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Protocol

Effect of enhanced external counterpulsation on heart rate variability in ischemic stroke patients: a pre-and post-interventional study protocol

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ABSTRACT

Background: Stroke is a prominent cause of mortality as well as disability globally. More than 40% of stroke survivors experience complications that last a lifetime. Following an ischemic stroke (IS), abnormalities in the autonomic nervous system (ANS) may influence the probability of another stroke and the healing process. Enhanced external counterpulsation (EECP) is a safe, effective, non-invasive treatment method that enhances blood circulation to the brain and manages ischemic cardiovascular and cerebrovascular diseases. There is a limited amount of literature exploring the effects of EECP on HRV specifically on stroke patients. Hence, the study aims to determine the impact of EECP on HRV in IS patients.
Methods: This single arm pre and post intervention study recruits 35 out of 45 subjects. The intervention will be given 5 days/week/45 minutes a session for 35 sessions. Pre-and post-intervention outcome measures will be measured. After collecting the data, statistical analysis will be done.
Conclusion: The application of EECP may be unlikely to cause any adverse effects in ischemic stroke patients, indicating that EECP may be a safe and effective treatment to improve hand grip strength and QOL in ischemic stroke patients.
Trial registration: Clinical trials (CTRI): CTRI/2023/11/060112.

Keywords: Ischemic stroke, Heart rate variability, Enhanced external counter pulsation, Autonomic dysfunction

INTRODUCTION

Stroke is a prominent cause of mortality and permanent disability globally, with over 40% of stroke survivors enduring lifelong complications. Annually, more than 7.6 million new cases of ischemic stroke occur. Cardiovascular events cause the majority of stroke-related fatalities, and 11% of stroke survivors are expected to experience another stroke within a year. These statistics place a heavy burden on public health.[1,2] People who have had a stroke frequently experience physical issues related to autonomic abnormalities, which limit their ability to perform activities of daily living (ADLs), decreased balance, and impairments in motor, sensory, and cognitive functions. The onset and progression of cerebrovascular disease (CVD) are inextricably related to the function of the (ANS) autonomic nervous system.

Autonomic dysfunction, reported in 25% to 76% of acute stroke patients, is regarded as a common risk factor within the stroke population.[2-5] The resurgence of homeostasis may exceed the ANS's capacity for adaptation, however, the precise pathophysiological mechanisms which entail an elevation of sympathetic activity and a reduce the vagal tone remain unclear.[4,6]

These changes may be attributed to brain lesions affecting the brain stem, the frontoparietal cortical areas, and the descending pathways. Notably, the middle cerebral artery contains the insular cortex, which is crucial for controlling the ANS.[6] In a recent study, the ANS function and HRV are associated with outcomes in individuals who have suffered distinct types of strokes. The researchers found that damage to the insular cortex was more common in large artery atherosclerotic infarcts than in lacunar infarcts.[7]

The vagus nerve, a vital component of the parasympathetic nervous system, establishes an intricate autonomic network between the central nervous system (CNS) and various peripheral organs. It is crucial in regulating energy metabolism and managing physiological or pathological processes like stroke. By linking several brain regions, the vagus nerve facilitates integration and responds appropriately to stimuli, and the heart and the brain have a reciprocal impact on hemodynamic and electrical connection.[8]

Epinephrine and non-epinephrine mechanisms can potentially harm the heart in 2 ways by altering the blood flow in cardiac arteries and directly affecting cardiac myocytes through activation of the beta 1-adrenergic receptor. In a recent study, the ANS function and HRV were associated with outcomes in individuals who had suffered distinct types of strokes. The researchers found that damage to the insular cortex was more common in large artery atherosclerotic infarcts than in lacunar infarcts.[7]

HRV acts as a dynamic, non–invasive marker for ANS function. Time-domain & frequency-domain indices of HRV evaluate the degree of variability in IBI (Inter beat interval) data and estimate absolute or relative power distribution into four frequency bands, respectively.[9] Numerous studies have shown that individuals with diminished or abnormal HRV are more likely to experience disability, post-stroke death, and other health problems.[10] According to Lakusic et al, the HRV is affected immediately following a stroke and may continue to be changed for a few months.[11]

