Clinical Study on the Treatment of Parkinson' s Disease with Transcranial Magneto-Electric Encephalopathy Therapeutic Apparatus

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Abstract

[Objective] To evaluate the therapeutic efficacy and safety of the transcranial magnetoelectric encephalopathy treatment instrument (brand name: AOBO Parkinson' s Treatment Instrument) for treating Parkinson' s disease. [Methods] Using a double-center, randomized, double-blind, self-crossover design, 22 Parkinson' s patients who met the inclusion criteria were randomly divided into group A and group B, after which therapeutic effect analysis was conducted and treatment efficacy was observed. [Results] In the treatment group of 22 cases, there were 0 completely cured cases, 9 markedly effective cases, 8 effective cases, and 5 ineffective cases. The total markedly effective rate and total effective rate were 40.91% (9/22) and 77.27% (17/22), respectively. In the control group of 22 cases, there were 0 completely cured cases, 2 markedly effective cases, 3 effective cases, and 17 ineffective cases. The total markedly effective rate and total effective rate were 9.09% (2/22) and 22.73% (5/22), respectively. The total markedly effective rate and total effective rate in the treatment group were higher than those in the control group, with statistically significant differences ($P<0.05$). Among the evaluations of main symptoms including resting tremor, rigidity, and bradykinesia, the treatment group showed significant differences ($P<0.01$); there was no significant difference in the control group ($p>0.05$); there was a significant difference between the treatment group and the control group ($p<0.05$). [Conclusions] Transcranial magnetoelectric stimulation can significantly improve resting tremor, muscle rigidity, bradykinesia, and other symptoms in patients with Parkinson' s disease, and its use is safe.

Full Text

Clinical Study of Transcranial Magnetoelectric Encephalopathy Treatment Instrument for Parkinson' s Disease

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Abstract

[**Objective**] To evaluate the efficacy and safety of the transcranial magnetoelectric encephalopathy treatment instrument (brand name: AOBO Parkinson' s Treatment Instrument) for treating Parkinson' s disease.

[**Methods**] Using a dual-center, randomized, double-blind, self-crossover design, 22 Parkinson' s patients who met the inclusion criteria were randomly divided into Group A and Group B for efficacy analysis and observation.

[**Results**] In the treatment group (22 cases), 0 cases were basically cured, 9 cases showed marked effectiveness, 8 cases were effective, and 5 cases were ineffective. The total efficiency rate and total effective rate were 40.91% (9/22) and 77.27% (17/22), respectively. In the control group (22 cases), 0 cases were basically cured, 2 cases showed marked effectiveness, 3 cases were effective, and 17 cases were ineffective. The total efficiency rate and total effective rate were 9.09% (2/22) and 22.73% (5/22), respectively. Both the total efficiency rate and total effective rate in the treatment group were significantly higher than those in the control group ($P<0.05$). Evaluation of the main symptoms—resting tremor, rigidity, and bradykinesia—showed significant improvement in the treatment group ($P<0.01$), while the control group showed no significant difference ($p>0.05$). There were significant differences between the treatment and control groups ($p<0.05$).

[**Conclusions**] Transcranial magnetoelectric stimulation can significantly improve resting tremor, muscle rigidity, bradykinesia, and other symptoms in patients with Parkinson' s disease, and is safe for clinical use.

Keywords: Transcranial magnetoelectric; Parkinson' s Treatment Instrument; Theory of brain cell activation; Dopamine; Voltage-gated Ca2+ channels

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Parkinson' s disease, first described by British doctor James Parkinson in 1817, is one of the most common degenerative diseases of the central nervous system in the elderly, characterized clinically by resting tremor, muscle rigidity,

bradykinesia, postural abnormalities, and loss of balance. Parkinson' s disease represents a worldwide medical challenge. With the aging population becoming increasingly serious, Parkinson' s disease has emerged as one of the most important diseases affecting human health.

Currently, drug treatment can only control the symptoms of Parkinson' s disease but cannot cure the disease or halt its progression [1]. The increasingly prominent limitations and adverse reactions of pharmacotherapy have drawn wide attention from the medical community. The main surgical treatments include lesioning, deep brain stimulation, and tissue cell transplantation. Because lesioning causes irreversible damage to cranial nerves and can lead to many complications, some causing lifelong disability, it is no longer advocated. Deep brain stimulation, which involves implanting a brain pacemaker, is limited by the risks of foreign body implantation in the brain, high costs, and strict requirements for both hospital facilities and patient conditions. Tissue cell transplantation, using stereotaxic techniques to transplant dopamine-producing brain cells such as fetal brain or neural stem cells into the brain, remains under investigation [2].

