ORIGINAL ARTICLE

The effects of transcranial direct current stimulation on serum superoxide dismutase levels in ambulatory ischaemic stroke patients: A randomised pilot study

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ABSTRACT

Introduction: Stroke is one of the leading causes of disability worldwide, imposing a significant public health and economic burden. Oxidative stress, which results from an imbalance between free radical production and antioxidant defences, exacerbates stroke outcomes via its role in promoting neuroinflammation and tissue damage. Superoxide dismutase (SOD), a critical antioxidant enzyme, plays a key role in mitigating oxidative stress. This study evaluates the effect of transcranial direct current stimulation (tDCS) on serum SOD levels in ambulatory ischaemic stroke patients with mild cognitive impairment.

Materials and Methods: In this randomized pilot study, 30 ischaemic stroke survivors (aged 20–65 years) were divided into two groups: control intervention physiotherapy (CIP, n=15) and tDCS combined with CIP (tDCS+CIP, n=15). Each group underwent 30-minute sessions, three times weekly, over four weeks. Serum SOD levels were measured pre- and post-intervention using SOD Activity Assay Kit. Paired t-test was used to evaluate within-group changes, and independent t-test assessed between-group differences and the influence of stroke risk factors such as body mass index and blood pressure.

Results: The tDCS+CIP group exhibited a significant increase in serum SOD levels post-intervention (289.02±64.94 U/L from 215.58±53.65 U/L, p=0.001), compared to the CIP group (216.67±45.02 U/L from 198.04±40.74 U/L, p=0.001). No significant association was observed between serum SOD levels and the studied risk factors.

Conclusion: tDCS combined with conventional therapy significantly improves serum SOD levels, suggesting its potential as an adjunctive treatment for reducing oxidative stress in stroke rehabilitation. Further studies with larger sample sizes and extended follow-up are recommended to validate these findings and explore long-term benefits.

KEYWORDS:
Brain stimulation, cerebrovascular accident, neuromodulation, oxidative stress, superoxide dismutase

INTRODUCTION

Stroke is a leading cause of disability worldwide, profoundly affecting the quality of life of patients and their caregivers.[1-3] This debilitating condition often results in motor, sensory, and cognitive impairments.[4] Oxidative stress, marked by an imbalance between the production of reactive oxygen species and the body's antioxidant defences, is a critical factor in stroke pathology.[5,6] Superoxide dismutase (SOD), an essential antioxidant enzyme, plays a pivotal role in neutralising superoxide radicals, thereby mitigating oxidative stress and reducing cellular damage.[7] Stroke patients often experience oxidative stress due to an imbalance between free radical production and antioxidant defences, especially in ischemic regions such as the penumbra, where excessive free radicals exacerbate tissue damage and hinder recovery.[5,6,8] Reduced serum antioxidant levels, including SOD, have been linked to poorer outcomes, such as larger infarct sizes and heightened neuroinflammation.[9,10] Moreover, SOD deficiency correlates with elevated systemic inflammatory biomarkers such as erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), and C-reactive protein (CRP), which exacerbate post-stroke complications.[11] Its deficiency has also been inversely correlated with recovery potential, as its depletion may lead to increased inflammation and the progression of neurological deficits.[12] Genetic mutations or defects affecting SOD expression have also been associated with unfavourable outcomes.[11] Enhancing SOD levels could, therefore, mitigate stroke-related complications and improve recovery.[12]

Non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and deep brain stimulation, have emerged as powerful tools to modulate brain function.[13,14] The use of electrical currents in neuromodulation has a long history, dating back nearly a century,[15] but inconsistent results led to a temporary decline in interest. Recent advancements and promising findings have revived enthusiasm for tDCS,[13,16,17,18,19] particularly anodal stimulation, which enhances neuroplasticity, modulates oxidative stress, and induces long-lasting alterations in cortical excitability.[20,21] It is a simple, cost-effective, and safe brain stimulation technique with proven benefits for conditions involving impaired neuroplasticity, such as stroke.[13,22,23] By

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applying low-amplitude electrical currents through epicranially positioned electrodes, tDCS modulates cortical excitability. Anodal stimulation depolarizes neurons to enhance excitability and promote neuroplasticity, while cathodal stimulation hyperpolarizes neurons, exerting inhibitory effects.[13,14,24,25]

Anodal tDCS has been shown to reduce proinflammatory cytokines, including interleukin-1 beta (IL-1β) and tumour necrosis factor-alpha (TNFα),[26,27] and promote neuronal growth by increasing the expression of neuronal growth-promoting proteins such as GAP-43 and microtubule-associated protein 2 (MAP-2) in peri-infarct regions.[27] These mechanisms collectively position tDCS as a promising adjunctive therapy for stroke rehabilitation. Evidence also indicates that anodal tDCS can improve cognitive and motor functions in disorders like depression, Parkinson's disease, and stroke.[13,22,23] However, its effects on oxidative stress biomarkers such as SOD in stroke patients remain underexplored.

