The Efficacy of Non-invasive Brain Stimulation on Cognitive Functions in Patients with Chronic Obstructive Pulmonary Disease: Double-Blinded Randomised Controlled Trial

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1. Introduction

1.1. Literature review

Chronic obstructive pulmonary disease (COPD) is a condition of diverse respiratory disorders exhibiting symptoms like sputum production, coughing and dyspnoea due to lung structural abnormalities.(1) In 2019, almost 455 million people received a diagnosis of COPD, which is considered a serious illness with a high death rate.(2) In addition to respiratory abnormalities, COPD can also develop non-respiratory diseases like cognitive impairment (CI), according to multiple studies.(3-5) Cognitive impairment is a disorder that significantly impairs a person's capacity to perform basic or complex tasks because of multiple deficiencies in cognitive function areas, including motor function, attention, memory, executive processes, language, and visuospatial function.(6) Approximately 36% of patients with COPD have CI, compared to 16.7% of healthy people with similar characteristics; as a result, the morbidity rate from CI is greater in COPD patients than in healthy people.(7) A meta-analysis found that because COPD patients with CI demonstrated poorer disease management and functional capacities, their socioeconomic burdens and mortality rates were higher.(8) According to a different meta-analysis including 14 studies, almost one in four individuals with COPD had mild cognitive impairment (MCI), and roughly 32% have CI.(9) It is yet unknown what causes CI in COPD. COPD may cause many physiological alterations, including hypoxia, systemic inflammation, and hypercapnia, that hasten cognitive ageing.(10) Nonetheless, research indicates that regardless of their hypoxemic state, people with COPD have reduced cognitive performance.(11) According to the researchers, CI may have detrimental effects on the treatment of patients with COPD, including influencing patients' compliance with therapy and their ability to use inhalation devices correctly.(12)

In patients with COPD, early intervention and management are important to improve their CI.

1.2. Gap of literature

Even though it's crucial to offer the proper intervention to enhance CI in patients with COPD, a conflict arises regarding interventions that can substantially improve their condition. According to specific research using PR as an intervention, cognitive skills significantly improved only in COPD patients with CI, while those without CI showed no discernible change.(13, 14) On the other hand, Andrianopoulos et al. demonstrated that COPD patients' cognitive performance improved significantly after PR, whether they had CI or not.(15) Potential causes of the conflicting results of PR's ability to improve cognitive function include variations in PR methods, patient demographics, or cognitive evaluation instruments.

Additionally, people with COPD who use a self-management behaviour modification (SMBM) method have been shown to have improved psychological and cognitive functioning.(16) Furthermore, Tabka et al. demonstrated that PR significantly improves cognitive performance in COPD patients with CI; nevertheless, it was also accepted that combining PR with CBT resulted in significant improvements over PR alone.(17) As a result, it is difficult to determine which intervention might significantly improve cognitive function in people with COPD. Conversely, noninvasive brain stimulation (NIBS), any form of neurostimulation for a brain region without the requirement for surgery or anaesthesia, showed a positive improvement in CI in a different disease population.(18-21) According to a systematic review and meta-analysis, non-invasive brain stimulation (NIBS) that uses transcranial alternating current stimulation (tACS) can help persons with Alzheimer's disease or moderate cognitive impairment (MCI) to improve their memory.(18) Additionally, NIBS has been authorised for therapeutic usage with patients with severe depression.(19) According

to another study, working memory and selective attention were found to improve in athletes with attention deficit hyperactivity disorder (ADHD) who received NIBS utilising tACS.(20) Although NIBS has been shown to enhance cognitive performance, its potential to do so in COPD has not yet been investigated. The dorsolateral prefrontal cortex (DLPFC) involves attention management and executive functions like planning, memory and decision-making. (22) As was already mentioned, the two cognitive domains with the greatest impairment in COPD patients were memory and attention. (7) Furthermore, structural MRI studies showed that the DLPFC area had damage, less grey matter, and a thinner DLPFC, which were positively connected with lower cognitive performance in the COPD population. (23)

According to supporting evidence from neuroimaging studies, NIBS targets and manipulates the frontoparietal network (FPN), which includes the DLPFC, by altering spontaneous neural network excitability, like transcranial electrical stimulation (tES) and, more specifically, tACS.(24) Transcranial alternating current stimulation is considered safe when certain parameters are followed without revealing significant adverse effects. (25) Dual-site tACS synchronisation of endogenous oscillations between FPN nodes via phase-amplitude coupling showed encouraging outcomes for enhancing executive and cognitive functioning. (26-28). However, no research has yet been done on using NIBS on DLPFC for COPD patients. Thus, the purpose of this study was to examine the effectiveness of NIBS, a novel intervention, in enhancing the cardiovascular parameters and cognitive function of patients with COPD. The effectiveness of NIBS on cognitive functioning in individuals with COPD is the study question for this review; the PICO is as follows:

