Am J Transl Res 2024;16(2):592-598
www.ajtr.org /ISSN:1943-8141/AJTR0154366

Original Article

Effects of scalp acupuncture combined with repetitive transcranial magnetic stimulation on post-stroke cognitive impairment at different time intervals

Daiyan Jiao[1,3*], Jianfeng Lian[2*], Fei Tian[2], Yaqing Zhou[4], Yujue Wang[5], Huiqian Xu[6]

[1]Department of Rehabilitation, Affiliated Hai'an Hospital of Nantong University, Hai'an County, Nantong 226600, Jiangsu, China; [2]Department of Acupuncture, Hai'an Hospital of Traditional Chinese Medicine Affiliated to Nanjing University of Chinese Medicine, Nantong 226600, Jiangsu, China; [3]Department of Acupuncture, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing 210029, Jiangsu, China; [4]Department of Critical Care Medicine, Affiliated Hai'an Hospital of Nantong University, Hai'an County, Nantong 226600, Jiangsu, China; [5]Department of Paediatrics, Rugao Hospital of Traditional Chinese Medicine, Rugao County, Nantong 226500, Jiangsu, China; [6]Department of Rehabilitation, Wuxi Eighth People's Hospital, Wuxi 214011, Jiangsu, China. [*]Equal contributors and co-first authors.

Received November 12, 2023; Accepted February 5, 2024; Epub February 15, 2024; Published February 28, 2024

Abstract: Objective: To investigate the therapeutic efficacy of scalp acupuncture combined with repetitive transcranial magnetic stimulation (rTMS) for post-stroke cognitive impairment at different time intervals. Method: This retrospective cohort study divided patients into two groups according to the timing of the scalp acupuncture combined with rTMS intervention. Group A received scalp acupuncture combined with rTMS at 1 month post-stroke and routine basic treatment and cognitive function training at two months post-stroke. Group B received routine basic treatment and cognitive function training at 1 month post-stroke and scalp acupuncture combined with rTMS at 2 months post-stroke. Both groups underwent cognitive assessment using the Montreal Cognitive Assessment (MoCA) before treatment and at the ends of the first and second months post-stroke. Results: The study population included 92 total stroke patients divided evenly into Groups A and B. Group A's total scores were higher at the end of the first month of treatment compared with baseline and remained stable at the end of the second month of treatment. By contrast, Group B's total score remained stable at the end of the first month of treatment compared with baseline and increased by the end of the second month. There were no significant differences in the scores at baseline or the end of the second month between the two groups. Conclusion: Scalp acupuncture combined with rTMS can effectively treat cognitive function in patients with post-stroke cognitive impairment, regardless of the timing of the intervention.

Keywords: Stroke, cognitive impairment, scalp acupuncture, repetitive transcranial magnetic stimulation

Introduction

In 2020, cerebrovascular diseases were the second most common cause of death in China, resulting in 1.57 million fatalities. According to the 2016 Global Burden of Disease study, China had the highest lifetime risk of stroke worldwide. The 2013 National Epidemiological Survey of Stroke in China reported a stroke prevalence of 1,596/100,000 people [1]. Post-stroke patients often suffer from sequelae, including hemiplegia, aphasia, and dysphagia, among other neurological disorders. Up to 71% of stroke patients experience cognitive dysfunction, and approximately 20% progress to dementia [2]. Moreover, cognitive impairment following a stroke directly affects the recovery of limb movement. Repetitive transcranial magnetic stimulation (rTMS) is an emerging painless, non-invasive therapeutic method that can regulate metabolic and neuroelectrophysiological activity [3]. Scalp acupuncture as a treatment modality adjusts the overall qi and blood of the viscera and meridians to alleviate mental and physical symptoms, restoring them to normalcy. Previous research has shown that scalp

https://doi.org/10.62347/GNWB8482

acupuncture combined with rTMS can improve cognitive impairment in stroke patients and the effect of rTMS lasted up to 18-week follow-up [4-7]. But complications or environmental reasons can hinder patients from receiving prompt and appropriate cognitive care. The current state of research does not appear to have conclusively determined whether acupuncture and rTMS exert varying levels of influence on therapeutic outcomes depending on specific treatment time windows. The novelty of our current research lies in finding the best treatment time window for scalp acupuncture and rTMS therapy in patients with stroke. Thus, the primary aim of this study is to provide robust evidence-based insight into the relationship between treatment timing and effectiveness, to guide more personalized and efficient healthcare strategies.

