Clinical Study of Transcranial Magnetic Electrical Brain Disease Therapeutic Apparatus for Alzheimer' s Disease

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Abstract

[Objective] To evaluate the efficacy and safety of the transcranial magnetoelectric therapeutic device (trade name: Aobo Alzheimer' s Treatment Device) for mild to moderate Alzheimer' s disease (AD). [Methods] A randomized, placebo-controlled, multicenter 8-week clinical trial was conducted on 80 patients with mild to moderate AD [Hachinski Ischemic Scale score 4 points, dementia severity (CDR=1.0) or (CDR=2.0)], with 40 cases in each of the treatment and control groups. All enrolled patients received standard internal medicine treatment and standardized nursing care; the treatment group was treated with the transcranial magnetoelectric therapeutic device, while the control group received simulated treatment with a placebo transcranial magnetoelectric therapeutic device. [Results] Clinical trial results demonstrated that at 8 weeks of treatment, the treatment group showed significant improvements compared with the control group in Mini-Mental State Examination (MMSE), Alzheimer' s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), and Activities of Daily Living (ADL) scores (inter-group differences $P<0.001$, $P<0.0001$, and $P<0.05$, respectively). At 4 weeks of treatment, MMSE and ADAS scores had already improved (inter-group differences $P<0.05$ and $P<0.01$, respectively). No adverse reactions were observed in either group. [Conclusion] According to the statistical results of the trial, the transcranial magnetoelectric therapeutic device has therapeutic effects in treating mild to moderate Alzheimer' s disease, demonstrating favorable improvement in patients' mental status, cognitive behavior, and daily living self-care ability, and the device is safe to use.

Full Text

Clinical Study on Transcranial Magnetoelectric Encephalopathy Treatment Instrument for Alzheimer' s Disease

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Abstract

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

[**Methods**] A randomized, placebo-controlled, multicenter 8-week clinical trial was conducted on 80 patients with mild to moderate AD [Hachinski Ischemia Scale score 4, dementia severity (CDR=1.0) or (CDR=2.0)], with 40 cases each in the treatment and control groups. All enrolled patients received standard internal medicine treatment and standardized nursing care. The treatment group was treated with the transcranial magnetoelectric encephalopathy treatment instrument, while the control group received simulated treatment with a placebo instrument.

[**Results**] Clinical trial results showed that after 8 weeks of treatment, the treatment group demonstrated significant improvement compared to the control group in Mini-Mental State Examination (MMSE), Alzheimer' s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), and Activities of Daily Living (ADL) scores (inter-group differences $P<0.001$, $P<0.0001$, and $P<0.05$, respectively). At 4 weeks, MMSE and ADAS scores had already improved (inter-group differences $P<0.05$ and $P<0.01$, respectively). No adverse reactions occurred in either group.

[**Conclusions**] Based on the statistical results, the transcranial magnetoelectric encephalopathy treatment instrument has therapeutic effects for mild to moderate Alzheimer' s disease, showing favorable improvement in patients' mental status, cognitive behavior, and daily living self-care ability, with safe usage.

Keywords: Transcranial magnetoelectric; Alzheimer' s disease; voltage-gated Ca2+ channels; best target; The theory of brain cell activation

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Alzheimer' s disease (AD), also known as senile dementia, is a neurodegenerative disease primarily manifested as cognitive dysfunction, loss of daily living abilities, and abnormal mental behavior. Currently, no truly effective drug can prevent or delay the progression of such diseases [1], and the increasing prevalence of AD has made exploring its treatment a hot topic among brain scientists worldwide.

Harbin Aobo Medical Apparatus Co., Ltd. has developed a patented product [3] (Invention Patent No.: ZL2009I0071875.X) based on the "Brain Cell Activation Theory [2]" —the transcranial magnetoelectric encephalopathy treatment instrument (brand name: AOBO Alzheimer' s Treatment Instrument [4], TME). This non-invasive physical therapy instrument integrates transcranial electrical stimulation (TES) technology for brain function rehabilitation [5,6] with transcranial magnetic stimulation (TMS) technology for AD rehabilitation. The instrument activates core area neuron groups through TES while simultaneously stimulating cerebral cortex functional areas through TMS, fully considering the fact that neurotransmitter neurons are distributed throughout the brain and that the skull has high impedance.

