and 12-month after intervention in other scales. The EEG results also dose.

2.6 Data collection

Inclusion and exclusion criteria will be assessed at screening. After written informed consent is acquired, the following data will be collected: demographic data (gender, age, education, and occupation); medical history; concomitant medications; and findings from a complete physical examination and neurological examination. Then, neuropsychological assessments, and EEG will be carried out. The follow-up assessments will be scheduled at 6-month and 12-month after intervention. The study schedule of the trial is shown in Table 1. The study flowchart is presented in Figure 1.

Table 1 Schedule of the trial

	Study period			
Time point	**screening**	**baseline**	**6-month intervention**	**12-month intervention**
Eligibility screen	×			
Informed consent	×			
Randomization		×		
Demographic data		×		
CDR	×			
Assessments				
MMSE	×	×	×	×
MoCA		×	×	×
WHO-UCLA AVLT		×	×	×
BNT		×	×	×
IADL		×	×	×
BI		×	×	×
HARS		×	×	×
GDS		×	×	×
CMAI		×	×	×
NPI		×	×	×
ZBI		×	×	×
EEG		×	×	×

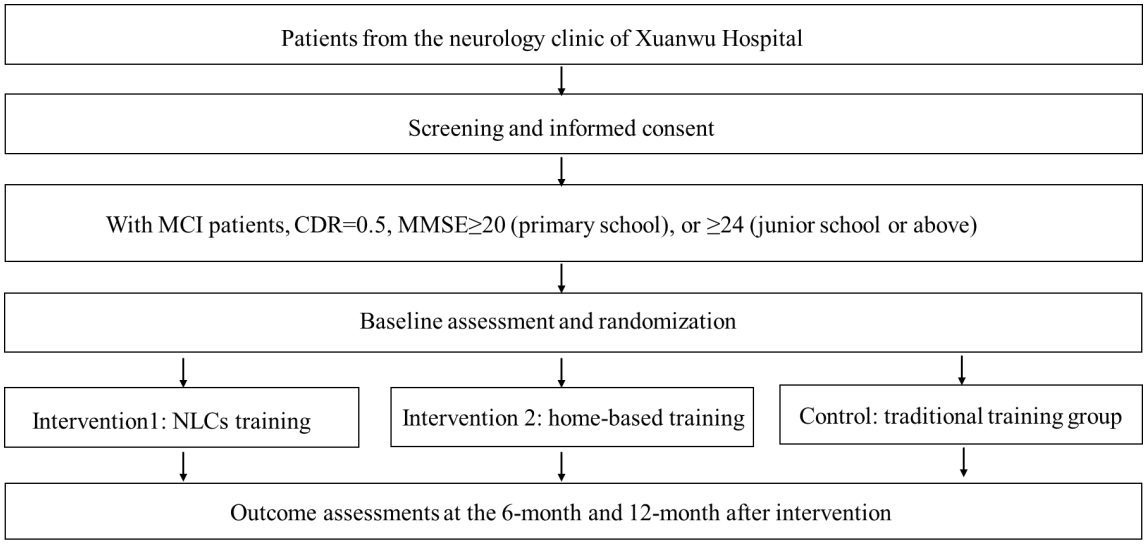

FIGURE 1 The flowchart of this trial

2.7 Data monitoring

The study will comply with the Declaration of Helsinki. The neuropsychological functions of all participants will be evaluated by the same trained neuropsychologists. EEG data will be acquired according to the same parameters and using the same scanner.

2.8 Sample size

There are no published randomized controlled trials on NLCs cognitive training or home-based cognitive training in MCI patients. In our preliminary experiments, the intervention resulted in improvement in MMSE scores (mean: 0.5 vs 0.04). According to these data, to obtain a statistical power of 90% with a significance level of 5%, the sample size needs to be 26 for each group. To allow for a maximum dropout rate of 20%, the sample size is set to 32 participants in each group.

2.9 Statistical analysis

All data will be analyzed according to intent-to-treat principles. Continuous data were reported as means ± standard deviation and were analyzed using one-way ANOVA or Kruskal-Wallis tests as appropriate. Categorical data were presented as frequency and percentages and were analyzed using the chi-squared test. A repeated-measures ANOVA was performed for 3-time points to evaluate the effect of group factors, time factors, and the interaction between time × group on the outcomes variables. A simple effect test was used to examine the difference among groups within each time point and between the 3-time points within each group when the interactions of time × group were significant. All statistical tests were two-sided, and statistical significance was considered at $p < 0.05$.

3 Discussion

The aims behind the introduction of nurse clinics were to contain costs and to better integrate the pathway of care from the acute to the rehabilitative phase,

particularly for shortened hospital stays. In the Irish, nurse clinics were introduced to provide intermediate care to patients discharged from hospital, yet in need of support to regain their maximum health.[25] In Hong Kong, the aim behind the establishment of nurse clinics was in line with the international trend, that is, to enhance continuity of care and access to care and to contain costs.[26] Recovery is often a protracted experience for MCI patients, warranting continuous, comprehensive training to manage cognitive training and support family members. Despite this great need, many patients discharged from an inpatient unit have limited access to outpatient training or comprehensive support. Thus, now more than ever, it is paramount to consider novel approaches to supporting persons training. The idea that NCLs can be established to balance out the rehabilitation technician deficit is not secret knowledge.The proposed study responds to a great need for ongoing professional support and, if successful, will provide evidence regarding an alternative pathway to organizing comprehensive professional support for MCI training.