Experimental methods

Source of cases

The study in question employed a retrospective cohort design. The research was conducted by retrieving information through an electronic medical record system at Hai'an People's Hospital. The subjects of the study were 263 post-stroke patients who received rehabilitation treatment within the time frame of July 1, 2018, to June 30, 2020.

Identification of outcomes

We identified people who met the diagnostic criteria for various cerebrovascular diseases specified by the 4th National Cerebrovascular Disease Academic Conference in 1995 and who had their diagnosis confirmed by cranial MRI or CT examination. To avoid including patients with multiple strokes, we defined the date of diagnosis as the date of the first recorded stroke.

Inclusion criteria

i) The case records of the eligible patients must be complete. ii) We estimated the patients' exposure to clear consciousness (i.e., no serious aphasia or significant cognitive dysfunction [MoCA score >24]) before the stroke onset to identify those with no significant cognitive dysfunction before the onset. iii) All participants were received rTMS stimulation and acupuncture treatment, The acupoints included Baihui, Shenting, Yintang, Sishencong, and bilateral Fengchi [8-10]. Stimulation parameters: site, the unaffected M1 region; stimulation frequency, 1 Hz; intensity, 120% of the motor threshold; stimulation time, 2 seconds; interval time, 20 seconds [11-14]. iv) All participants were younger than 70 years old, right-handed, and able to cooperate with treatment and evaluation.

Exclusion criteria

The exclusion criteria were i) multiple onsets of the disease, ii) history of transcranial surgery, iii) previous history of brain trauma, cerebral hemorrhage, epilepsy, cognitive impairment, or mental illness, iv) cognitive defects due to reasons other than stroke (e.g., drug abuse, excessive alcohol consumption), v) serious liver, kidney, heart diseases or other significant physical ailments, and vi) inability to cooperate with clinical examinations due to, e.g., severe hearing, or vision impairments.

Data collection

Data from eligible patients, included each participant's age, sex, occupational status, MoCA score, and highest level of education attained. The MoCA includes seven components, which were considered primary outcomes: visuospatial and executive functions, naming, attention, language, abstraction, delayed recall, and orientation.

The data from eligible patients were divided into two groups according to the time of the scalp acupuncture combined with rTMS intervention. Group A received scalp acupuncture combined with rTMS at 1 month post-stroke and routine basic treatment and cognitive function training at 2 months post-stroke. Group B received routine basic treatment and cognitive function training at 1 month post-stroke and scalp acupuncture combined with rTMS at 2 months post-stroke.

Outcome measures and statistical analysis

Patients were evaluated using the MoCA before treatment and at the ends of the first and second months post-stroke. The MoCA includes seven components and each correct answer on the assessment was scored as 1 point, and

Table 1. Baseline characteristics of all enrolled post-stroke patients

Variable	Group A	Group B	P	t/χ²
Sex (male/female)	24/22	22/24	0.527	0.400
Age, mean (SD), years	59.90 (17.8)	65.20 (12.75)	0.343	0.733
Type of stroke (hemorrhagic/ischemic)	23/23	10/36	0.43	-0.7824
Education, mean (SD), years	8.35 (3.12)	9.00 (4.15)	0.22	-1.2193
Disease duration (days)	20.80 (6.09)	21.85 (9.84)	0.437	-0.786
MoCA (score)	14.50 (2.27)	14.00 (2.91)	0.410	-0.872

MoCA: Montreal Cognitive Assessment.

each incorrect or unanswered item was scored as 0 points, such that higher scores indicated better cognitive function. The highest possible score was 30 points, and the total score was the main outcome measurement.

Statistical analyses were performed using SPSS 22.0. P-P plots were used to analyze the normality of the quantitative data. Data conforming to a normal distribution were represented as the mean ± standard deviation. Independent sample t-tests were used for comparisons between the two groups. The scores for each MoCA dimension were subjected to a sphericity test, and those exhibiting sphericity were analyzed using repeated measures analysis of variance. Counted data were analyzed using Fisher's exact test. *P*-values less than 0.05 were considered significant.

Quality control

As this was a retrospective study, no patients or members of the public were involved in the design, conduct, reporting, or dissemination plans of our research. All doctors and rehabilitation therapists underwent standardized training and had over 10 years of work experience. This research has been approved by the Ethics Committee of Hai'an People's Hospital. The ethical approval number is (HKL2018029).

Results

We identified 263 people with stroke from the target population. After excluding patients with a diagnosis or previous history of brain trauma, cerebral hemorrhage, epilepsy, cognitive impairment, or mental illness before baseline, the final study population comprised 46 participants in Group A and 46 participants in Group B.