TME can also be understood as an endogenous neurotransmitter regulation technology. This paper evaluates the safety and efficacy of TME in treating mild to moderate AD patients in clinical settings. The relevant data was recognized by national drug regulatory authorities in 2014 as part of the clinical basis for certification and registration of the transcranial magnetoelectric encephalopathy treatment instrument (brand name: AOBO Alzheimer's Treatment Instrument). TME Registration No.: Heilongjiang Food and Drug Administration Medical Device (Approval) 2014 No. 2260036.

1.1 Study Subjects

(1) General Patient Information: This multicenter, randomized, placebo-controlled clinical study included 80 patients. The treatment group (using the transcranial magnetoelectric encephalopathy treatment instrument) had 40 cases, including 13 males and 27 females, aged 50-75 years (59.93±7.22), with Mini-Mental State Examination (MMSE) scores of 10-22 (17.35±2.89) and Alzheimer's Disease Assessment Scale (ADAS) scores of 19-45 (29.53±6.72). The control group (using the placebo transcranial magnetoelectric encephalopathy treatment instrument model) had 40 cases, including 16 males and 24 females, aged 50-78 years (62.48±7.73), with MMSE scores of 11-23 (17.48±2.94) and ADAS scores of 20-45 (31.70±7.42). No significant differences were observed between the treatment and control groups in terms of gender, age, and MMSE or ADAS scores.

(2) Diagnostic Criteria: All AD patients met the diagnostic criteria for AD in *Neurology* [7] and the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition) (DSM-IV) [8].

(3) Inclusion Criteria: Met DSM-IV diagnostic criteria for Alzheimer' s disease; Hachinski Ischemia Scale score 4; Dementia severity of mild (CDR=1.0) or moderate (CDR=2.0); Age between 50-80 years, both genders eligible; All patients signed informed consent forms.

(4) Exclusion Criteria: Mixed dementia with Hachinski Ischemia Scale (HIS) scores of 5-6 or vascular dementia with scores 7, and Cornell Depression Scale scores 8; Severe (CDR=3.0) or questionable dementia (CDR=0.5) patients; Patients with severe primary diseases of the heart, brain, liver, kidney, or hematopoietic system, or psychiatric patients; Age under 50 or over 80; Participants in other clinical trials; Patients with severely abnormal safety indicators before treatment (laboratory indicators exceeding normal upper limits by 20%); Patients intolerant to instrument treatment, with severe side effects, or allergic constitution; Patients non-compliant with the study protocol.

1.2 Trial Methods

(1) Trial Units: The leading clinical research unit was the Second Affiliated Hospital of Heilongjiang University of Chinese Medicine, with the First Affiliated Hospital of Heilongjiang University of Chinese Medicine as a participating unit, and the School of Public Health of Harbin Medical University responsible for statistical analysis.

(2) Treatment Methods: Both the transcranial magnetoelectric encephalopathy treatment instrument and its placebo model had identical appearance and treatment methods, both provided by Harbin Aobo Medical Apparatus Co., Ltd. Specially trained medical staff operated the devices. Strictly following the methods specified in the product *Investigator' s Brochure*, treatment sites were selected, treatment terminals were fixed, and treatment parameters were set. Based on the grouping of enrolled cases, either standard treatment mode (with normal therapeutic dose output) or simulated treatment mode (without actual therapeutic dose output) was selected for patient treatment. Patients were treated twice daily for 30 minutes each session, with intervals of at least 10 minutes between sessions. Seven consecutive days of treatment constituted one course, with a total of 8 courses administered.

(3) Efficacy Evaluation: Primary indicators: Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and Alzheimer' s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog); Secondary indicator: Activities of Daily Living assessment (ADL: Barthel Index).

(4) Safety Evaluation: Evaluations were conducted once before treatment (0 weeks) and once at the end of treatment (8 weeks), including: General physical examination; Blood routine, urine routine, liver function, and kidney function

tests; Electrocardiogram examination.

(5) Statistical Analysis: SAS 9.1.3 statistical analysis software was used. Efficacy evaluation was calculated for both the Full Analysis Set (FAS) and Per Protocol Set (PPS), while safety evaluation was analyzed using the Safety Set (SAS).

2 Results

The PPS analysis results of this trial were similar to the FAS analysis results; therefore, only the FAS analysis statistical results are presented.

