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# Application of Low-frequency Repetitive Transcranial Magnetic Stimulation in Patients with Sleep Disorders after Traumatic Brain Injury

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**Abstract**

**Objective:** Our study aims to explore the application of low-frequency repetitive transcranial magnetic stimulation (rTMS) in patients with sleep disorders after traumatic brain injury (TBI). **Methods:** 47 patients with sleep disorders after TBI, who received rTMS combined with conventional treatment in our hospital from January 2022 to May 2023, were allocated into the observation group, and 43 patients with sleep disorders after TBI receiving conventional treatment during the same period were assigned into the control group. The clinical efficacy and adverse reaction in the two groups were compared, and the differences of sleep disorder score and neurotrophic factor expression before and after treatment were observed. **Results:** The total effective rate of clinical efficacy was significantly higher and the total incidence of adverse reaction was obviously lower in observation group than those in control group ($p < 0.05$). After treatment, pittsburgh sleep quality index was visibly decreased in both groups ($p < 0.05$), and that in the observation group was significantly lower than that in the control group ($p < 0.05$). The levels of brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor were markedly increased in both groups ($p < 0.05$), and those in the observation group was significantly higher than those in the control group ($p < 0.05$). **Conclusion:** RTMS has a good clinical efficacy in the treatment of sleep disorders after TBI, which has a good effect in improving sleep disorders and expressions of neurotrophic factors, with high safety.

## 1 Introduction

Traumatic brain injury (TBI) is a disease in which the normal function of the brain is impaired by a penetrating injury after a hit or bump to the head, with the characteristics of high morbidity, disability, and mortality [1]. TBI can be classified as mild (GCS 13-15), moderate (GCS 9-12), and severe (GCS 3-8) [2]. Patients often experience varying degrees of impaired consciousness or mental changes, and in severe cases they may even experience prolonged unconsciousness, coma, or death [3]. Sleep disorders are a common complication of TBI, with insomnia being the predominant sleep disorder in patients with mild TBI and somnolence being the predominant sleep disorder in patients with moderate and severe TBI [4].

The treatment of sleep disorders in TBI mainly includes drug treatment and non-drug treatment. Physical therapy, as a common method for this disease, has a good therapeutic effect in clinical application [5,6]. Low-frequency repetitive transcranial magnetic stimulation (rTMS) is a non-invasive physical therapy commonly used in the treatment of neurological disorders, including stroke, TBI, etc., and mental disorders such as depression and insomnia [7]. Previous study showed that rTMS can improve neural function, motor function and cortical excitation in ischemic stroke [8]. rTMS also can target the prefrontal cortex to treat anxiety disorders [9]. Moreover, Nardone et al. have showed that rTMS can reduce cortical hyperexcitability and improve sleep quality in patients with sleep disorders by stimulating the right dorsolateral prefrontal cortex or posterior parietal cortex [10].

Based on these, this study applied rTMS in patients with sleep disorders after TBI, explored the clinical efficacy and adverse reaction of this method, and compared the changes in sleep disorder score and neurotrophic factor expression before and after the treatment, aiming to provide more references for the treatment of sleep disorders in TBI.

## 2 Methods and methods

### 2.1 General data

47 patients with sleep disorders after TBI, who received rTMS combined with conventional treatment in our hospital from January 2022 to May 2023, were allocated into the observation group, and 43 patients with sleep disorders after TBI receiving conventional treatment during the same period were assigned into the control group. The difference between the two groups of patients in terms of gender, age, and degree of disease was not statistically significant ($p > 0.05$), but was comparable, as seen in Table 1.

**Table 1** Comparison of general data in the two groups (mean ± standard deviation).

| Groups | Cases | Gender (cases) | | Age (years old) | Degree of disease (cases) | |
|---|---|---|---|---|---|---|
| | | Male | Female | | Mild | Moderate |
| Control group | 43 | 22 | 21 | 38.77 ± 7.06 | 35 | 8 |
| Observation group | 47 | 25 | 22 | 37.57 ± 5.98 | 37 | 10 |
| $t/\chi^2$ | | 0.037 | | 0.873 | 0.100 | |
| $p$ | | 0.847 | | 0.385 | 0.752 | |

### 2.2 Inclusion and exclusion criteria

#### 2.2.1 Inclusion criteria

(1) Patients met the diagnostic criteria for sleep disorders in Guidelines for the diagnosis and treatment of adult insomnia in China (2017 edition) [11]. (2) Patients were diagnosed with mild to moderate TBI after imaging examination. (3) Patients were diagnosed for the first time and had not received

systemic treatment. (4) Patients with a quiet sleep environment.

#### 2.2.2 Exclusion criteria

(1) Patients with a history of sleep disorders such as severe insomnia. (2) Patients with serious complications such as intracranial infections. (3) Patients with unstable vital signs and unconsciousness. (4) Patients with insufficiency in vital organs such as liver and kidney. (5) Patients with psychiatric disorders and poor treatment compliance. (6) Patients with alcohol or psychotropic substance abuse.