We compared the patients' sex, type of stroke, age, education, and time since stroke and found no significant difference between the two groups (P>0.05; **Table 1**). Next, we evaluated the MoCA scores (**Table 2**). Group A's total scores were higher at the end of the first month of treatment compared to baseline and remained stable at the end of the second month of treatment. By contrast, Group B's total scores remained stable at the end of the first month of treatment compared to baseline and increased by the end of the second month of treatment. Both groups showed significant main effects over time in visuospatial and executive functions, naming, attention, language, abstraction, delayed recall, and orientation. Group A's scores at the ends of the first and second months were higher than those at baseline, whereas Group B's scores at the end of the second month were higher than both the baseline scores and those at the end of the first month (both P<0.05). Group B's score at the end of the first month was lower than Group A's (P<0.05). However, there were no significant differences between groups in the scores at baseline or the end of the second month (P>0.05).

Discussion

Cognitive impairment is frequently associated with stroke. A stroke occurs when the blood supply to a part of the brain is interrupted or reduced, depriving brain tissue of oxygen and nutrients. This can lead to the death of brain cells in the affected area, which may result in various cognitive deficits depending on the location and extent of the damage. Cognitive function is a complex mental activity that enables humans to understand, interpret, and respond to the world around them. It involves various psychological processes including at-

Table 2. Comparison between the two groups before treatment, at 1 month post-stroke, and at 2 months post-stroke

Group	Visuospatial & executive function			Naming			Attention		
	Baseline	First month	Second month	Baseline	First month	Second month	Baseline	First month	Second month
A	2.30±0.48	3.70±0.48[a]	3.60±0.52[a]	1.80±0.79	2.40±0.70[a]	2.50±0.53[a]	3.00±0.47	4.10±0.99[a]	4.30±0.82[a]
B	2.40±0.52	2.80±0.79	3.50±0.53[a,b]	1.70±0.67	1.80±0.79	2.40±0.52[a,b]	2.90±0.74	3.10±0.57	4.20±1.14[a,b]

Group	Language			Abstraction			Delayed recall		
	Baseline	First month	Second month	Baseline	First month	Second month	Baseline	First month	Second month
A	1.70±0.82	2.40±0.70[a]	2.30±0.82[a]	0.40±0.52	1.10±0.74[a]	1.20±0.79[a]	1.70±0.48	2.80±0.79[a]	2.90±0.74[a]
B	1.60±0.70	1.90±0.99	2.40±0.70[a,b]	0.60±0.52	0.60±0.52	1.50±0.71[a,b]	1.50±0.53	1.60±0.70	2.60±0.70[a,b]

Group	Orientation			Scores		
	Baseline	First month	Second month	Baseline	First month	Second month
A	3.60±0.70	4.30±0.67[a]	4.50±0.85[a]	14.50±1.27	20.80±1.48[a]	21.10±1.45[a]
B	3.30±0.95	3.30±0.95	4.40±1.17[a,b]	14.00±1.91	15.10±1.14[*]	20.30±1.26[a,b]

Notes: a = Significant compared with baseline in the same group, P<0.05; b = Significant compared with the end of the first month in the same group, P<0.05; * = Significant compared with Group A at the same time, P<0.05.

tention, memory, perception, reasoning, and language [15]. When these functions are impaired due to conditions such as stroke, traumatic brain injury, or neurodegenerative diseases like Parkinson's, this can significantly affect an individual's quality of life [16]. Traditional Chinese Medicine (TCM) has a deep historical background in addressing cognitive dysfunction following strokes [17]. Early TCM texts, such as "Za Bing Yuan Liu Xi Zhu·Zhong Feng", provide records of post-stroke forgetfulness, recognizing it as a cognitive impairment [18]. The classic medical text "Ben Cao Bei Yao" by Wang Ang underscores the role of the brain in memory storage, while Wang Qingren's "Yi Lin Gai Cuo·Nao Sui Shuo" explains memory capacity through the concept of brain marrow development across different life stages [19, 20].

The "Huangdi Neijing", one of the foundational classics of TCM, describes the Du meridian - a key energy pathway in acupuncture theory - which originates at the base of the spine and ascends to connect with the brain [21]. This meridian is metaphorically known as the 'Sea of Yang Meridians' and its trajectory corresponds closely to the anatomic location of the frontal lobe and midbrain regions which play significant roles in cognitive function in modern neuroscience [22]. In this context, specific acupuncture points along the Du meridian such as "Bai Hui", "Shen Ting", and "Si Shen Cong" are believed to have a direct connection to the brain and thus may be used to stimulate cognitive improvement. These points are strategically located where they might influence the brain's activities, aligning with the TCM principle of harmonizing and awakening the functions of the brain and marrow sea. Through acupuncture and other TCM treatments, practitioners aim to restore cognitive function by stimulating these pathways, enhancing blood flow, and promoting the body's natural healing process.