A non-invasive aided circulation technique called enhanced external counter pulsation (EECP) treats and rehabilitates ischemic cerebrovascular and cardiovascular illnesses. The EECP device, synchronized with the R wave of the electrocardiograph (ECG), sequentially inflates cuffs that cover the lower leg, thigh, and hip of the patient. This inflation occurs from the bottom to the top. By inflating the cuffs during diastole, the arterial system of the lower body is compressed, thus restoring blood flow to the upper body and increasing blood circulation to vital organs such as the heart, brain, and others. This process boosts cardiac output and stroke volume, ultimately increasing the volume of blood returning to the heart. During the systolic phase of the heart, the three-stage cuffs are deflated simultaneously, reducing the resistance to ejecting blood from the heart.[12,13]

There is not enough evidence on the impact of EECP on HRV in stroke patients. Previous research indicates that EECP has a favourable impact on HRV in sub-acute stroke patients.[14] As a consequence; further study is needed to evaluate the long-term effects of EECP on HRV. Therefore, this study aims to investigate the effects of enhanced external counter-pulsation on heart rate variability in stroke patients.

METHODS

In this single-arm pre-and post-intervention study, a total of 35 ischemic stroke patients (Confirmatory diagnosis for Ischemia will be taken by CT scan & MRI Scan) will be recruited from the Srinivas Institute of Physiotherapy, Mangalore, Karnataka. The inclusion criteria will be: first-ever ischemic stroke; based on an Age-appropriate SDNN value; ages between 20 and 65 years old; both genders will be recruited after signing informed consent.[15-18] Those with any of the following will be excluded from the study: previous CVA history; history of brain tumour; history of cardiovascular diseases; duration of diabetic mellitus; history of diabetic neuropathy; history of any kidney or liver diseases; history of PVD; history of active thrombophlebitis; sustained hypertension (systolic >180 mm Hg or diastolic >100 mmHg); Apraxia and (k) patients who are under medication of beta-blockers, anticholinergic, muscle relaxants, antiadrenergic, and diuretics drugs.[14,18,19]

Eligible participants who meet the predefined inclusion and exclusion criteria will be carefully chosen for study inclusion. Written informed consent will be obtained before their involvement to ensure their voluntary participation. The demographic information (i.e., age, gender, dominancy of hand, and other details) will be collected from all selected subjects. All the subjects will be briefly explained about the procedure, and then the treatment will be given to the patients. After, collecting the data, statistical analysis will be done (Figure 1).

Study duration

The study duration was of 22 months from August 2023 to May 2025.

Sample size

The sample size was calculated using the formula,

$$N = \frac{Z_{\alpha}^2 \sigma^2}{d^2}$$

where, Z α =1.96 at a 95% confidence level, σ =Standard deviation =15, X =Mean = 40.9, d =10% of the mean.

With a 95% confidence level and 90% power concerning the below-mentioned article by Xiong et al, the sample size comes to be 35 participants. With a 20% dropout sample size comes to be 42 participants.[18]