Given the potential of tDCS to improve stroke outcomes, this pilot study was designed to investigate its impact on serum SOD levels in ambulatory stroke patients. Pilot studies are essential to assess feasibility, optimize study design, and generate preliminary data for subsequent trials. Accordingly, this pilot study aims to evaluate the effect of a four-week tDCS intervention on serum SOD levels in ambulatory stroke patients with mild cognitive impairment. We hypothesize that tDCS combined with conventional therapy will significantly enhance serum SOD levels compared to conventional therapy alone, providing a foundation for future research.

MATERIALS AND METHODS

Study Design and Participant Selection

This randomised, assessor-blinded, pilot-controlled study was conducted at Imamu Wali General Hospital, Kano, Nigeria, following ethical approval from the Kano State Ministry of Health (Ref. No.: SHREC/2023/3901, Approval No.: NHREC/17/03/2018) and was performed in accordance with the Declaration of Helsinki. Thirty ambulatory ischaemic stroke patients were recruited and randomly assigned into two groups: the control intervention physiotherapy group (CIP, n = 15) and the combined intervention group receiving tDCS with control intervention physiotherapy (tDCS+CIP, n = 15) (Figure 1). The study was conducted over a four-week period, with all participants giving written informed consent prior to the enrolment.

Eligible participants were male and female ischaemic stroke survivors, aged 20 - 65 years, with a Mini-Mental State Examination (MMSE) score of 22 or higher. Inclusion criteria required patients to be free of drug abuse, psychiatric comorbidities, visual or auditory deficits, and able to walk unaided or with mild assistive devices. Patients were required to achieve controlled systemic hypertension or diabetes with medication, and without the use of antidepressants. The onset of stroke was at least six months prior, and participants had to be responsive to verbal commands.

Participants were excluded if they had engaged if they had engaged in regular exercise or physiotherapy three months prior to enrolment, had moderate to severe musculoskeletal disorders in the upper or lower extremities, balance impairments, or concurrent participation in any other clinical research.

Randomisation, Allocation Concealment, and Blinding

The randomisation sequence was computer-generated using Microsoft Excel's random number function (=RAND( )) by an independent statistician not involved in the trial. The generated random number was sorted from smallest to largest, which was used to allocate the two studied groups repeatedly. To minimise selection bias, allocation concealment was ensured by using sequentially numbered, opaque, sealed envelopes (SNOSE) prepared by an independent researcher not involved in participant recruitment, intervention, or assessment. The envelopes were opened by the independent researcher only after the enrolled participant had completed all baseline assessments.

Due to the nature of the non-invasive brain stimulation, participants could not be blinded to their group assignment. This lack of blinding may introduce performance and detection bias, which is acknowledged as a limitation. However, to minimise assessment bias, the research personnel responsible for collecting blood samples, conducting laboratory analyses (serum SOD measurement), and performing all outcome assessments were blinded to group allocation throughout the study.

Intervention Protocol

Both groups participated in 30-minute sessions of control intervention physiotherapy three times a week for four weeks. These included 10 minutes of infrared radiation (IRR) to the affected limb and 20 minutes of static cycling using a Reebok (Z9BIKE) set at zero resistance. Stretching exercises were performed pre- and post-cycling.

Additionally, participants in the combined intervention group underwent anodal stimulation of the primary motor cortex (PMC) using the International 10-20% EEG electrode placement system.28 The anodal electrode was positioned over the PMC at a point 1 cm anterior and 4 cm lateral to the cortical vertex, which corresponds to the C3/C4 site in the EEG system.[28] To complete the circuit, the cathodal electrode was placed over the contralateral supraorbital region. A constant 2 mA current was delivered for 20 minutes using a tDCS stimulator (Medisystems tDCS DC-Stimulator Plus). Electrodes were secured with elastic straps and moistened with saline to ensure proper contact.

