Assessing the Effects of Oxiracetam Conjoined with rTMS in Mild Cognitive Impairment Following Craniocerebral Injury

JIAYOU LU, C. SONG[1], YONGLIN ZHONG[2], KE LIU[2] AND FASEN LU[3]*

Department of Surgery, [1]Department of Traditional Chinese Medicine, [2]Department of Rehabilitation Medicine, [3]Department of Internal Medicine, Chongqing Western Rehabilitation Hospital, Yuzhong, Chongqing 400331, China

In an effort to evaluate the therapeutic impact of oxiracetam in conjunction with repetitive transcranial magnetic stimulation, the current research endeavors to assess patients with mild cognitive impairment after craniocerebral injury. Over a period spanning from March 2020 to March 2023, 160 patients diagnosed with mild cognitive impairment were involved in this research and randomly separated into either the control group treated exclusively with oxiracetam or the study group receiving a combined treatment of oxiracetam and repetitive transcranial magnetic stimulation. The changes of intelligence, cognitive function and neurotransmitter indexes were observed. Upon completion of the treatment regimen, the study group displayed substantial increases in both mini mental state examination and Montreal cognitive assessment scores than the control group. Additionally, the study group exhibited markedly higher levels of neurotransmitters such as norepinephrine, serotonin and dopamine compared to the control ($p<0.05$). The improvement rate of the study group was remarkably higher at 88.75 % as compared to their counterparts in the control group who exhibited an improvement rate of 65.00 %. This difference was statistically significant between the two groups ($p<0.05$). The implementation of a combined treatment strategy featuring both oxiracetam and repetitive transcranial magnetic stimulation in patients diagnosed with mild cognitive impairment yielded promising results, effectively mitigating cognitive impairment, enhancing neurotransmitter function and expediting overall improvement of patient wellbeing.

Key words: Craniocerebral injury, cognitive dysfunction, oxiracetam, repetitive transcranial magnetic stimulation, neurotransmitter

Mild Cognitive Impairment (MCI) after craniocerebral injury refers to the mild cognitive decline caused by craniocerebral injury. The main symptoms of patients are mild impairment in attention, memory and learning ability, but have not yet reached obvious dementia symptoms[1]. At present, there are many clinical studies on MCI treatment, but it has not yet formed a standardized treatment plan. The treatment methods mainly include drug therapy, cognitive rehabilitation training, psychological intervention, lifestyle adjustment and so on, but the therapeutic effects are different and need to be further explored. Non-invasive neuroregulatory methods such as repetitive Transcranial Magnetic Stimulation (rTMS) have been receiving significant attention in recent years for their potential in the management of nervous system diseases. Some recent studies have shown that rTMS has potential clinical significance in the treatment of MCI[2,3]. However, the related research is still in the preliminary stage, warranting the need for additional studies to confirm its safety and effectiveness. This study mainly discusses the clinical effect and effect of oxiracetam+rTMS regimen in the treatment of MCI patients. A total of 160 MCI patients were randomly selected from March 2020 to March 2023 in our hospital. Allocation of participants into two groups was random using a numbered table. The control group included 48 male and 32 female participants, aged between 30 y-60 y, with an average age of (48.73±5.39) y. The average Glasgow Score (GCS) for the control group was 13.73±1.26 points, with a score range of 12-15 points. Within the study group were 49 males and 31 females, with ages ranging between 30 y-65 y and an average age of (48.88±6.61) y old. The average GCS for the study group was 13.66±1.97 points, with a score range of 12-15 points. The statistical analysis revealed no significant difference between groups