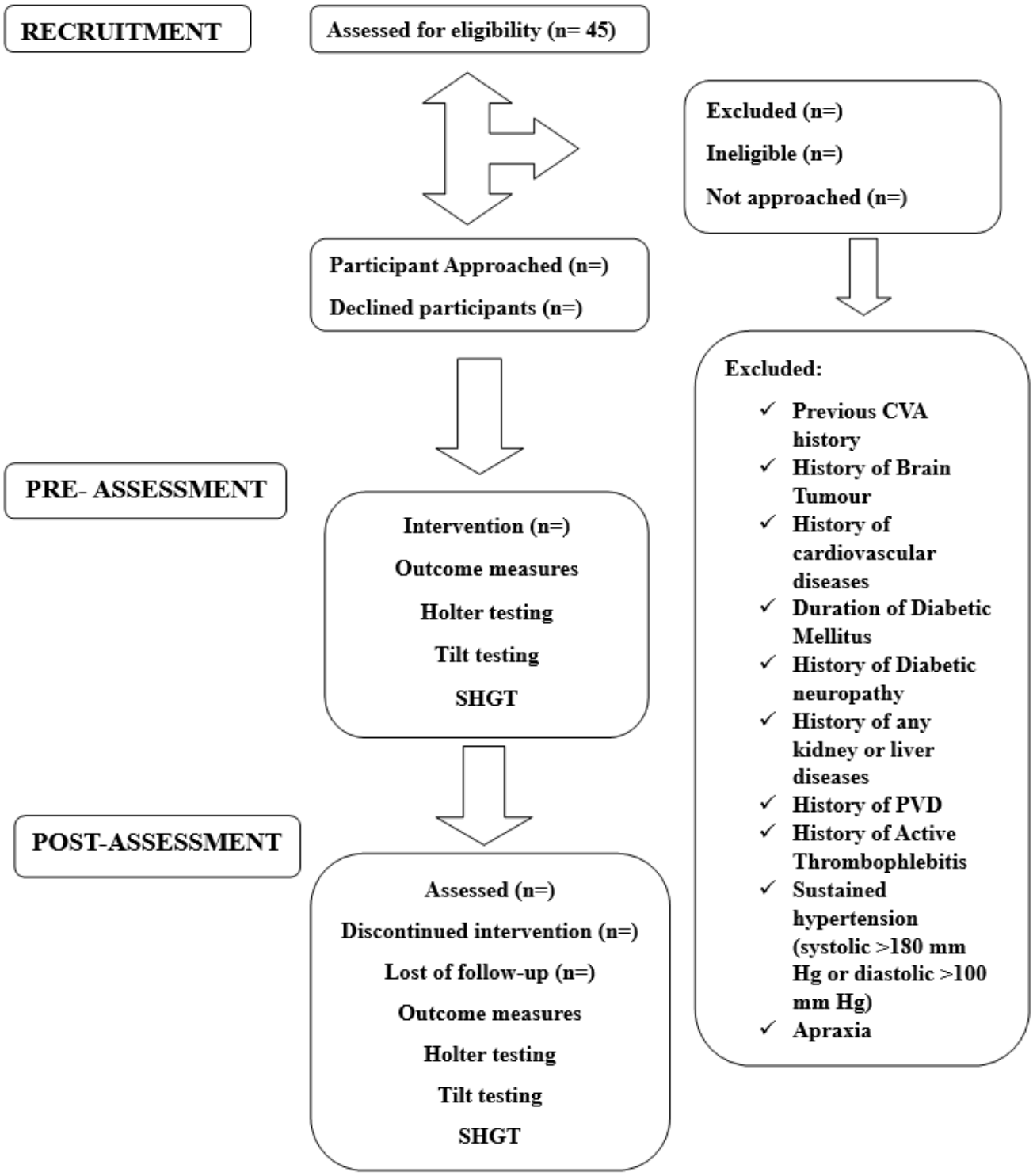

Figure 1: Modified consort flow chart for pre- and post-interventional study.

EECP intervention

The intervention will be administered to all patients for 45 minutes daily with a frequency of 5 sessions/week for a period of 7 weeks with a cuff inflation pressure of 150 mmHg using the EECP system (RIYATI MEDIQUIP PVT.LTD) (Figure 2 and 3).[19,20]

Before implementing the intervention, the baseline data will be collected for all the outcome measures. The patients will be positioned in a supine (lying face-up) position. Digital Holter ECG (BPL Version A) leads will be placed on the patient's chest and 3 sets of inflatable cuffs will be wrapped tightly around the calf, thigh, and hip regions. These cuffs will be connected to air hoses. The inflation pressure will start at a low level and

gradually increase to the target range. Holter ECG will record both heart rate variability (HRV) & heart rate (HR) simultaneously (Figure 2 and 3). Conservative physiotherapy treatment will be continued according to the prescribed plan by the physiotherapist. Follow-up will be done after 1 and 3 months.

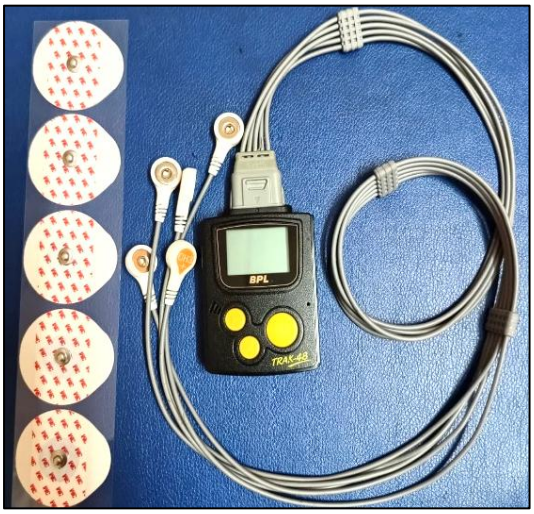

Figure 2: Holter device with 5 ECG leads.

Figure 3: EECP system (Riyati Medi Quip Pvt. Ltd).