Monitoring of Adverse Events

tDCS is generally safe. However, participants were actively monitored for any adverse effects (e.g., skin redness, itching, burning sensation, headache, dizziness) during and after each tDCS session. Any reported adverse events were recorded.

Data Collection

Socio-demographic characteristics of the participants were recorded using a structured data collection sheet, capturing variables such as age, gender, marital status, education level,

Table I: Socio-demographic and clinical characteristics of participants in the combined intervention and control groups

Characteristics	Combined Intervention		Control		p-value
	n (%)	Mean + SD	n (%)	Mean + SD	
Age (years)		56.70 ± 6.19		56.87 ± 4.97	0.396
20-34	0 (0)		0 (0)		
35-49	3 (20)		2 (13.3)		
50-65	12 (80)		13 (86.7)		
Gender					
Male	11 (73.3)		10 (53.3)		
Female	4 (26.7)		5 (46.7)		
Marital status	Single	0 (0)		0 (0)	
Married	9 (60.0)		12 (80)		
Divorced	5 (33.3)		2 (13.3)		
Widow	1 (6.7)		1 (6.7)		
Residence	Rural	8 (53.3)		9 (60)	
Urban	7 (46.7)		6 (40)		
Occupation					0.090
Small traders	10 (66.7)		8 (53.3)		
Civil servant	3 (20.0)		4 (26.7)		
Skilled labourers	2 (13.3)		0 (0)		
Unemployed	0 (0)		3 (20.0)		
Retired	0 (0)		0 (0)		
Education					0.703
Post-secondary	4 (26.7)		4 (26.7)		
Secondary	7 (46.7)		5 (33.3)		
Primary	2 (13.3)		3 (20.0)		
Non-formal	2 (13.3)		3 (20.0)		
None	0 (0)		0 (0)		
Laterality					0.819
Right hemiparesis	13 (86.7)		12 (80.0)		
Left hemiparesis	2 (13.3)		3 (20.0)		
SBP (mmHg)					0.675
< 140	7 (46.7)		10 (66.7)		
> 140	8 (52.3)		5 (23.3)		
DBP (mmHg)					0.546
< 90	14 (93.3)		12 (80)		
> 90	1 (6.7)		3 (20)		
BMI					0.066
Underweight	0 (0)		0 (0)		
Normal	8 (53.3)		8 (53.3)		
Pre-obesity	7 (46.7)		7 (46.7)		
Obesity	0 (0)		0 (0)		
Baseline SOD level (U/L)	-	215.58 ± 53.60	-	198.04 ± 40.74	0.292
MMSE	-	23.27 ± 1.27	-	24.30 ± 1.09	0.432

Data analysed by paired t-test (within-group) and independent t-test (between-group). A *p-value of <0.05 was considered statistically significant.
BMI: body mass index, DBP: diastolic blood pressure, MMSE: Mini-Mental State Examination, SBP: systolic blood pressure, SD: standard deviation, SOD: superoxide dismutase.

Table II: Within-group and between-group comparison of serum SOD levels pre- and post-intervention

Group	n	Serum SOD (U/L) Mean + SD		Difference in serum SOD (U/L)	p-value	
		Pre-intervention	Post-intervention	Mean + SD	Within-group	Between-group
Combined intervention	15	215.58 ± 53.65	289.02 ± 64.94	73.44 ± 37.86	0.001*	0.001*
Control	15	198.04 ± 40.74	216.67 ± 45.02	18.63 ± 15.21	0.001*	

Data analysed by paired t-test (within-group) and independent t-test (between-group). A *p-value of <0.05 was considered statistically significant.
SD: standard deviation, SOD: superoxide dismutase.

Statistical Analysis

Data were analysed using IBM SPSS 23.0 software. Descriptive statistics summarized demographic variables as means and standard deviations (SD). The Shapiro-Wilk test was employed to assess the normality of continuous variables. Paired t-tests compared pre- and post-intervention serum SOD levels within groups, while independent t-tests assessed between-group differences and associations with risk factors. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 30 participants were included in the study, with 15 participants in each of the two groups. The mean age of participants was approximately 57 years. The age distribution varied, with the majority (80%) of participants in the combined intervention group aged 50–65 years,

Table III: The effect of studied risk factors on serum SOD levels of participants