P: COPD patient with CI

I: NIBS

C: None

O: Cognitive Function and Cardiopulmonary parameters

2. Method and Materials

2.1. Study design

A double-blind randomised controlled trial design will be used, where the result assessor and the subjects will be blinded. The King Fahad University Hospital will serve as the recruitment site for participants. In addition to receiving formal agreement to participate, patients will be made aware that participation in the program is completely optional and that they can discontinue at any moment without facing repercussions. The study protocol was authorised by the Imam Abdulrahman Bin Faisal institutions' Institutional Review Board

2.2. Sample size and power calculation

The following sites is used to determine the sample size: https://clincalc.com/stats/samplesize.aspx using data from earlier studies, which used the Montreal Cognitive Assessment Test (MoCA) to evaluate cognitive performance in people with COPD. (29) This necessitated a sample size of 22 patients with 80% power and $p<0.05$. The estimated variability will be 4.5, which is the pooled standard deviation (SD_{pooled}).

2.3. Participants

A computer generator will randomly assign participants, and the assignment will be kept concealed. Inclusion Criteria; Adult age from eighteen years old and above; Patients with confirmed COPD via pulmonary function test (PFT) according to the classifications of GOLD; All stages of GOLD will be included; Stable patients, which means they were not admitted to the hospital in the last 3 months; Patients with COPD with confirmed cognitive impairment by the MoCA test; All MoCA stages will be included. Exclusion Criteria; Patients without COPD; Unstable patients with several admissions in the last 3 months; Patients with COPD but without cognitive impairment; COPD patients who suffered from any neurological

problems; COPD patients who are contraindicated for using brain stimulation like psychiatric disorders.

2.4. Outcome measures

A. Stratification outcome measure

Montreal Cognitive Assessment Test(30); MoCA was employed as a stratification result measure at the start of the enrolment process. MoCA is used to examine various cognitive areas to detect participants' CI. MoCA test scores range from zero to 30, with a score of more than 26 considered CI(31). The previously trained researcher will administer the test.

B. Primary outcome measure

The battery of neurocognitive tests: Neuropsychological tests are going to be utilised to evaluate cognitive function. The two key domains to be evaluated are memory and attention. The Flanker Task will test the attention domain by examining how well the executive control network can be modulated by focusing on one stimulus while concurrently preventing the detection of another stimulus. (32) The Memory Automaticity Task will be used to evaluate working memory, requiring participants to complete Sternberg-style memory searches in order to attain automaticity; Recalling the existence of a specific letter in the memory set and accurately classifying it are prerequisites for this task. (33) The previously trained researcher will administer the test

C. Secondary outcome measure

Cardiopulmonary exercise test (CPET)(34): The gold standard exercise test for calculating VO2 max is the CPET. It will be used to evaluate COPD patients' functional capacity and VO2max. Each subject will be assessed using incremental CPET at maximal effort. The modified Bruce procedure will be used to conduct the test on a treadmill. Breath-by-breath analysis will be used to evaluate the following gas-exchange and ventilation

measurements: VO2, end-tidal pressures for carbon dioxide and oxygen (PETCO2 and PETO2), ventilatory equivalents for carbon dioxide (VE/VCO2), and minute ventilation (VE). The previously trained researcher will administer the test.

Transcranial Doppler (TCD) ultrasound(35, 36)**:** It allows for the real-time monitoring of cerebrovascular haemodynamic and blood flow parameters throughout the brain's basal arteries. - Taking into account both the end-diastolic and peak systolic flow velocities, the mean flow velocity (MFV) is calculated, and a few important intracranial arteries are evaluated using the temporal bone window. - Qualified neurologists and vascular technologists will conduct the exam.am.

Arterial blood gas analysis (ABGs)(37, 38): The acid-base balance and arterial blood oxygenation are measured by ABGs, which uses blood drawn from an artery. We shall test the arterial carbon dioxide tension (PCO2), arterial blood gas oxygen tension (PO2), and pH. Patients requiring oxygen will be assessed while using their typical inspiratory oxygen fraction. The test will be done as part of a hospital's routine.

2.5. Procedure

All patients with COPD will undergo MoCA testing and be added to the study when CI is approved. Following their inclusion, participants will be divided into four blocks based on their GOLD grades, which FEV1 determines; these grades are mild, moderate, severe, and very severe. (39) Each block will then be assigned to either the experimental or control group using a block randomisation technique. A researcher who is not involved in the assessment or recruitment process will carry out the randomisation procedure for each group. A computer-generated random number schedule will conceal the randomisation from all other investigators. The participants as well as the outcome assessors will be both blind to the group assignment. The allocation of concealment will be provided through sealed envelopes

with sequential numbers. Following that, both groups will be evaluated at baseline and the end of the intervention using the following outcome measures: the battery of neurocognitive tests, the CPET, the TCD and ABGs. The participants will be blinded because the experimental group will be given five NIBS treatments per week, while the control group will be given five sham-NIBS treatments per week for three weeks. The results will be compared within and across groups, and the relationship between the pulmonary and cognitive parameters will be examined.