4 Conclusions

Nurse-led clinics cognitive training has the potential ability to enhance cognitive functions in MCI patients. This single-blind, randomized-controlled trial will verify these effects.

REFERENCES

1. Sanford AM. Mild Cognitive Impairment[J]. Clin Geriatr Med. 2017 Aug;33(3):325-337.
2. Jia L, Du Y, Chu L, et al. Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: a cross-sectional study[J]. Lancet Public Health, 2020, 5(12):e661-e671.
3. Wang Q, Zhang Z, Li L, et al. Assessment of cognitive impairment in patients with Parkinson′s disease: prevalence and risk factors[J]. Clin Interv Aging, 2014, 9:275-281.
4. Benedict R, Amato MP, DeLuca J, et al. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues[J]. Lancet Neurol, 2020, 19(10):860-871.
5. How Many People Have Dementia and What Is the Cost of Dementia Care? Alzheimer's Society. 2019. URL: https://www. alzheimers.org.uk/about-us/policy-and-influencing/dementia-scale-impact-numbers.
6. World Health Organization. Global action plan on the public health response to dementia 2017–2025. 2017; Geneva, Switzerland.
7. Li R, Geng J, Yang R, Ge Y, Hesketh T. Effectiveness of Computerized Cognitive Training in Delaying Cognitive Function Decline in People With Mild Cognitive Impairment: Systematic Review and Meta-analysis[J]. J Med Internet Res. 2022 Oct

27;24(10):e38624.
8. Wang YY, Yang L, Zhang J, et al. The effect of cognitive intervention on cognitive function in older adults with Alzheimer′s disease: a systematic review and meta-analysis[J].Neuropsychol Rev, 2022, 32(2):247-273.
9. Nguyen L, Murphy K, Andrews G. Immediate and long-term efficacy of executive functions cognitive training in older adults: a systematic review and meta-analysis[J]. Psychol Bull, 2019, 145(7): 698-733.
10. Kalbe E, Folkerts AK, Ophey A, et al. Enhancement of executive functions but not memory by multidomain group cognitive training in patients with Parkinson′s disease and mild cognitive impairment: a multicenter randomized controlled trial[J]. Parkinsons Dis, 2020, 2020:4068706.
11. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology[J]. Neurology. 2018 Jan 16;90(3):126-135.
12. Wong FK, Chung LC. Establishing a definition for a nurse-led clinic: structure, process, and outcome[J]. J Adv Nurs. 2006 Feb;53(3):358-69.
13. Chang YL, Bondi MW, McEvoy LK, et al. Global clinical dementia rating of 0.5 in MCI masks variability related to level of function[J]. Neurology. 2011 Feb 15;76(7):652-9.
14. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician[J]. J Psychiatr Res. 1975;12:189-198.
15. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment[J]. J Am Geriatr Soc. 2005;53:695-699.
16. Zhou A, Jia J. A screen for cognitive assessments for patients with vascular cognitive impairment no dementia[J]. Int J Geriatr Psychiatry. 2009 Dec;24(12):1352-7.
17. Bezdicek O, Rosická AM, Mana J, et al. The 30-item and 15-item Boston naming test Czech version: Item response analysis and normative values for healthy older adults[J]. J Clin Exp Neuropsychol. 2021 Nov;43(9):890-905.
18. Graf C. The Lawton instrumental activities of daily living scale[J]. Am J Nurs. 2008 Apr;108(4):52-62; quiz 62-3.
19. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. J Clin Epidemiol. 1989;42(8):703-9.
20. Bruss GS, Gruenberg AM, Goldstein RD, et al. Hamilton Anxiety Rating Scale Interview guide: joint interview and test-retest methods for interrater reliability[J]. Psychiatry Res. 1994 Aug;53(2):191-202.
21. Montorio I, Izal M. The Geriatric Depression Scale: a review of its development and utility[J]. Int Psychogeriatr. 1996 Spring;8(1):103-12.
22. Kupeli N, Vickerstaff V, White N, et al. Psychometric evaluation of the Cohen-Mansfield Agitation Inventory in an acute general hospital setting[J]. Int J Geriatr Psychiatry. 2018 Jan;33(1):e158-e165.

23. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia[J]. Neurology. 1994 Dec;44(12):2308-14.
24. Lu L, Wang L, Yang X, et al. Zarit Caregiver Burden Interview: development, reliability and validity of the Chinese version[J]. Psychiatry Clin Neurosci. 2009 Dec;63(6):730-4.
25. Rosalim JP. Service Provision Study on the Implementation of Nurse-Led Clinic in the Irish Judicial System[J]. J Correct Health Care. 2020 Jul;26(3):258-266.
26. Wiles R, Postle K, Steiner A, et al. Nurse-led intermediate care: an opportunity to develop enhanced roles for nurses?[J] J Adv Nurs. 2001 Jun;34(6):813-21.