Variables	n (%)	Serum SOD (U/L)	Mean + SD	t-value	p-value
Age (years)	35-49	5 (16.7)	56.99 + 34.82	0.665	0.511
	50-65	25 (83.3)	43.85 + 40.69		
BMI (kg/m^2)	18.2-24.9	13 (43.3)	53.23 + 47.10	0.885	0.398
	25.0-34.9	17 (56.7)	40.54 + 33.18		
SBP (mmHg)	< 140	17 (56.7)	41.72 + 32.33	-0.671	0.508
	> 140	13 (33.3)	51.69 + 49.17		
DBP (mmHg)	< 90	26 (86.7)	42.99 + 34.82	-1.069	0.294
	> 90	4 (13.3)	65.87 + 68.69		
Laterality	Right hemiparesis	24 (80)	43.85 + 40.55	0.382	0.705
	Left hemiparesis	6 (20)	40.45 + 40.58		

Data analysed by an independent t-test. A *p-value of <0.05 was considered statistically significant.
BMI: body mass index, DBP: diastolic blood pressure, SBP: systolic blood pressure, SD: standard deviation, SOD: superoxide dismutase

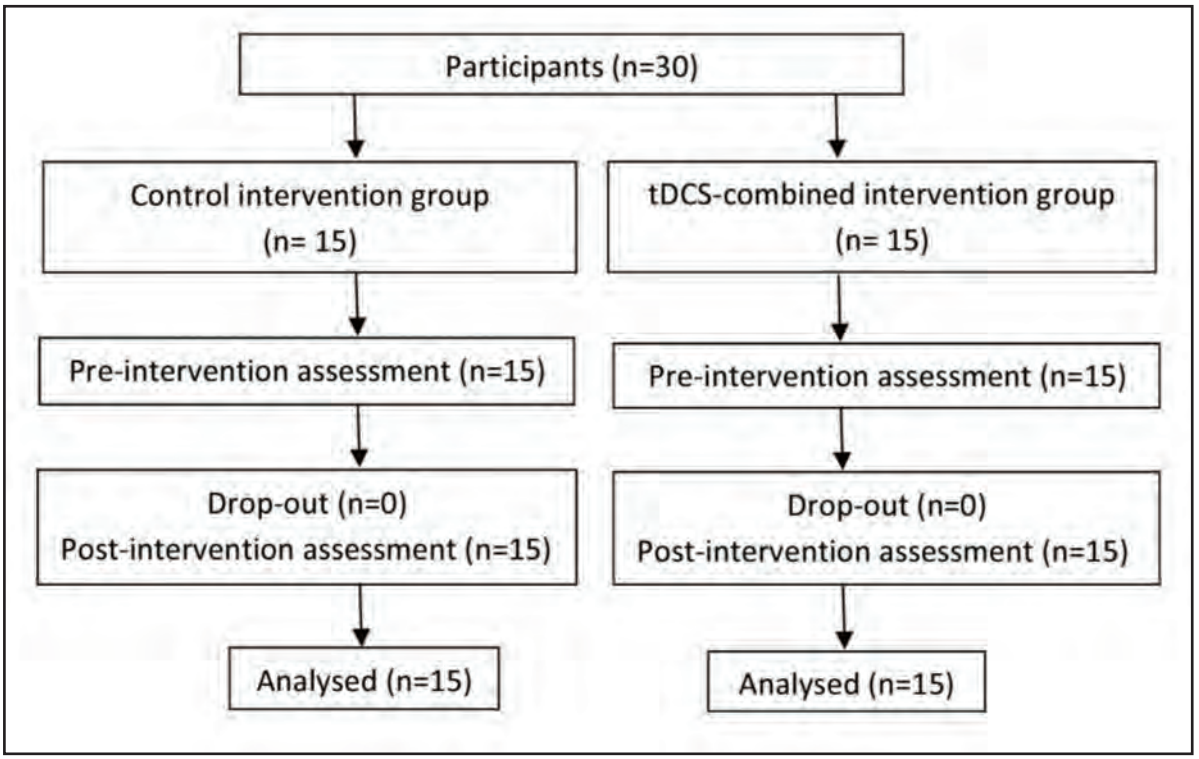

Fig. 1: Study flow chart

and residence. Blood pressure measurements were taken twice for each participant using validated and calibrated mercury and digital sphygmomanometers. The average values of systolic (SBP) and diastolic (DBP) blood pressure readings were recorded. Body mass index (BMI) was calculated based on each participant's weight and height. Weight was measured using a digital scale, with participants standing barefoot in the centre of the scale. Height was recorded against a calibrated wall-mounted stadiometer. BMI was then calculated using the standard formula: BMI = weight (kg) / [height (m)]^2.