***Address for correspondence**
E-mail: NEURO-REHAB@mail.bnu.edu.cn

($p>0.05$). Inclusion criteria meet the diagnostic criteria of MCI[4]; mild symptoms, no impact on daily life and work; over 18 y old, no gender restrictions; stable condition, normal cognitive and understanding ability, can cooperate with the completion of treatment and evaluation; a signed informed consent form was obtained from the patient and their family members. Exclusion criteria have allergic or adverse reactions to oxiracetam or rTMS; severe cognitive disorders such as moderate and severe dementia; severe emotional and mental disorders such as depression and anxiety disorders; severe history of craniocerebral trauma or other neurological diseases; receiving other therapeutic interventions, such as other brain electrical stimulation, drug therapy, etc.; severe intellectual or language disorders. The treatment protocol for patients in the control group included the administration of oxiracetam (Stone Pharmaceutical Group Ouyi Pharmaceutical Co., Ltd., H20100040). 4.0 g of the drug was added to 5 % glucose in 250 ml or 0.9 % sodium chloride injection in 250 ml, and then injected intravenously once a day. The time of drug treatment was 21 d, and other brain nutrients were not used at the same time. Oxiracetam was administered to patients in the study group along with rTMS as part of their treatment. The specific use of oxiracetam was the same as that of the control group. The instrument used in rTMS treatment is Magstim® transcranial magnetic stimulation instrument (made in United Kingdom (UK)). During the treatment, the coil was placed horizontally in the dorsolateral area of the left forehead and the stimulation frequency was 0.5Hz, the stimulation time was 2 s, and the interval was 8 s. The treatment regimen consisted of a 20 min session administered once daily for a duration of 21 d. In the course of treatment, psychiatric rehabilitation specialists monitor the whole process of patients, timely understand the condition of patients, and find out that patients have obvious discomfort reactions and deal with them in time. Cognitive function assessment including the Mini-Mental State Examination (MMSE) and Montreal Cognitive Function Scale (MoCA) were used to evaluate the cognitive function of the patients both prior to and following treatment. MMSE scores range from 0-30, with scores of 0-9 indicating severe cognitive impairment; 10-20 indicating moderate cognitive impairment; 21-26 indicating MCI and 27-30 indicating normal cognitive function[5]. The MoCA has a total score of 30, with scores ≥26 considered normal. Higher scores on the assessment correspond with better cognitive function[6]. Evaluation of neurotransmitter level including the prior to treatment and after treatment, patients provided fasting venous blood samples which were centrifuged at 3000 r/min for 10 min. The supernatant was then stored at -70° for subsequent testing. The levels of plasma neurotransmitters were detected by Ultra-Fast Liquid Chromatography (UFLCXR) high performance liquid chromatograph produced by Shimadzu Company of Japan. The detection indexes were Dopamine (DA), Norepinephrine (NE) and 5-Hydroxytryptamine (5-HT). Evaluation of total curative effect including the after treatment, the main clinical symptoms, and the assessment of cognitive and neurological function following treatment revealed significant improvement in the patient group, with a degree of improvement exceeding 90 %. This improvement was considered to be significant; after treatment, the clinical symptoms, cognitive and neurological function were significantly improved and the degree of improvement was more than 50 %, which was determined to be a partial improvement. After treatment, the improvement of symptoms, nerve and cognitive function did not reach the above standard, which was judged as no improvement[7]. Significant improvement rate+partial improvement rate=improvement rate. Descriptive statistics for the counting data were presented as percentages, and a Chi-square (χ^2) test was performed to assess differences. For measurement data, the mean±standard deviation was analyzed using a paired t-test for within-group comparison. Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) 25.0, with a $p<0.05$ considered significant. Prior to treatment, no significant differences were observed in MMSE or MoCA scores between the two groups. However, following the respective treatments, the study group exhibited significantly higher MMSE and MoCA scores compared to the control group ($p<0.05$) as shown in Table 1. Before treatment, there were no significant differences found in the levels of NE, 5-HT, and DA between the study and control groups. However, after treatment, the levels of NE, 5-HT and DA were notably elevated in the study group as compared to the control group, with a statistically significant difference as shown in Table 2. Table 3 indicates that the clinical improvement rate observed in the study group was significantly better than that of the control group following treatment, with a

