Effect of Transcranial Direct Current Stimulation Plus Early Rehabilitation Therapy on Cerebral Cognitive Function, Hemodynamics and Life Qualityin Patients

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With the implementation of Health China strategy, rehabilitation medicine, as an important branch of medicine, plays an increasingly important role in China's health. Objective: This paper aims to inquire into the effects of transcranial direct current stimulation (TDCS) plus early rehabilitation therapy on cerebral cognitive function, hemodynamics and quality of life (QOL) in patients with cerebral infarction (CI). Methods: One hundred and eight CIpatients treated in our hospital were randomized into the observation group (OG; n=63) for TDCS plus early rehabilitation therapy and the control group (CG; n=45) for early rehabilitation therapy alone. The changes of hemodynamic index before and after treatment were observed. The eurological deficit [neurological deficit score (NDS)] and cognitive impairment [mini-mental state examination (MMSE)], as well as activity of daily living (ADL; Barthel score) and motor function [Fugl Meyer assessment (FMA)] were compared between the two series. The assessment of neurological function recovery of patients in the two cohors was performed by the National Institutes of Health Stroke Scale (NIHSS). The therapeutic effect of the two groups was compared, as well as the post-treatment QOL referring to the questionnaire of QOL of patients with acute CI. Results: The post-treatment hemodynamic indexes increased in both OG and CG, and the increase was more profound in OG ($p<0.05$). After treatment, the NDS score in OG was lower while the MMSE score was higher as compared to CG ($p<0.05$). The Barthel score and the FMA score increased in both groups after treatment, with higher scores in OG ($p<0.05$). The NIHSS score of both groups decreased post treatment, and the score was lower in OG ($p<0.05$). OG presented with notably higher total effective rate ($p=0.028$) and superior QOL than CG ($p<0.05$). Conclusions: TDCS plus early rehabilitation therapy is effective for patients with early CI, which can enormously improve the neurological function, hemodynamics, activity ability and QOL of patients.

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INTRODUCTION

Cerebral infarction (CI), or ischemic stroke, is a cerebral blood circulation disorder caused by ischemia and hypoxia and the world's third leading cause of death and disability [1]. Similarly, CI is the primary cause of disability [2]. It occurs mostly in middle-aged and elderly and is also the first killer causing disability or death in this population [3]. Statistics reveals an ongoing incidence of CI across the globe, and the incidence goes in parallel with population aging [4, 5]. In clinic, patients with early CI generally need long-term clinical standard treatment, and antiplatelet and anticoagulant therapy to control the disease [6]. While for advanced or severe patients, surgery is the only option [7]. However, CI often causes obstruction or necrosis of cerebral vessels and nerves, which has a significant impact on patients' cognitive function and hemodynamics [8]. Moreover, some investigations have pointed out that after suffering from CI, patients' quality of life (QOL) will be significantly reduced [9]. Therefore, the ends of CI treatment are not limited to the control of disease symptoms, but also to ameliorate patients' cognitive function and hemodynamics.

Attributing to the deepening of research, transcranial direct current stimulation (TDCS) has been found to confer benefits against nervous system diseases, especially the cognitive function of patients [10, 11]. In addition, evidence has shown that TDCS also exerts a relatively stable therapeutic effect on patients with early CI [12]. Therefore, we speculated that TDCS plus rehabilitation therapy could achieve excellent nerve repair for patients with early CI and greatly reduce the nerve damage caused by CI. Unfortunately, there is currently a lack of relevant research to support our conjecture. Accordingly, we explored the impact of TDCS plus early rehabilitation therapy on cognitive function and hemodynamics of patients with CI, and conducted prognostic follow-up to investigate the changes in patients' QOL, so as to clarify the clinical implications of the combination for future CI treatment.

MATERIALS AND METHODS

Baseline Data

One hundred and eight CIpatients referred to our hospital were collected and randomized into two groups: 63 casesin the observation group (OG) were given TDCS plus early rehabilitation therapy, and 45 cases in the control group (CG) received early rehabilitation therapy alone. The Ethics Committee and the attending gynecologist of our hospital approved this experiment.

Eligibility Criteria

Inclusion criteria: All included patients 1) were diagnosed as ischemic stroke by attending physicians of the department of Neurology of our hospital with reference to the diagnostic criteria of Chinese Guidelines for Diagnosis and Treatment of Ischemic Stroke, as well as laboratory and imaging examination reports; 2) had complete case data; 3) were in the early stage of the disease with mild symptoms.

Exclusion criteria: Patients excluded were those 1) who do not cooperate and cannot communicate normally; Patients with drug allergy; 2) with other serious diseases; 3) complicated with severe somatic behavior disorder; 4) who could not receive complete treatment for various reasons.