Contemporary research shows that acupuncture may exert its effects on neurological conditions like post-stroke cognitive impairment through modulation of several molecular pathways. The six key signaling pathways mentioned-NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), PI3K/Akt (phosphoinositide 3-kinase/protein kinase B), MAPK (mitogen-activated protein kinases), JAK/STAT (Janus kinase/signal transducer and activator of transcription), CREB (cAMP response element-binding protein), and Notch - are all involved in various cellular processes including inflammation, cell survival, proliferation, differentiation, and synaptic plasticity, all of which play critical roles in neuronal recovery after stroke [23-28]. Acupuncture has shown potential to positively regulate these pathways, thus enhancing neuroprotection, reducing inflammation, promoting neural regeneration, and improving cognitive function. This highlights the therapeutic use of acupuncture in treating post-stroke cognitive dysfunction and contributes to the growing body of evidence supporting integrative medicine approaches for neurological disorders.

Neuroplasticity, the brain's ability to reorganize and form new neural connections throughout life, is a fundamental mechanism underlying recovery from neurologic conditions such as post-stroke cognitive impairment. High-frequency transcranial magnetic stimulation (HF-TMS) stimulates neuroplastic changes by increasing calcium levels, upregulating AMPA receptors, and inducing long-term potentiation (LTP), which enhances cortical excitability and can improve cognitive function when targeted at specific areas like the left dorsolateral prefrontal cortex (DLPFC) [29, 30]. On the other hand, low-frequency TMS (LF-TMS) tends to decrease calcium concentration, downregulate AMPA receptors, and induce long-term depression (LTD), thereby reducing cortical excitability [31, 32]. This reduction in excitability has been associated with improvement in certain cognitive domains, particularly memory, speech, attention, and executive function. Studies (e.g., Kwon et al. [33]) have shown that high-frequency transcranial magnetic stimulation (TMS) on the left dorsolateral prefrontal cortex significantly improves cognitive function, facilitating patients' learning processes and daily activities, such as dressing and eating. High-frequency TMS can increase the calcium ion concentration in post-synaptic neurons, elevate AMPA receptor levels, induce LTP, and enhance the excitability of the affected cerebral cortex. Low-frequency TMS has the opposite effect, decreasing the calcium ion concentration in post-synaptic neurons, reducing AMPA receptor levels, inducing LTD, and reducing the excitability of the unaffected cerebral cortex [34].

In this cohort study of stroke patients in the acute or recovery phase, we found that combined treatment with scalp acupuncture and rTMS could improve cognitive function, accelerate the overall recovery process after a stroke, and enhance patients' quality of life. It was shown that while there might not be significant differences between the combined therapy group and control groups at baseline or after eight weeks of treatment, there was a significant improvement observed after four weeks of treatment. The fact that both treatments led to significant improvement in cognitive function after eight weeks suggests that this integrative therapeutic strategy may have a lasting impact on cognitive recovery post-stroke. Moreover, these findings imply that even if the treatment is initiated later, it can still yield positive outcomes, emphasizing the potential for acupuncture and LF-rTMS as effective and possibly time-flexible interventions in managing post-stroke cognitive impairment. However, more research is necessary to further validate these results and understand the exact mechanisms through which these two modalities interact to promote neuroplasticity and cognitive rehabilitation. Late treatment time did not reduce the therapeutic effect of the combined treatment. If these findings are confirmed in future studies, they may substantially improve the estimation of the best intervention time.

One limitation in the study's methodology was that we did not deeply explore or find all relevant factors, and the data records may not have been accurate enough, resulting in increased data errors. Additionally, the research did not delve deeply enough into identifying and incorporating all pertinent variables that could influence the outcome. The absence of comprehensive data on lifestyle factors, known to play a crucial role in cognitive impairment risk, introduces another layer of methodologic constraint. This oversight may result in exposure misclassification, where participants might be categorized incorrectly with regard to their actual risk level due to the lack of information on these critical factors. In essence, the limitations encompass both the precision of collected data and the comprehensiveness of considered risk factors, thereby possibly affecting the validity of the study's conclusions.

Disclosure of conflict of interest

None.

Address correspondence to: Huiqian Xu, Department of Rehabilitation, Wuxi Eighth People's Hospital, Wuxi 214011, Jiangsu, China. E-mail: maxiaqing@sjtu.edu.cn

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