### 2.3 Method

#### 2.3.1 Control group

Patients took estazolam tablets (National Medical Products Administration (NMPA) approval No.: H44022484, specification: 1 mg/tablet) orally at bedtime, with 1 tablet per day for a total of 7 days.

#### 2.3.2 Observation group

Based on the treatment in Control group, patients were treated by rTMS using magnetic field stimulator (CCY, Yiruide, Wuhan, China). Patients were asked to take the supine position, and their bilateral dorsolateral prefrontal cortex and parieto-occipital regions were stimulated. The parameters were set at a stimulation time of 10 s, an interval of 5 s, a frequency of 1 Hz, a repetition rate of 100 times, and duration of 25 min. The treatment period was 7 days.

### 2.4 Observational indicators

#### 2.4.1 Clinical efficacy

Clinical efficacy was evaluated according to the Pittsburgh Sleep Quality Index (PSQI) score [12]. Criteria were detailed below. Cured: PSQI score with a decrease of more than 75% after treatment; significant effective: PSQI score with a decrease of more than 50% after treatment; effective: PSQI score with a decrease of more than 25% after treatment; ineffective: PSQI score did not decrease by more than 25% or even increased after treatment. The clinical total effective rate = the number of (cured + significantly effective + effective) cases / total number of cases × 100%.

#### 2.4.2 Sleep disorder score

PSQI score (total score: 21 points) was used to assess the sleep quality of patients in the two groups, which consisted of seven dimensions, with each dimension scored 0 to 3 points. PSQI score was negatively correlated with the sleep quality of patients.

#### 2.4.3 Neurotrophic factors

Before and after 7 days of treatment, 5 ml of fasting peripheral venous blood was collected from the two groups of patients in the early morning, left at room temperature for 30-60 min, and centrifuged at 3,000 r/min for 10 min. Afterwards, the serum was separated and stored at -20 ℃ for measurement. The levels of brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) were detected by enzyme-linked immunosorbent assay using a kit (YS01139B, YS01120B) purchased from Shanghai YaJi Biotechnology Co., Ltd. All operations were carried out with strict reference to the instructions of the kits.

#### 2.4.4 Adverse reaction

The occurrence of fatigue, dizziness, nausea, vomiting, and drowsiness was recorded in both groups.

### 2.5 Statistical methods

Statistical analysis was performed using SPSS 20.0. Count data were expressed as cases (%), comparisons between the two groups were carried out using $\chi^2$ test, and measurement data were denoted as mean ± standard deviation. Independent samples *t*-test was used for the comparison between the two groups, and paired samples *t*-test was utilized for the comparison in the same group at different time points. Differences

were considered to be statistically significant at $p < 0.05$.

## 3 Results

### 3.1 Comparison of clinical efficacy between the two groups

The total effective rate of clinical efficacy was significantly higher in observation group than that in control group ($p < 0.05$), as displayed in Table 2.

**Table 2** Comparison of clinical efficacy between the two groups [cases (%)].

| Groups | Cases | Cured | Significantly effective | Effective | Ineffective | Total effective rate |
|---|---|---|---|---|---|---|
| Control group | 43 | 13 (30.23) | 15 (34.88) | 6 (13.95) | 9 (20.93) | 34 (79.07) |
| Observation group | 47 | 21 (44.68) | 18 (38.30) | 5 (10.64) | 3 (6.38) | 44 (93.62) |
| $\chi^2$ | | | | | | 4.112 |
| $p$ | | | | | | 0.043 |

### 3.2 Comparison of sleep disorder score between the two groups

Before treatment, the difference between PSQI score in the two groups was not statistically significant ($p > 0.05$). After treatment, PSQI score in the two groups was obviously lower ($p < 0.05$), and the score in the observation group was significantly lower than that in the control group ($p < 0.05$). The results were seen in Table 3.

**Table 3** Comparison of sleep disorder score between the two groups (mean ± standard deviation).

| Groups | Cases | PSQI (score) | |
|---|---|---|---|
| | | Before treatment | After treatment |
| Control group | 43 | 13.57 ± 2.64 | 9.04 ± 2.43 * |
| Observation group | 47 | 13.34 ± 2.48 | 5.21 ± 2.16 * |
| $t$ | | 0.426 | 7.916 |
| $p$ | | 0.671 | < 0.001 |

Note: Comparison with before treatment: * $p < 0.05$.

### 3.3 Comparison of serum indicators between the two groups

Before treatment, there was no statistically significant difference between the levels of BDNF and GDNF in the two groups ($p > 0.05$). After treatment, the levels of BDNF and GDNF in the two groups were significantly elevated ($p < 0.05$), and the levels in the observation group were significantly higher than those in the control group ($p < 0.05$), as shown in Table 4.