2.1 Scores of MMSE, ADAS, CDR, and ADL Before, During, and After Treatment

See Table 1 , Table 2 , and Table 3 .

Table 1 Pre-treatment scale scores ($\bar{x}\pm s$, points), test statistics (t-value), and P-value for treatment and control groups

Group	n	MMSE	ADAS	CDR	ADL
Treatment	40	17.35±2.89	29.53±6.72	1.33±0.47	77.63±14.50
Control	40	17.48±2.94	31.70±7.42	1.35±0.48	74.75±13.63
Test statistic		-0.192	-1.375	-0.234	0.914

Table 2 Scale scores ($\bar{x}\pm s$, points), test statistics (t-value), and P-value for treatment and control groups after 4 weeks of treatment

Group	n	MMSE	ADAS	CDR	ADL
Treatment	40	17.95±3.01	28.73±6.56	1.29±0.48	78.25±14.30
Control	40	17.65±2.89	31.65±7.57	1.34±0.50	74.63±13.22
Test statistic		0.455	-1.846	-0.457	1.177

Table 3 Scale scores ($\bar{x}\pm s$, points), test statistics (t-value), and P-value for treatment and control groups after 8 weeks of treatment

Group	n	MMSE	ADAS	CDR	ADL
Treatment	40	18.93±3.37	27.78±7.35	1.19±0.46	79.25±14.08
Control	40	17.75±3.05	31.68±7.76	1.31±0.49	74.75±13.06
Test statistic		1.634	-2.308	-1.174	1.482

2.2 Cognitive Function (Assessed by MMSE Scores)

Efficacy observation showed that after treatment, the treatment group had significantly improved MMSE scores compared to the control group (P<0.001), see Table 5 ; and MMSE scores had already significantly improved at 4 weeks of treatment (P<0.05), see Table 4 .

Table 4 Scale score differences ($\bar{x}\pm s$, points), test statistics (t-value), and P-value for treatment and control groups at 4 weeks (during treatment - before treatment)

Group	n	MMSE	ADAS	CDR	ADL
Treatment	40	0.60±0.96	-0.80±0.99	0.00±0.00	0.63±2.82
Control	40	0.18±0.84	-0.05±1.24	0.00±0.00	-0.13±2.65
Test statistic		2.109	-2.988		1.226

Table 5 Scale score differences ($\bar{x}\pm s$, points), test statistics (t-value), and P-value for treatment and control groups at 8 weeks (after treatment - before treatment)

Group	n	MMSE	ADAS	CDR	ADL
Treatment	40	1.58±1.53	-1.78±1.68	-0.14±0.32	1.63±3.47
Control	40	0.28±1.45	-0.03±1.53	-0.04±0.17	0.00±3.00
Test statistic		3.895	-4.812	-1.734	2.242

2.3 Alzheimer' s Disease Assessment (Assessed by ADAS Scores)

After treatment, the treatment group showed significantly improved ADAS scores compared to the control group (P<0.0001), see Table 5; and ADAS scores had already significantly improved at 4 weeks of treatment (P<0.005), see Table 4.

2.4 Dementia Severity (Assessed by CDR Scores)

After treatment, the treatment group showed some improvement in CDR scores compared to the control group (P=0.0880), see Table 5.

2.5 Activities of Daily Living (Assessed by ADL Scores)

After treatment, the treatment group showed significantly improved ADL scores compared to the control group (P<0.05), see Table 5; however, no significant improvement was observed at 4 weeks of treatment (P>0.05), see Table 4.

2.6 Safety Evaluation

Among the 40 cases in the treatment group and 40 cases in the control group, no adverse reactions or events occurred. During the use of the transcranial magnetoelectric encephalopathy treatment instrument, all patients maintained stable vital signs, and no significant changes were observed in blood and urine routine tests or blood biochemical examinations before and after treatment (P>0.05).

This trial demonstrated that the transcranial magnetoelectric encephalopathy treatment instrument can improve mild to moderate cognitive dysfunction, with certain improvements in cognitive function as measured by MMSE and ADAS observed at 4 weeks of treatment, and significant improvements at 8 weeks. Patients showed enhanced word recall, attention, memory, and calculation abilities, with statistically significant differences compared to the control group. The transcranial magnetoelectric encephalopathy treatment instrument can also improve the self-care ability of AD patients and reduce dementia severity. The multicenter, randomized, placebo-controlled trial results for AD patients showed that significant therapeutic effects appeared after 8 weeks of treatment, with statistically significant differences and high clinical safety, and no adverse reactions.