The transcranial magnetoelectric encephalopathy treatment instrument (brand name: AOBO Parkinson' s Treatment Instrument [3], TME) is a non-invasive physical therapy apparatus for rehabilitation treatment based on the "Theory of brain cell activation [2]" and integrated with transcranial magnetic stimulation (TMS) as its core technology, building upon transcranial electric (TES) brain function rehabilitation therapy instruments [5,6]. By activating core region neurons and cortical functional areas through TMS, the instrument fully accounts for the fact that neurotransmitters are distributed throughout the brain and must overcome the high impedance of the skull, which can be achieved through TES.

TME can also be understood as endogenous neurotransmitter control technology (patent number: ZL200910071875.X [11]). This paper evaluates the safety and effectiveness of TME in treating patients with mild to moderate Parkinson' s disease. The relevant data were approved by the State Drug Administration in 2011 and provide partial clinical basis for the registration of the Transcranial magnetoelectric encephalopathy treatment instrument (registration number: Hei Shi Yao Jian Xie (Zhun) Zi 2011 No. 226001th).

1.1 Clinical General Data

Diagnostic Criteria: Referring to the Diagnostic Criteria and Differential Diagnosis of Parkinson' s Disease and Parkinson' s Syndrome formulated by the National Symposium on Extrapyramidal Diseases in October 1984: (a) Patients must exhibit at least 2 of 4 typical symptoms and signs (static tremor, hypokinesia, muscle rigidity, and postural reflex disorder); (b) The diagnosis of idiopathic Parkinson' s disease does not support atypical symptoms and signs such as pyramidal signs, gait apraxia, cerebellar syndrome, intention tremor,

gaze palsy, severe autonomic dysfunction, or mild dementia associated with extrapyramidal symptoms.

Total Number of Cases: Based on the characteristics of the Transcranial magnetoelectric encephalopathy treatment instrument and Parkinson' s disease, obtaining a large sample is not easy with fewer cases. Under the assumption that the treatment group would be significantly better than the placebo group, we determined 22 cases for the treatment group and 22 cases for the control group. Due to the crossover design, the total sample size was 22 cases, which provides adequate statistical power for the clinical trial results to be statistically significant.

Case Selection Criteria: - **Inclusion criteria:** (a) Compliance with Parkinson' s disease diagnostic criteria; (b) Age between 45-70 years; (c) Modified Hoehn-Yahr staging of mild to moderate disease (grades 1-3); (d) Discontinuation of benserazide during the examination period; (e) Both males and females eligible according to the purpose of the clinical trial and disease characteristics; (f) All patients signed informed consent. - **Exclusion criteria:** (a) Parkinson' s syndrome, etc.; (b) Combined with other serious diseases of the heart, brain, liver, kidney, endocrine, and hematopoietic systems; (c) Persons under 45 or over 70 years of age; (d) Psychiatric patients; (e) Pregnant women, women preparing for pregnancy, or lactating women. - **Case rejection criteria:** (a) Persons forced to discontinue treatment due to adverse effects; (b) Those who fail to make follow-up visits or whose data cannot be obtained may not be able to judge efficacy or have data that affects therapeutic evaluation; (c) Those who do not comply with the study protocol.

1.2 Test Method

Trial Participation: Clinical research participation by Second Affiliated Hospital, Heilongjiang University of Chinese Medicine; Clinical research unit: First Affiliated Hospital, Heilongjiang University of Chinese Medicine; Statistical analysis unit: School of Public Health, Harbin Medical University.

Trial Method: In accordance with a dual-center, randomized, double-blind, crossover controlled design, 22 patients were randomly divided into Group A and Group B. Group A served as the treatment group for 10 days, receiving treatment 2 times daily, with each treatment lasting 30 minutes and a 10-minute break in between; then Group A served as the control group for 10 days, totaling 20 days. Group B served as the control group for 10 days, then as the treatment group for 10 days, also totaling 20 days.

Before treatment, anti-Parkinson' s drugs were discontinued for 12 hours, and patients did not take anti-Parkinson' s medication in the morning. Treatment began 2 hours after breakfast.

Blinding Implementation: Each trial was attended by 2 individuals: 1 who administered treatment and 1 who evaluated outcomes. Patients did not know

whether they were receiving the experimental instrument or placebo control instrument, and the evaluators did not know the actual group assignment, thus simulating a double-blind effect.

Efficacy Determination: The Unified PD Rating Scale (UPDRS) Part III was used.

Safety Evaluation: Conducted once before treatment (0 weeks) and at the end of treatment (8 weeks), including: (a) General physical examination; (b) Blood routine and urine routine examination; (c) ECG examination, liver function, and kidney function examination.

Statistical Analysis: SAS 9.1.3 statistical analysis software was used to evaluate the main curative effects. Both the Full Analysis Set (FAS) and Per Protocol Set (PPS) datasets were calculated, and safety evaluation was performed using SAS data analysis.