Treatment Methods

Patients in both groups were given routine interventions such as dilating blood vessels, lowering intracranial pressure and anticoagulation. CG: the patient was provided with a comfortable position and instructed the body placement according to his/her own physical conditions. Also, the patient was guided to do some simple joint activities and sitting-up training. In the later stage, taken the status quo of the patient's condition into consideration, the patient was trained on the affected limb and guided by fine movements such as sitting position and walking, so as to gradually guide the recovery of ADL and functions. The training was conducted for 30min each time, once a day for two weeks.

OG: All patients in OG were treated with TDCS on the basis of CG. Methods: the patient was treated with TDCS with an IS200 intelligent stimulator. The anode electrode was placed on the scalp of C3/C4 in the cerebral hemisphere, and the stimulation current was 1.2mA for twice/d, 20min/time. The stimulation electrode was a 3cm×7cm isotonic gelatin sponge electrode, and the reference electrode was placed on the shoulder of healthy side. The treatment lasted for two weeks.

Outcome Measures

The changes of hemodynamic indexes [anterior/middle/posterior cerebral artery (ACA/MCA/PCA; Vm), and basilar artery (BA; Vm)] were observed pre- and post-treatment. The neurological deficit [neurological deficit score (NDS)] and cognitive impairment [mini-mental state examination (MMSE)], as well as ADL (Barthel score) and motor function [Fugl Meyer assessment (FMA)] were compared between the two series. The assessment of neurological function recovery of patients in the two cohorts was performed by the National Institutes of Health Stroke Scale (NIHSS).The therapeutic effect [13] of the two groups was compared, and the QOL after treatment was compared according to the questionnaire of QOL of patients with acute CI.

STATISTICAL PROCESSING

The statistical analysis and image rendering of the experimental results were undertaken by SPSS 24.0 (Yuchuang Network Technology Co., Ltd., Shanghai, China) and Graphpad8 (Softhead Technology Co., Ltd., Shenzhen, China) respectively. The categorical variables were recorded as (%) and compared by the Chi-square test. The continuous variables were given (mean ± standard deviation) and compared by t test or one-way analysis of variance (ANOVA) and LSD post-hoc test, as appropriate; repeated measures ANOVA and Bonferroni post-hoc test were applied for comparisons of multiple time points. The significance level was set at p-value <0.05.

RESULTS

Patient Baseline Data

Patient baseline data including age, sex, BMI, living environment, smoking history, drinking history, family history, ethnicity, hypertension history and diabetes history differed insignificantly between OG and CG (p>0.05). (Table 1)

Table 1. General data [n(%)]

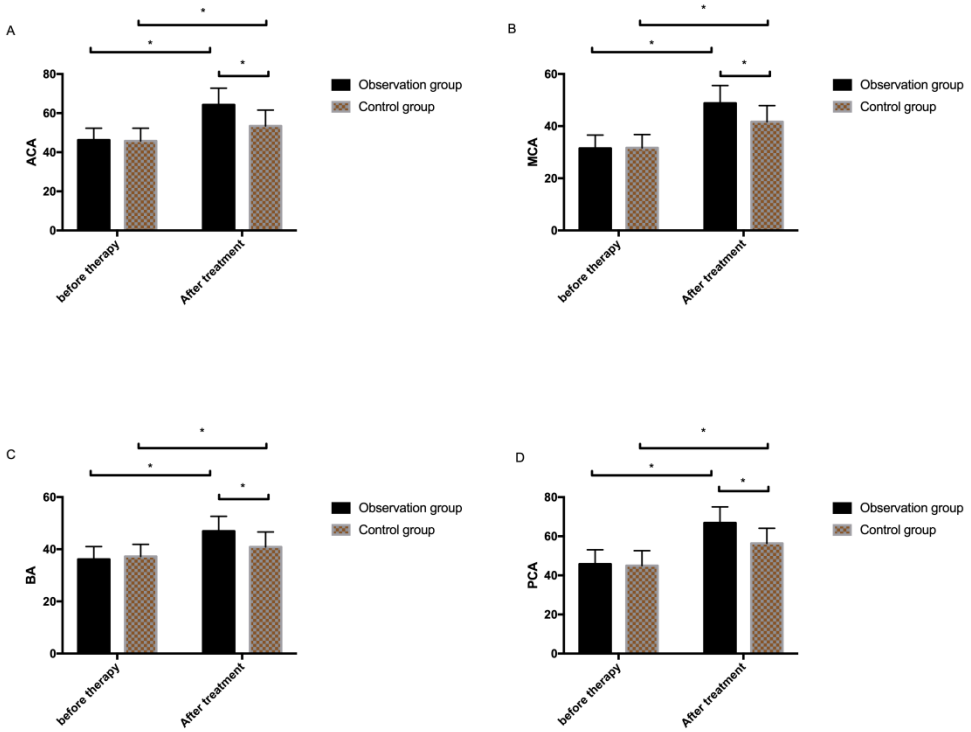
	Observation group (n=63)	Control group (n=45)	t or X^2	P
Age (years old)			0.358	0.721
	47.8±5.6	48.2±5.9		
Gender			0.187	0.666
Male	39 (61.90)	26 (57.78)		
Female	24 (38.10)	19 (42.22)		
BMI (KG/cm^2)			0.312	1.016
	24.52±3.05	23.76±4.72		
Living environment			0.228	0.633
Urban	45 (71.43)	34 (75.56)		
Rural	18 (28.57)	11 (24.44)		
History of smoking			0.073	0.788
Yes	39 (61.90)	29 (64.44)		
No	24 (38.10)	16 (35.56)		
History of drinking			0.207	0.648
Yes	35 (55.56)	23 (51.11)		
No	28 (44.44)	22 (48.89)		
Family medical history			0.020	0.888
Yes	9 (14.29)	6 (13.33)		
No	54 (85.71)	39 (86.67)		
History of hypertension			0.108	0.742
Yes	26 (41.27)	20 (44.44)		
No	37 (58.73)	25 (55.56)		
History of diabetes			0.040	0.841
Yes	24 (38.10)	18 (40.00)		
No	39 (61.90)	27 (60.00)		