2.6. Intervention: Non-invasive Brain Stimulation

Non-invasive brain stimulation (NIBS) modifies brain activity without surgery using electric currents. (21) Transcranial alternating current stimulation (tACS) is one type of NIBS that modifies neuronal oscillations in the brain by applying alternating electrical currents to the scalp through electrodes. (40-42) A sinusoidal current with alternating polarity and a sine wave pattern is applied between two electrodes in tACS. (40, 43) The electrodes will be positioned on the DLPFC region, which has been shown to be affected in COPD patients. (23) This method can enhance motor abilities, improve cognitive functions, and be used in rehabilitation and it does this by entraining neurones, which synchronise their firing to the applied sinusoidal frequency. To guarantee no apparent distinction between the experimental and control groups, the experimental group will be given 40 Hz gamma-tACS of 2 mA. In contrast, the control group will get an electric current that ramps down 60 seconds after the stimulation begins. (44) Both groups will undergo the treatment sessions five times a week for three weeks, each lasting 20 minutes. (44)

2.7. Safeguards for adverse effects in using tACS in COPD patients:

If specific parameters are adhered to, transcranial alternating current stimulation is considered safe.(25) Most studies have employed stimulation frequencies ranging from 1 to

80 Hz and currents reaching up to 2 mA without detecting any appreciable negative effects. (45) Higher tACS frequencies, such as 5 kHz, have been utilised safely in human studies. For instance, a study that employed 10-minute periods of 1 mA tACS at 5 kHz revealed no pathological changes in EEG or MRI, or an increase in neural-specific enolase levels, indicating no neuronal harm. (46). Nevertheless, a systematic review on Alzheimer's disease and MCI found that 40 Hz gamma-tACS was the safest parameter. It also found that, even with the wide range of stimulation protocols and parameter variations, all evaluated studies confirmed the multi-session tACS program's safety, feasibility, and tolerability, with no subjects reporting serious adverse effects. (47) Light flashes and itching or tingling beneath the electrodes are among the mild side effects, particularly at frequencies between 10 and 30 Hz, which peak nearly at 20 Hz. (48) Conversely, when using the accepted tACS protocol, functional or structural damage is not regarded as a potentially developed adverse event; for example, there have been no reports of tACS inducing seizures. (48) According to an application guideline, safety for transcranial electric stimulation is defined as below four mA for up to 60 minutes per day. (48) Each patient will undergo the following process for this work: Prior to tACS application, each participant will go through a pre-treatment evaluation through a comprehensive medical assessment, primarily to verify the stability of their COPD status.(49, 50). Vital markers like oxygen saturation, heart rate, and respiration rate will be tracked while tACS is applied, and symptoms like headaches, dizziness, and respiratory distress will be evaluated. (50) If there are negative effects, such as worsening respiratory condition, an emergency plan will be implemented, and the application will be stopped if necessary. (49) Bronchodilators and supplemental oxygen will be available, especially for patients with severe COPD. (50)

2.8. Data Analysis

Version 21 of the SPSS Statistics program will be utilised for all analyses. The mean and standard deviation (SD) for the continuous variables and percentages for the categorical variables will be used to report demographic characteristics. We will assess the significant relationships between category variables using chi-square tests. To assess whether the outcome measures are normally distributed, the Shapiro-Wilk test will be used. Group differences at baseline will be adjusted for using the analysis of covariance (ANCOVA). A one-way repeated measures Analysis of Variance (ANOVA) will be used to determine how effective the study's intervention was. Post-treatment outcomes will be analysed for repeated measures using a mixed effects model. The association between improved levels of cognitive function and certain factors will be ascertained using the Pearson correlation coefficient. The significance level will be set at a p-value of less than 0.05.

3. Expected result, possible clinical implication, and significant

The results of this study will provide a valuable framework for making decisions about improving CI in patients with COPD and creating a more effective treatment plan for this group. The therapy of COPD will undergo a paradigm shift if NIBS becomes approved for its ability to improve CI in patients with the disease. This will emphasise the significance of incorporating NIBS into a treatment regimen at a certain point in time. Enhancing cognitive function in individuals with COPD may help them better control their illness, follow their treatment plans, take part in rehabilitation programs, live better lives, and save money on medical expenses.

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