statistically significant difference ($p<0.05$). Craniocerebral injury is a kind of brain injury caused by violent blow or impact on the head. Craniocerebral injury can not only seriously endanger human health, but also directly endanger life. Craniocerebral injury will cause direct or indirect damage to the brain, which is easy to cause different degrees of cognitive dysfunction. The impact of craniocerebral injury on cognitive function has been well-documented in multiple studies[8,9]. In recent years, more and more researchers continue to strengthen in-depth research on the effective and safe treatment of patients with cognitive impairment after craniocerebral injury. At present, the main clinical methods for the treatment of MCI patients are drug therapy, comprehensive treatment and rehabilitation training, while the research of rTMS combined with drug therapy is still relatively few and the effect and effect are not clear. Therefore, this study strengthens the in-depth study of this aspect, in order to further clarify the application effect and value of this treatment. Oxiracetam is a commonly used antiepileptic drug in clinic, and its chemical structure is similar to that of piracetam. After intravenous infusion of oxiracetam, the drug can get through the blood-brain barrier and be distributed in different regions of the brain to regulate the ascending activation of cholinergic neurons and promoting the release of acetylcholine[10]. At the same time, oxiracetam can also act on proline endopeptidase to improve the patient's memory. Prior research has suggested that the addition of oxiracetam to other drugs can be effective in improving cognitive function and activities of daily living in elderly patients with MCI and those suffering from cognitive impairment after cerebral infarction[11]. rTMS is a non-invasive brain stimulation technique, its principle is through the principle of electromagnetic induction acting on the human head surface, in order to change the neural excitability of the brain region[12]. At present, rTMS is widely applicant in treating depression and other neuropsychiatric diseases[13]. It is showed in this research that after 60 MCI patients were treated with rTMS+oxiracetam regimen, resulted in significant increases in MMSE and MoCA scores, with these improvements found to be significantly greater than those observed in the control group receiving oxiracetam alone. Furthermore, the study group exhibited significantly more prominent levels of NE, 5-HT and DA in comparison with the control group, suggestive of a positive impact of the rTMS+oxiracetam regimen on both cognitive function and neurotransmitter levels. The reason may be that oxiracetam is a selective cholinergic M1 receptor agonist, which can improve cognitive function by regulating the transmitter level of the cholinergic system. Studies have reported that oxiracetam can lead to increased levels of acetylcholine in the brain, thereby facilitating improved neuronal signal transmission[14]. In addition, oxiracetam can also affect a variety of neurotransmitter systems, such as increasing the release of DA and NE, reducing the release of glutamic acid and aspartic acid, and increasing the level of neurotransmitters in this way. rTMS is a non-invasive method to stimulate brain regions and its mechanism involves a variety of neurotransmitter systems. rTMS can promote the activity of neurons in the brain, and change the connection and signal transmission between neurons through long-term inhibition and enhancement, thus affecting the level of a variety of neurotransmitters. Previous studies have shown that rTMS can significantly affect the levels of glutamate and serotonin[15]. Therefore, oxiracetam combined with rTMS regimen is used in the treatment of MCI patients, both of them can enhance patient cognitive function and neurotransmitter levels through their own ways. The resultant synergistic effect of these interventions manifests in significantly improved cognitive function and neurotransmitter indicators, producing a more holistic and effective therapeutic outcome for patients. Notably, the study group demonstrated a significantly superior total improvement rate compared to the control group. To sum up, rTMS joints oxiracetam in treating MCI patients can help to enhance the cognitive function of patients, and can efficiently regulate the level of neurotransmitters and improve the overall efficacy.

TABLE 1: COMPARISON OF VAS AND ODI SCORES ($\bar{x}\pm s$)

Group	n	MMSE score		MoCA score	
		Before	After	Before	After
Control	80	22.31±3.84	23.74±3.53	18.37±4.52	20.74±4.09
Study	80	22.46±4.77	27.84±2.17	18.30±3.60	24.36±2.75
t		0.219	8.850	0.108	6.570
p		0.827	<0.05	0.914	<0.05

TABLE 2: COMPARISON OF THE IMPROVEMENT OF PLASMA NEUROTRANSMITTER LEVELS (x̄±s)

Group	n	NE		5-HT		DA	
		Before	After	Before	After	Before	After
Control	80	7.70±2.07	12.12±3.73	8.15±1.36	11.85±2.49	9.98±2.42	10.63±2.39
Study	80	7.74±2.13	16.16±4.88	8.18±1.25	14.09±2.68	9.95±2.39	13.56±3.51
t		0.120	5.883	0.145	5.477	0.079	6.171
p		0.904	<0.001	0.885	<0.001	0.937	<0.001

TABLE 3: COMPARISON OF SERUM INFLAMMATORY FACTORS (x̄±s)

Group	n	Significant improvement	Partial improvement	No improvement	Improvement rate
Control	80	27 (33.75)	25 (31.25)	28 (35.00)	52 (65.00)
Study	80	49 (61.25)	22 (27.50)	9 (11.25)	71 (88.75)
χ^2					12.692
p					<0.001

Author's contributions:

Jiayou Lu and Changpeng Song have contributed equally to this work.

Conflict of interests:

The authors declared no conflict of interests.

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This article was originally published in a special issue, "Drug Development in Biomedical and Pharmaceutical Sciences" Indian J Pharm Sci 2023:85(5) Spl Issue "154-157"