Ethnicity			0.281	0.596
Han	57 (90.48)	42 (93.33)		
Ethnic minorities	6 (9.52)	3 (6.67)		

Changes of Hemodynamic Indexes before and after in the Two Groups

Detection of pre- and post-treatment hemodynamic indexes revealed no evident differences in theaverage blood flow velocities of ACA, MCA, BA and PCA between OG and CG before treatment, but the hemodynamic indexes elevated in both groups after treatment, and the increase was more notable in OG ($p<0.05$). (Figure 1)

Figure 1. Pre- and post-treatment hemodynamic indexes in the two groups.

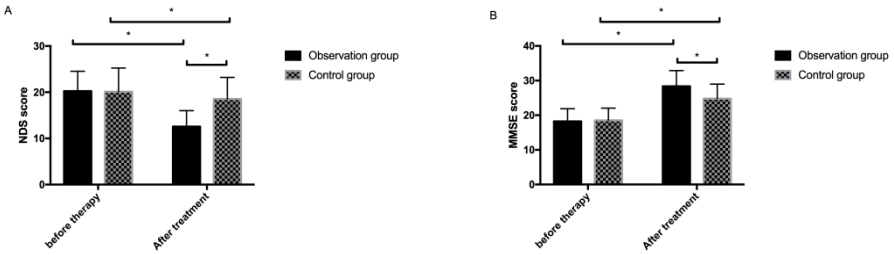


A. BFVs of ACA before and after treatment in the two groups.
B. BFVs of MCA before and after treatment in the two groups.
C. BFVs of BA before and after treatment in the two groups.
D. BFVs of PCA before and after treatment in the two groups.
BFVs: blood flow velocities; ACA: anterior cerebral artery; MCA: middle cerebral artery; BA: basilar artery; PCA: posterior cerebral artery.

Scores of Neurological Deficits and Cognitive Impairment in the Two Groups

NDS and MMSE score were used for the evaluation of neurological deficits and cognitive impairment of patients pre- and post-treatment. Notably difference was observed in neither NDS score nor MMSE score between the two series before treatment. However, the post-treatment NDS decreased in both groups, and the reduction was more evident in OG ($p<0.05$). While the MMSE score was increased in both OG and CG, and the increase was more evident in OG ($p<0.05$). (Figure 2)

Figure 2. Neurological deficitsand cognitive impairment scores in the two groups.

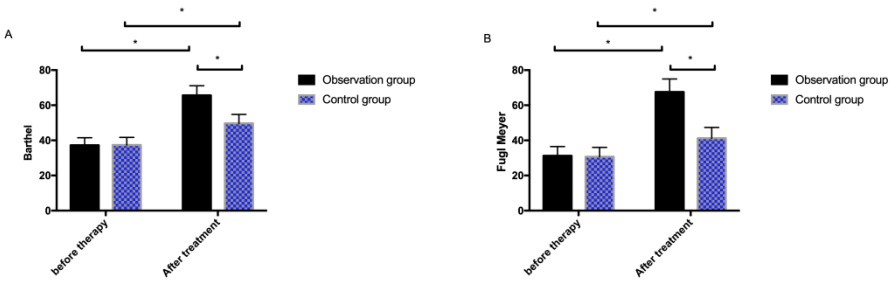


A. Neurological impairment scores (NDS).
B. Cognitive impairment scores (MMSE).
NDS: neurological deficit score; MMSE: mini-mental state examination.