Serum SOD Measurement

The serum SOD levels of stroke patients were measured both before and after the 4-week tDCS intervention using the Superoxide Dismutase (SOD) Activity Assay Kit. The microplate reader was preheated to 560 nm for 30 minutes to ensure stable wavelength detection. Working reagents (Reagents I, II, and V) were equilibrated in a water bath at 37°C for 5 minutes before use. Additionally, Reagent IV was mixed with Reagent V by oscillation to ensure proper dissolution immediately before application.

The assay utilized four types of tubes: two blank tubes (B1 and B2), a test tube (T), and a control tube (C). Reagents were added to the respective tubes according to the manufacturer's instructions, and the mixtures were thoroughly combined. The tubes were then incubated at 37°C for 30 minutes. After incubation, the solutions were transferred into an ultra-micro cuvette or a 96-well flat-bottom plate to measure absorbance at 560 nm using the microplate reader. Serum SOD concentrations were calculated based on the absorbance values using the manufacturer's formula:

SOD (U/mL) = [P÷ (1-P) ×Vrv] ÷Vs×F=11.11×P÷ (1-P) ×F

compared to only 20% in the control group within the same age category. Gender distribution showed a higher proportion of males in the tDCS group (73.3%) compared to the control group (53.3%).

Educational attainment among participants varied, with most having received non-formal, primary, secondary, or post-secondary education. Secondary school education was the most common, with 46.7% and 33.3% in the combined intervention and control groups, respectively. A large proportion of participants resided in rural areas (53.3% in the combined intervention group, 60% in the control group) and were married (80% in the combined intervention group, 60% in the control group). Small-scale trading was the primary occupation for most participants, comprising 66.7% in the combined intervention group and 53.3% in the control group.

The baseline serum SOD levels were comparable between the groups, with mean values of 215.58 ± 53.60 U/L for the combined intervention group and 198.04 ± 40.74 U/L for the control group ($p>0.05$). Most participants presented with right-sided hemiparesis, indicative of left hemispheric cerebral involvement. Elevated SBP was more common in the combined intervention group (52.7%) than in the control group (33.3%), while DBP was within the normal range (<90 mmHg) for most participants. The mean BMI was 24.23 kg/m² in the combined intervention group and 25.11 kg/m² in the control group. These baseline characteristics were recorded to ensure group comparability and to explore potential confounding influences on the primary outcome (serum SOD). Table I summarises the socio-demographic and clinical characteristics of participants of both groups.

Within the combined intervention group, serum SOD levels increased significantly from 215.58 ± 53.65 U/L at baseline to 289.02 ± 64.94 U/L post-intervention ($p<0.001$). Similarly, the control group showed a smaller but significant increase, with serum SOD levels rising from 198.04 ± 40.74 U/L to 216.67±45.02 U/L post-intervention ($p<0.001$) (Table II). A statistically significant increase in serum SOD levels was observed in the combined intervention group compared to the control group (mean increase of 73.44 U/L vs. 18.63 U/L, $p<0.05$) (Table III). No adverse events related to the tDCS or physiotherapy interventions were reported throughout the study period.

No statistically significant effects were observed for the studied risk factors, including age, SBP, DBP, stroke laterality, or BMI, on serum SOD levels ($p>0.05$). Younger participants (aged 35–49 years) had slightly higher serum SOD levels (56.99 U/L) than those aged 50–65 years (43.85 U/L). Participants with elevated SBP and DBP demonstrated slightly higher serum SOD levels (51.69 U/L and 65.87 U/L, respectively) compared to those with normal SBP and DBP (41.72 U/L and 42.99 U/L, respectively). Additionally, participants with normal BMI showed higher serum SOD levels (53.23 U/L) compared to those in the pre-obesity category (40.54 U/L) (Table IV).

DISCUSSION

This pilot study demonstrated a statistically significant increase in serum SOD levels following a four-week intervention of combined tDCS and CIP, with a markedly greater improvement compared to CIP alone. The observed increase in serum SOD levels, approximately a 34% rise in the tDCS+CIP group compared to a 9.4% increase in the CIP group, may have substantial clinical relevance. Higher antioxidant capacity is theorised to mitigate neuronal damage in the ischemic penumbra, potentially slowing infarct expansion and creating a more favourable environment for neuroplasticity. This biochemical improvement could translate to enhanced recovery of cognitive and motor functions,[9,10] although direct correlation between SOD levels and functional outcomes requires larger study trials.