Outcome measures

Holter testing

The 5-lead ECG system requires placing electrodes as follows: the white lead below the right clavicle, the black lead below the left clavicle, the red lead on the left side of the abdomen below the ribcage, the green lead on the right side of the abdomen below the ribcage, and the brown lead in the 4th intercostal space to the right of the sternum. Attach the corresponding lead wires to the Holter monitor, turn it on, and verify it is recording correctly (Figure 4). Baseline data will be recorded for 30 minutes in a resting position upon admission, serving as pre-intervention data. After completing the treatment, another ECG recording will be taken at the end of 35 sessions for post-intervention analysis.

Figure 4: Application of EECP intervention.

Tilt testing

The digital sphygmomanometer (Omron's HEM 7124) blood pressure sensor will be properly placed during a tilt test to ensure accurate measurement. Baseline blood pressure will be measured from the brachial artery. The patient can rest comfortably for 5-10 minutes before proceeding.[21] Then, the patient will smoothly transition from a supine position to a 70-degree tilt position within 5-10 seconds. Throughout the 10-minute test duration, the patient's blood pressure will be continuously monitored and recorded every minute using a digital sphygmomanometer (Omron's HEM 7124). If the patient experiences any discomfort such as dizziness, chest pain, or shortness of breath, the treatment will be terminated. If there are no obvious abnormalities, the procedure will continue. When the test is over, the patient will be gently tilted back to the original position (Figure 5).

Figure 5: 70⁰ tilt position.

Sustained hand grip test

The patient will be instructed to initially hold the JAMAR hand dynamometer with their dominant hand as hard as possible for a few seconds. Afterward, they will be asked to sustain the grip steadily at 30 percent of their T_{max}. For up to five minutes. During the test, a digital sphygmomanometer will be used to continuously monitor blood pressure on the non-exercising arm. The diastolic blood pressure (DBP) will be recorded just before releasing the handgrip. To determine the index of DBP response to the Sustained Handgrip test, the difference between the DBP just before release and the average of three resting DBP readings (Figure 6).

Figure 6: SHGT in a sitting position.

Timeline of this trial

Ethical approval was obtained on - 16th August 2023, CTRI Registered on–22nd November 2023. 1st Enrolment of the patient was done on–5th December 2023. Completion of Trial will be on–31st May 2025.

Data analysis

Evaluation of the data will be performed using the SPSS statistic version 25.0. The normality of the data will be analyzed using the Shapiro-Wilk test. If the data is normally distributed then repeated measure ANOVA will be used, if contrary, the Friedman test's non-parametric test will be used to demonstrate the statistical significance. $p<0.05$ and CI 95% will be considered statistically significant.

DISCUSSION

The EECP program represents the first brief standard protocol that combines various advantages with physical health, aimed at enhancing autonomic function in individuals with ischemic stroke. It involves the interaction of cardiac parameters during EECP intervention, which will influence heart-brain axis control.[14] This research will explore how the intervention can be applied to patients with neurological disorders, its impacts on HRV, and its influence on the grip strength of the affected individual.

Initially, when application of EECP, there are no undesirable or alarming changes in HRV and related physiological responses. Additionally, without compromising the hemodynamic response EECP might be beneficial in improving the neuromuscular function. Moreover, the physiological modifications may increase cerebral perfusion, enhance collateral circulation, oxygen supply to affected tissues in the brain, autonomic modulation, and blood pressure stability, all of which will contribute to an overall improvement in the QOL for stroke patients.

Aerobic training, exercise therapy, and biofeedback training can improve cardiac health through HRV, but optimal exercise regimens and long-term effects on ANS stimulation in stroke patients remain unclear.[23-25] A Hong Kong study on 155 individuals with ICAD found that EECP predicted favourable outcomes after three months.[26] In 2017, Li Xiong et al. showed the beneficial effects of EECP on HRV in sub-acute stroke patients, though the study used only 3 minutes of EECP instead of the standard 35 sessions.[18] The study's strength includes the use of validated assessment tools and a thorough explanation of the study design. The wealth of information gathered will offer important new understandings about how EECP impacts HRV in ischemic stroke patients. The individualized conservative care plan will be administered under supervision. Research can shed light on the intricate relationship between the brain-heart axis. Improving autonomic function can help individuals avoid difficulties following a stroke and potentially lead to better physical health.[27]

Our intervention has some limitations, including the possibility that the expected small size may be insufficient to identify changes in the brain and the absence of an active control group because this is the first promising protocol that aims to assess the feasibility of the intervention. Therefore, further RCTs are required for high-quality research.

CONCLUSION

The application of EECP may be unlikely to cause any adverse effects in ischemic stroke patients, indicating that EECP may be a safe and effective treatment to improve hand grip strength and QOL in ischemic stroke patients.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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