ADL and Motor Function in the Two Groups

ADL and motor function of patients before and after treatment were assessed by Barthel score and FMA respectively. It revealed similar Barthel and FMA scoresin the two series before treatment; however,the two scores elevated in both series after treatment, and the increase was more significant in OG ($p<0.05$). (Figure 3)

Figure 3. Activity of daily living and motor function in the two groups.

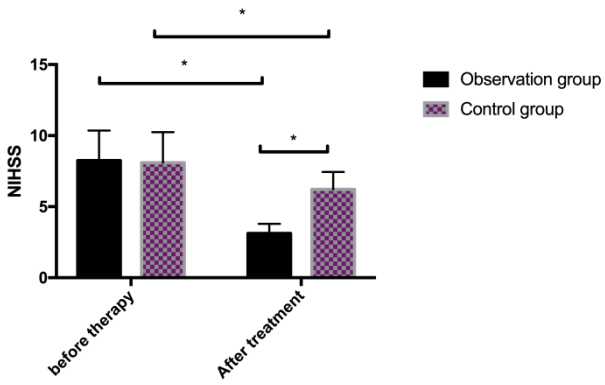


A. Activity of daily living scores (Barthel score).
B. Motor function scores (Fugl Meyer assessment).

Neurological Function Recovery in the Two Groups

The NIHSS for the evaluation of neurological function recovery identified no evident difference between the two groups before treatment; whereas, the score decreased in bothOG and CG after treatment, and the decrease was more profound in OG ($p<0.05$). (Figure 4)

Figure 4. Neurological function recoveryin the two groups



Therapeutic Effects in the Two Groups

Comparing the post-treatment efficacy, it was found that OG was basically cured in 38.10% of the cases, markedly effective in 31.75%, effective in 25.40%, and ineffective in 4.76%, with a total effective rate of 95.24%; while CG was basically cured in 22.22% of the cases, markedly effective in 33.33%, effective in 26.67% and ineffective in

17.78, with a total effective rate of 82.22%. OG had an evident superiortotal effective rate than CG (P=0.028). (Table 2)

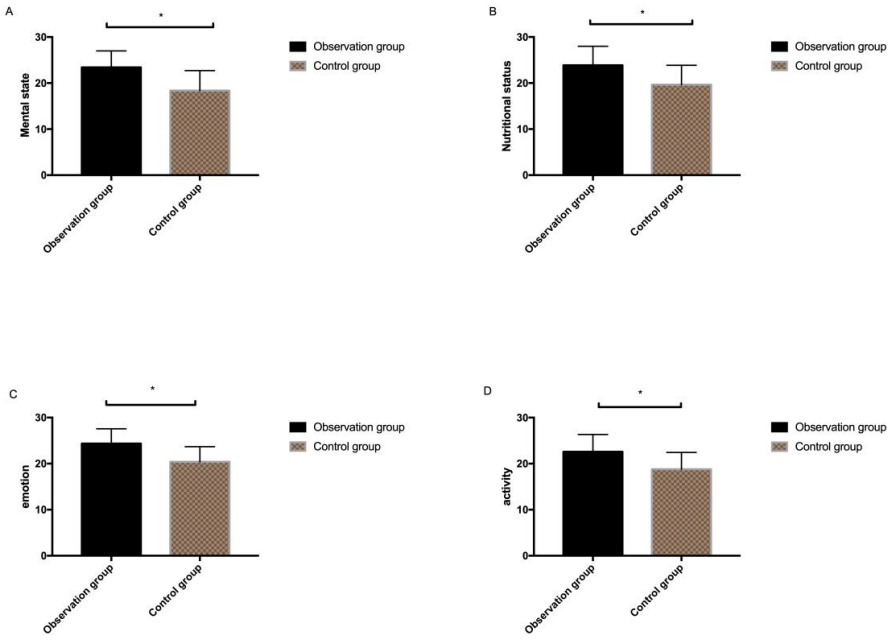
Table 2. Treatment efficacy in the two groups

	Observation group (n=63)	Control group (n=45)	X^2	P
Basically cured	24 (38.10)	10 (22.22)		
Markedly effective	20 (31.75)	15 (33.33)		
Effective	16 (25.40)	12 (26.67)		
Ineffective	3 (4.76)	8 (17.78)		
Total effective rate	60 (95.24)	37 (82.22)	4.861	0.028

QOL after Treatment in the Two Groups

Patients' QOL, which was divided into four aspects: mental, nutrition, emotion, and activity was compared between the two series after treatment. The results demonstrated that the scores of mental, nutrition, emotion and activity were enormously higher in OG than in CG ($p<0.05$). (Figure 5)

Figure 5. Post-treatment quality of life in the two groups.