**Table 4** Comparison of serum indicators between the two groups (mean ± standard deviation).

| Groups | Cases | BDNF (ng/L) | | GDNF (ng/L) | |
|---|---|---|---|---|---|
| | | Before treatment | After treatment | Before treatment | After treatment |
| Control group | 43 | 13.06 ± 2.62 | 15.34 ± 3.12 * | 334.54 ± 26.15 | 414.79 ± 30.58 * |
| Observation group | 47 | 12.88 ± 2.13 | 18.64 ± 3.55 * | 338.44 ± 27.38 | 468.66 ± 43.45 * |
| $t$ | | 0.359 | 4.666 | 0.690 | 6.743 |
| $p$ | | 0.721 | < 0.001 | 0.492 | < 0.001 |

Note: Comparison with before treatment: * $p < 0.05$.

### 3.4 Comparison of adverse reaction between the two groups

The total incidence of adverse reaction was obviously lower in observation group than that in control group ($p < 0.05$), as displayed in Table 5.

**Table 5** Comparison of adverse reaction between the two groups [cases (%)].

| Groups | Cases | Fatigue | Dizziness | Nausea and vomiting | Drowsiness | Total incidence |
|---|---|---|---|---|---|---|
| Control group | 43 | 2 (4.65) | 1 (2.33) | 2 (4.65) | 5 (11.63) | 10 (23.26) |
| Observation group | 47 | 1 (2.13) | 1 (2.13) | 0 (0.00) | 1 (2.13) | 3 (6.38) |
| $\chi^2$ | | | | | | 5.173 |
| $p$ | | | | | | 0.023 |

## 4 Discussion

In order to investigate the clinical efficacy of rTMS for the treatment of patients with sleep disorders after TBI, this study used different treatment methods for 90 patients with sleep disorders after TBI. Our results revealed that the total effective rate of clinical efficacy was significantly higher in observation group than that in control group, suggesting that rTMS has a good clinical efficacy in the treatment of sleep disorders after TBI.

Sleep disorder is a common complication in patients with TBI, which is often caused by nausea, vomiting, and pain, seriously affecting patients' health and quality of life [13,14]. PSQI score is a commonly used scale to clinically assess the severity of sleep disorders, and a higher score can indicate a more severe sleep disorder of the patients [15]. Our study revealed that rTMS can improve sleep disorders of patients after TBI, with a better effect. rTMS is a non-invasive neuromodulation technique that can reduce sleep disorders in patients by improving cerebral blood flow, regulating melatonin production, and decreasing patients' cortical excitability [16,17]. Yuan et al. found that rTMS was effective in improving sleep quality in patients with chronic insomnia, and their experimental results were similar to the results of this experiment [18]. Therefore, rTMS has a role in reducing sleep disorders of patients after TBI.

BDNF is a neuropeptide that is distributed in the brain and has an important role in neural development and differentiation [19]. Rahmani et al. demonstrated that the expression of BDNF is also associated with sleep deprivation- and insomnia-related changes in the central nervous system, and down-regulation of BDNF expression can indicate the damage of nervous system and occurrence of sleep disorders [20]. GDNF is a protein that promotes neuronal cell development, survival and maintenance and has a neuroprotective effect [21]. The research of Wang et al. concluded that GDNF and related neurotransmitters have an important role in sleep-wake regulation and low level of GDNF may lead to exacerbation of sleep disorders [22].

This study uncovered that rTMS can repair neurological damage and reduce sleep disorders of patients after TBI, and its efficacy was better. rTMS can inhibit cortical excitability by affecting the release of neuroendocrine substances, such as BDNF [23]. At the same time, rTMS is also able to activate the cortex-subcortical neural network structure, induce the electric field in the brain, and formed induced currents, which promotes the functional reconstruction of the brain tissue and the repair of neurological damage, and thus reduces the sleep disorders [24]. The study of Wang et al. showed that

rTMS increased BDNF and GDNF levels in patients, and their experimental results were similar to the results of the present experiment [25]. Therefore, rTMS plays a part in repairing neurological damage and reducing sleep disorders of patients after TBI.

In addition, it has been found that rTMS can reduce adverse reaction of patients [26]. Our study unveiled that the total incidence of adverse reaction, such as fatigue, dizziness, nausea, vomiting, and drowsiness, was obviously lower in observation group than that in control group. These findings indicated that rTMS had high safety in the treatment of patients with sleep disorders after TBI, and can be popularized in the clinic.

## 5 Conclusion

RTMS has a good clinical efficacy in the treatment of sleep disorders after TBI, which has a good effect in improving sleep disorders and expressions of neurotrophic factors, with high safety.

## Acknowledgements

Not applicable.

## Conflicts of Interest

The authors declare no conflict of interest.

## Author Contributions

Conceptualization: J.X.; Data curation: L.Z.; Formal analysis: J.X.; Methodology: L.Z.; Writing – original draft: J.X.; Writing – review and editing: L.Z.; All authors have read and agreed to the published version of manuscript.

## Ethics Approval and Consent to Participate

This study was approved by Medical Ethics Committee, and patients were informed and agreed.

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## Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

## Supplementary Materials

Not applicable.

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