

Effect of Vagal Nerve Stimulation on Cognitive Impairment Among Subjects with Anterior Cerebral Artery Syndrome: A Pilot Study

Santhana Lakshmi. S¹, Vignesh Srinivasan², Prathap Suganthirababu³, Priyadharshini Kumar⁴, Dhanusia S⁵, Kumaresan A⁶, Surya Vishnuram⁷

¹Post Graduate, ²Assistant Professor, ^{3,6}Professor, ^{4,5,7}Tutor, Saveetha College of Physiotherapy, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India.

How to cite this article: Santhana Lakshmi. S, Vignesh Srinivasan, Prathap Suganthirababu et. al. Effect of Vagal Nerve Stimulation on Cognitive Impairment Among Subjects with Anterior Cerebral Artery Syndrome: A Pilot Study. Indian Journal of Physiotherapy and Occupational Therapy / Volume 18, Year 2024.

Abstract

Background: Cognitive dysfunction, including impairments in attention, memory, executive function, and processing speed. This study was developed to determine the effectiveness of transcutaneous auricular vagal nerve stimulation on cognitive impairment among subjects with anterior cerebral artery syndrome.

Purpose: The purpose of the study is to compare and evaluate the effectiveness of two non-pharmacological methods of treatment for cognitive impairment patients with ACA syndrome.

Material and Methods: The project was conducted as a pilot study in a private hospital in Chennai. The experimental group (group A) received transcutaneous auricular vagal nerve stimulation for 20 minutes and conventional strengthening exercises for the affected limb for 10 minutes. Group B got conventional cognitive training (20 minutes) and strengthening exercises (10 minutes). Following the four-week treatment, a post-test analysis was performed using the Montreal cognitive assessment scale.

Results: The post-test analysis obtained a mean value of about 27.25 and SD 1.5 for group A, whereas group B revealed 22.75 ± 1.25 , mean \pm SD, and a significant P value of 0.004.

Conclusion: Non-invasive transcutaneous auricular vagal nerve stimulation has been proven to be an effective approach for preventing vascular dementia.

Keywords: Cognition therapy, vascular dementia, electrical stimulation, nerve stimulation

Introduction

Cognitive impairment is seen as a step that occurs between healthy aging and brain cell damage^{1,2}. Cognition is a mental action or a set of phases including learning, comprehension, and the senses. It also involves high cognitive abilities, such as focus, memory storage, decision-making, planning, judgment, and reasoning³.

According to data, there is a 1.8 percent incidence of cognitive impairment in senior adults around the age of 60, a 5.1 percent incidence in those around the age of 70, a 15.1 percent risk in those in their 80s, and a 35.7 percent risk in those in their 90s⁴⁻⁷. Cognitive impairment is caused by various factors, such as any disease process, hereditary factors, mutations in the genes due to poor lifestyles, and nutrition deficits⁸.

Corresponding Author: Vignesh Srinivasan, Assistant professor, Saveetha College of Physiotherapy, Saveetha Institute of Technical and Medical Sciences, Chennai, Tamil Nadu, India.

E-mail: vigneshphysio1989@gmail.com

If the frontal lobe is damaged, the patient will have difficulty planning and understanding. Injury to the parietal lobe manifests as a decrease in dressing ability and visual-spatial function. When the temporal lobe is involved, language and memory issues arise³. To be more precise, cognitive impairments are seen following an acute ischemic stroke, which is due to atherosclerosis of the large artery. The cognitive decline resulting in dementia following brain infarcts is collectively called multi-infarct dementia⁸. More evidence points to the probability that Alzheimer's disease may emerge as a result of vascular cognitive impairment⁹. Post-stroke cognitive impairment is linked to demographic and vascular origin variables such as age, education, and job¹⁰.

Typical ACA infarct symptoms include changed mental status, verbal fluency issues, incontinence, reduced responsiveness, and a difficulty or desire to communicate¹¹. Focus, executive function, memory storage, and visuomotor speed limitations are signs of the gradual cognitive decline caused by cerebrovascular disease¹². Damage to the brain parenchyma, including hyperintensities of white matter in radiological data and the improper functioning of perforating arterioles, venules, and capillaries, are features of vascular cognitive impairment¹³. It ultimately became clear that a systematic strategy was needed for investigating people with cognitive impairment. The examination, radiological tests, and laboratory testing all contribute to a thorough assessment of cognitive impairment. A diagnosis is made to evaluate the severity of the impairment and the source of the cognitive deficit⁴.