The synergistic effect observed in the tDCS+CIP group may be attributed to the complementary mechanisms of both therapies. While conventional physiotherapy promotes use-dependent plasticity through repetitive task training, anodal tDCS primes the motor cortex by increasing neuronal excitability and facilitating long-term potentiation (LTP)-like mechanisms, thereby enhancing the effects of subsequent physiotherapy.[12,20] This heightened cortical responsiveness may not only improve motor learning but also upregulate endogenous neuroprotective pathways, including the expression of antioxidant enzymes such as SOD. These findings are consistent with previous research demonstrating that tDCS reduces proinflammatory cytokines and promotes neurotrophic factor expression.[17,26,27] In our study, the significant increment in serum SOD after the intervention suggests that tDCS amplifies rehabilitation benefits at a biochemical level.[20,21,26] Despite challenges in comparing studies due to variations in stimulation protocols (such as electrode montage, current intensity, frequency, and session number), the consistent findings that neuroplasticity enhancement by tDCS through increased cortical excitability, synaptic plasticity modulation, current calcium increments, and oxidative stress regulation support its clinical relevance in neurological recovery.

There are no identified risk factors demonstrating a statistically significant association with changes in SOD levels. The gender distribution and BMI range in this study are consistent with previous research on stroke populations.[29] The slightly higher mean increase in SOD among younger participants (35-49 years) may reflect age-related declines in neuroplasticity or antioxidant regulatory mechanisms in older cohorts.[12] Similarly, participants with a normal BMI showed a greater, though non-significant, increase than those in the pre-obesity category, which aligns with literature suggesting obesity is associated with chronic inflammation and oxidative stress that may blunt intervention efficacy.[11] However, this contrasts with prior findings reporting increased levels of SOD isoenzymes (manganese (Mn) SOD and copper-zinc (CuZn) SOD) in obese individuals.[30] Regarding blood pressure, previous studies have reported significantly lower SOD activity in hypertensive patients compared to normotensive controls.[31,32] In contrast, our study found no association between blood pressure or stroke laterality and changes in SOD levels, which may be due to

the small sample size. The absence of significant effects from blood pressure and laterality suggests that the combined tDCS and physiotherapy intervention benefits were consistent across these clinical subgroups, indicating its potential broad applicability. Nonetheless, these trends should be interpreted cautiously and require validation in larger, more diverse cohorts.

This pilot study provides preliminary evidence supporting the potential benefits of tDCS in reducing oxidative stress among stroke patients. However, several limitations should be acknowledged. The small sample size and single-centre design may restrict the generalisability of the findings. Although assessor blinding was maintained for the primary outcome (serum SOD levels), the absence of participant blinding introduces the possibility of performance bias. The fixed stimulation parameters used may not reflect the full therapeutic potential achievable with varied intensities, session frequencies, or electrode placements. Furthermore, outcome assessment was limited to the four-week intervention, with no extended follow-up to evaluate the durability of effects. The study did not correlate serum SOD levels with cognitive function measures, and the variability in stroke subtypes lack systematic control, which may have confounded the findings. While no adverse events were reported, future studies should incorporate standardised monitoring tools to comprehensively assess safety.

To build on these findings, future studies should recruit larger and more diverse populations to enhance generalisability. An extended intervention period and long-term follow-ups would help elucidate the sustainability of the tDCS effects. Combining tDCS with other neuroplasticity-focused rehabilitation strategies may reveal synergistic benefits. Importantly, subsequent studies should integrate functional, cognitive, and quality-of-life assessments alongside biomarker analysis to better determine the clinical relevance of biochemical changes observed.

CONCLUSION

This pilot study demonstrated that anodal tDCS, when combined with conventional therapy, increases SOD levels in ambulatory stroke patients. The findings highlight the potential of tDCS as a non-invasive and adjunctive therapeutic approach to reduce oxidative stress and support recovery in stroke rehabilitation. While these results are promising, further research with larger sample sizes, incorporating functional outcomes, and employing longer-term follow-up is necessary to validate the findings and optimise the clinical application of tDCS in managing post-stroke complications.

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