2 Result

The PPS dataset of this experiment is identical to the FAS dataset, so the statistical results of the PPS and FAS datasets are presented together.

2.1 Statistical Analysis of Efficacy of Main Endpoints in Effectiveness Evaluation

The treatment group showed a total efficiency rate of 40.91% (9/22) and total effective rate of 77.27% (17/22), with 95% confidence intervals of (20.36 ~ 61.45) and (59.76 ~ 94.78), respectively. The control group showed a total efficiency rate of 9.09% (2/22) and total effective rate of 22.73% (5/22), with 95% confidence intervals of (0 ~ 21.10) and (5.22 ~ 40.24), respectively. There was a significant center effect (P=0.0006). After adjusting for center, the total efficiency rate showed an adjusted P=0.0003. Both the total efficiency rate and total effective rate in the treatment group were significantly higher than in the control group, demonstrating that the treatment group outperformed the control group. See Table 1 through Table 5 .

2.2 Effectiveness Evaluation: Statistical Analysis of Main Individual Indicators

Evaluation of the main symptoms—resting tremor, muscle rigidity, and bradykinesia—showed significant improvement in the treatment group ($P<0.01$), while the control group showed no obvious improvement ($p>0.05$). There were significant differences between the treatment and control groups ($p<0.05$). From the UPDRS Part III scale for Parkinson' s disease, which contains 36 individual indicators, three representative symptoms were selected for individual analysis. See Table 6 .

2.3 Statistical Analysis of Clinical Safety

Neither the treatment group nor the control group experienced any adverse reactions or adverse events during the clinical trials.

In summary, the experimental statistics demonstrate that the Transcranial magnetoelectric encephalopathy treatment instrument (brand name: AOBO Parkinson' s Treatment Instrument) has short-term efficacy in treating mild to moderate Parkinson' s disease, particularly in improving static tremor, muscle rigidity, bradykinesia, and other symptoms, and is safe for use.

3 Discussion

The main clinical symptoms of Parkinson' s disease are static tremor, muscle rigidity, and bradykinesia. The primary pathological changes involve degeneration and death of dopaminergic neurons in the substantia nigra, resulting in decreased dopamine (DA) content in the striatum. The process of DA formation involves tyrosine (obtained directly or indirectly from food) being converted to DOPA under the action of tyrosine hydroxylase in neurons, which is then converted to DA by dopa decarboxylase.

DA is stored in synaptic vesicles surrounding dopaminergic neuron axon terminals, and dopamine release from these vesicles is accomplished through Ca2+-dependent rapid regulation of vesicular exocytosis [13,14]. When intracellular Ca2+ concentration increases to a certain level, it triggers dopamine release from vesicles. Ca2+ influx occurs through the opening of voltage-gated Ca2+ channels during cell membrane depolarization. Vesicular exocytosis is divided into Ca2+-dependent rapid regulation exocytosis and basal exocytosis, with basal exocytosis not being regulated by action potentials or Ca2+ [15]. In addition to extracellular Ca2+ influx, axoplasmic Ca2+ also originates from intracellular calcium stores in synapses [16]. The influx Ca2+ plays a role after accumulating with basic calcium ions.

If dopaminergic neurons sustain high-frequency DA release, the accompanying increase in presynaptic Ca2+ will enhance the catalytic activity and expression of tyrosine hydroxylase, and can also increase transcription of mRNA synthase genes and tyrosine hydroxylase [17]. Conversely, if dopaminergic neurons fail to release dopamine at a normal rate in a timely manner, degenerative disease will develop, and increased axoplasmic dopamine can inhibit tyrosine hydroxylase activity. This feedback regulation can lead to time-dependent inhibition of dopamine synthesis, which may be related to the "wearing-off" effect observed with clinical levodopa treatment of Parkinson' s disease. Dopaminergic neurons undergoing degenerative changes gradually lose function, and apoptosis represents the basal state before cell death, with exocytosis being the essential metabolism that maintains neuronal function.

Exogenous dopamine alleviates patient symptoms but further reduces tyrosine hydroxylase activity, decreasing the rate of vesicle fusion in basal state exo-

cytosis that is normally independent of action potential and Ca2+ regulation. This replacement therapy is equivalent to abandoning rescue efforts for degenerative dopaminergic neurons. The dopaminergic neuron death signaling pathway becomes upregulated, initiating the apoptotic program [19]. The death of dopaminergic neurons is probably not solely due to dopamine deficiency. This may explain why patients with Parkinson' s disease develop severe dysfunction after 2-5 years of levodopa use. Numerous experiments have indirectly proved that TME is related to endogenous dopamine production, and the effect of TME is much better than simple transcranial magnetic or transcranial electrotherapy.