The Montreal Cognitive Assessment (MoCA) is a screening exam used to evaluate mild cognitive impairment in the elderly. When compared to another commonly used cognitive evaluation test, two possible benefits of MoCA are the evaluation of execution abilities and the presence of more complex visual building task¹⁴.

The intervention for cognitive impairment is expected to focus on the relationship between neuronal activity/neurovascular coupling and blood vessels, the organization of molecular clearance and leukocyte trafficking, the related macroscopic waste clearance system, and the function of the blood-brain barrier¹⁵. Non-pharmacological cognitive impairment

management aims to address a broad variety of disciplines that improve cognition, behavior, mood, and psychological symptoms. According to authors, treatments are classified into four types: holistic approaches, cognitive methods, alternative approaches, and short psychotherapy^{16,17}.

Non-pharmacological intervention is found to be more effective than the pharmacological treatment method in treating cognitive decline¹⁸. Transcutaneous auricular vagal nerve stimulation (taVNS) has been proven to be effective in improving cognition in patients with cognitive impairment. The Food and Drug Association authorized vagus nerve stimulation at the cervical level as a therapy for refractory epilepsy in 1997, and it was approved as a longer-term treatment for refractory depression in 2005¹⁹.

Despite its effectiveness, the surgical strategy of vagal nerve stimulation has significant technical challenges and, as a result, a limited spectrum of usage. As a result, non-invasive vagus nerve stimulation was developed. The two non-invasive treatments employed were stimulating the ear and applying superficially to the cervical nerve^{20, 21}. The aim of this study is to determine the effectiveness of transcutaneous auricular vagal nerve stimulation on cognitive impairment in anterior cerebral artery syndrome.

Aim

To analyze the effect of transcutaneous auricular vagal nerve stimulation on cognitive impairment among subjects with anterior cerebral artery syndrome.

Material and Methods

The research project was conducted as a pilot study in a private hospital in Chennai to investigate the efficacy of transcutaneous auricular vagal nerve stimulation in improving cognitive abilities in patients with anterior cerebral artery syndrome. A private college's Scientific Study Board approved a human population study in line with all applicable laws and regulations (01/027/2022/ISRB/PGSR/SCPT). Following a thorough description of the procedure, individuals were selected from the private hospital with their signed consent. There was

blinding of both the participant and the evaluated participant involved in this study. The study duration is from January 2023, and treatment sessions began in February 2023 for four weeks.

Selection criteria: Eight participants were selected, representing both genders, based on the following eligibility criteria: **Inclusion criteria:**

- Participants with ACA syndrome,
- Participants with a pre-test Montreal cognitive assessment scale score of less than 25, were eligible to participate.

Exclusion criteria:

- Participants who had a history of various neurological diseases,
- recent injuries, mental instability,
- lack of interest in participating in the study were excluded.

Outcome measure: A fast screening assessment tool, the Montreal Cognitive Screening, was developed to identify MCI in elderly people. MoCA is a 30-point test that can be finished in under 10 minutes and evaluates a number of skills, including execution, short-term recall of memory, visuospatial abilities, focus, concentration, memory of work, language, and time and space orientation. MoCA has a Cronbach's Alpha of 0.715, which indicates strong internal consistency. At a cutoff of 26, the MoCA area under the curve has a sensitivity of 97.8%, a specificity of 67.2%, and a 95% confidence interval of 0.672-0.849 [22].

Procedure

The participants were separated into two groups, A and B, using the closed envelope method. Both groups received 30-minute therapy sessions three days a week for four weeks. The experimental group (group A) received transcutaneous auricular vagal nerve stimulation for approximately 20 minutes (30 seconds ON and 5 minutes OFF), with clip electrodes placed on the Cymba concha of the left ear at a frequency of 25 Hz, amplitude: 1 mA, pulse width: 330 s, and conventional strengthening exercises for the affected hemiparetic limb for 10 minutes. Group B got conventional cognitive training (20 minutes) and strengthening exercises (10 minutes). Following the four-week treatment period, a post-test analysis was

performed using the Montreal cognitive assessment scale.

Data analysis

A statistical analysis was done with the Intention of treating the cognitive impairment after the stroke (ACA syndrome). Pre- and post-test values for MOCA were noted. A paired t-test was used for within-group analysis, and a Mann-Whitney U test was used for between-group analysis.

Table 1: Baseline characteristics of population included.

CHARACTERISTICS	GROUP A	GROUP B
AGE (mean \pm SD)	43.25 \pm 2.38	44.5 \pm 2.29
DURATION (mean \pm SD)	7.75 \pm 1.47	7.82 \pm 1.11
MoCA	20.25 \pm 2.38	20.25 \pm 1.47

Table 2: Pre and Post-test comparison of Group A (taVNS)

Group A	MEAN \pm SD	t value	p value
Pre-test	20.25 \pm 2.75	-9.89	0.002
Post-test	27.25 \pm 1.5		

Table 3: Pre and post-test comparison of Group B (conventional cognitive training).