A. Post-treatmentmental scores.
B. Post-treatmentnutritional scores.
C. Post-treatmentemotion scores.
D. Post-treatmentactivity scores.

DISCUSSION

CI is the primary disease that causes death and disability in middle-aged and elderly people, so the prevention and treatment of the disease carries huge implications [14, 15]. Given that TDCS is a commonly used means in clinical treatment of nervous system diseases [16], we combined it with early rehabilitation therapy to treat patients with early CI, aiming to confirm the therapeutic value of the combination therapy for CI, which yields essential reference significance for future clinical treatment of CI.

Firstly, we compared patient general data and found no statistical difference between the two series, confirming the comparability. This is also the result of our rigorous screening in accordance with the inclusion and exclusion criteria, which can greatly reduce the probability of other factors affecting our experimental results. Subsequently, we made a preliminary study on the clinical efficacy of the two cohorts. By comparing the hemodynamics

of patients, we found that the post-treatment average blood flow velocities of ACA, MCA, BA and PCA were higher in OG than in CG, suggesting that TDCS plus early rehabilitation has a significant effect on improving intracranial hemodynamics of CI patients. This also agrees with the basic effect of cranial direct current stimulation in previous studies [17, 18], which supports the accuracy of our experimental results. Then, we used NDS and MMSE to evaluate the neurological function of patients. The results revealed decreased NDS scores and increased MMSE scores in OG as compared to CG, indicating that TDCS is also effective in repairing the neurological function of patients with CI. TDCS consists of two surface electrodes: anode and cathode, and the output of stimulation type is set by control software, which acts on the cerebral cortex with weak polarized direct current [19]. TDCS does not trigger neuronal discharge through suprathreshold stimulation, but by modulating the activity of neuronal cell network in cerebral cortex, which is quite different from other non-invasive brain stimulation techniques such as transcranial electrical stimulation and transcranial magnetic stimulation [16]. However, the occurrence of CI is strongly associated with the apoptosis and necrosis of neuron cells in that the injury of neuron cells lead to the obstruction or necrosis of nerves and blood vessels, thus causing the occurrence of disease [20]. Conventional conservative treatment for CI gradually repairs the damaged nerve tissue of patients only by lowering intracranial pressure or controlling internal circulation, which underlies the overwhelmingly long course of treatment [21]. On the contrary, TDCS can directly and fundamentally treat CI in a faster and more effective manner, with higher safety via non-invasive operation, which enjoys great clinical application prospect. However, CI is usually accompanied by a certain degree of limb dyskinesia due to neurological damage [22-23], so the influence on patients' ability of daily activities is also one of the vital indicators to evaluate the curative effect of CI. Accordingly, to further evaluate the impact of TDCS on clinical symptoms of patients with CI, we used Barthel score and FMA to evaluate patients' ability of daily activities. Consistent with our inference, the results showed that the scores in OG were higher than those in CG after treatment, suggesting that TDCS can improve patients' ability to do daily activities. Further, by observing the NIHSS scores of the two groups, we observed lower post-treatment NIHSS scores in OG than in CG, which further confirmed that the recovery of patients' nerve function after TDCS was more significant. Based on the above, we compared the clinical efficacy of the two groups, and found a much superior total effective rate in OG as compared to CG, suggesting that TDCS plus early rehabilitation therapy can greatly improve the clinical efficacy of patients with early CI, which is one of the important application directions of TDCS in neurological diseases in the future. What's more, the QOL in OG was found to be better than that in CG after treatment, which verified our views and results again.

To sum up, TDCS plus early rehabilitation therapy confers benefits against early CI, which can ameliorate neurological function, hemodynamics, mobility and QOL of patients to a great extent. However, as we only included patients with early CI, and the influence of TDCS on patients with advanced CI remains to be investigated. In addition, the patient base of this study is small, so the sample size of our study needs to be expanded in future research. Moreover, due to the short time frame, we were unable to clarify the influence of TDCS plus early rehabilitation on the long-term prognosis of CI patients. We will carry out more complete experimental analysis to address the aforementioned shortcomings to obtain more convincing experimental results.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, author- ship, and/or publication of this article.

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