The optimal target of TME is the voltage-gated Ca2+ channel. The improvement in clinical symptoms of Parkinson' s disease may be due to activation of neurotransmitter neurons, particularly dopaminergic neurons. Approximately 80% of dopaminergic neurons in the midbrain are located in the substantia nigra, with 20% remaining in other brain regions [2]. The shortest non-invasive way to stimulate calcium channels is through TME, which primarily acts in the form of voltage. The TMS component of TME generates microcurrents through magnetoelectric energy, and these microcurrents act on calcium channels. The effectiveness of TME in treating Parkinson' s disease is based on the theory of brain cell activation.

Regarding the safety of TME, new advances in biological magnetoelectric technology can activate the central nervous system (CNS) without causing damage, reflecting the potential for research and treatment. This method is based on the application of external pulsed electromagnetic fields that penetrate the skin in an exponentially decaying manner, enabling excitation of specific CNS regions. The human brain is extremely complex and valuable. In principle, it cannot be directly subjected to high-intensity electromagnetic stimulation. Because the cerebral cortex and brain medulla lack pain nerves, pure nociceptive stimulation of these tissues does not cause pain (such as using tweezers). High-intensity deep brain stimulation or high-intensity transcranial magnetic stimulation, equivalent to electroshock or magnetic shock therapy, may cause uncertain long-term brain injury. Inappropriate use of deep brain stimulation can damage the brain. Although pacemakers are widely used, brain pacemakers are rarely encouraged because the heart is a simple organ with only one main function—contracting to eject blood—whereas the brain is far more complex. Electricity is a monotonous, non-specific stimulus that can stimulate existing functions but cannot build these functions. High-intensity transcranial magnetic stimulation uses magnetic field strengths of 1-3T. Although there is no real electrode in the brain, this high-intensity magnetic field can propel a one-yuan coin 1-2 meters. Penetrating the skin and skull, it can stimulate cerebral cortex regions at a depth of about 2.5cm, causing thumb responses. Due to unclear mechanisms and safety concerns, its application is limited to clinical hospitals, operated by professionals, and restricted to serious mental illness.

The magnetic field strength of TME does not exceed 50mT. Compared with high-voltage low-frequency pulsed magnetic fields, the purpose, mechanism, strength,

and safety of TME' s magnetic field are different. TME uses a multi-turn magnetic field generator with multi-position low-frequency and low-intensity alternating magnetic fields. The direct action is on the "head"rather than the "brain," and stimulation of targets in the brain is flexible, targeting the superficial cortical layer. Monkey studies have shown that cortical magnetic stimulation of the brain reaching 1-2G increases hippocampal activity and reduces the threshold of the motor cortex. The transcranial direct current of TME is a non-invasive transcranial electrical stimulation that delivers microcurrents through the core area of neurons. Three pairs of electrodes are symmetrically distributed on the upper edge of the ear, with strength set at a level tolerable to scalp nerve pain perception, allowing a small portion of the current to reach the substantia nigra. The conventional version is incorrect because the presence of the skull prevents current from passing through or across it. In this way, TME can avoid potential harm to the human brain from high-intensity pulsed electromagnetic fields while achieving the desired therapeutic effect. It is not limited by treatment conditions, is safe without side effects, and can be used in both family and hospital settings.

The theory of brain cell activation and the safety and efficacy of TME in treating mild to moderate Parkinson' s disease suggest a need for reorientation of clinical experts regarding Parkinson' s disease treatment. The principle of treatment choice for patients with mild to moderate Parkinson' s disease should be non-invasive physical means (such as TME, also known as an in vitro brain pacemaker) instead of L-dopa. When non-invasive physical means (such as TME) cannot completely control symptoms, L-dopa should be used as supplementary therapy, with levodopa dosage reduced and eventually discontinued as the course of treatment progresses. When Parkinson' s disease patients are treated with physical therapy alone (such as TME) or take levodopa, or both, the use of deep brain stimulation (DBS, installation of brain pacemakers) will certainly not be effective. At this point, brain damage may be the last and most helpless option.

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Author Contribution Statement

Qiang Tang and Wei Zou: Proposed research ideas and master design of the clinical trial program. Zuodong Sun: Participated in proposing research ideas and clinical trial design; inventor of the transcranial magnetic therapy instrument for computer disease; primary author of the "Preamble" and "Discussion" sections; responsible for drafting and revising the final version. Wuyi Sun and Wenhua Wang: Authors of the "Preamble" and "Discussion" sections. Yanli Xing and Xueping Yu: Main participants in clinical trial design and implementers of clinical trials. Jing Bai and Xiuying Teng: Implementers of the clinical trial program. Kang Li: Principal participant in clinical trial program design and head of mathematical statistical analysis. Yan Hou: Responsible for statistical analysis of clinical trial data.

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Note: Figure translations are in progress. See original paper for figures.