Group A	MEAN \pm SD	t value	p value
Pre-test	27.25 \pm 1.5	4.7	0.018
Post-test	22.75 \pm 1.25		

Table 4: post-test comparison of both Group A and B (taVNS and Conventional cognitive training).

PARAMETRICS	Mean \pm SD	t value	p value
Group A	27.25 \pm 1.5	4.59	0.004
Group B	22.75 \pm 1.25		

Results

The collection of data began in January 2023, and treatment sessions began in February 2023 for four weeks. Following the treatment phase, the post-test analysis was carried out using the Montreal Cognitive Assessment.

The statistical analysis of the study revealed a significant p value of less than 0.004 (Table 4) for

those who underwent transcutaneous auricular vagal nerve stimulation in addition to conventional strengthening training. Both groups had the same baseline characteristics in the pre-test (Table 1).

MoCA testing was done on both Group A and B before the therapy started. Group A underwent conventional strengthening training for 10 minutes each week for four weeks while also receiving transcutaneous auricular vagal nerve stimulation for 20 minutes. The patient's post-test analysis then made use of the same outcome. The data collected before and after the treatment was recorded, and the paired t-test was used to look into the difference. The statistical analysis shows that $P = 0.002$ is significant (Table 2).

Group B received standard cognitive training and muscle-strengthening exercises. The paired t-test was used to examine the differences between the data acquired before and after the test. With a p value of 0.018, it also showed statistical significance (Table 3).

On comparing, the post-test values obtained in both group A and B was analyzed using Mann-Whitney U test and it revealed a statistically significant p value of 0.004 (Table 4).

Discussion

The study aimed to find out the effectiveness of transcutaneous auricular vagal nerve stimulation on cognitive impairment in ACA syndrome. There are various complications that occur following a stroke. Post-stroke cognitive impairment is common in stroke survivors and has a negative impact on their health. Stroke-related cognitive impairment is usually accompanied by other disorders, such as depression²³. The most uncommonly addressed area of cognitive decline that requires substantial attention in order to avoid dementia is cognitive decline of vascular origin. Clancy U. et al. conducted research on cognitive damage caused by small vessel disease, the neuropsychiatric symptoms of small vessel disease as an indication of cognitive impairment. The research discovered a progression in white matter hyperdensities linked to neuropsychiatric symptoms²⁴.

Looking into the available therapeutic methods or preventive measures for vascular dementia, we

studied certain studies that discussed the management of cognitive impairment. The pharmaceutical intervention included the administration of donepezil, galantamine, and rivastigmine, as well as cholinesterase inhibitors. An author conducted a double-blind trial in 2003 with a focus on vascular cognitive impairment and discovered the significant effect of donepezil on cognition. However, there was still a discrepancy in global cognitive functioning^{25,26}. In 2010, Similarly others attempted to develop preventive strategies for post-stroke cognitive impairment. The author observed that there is no obvious treatment option for preventing post-stroke cognitive decline. The author suggests that further study is needed to develop a clear strategy for preventing cognitive loss after a stroke²⁷.

Because there was not much significance to be found in pharmaceutical therapy, a special emphasis was placed on the non-pharmacological approach to cognitive impairment. Berg-Weger M. et al., 2017 revealed evidence-based non-pharmacological therapy to be a cost-effective therapeutic strategy with no adverse effects. Stimulation therapy has been shown to be more effective in terms of improving cognition and quality of life¹⁸.

In addition to this, there is another emerging effective non-invasive therapeutic method for improving cognitive function: transcutaneous auricular vagal nerve stimulation, a modulating method that uses electrical stimulation to stimulate the branch of the afferent vagal nerve. taVNS differs from transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). Boon P. et al. investigated the effect of vagal nerve stimulation on cognition in 2006. The author concluded that vagal nerve stimulation is a potential therapy in the management of cognitive decline after analyzing the literature on the effect of vagal nerve stimulation on cognition²⁸. On the other hand, Ruhnau P. et al., in 2021, studied the effect of transcranial auricular vagus nerve stimulation in combination with ear-EEG. The author found that this closed-loop combination of taVNS and ear-EEG has been demonstrated to be a supportive device for the healthy population as well as a potential tool for the treatment of neuropsychiatric illnesses. The author also recommended that future studies concentrate on maximizing the long-term efficacy of taVNS²⁹.

As a result, we decided to administer the effective therapeutic technique taVNS to patients who were diagnosed with ACA syndrome—cognitive decline. We had a desire to conduct an experimental investigation to determine the efficacy of non-invasive vagal nerve stimulation, which would reduce the danger of adverse effects. Prior to that, we decided to take a chance and perform this pilot research to see if transcutaneous auricular vagal nerve stimulation improved cognitive ability.

The Montreal Cognitive Assessment Scale (MoCA), the most reliable and precise tool for detecting mild cognitive impairment, was employed as the outcome measure in this study. MoCA was used for both the pre- and post-test analyses. In 2021, research compared the MoCA with the Oxford Cognitive Screen, finding that the Oxford Cognitive Screen was not any better at detecting cognitive impairment in post-cognitive impairment than the MoCA³⁰.

Since this study was self-funded, authors haven't performed any quantitative analysis, like biological markers. The study is unique since it addressed the population's post-stroke cognitive loss and vascular dementia by providing a special non-invasive, efficient, and safer treatment approach. This research helps in the prevention of dementia in people with cognitive impairment.

Conclusion

According to the results of the current study, non-invasive vagal nerve stimulation performed trans-auricularly resulted in a greater improvement in cognitive function than conventional cognitive training, with a significant value of $p = 0.004$. Participants who underwent conventional cognitive training also showed improvement. But when comparing the two groups, those in group A who received transcutaneous auricular vagal nerve stimulation showed a more significant improvement in treating the cognitive symptoms of ACA syndrome.

Ethical clearance: The ISRB committee of a private hospital and institution in Chennai has provided its clearance for the conduct of human research that complies with all applicable national laws, institutional regulations. (Application Number

01/027/2022/ISRB/PGSR/SCPT).

Funding: none

Acknowledgements: The author would like to express their sincere thanks to the study participants, the authors whose works are referenced and cited in our manuscript, and the creators of the MoCA.

Conflict of interest: The authors state that there is no conflict of interest.

References

1. Patel RM, Singh US. Prevalence study of cognitive impairment and its associated sociodemographic variables using mini-mental status examination among elderly population residing in field practice areas of a medical college. *Indian journal of community medicine: official publication of Indian Association of Preventive & Social Medicine*. 2018 Apr;43(2):113.
2. Burns A, Zaudig M. Mild cognitive impairment in older people. *Lancet*. 2002; 360:1963-5.
3. Blanchette I, Richards A. The influence of affect on higher level cognition: A review of research on interpretation, judgement, decision making and reasoning. *Cognition & Emotion*. 2010 Jun 1;24(4):561-95.
4. McCollum L, Karlawish J. Cognitive impairment evaluation and management. *Medical Clinics*. 2020 Sep 1;104(5):807-25.
5. Hu C., Yu D., Sun X., et al. The prevalence and progression of mild cognitive impairment among clinic and community populations: a systematic review and meta-analysis. *Int Psychogeriatr*. 2017;29(10):1595-1608.
6. Petersen RC, Lopez O, Armstrong MJ, Getchius TS, Ganguli M, Gloss D, Gronseth GS, Marson D, Pringsheim T, Day GS, Sager M. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018 Jan 16;90(3):126-35.
7. Cao Q., Tan C.C., Xu W., et al. The prevalence of dementia: a systematic review and meta-analysis. *J Alzheimers Dis*. 2020;73(3):1157-1166.
8. Deary IJ, Corley J, Gow AJ, Harris SE, Houlihan LM, Marioni RE, Penke L, Rafnsson SB, Starr JM. Age-associated cognitive decline. *British medical bulletin*. 2009 Dec 1;92(1):135-52.

9. Erkinjuntti T. Cerebrovascular Dementia: Pathophysiology, Diagnosis and Treatment. *CNS Drugs* 1999;12:35-48
10. Sun JH, Tan L, Yu JT. Post-stroke cognitive impairment: epidemiology, mechanisms and management. *Annals of translational medicine*. 2014 Aug;2(8).
11. Al-Qazzaz NK, Ali SH, Ahmad SA, Islam S, Mohamad K. Cognitive impairment and memory dysfunction after a stroke diagnosis: a post-stroke memory assessment. *Neuropsychiatric disease and treatment*. 2014;10:1677.
12. Park H, Jeong YS, Lee SH, Jang SH, Kwon DH, Hong JH, Sohn SI, Yoo J. Clinical prognosis of isolated anterior cerebral artery territory infarction: a retrospective study. *BMC neurology*. 2021 Dec;21(1):1-9.
13. Boomsma JM, Exalto LG, Barkhof F, Leeuwis AE, Prins ND, Scheltens P, Teunissen CE, Weinstein HC, Biessels GJ, van der Flier WM. Vascular Cognitive Impairment and cognitive decline; a longitudinal study comparing different types of vascular brain injury-The TRACE-VCI study. *Cerebral Circulation-Cognition and Behavior*. 2022 Jan 1;3:100141.
14. Clancy U, Ramirez J, Chappell FM, Doubal FN, Wardlaw JM, Black SE. Neuropsychiatric symptoms as a sign of small vessel disease progression in cognitive impairment. *Cerebral Circulation-Cognition and Behavior*. 2022 Jan 1;3:100041.
15. Howland RH. Vagus nerve stimulation. *Curr Behav Neurosci Rep* 1, 64-73.
16. Hainsworth AH, Elahi FM, Corriveau RA. An introduction to therapeutic approaches to vascular cognitive impairment. *Cerebral Circulation-Cognition and Behavior*. 2021 Jan 1;2:100033.
17. Cammisuli DM, Danit S, Bosinelli F, Cipriani G. Non-pharmacological interventions for people with Alzheimer's disease: A critical review of the scientific literature from the last ten years. *Eur Geriatr Med*. 2016;7:57-64.
18. Berg-Weger M, Stewart DB. Non-pharmacologic interventions for persons with dementia. *Missouri medicine*. 2017 Mar;114(2):116.
19. Wang L, Zhang J, Guo C, He J, Zhang S, Wang Y, Zhao Y, Li L, Wang J, Hou L, Li S. The efficacy and safety of transcutaneous auricular vagus nerve stimulation in patients with mild cognitive impairment: A double blinded randomized clinical trial. *Brain stimulation*. 2022 Nov 1;15(6):1405-14.
20. Yuan H, Silberstein SD. Vagus nerve and vagus nerve stimulation, a comprehensive review: part I. *Headache* (2016) 56(1):71-8. doi:10.1111/head.12647
21. Kong J, Fang J, Park J, Li S, Rong P. Treating depression with transcutaneous auricular vagus nerve stimulation: state of the art and future perspectives. *Frontiers in psychiatry*. 2018 Feb 5;9:20.
22. Thomas PE, Adhikari P, Kotian S. Validity and Reliability of Montreal Cognitive Assessment and Its Comparison with the Translated Hindi Mental Status Examination in a South Indian Geriatric Population. *Indian Journal of Public Health Research & Development*. 2018 Mar 1;9(3).
23. El Husseini N, Katzan IL, Rost NS, Blake ML, Byun E, Pendlebury ST, Aparicio HJ, Marquine MJ, Gottesman RF, Smith EE, American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Radiology and Intervention; Council on Hypertension; and Council on Lifestyle and Cardiometabolic Health. Cognitive Impairment After Ischemic and Hemorrhagic Stroke: A Scientific Statement From the American Heart Association/American Stroke Association. *Stroke*. 2023 Jun;54(6):e272-91.
24. Clancy U, Ramirez J, Chappell FM, Doubal FN, Wardlaw JM, Black SE. Neuropsychiatric symptoms as a sign of small vessel disease progression in cognitive impairment. *Cerebral Circulation-Cognition and Behavior*. 2022 Jan 1;3:100041.
25. Sun JH, Tan L, Yu JT. Post-stroke cognitive impairment: epidemiology, mechanisms and management. *Annals of translational medicine*. 2014 Aug;2(8).
26. Wilkinson D, Doody R, Helme R, et al. Donepezil in vascular dementia: a randomized, placebo-controlled study. *Neurology* 2003;61:479-86
27. Ankolekar S, Geeganage C, Anderton P, Hogg C, Bath PM. Clinical trials for preventing post stroke cognitive impairment. *Journal of the neurological sciences*. 2010 Dec 15;299(1-2):168-74.
28. Boon P, Moors I, De Herdt V, Vonck K. Vagus nerve stimulation and cognition. *Seizure*. 2006 Jun 1;15(4):259-63.
29. Ruhnau P, Zaehle T. Transcranial auricular vagus nerve stimulation (taVNS) and ear-EEG: potential for closed-loop portable non-invasive brain stimulation. *Frontiers in human neuroscience*. 2021 Jun 14;15:699473.
30. Brambilla M, Cerasetti M, Pepe F, Pini E, Pomati S, Magni E, Berlingeri M, Pantoni L. Comparison of Oxford Cognitive Screen and Montreal Cognitive Assessment feasibility in the stroke unit setting. A pilot study. *Cerebral Circulation-Cognition and Behavior*. 2021 Jan 1;2:100021.