In summary, according to the trial statistical results, the transcranial magnetoelectric encephalopathy treatment instrument (brand name: AOBO Alzheimer' s Treatment Instrument) has therapeutic effects for mild to moderate Alzheimer' s disease, showing favorable improvement in patients' mental status, cognitive behavior, and daily living self-care ability, with safe usage [4].

3 Discussion

Alzheimer' s disease affects nearly 35.6 million people worldwide, with 4.6 million new cases annually. In China alone, there are 10 million patients, with a prevalence rate of 30% among people over 80 years old. Unfortunately, the pathogenesis of AD remains unclear, and no truly effective drugs have been developed [9], leading to various hypotheses such as the -amyloid hypothesis, Tau protein hypothesis (with Tau pathology considered downstream of A), inflammatory hypothesis, and cholinergic hypothesis. The mainstream direction of AD research has primarily focused on A [10]. However, since Glenner and Wong purified and isolated A from senile plaques and decoded its protein sequence in 1984, all drugs developed based on A worldwide have failed over the past 30+ years. Existing AD drugs such as cholinesterase inhibitors and NMDA receptor antagonists target not the degenerated cholinergic neurons themselves, which may explain why these drugs cannot prevent or delay disease progression. Most drugs under development also target upstream or downstream events of already degenerated cholinergic neurons. The -amyloid hypothesis may have misled mainstream research directions.

The clinical efficacy of TME, developed based on the "Brain Cell Activation Theory" hypothesis, supports the cholinergic hypothesis [10]. The cholinergic hypothesis posits that the reduction of cholinergic neurons in the brain leads

to decreased synthesis, storage, and release of acetylcholine (ACh), resulting in a series of clinical manifestations primarily characterized by memory and recognition dysfunction. Evidence has shown that ACh deficiency is the main cause of memory impairment, though possibly not the only one.

The death of cholinergic neurons may involve the loss of not only ACh but also neuropeptides, which coexist with neurotransmitters [11-13]. Neuropeptides are suitable for regulating slow and lasting functional changes and have neurotrophic effects. The main reason for TME' s efficacy may be the activation of corresponding neurotransmitter neurons, such as cholinergic neurons and peptidergic neurons.

Additionally, TME' s target of action is not limited to voltage-gated ion channels. For AD, its effects may also involve the de-polarization of -amyloid peptides (A), the main component of senile plaques, and de-acidification of Tau protein through externally applied specific electromagnetic fields, eliminating inflammatory reactions, clearing A or blocking A aggregation, and protecting microtubule assembly and axonal transport systems [1].

The above explains TME' s efficacy for AD. Regarding TME' s safety, new developments in biomagnetoelectric technology allow non-harmful activation of the central nervous system (CNS), demonstrating research and therapeutic possibilities. This method is based on the external application of pulsed electromagnetic fields, which excite specific CNS regions by penetrating the skin in an exponentially decaying manner. The human brain is extremely delicate and should not, in principle, receive high-intensity electromagnetic stimulation directly. High-intensity deep brain electrical stimulation or high-intensity transcranial magnetic stimulation is equivalent to electroconvulsive or magnetoconvulsive therapy, with uncertain long-term damage to the brain. For example, improper application of deep brain electrical stimulation may have consequences equivalent to brain lesioning surgery. Compared with high-voltage low-frequency pulsed magnetic fields, TME' s transcranial magnetism differs in purpose, mechanism, and intensity, and thus has different safety profiles. TME employs multi-turn magnetic field generators and multi-point low-frequency low-intensity alternating magnetic fields, with the direct action site being the "head" rather than the "brain," providing gentle stimulation to intracerebral targets with the cerebral cortex superficial layer as the target. TME' s transcranial electricity is also non-invasive, with microcurrents passing through core area neuron groups in the brain. This approach not only avoids potential damage to the human brain from high-intensity pulsed electromagnetic fields but also achieves the expected therapeutic effects without being limited by the treatment environment, making it safe with no side effects and suitable for both home and hospital use.

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Author Contributions Statement:

Tang Qiang, Zou Wei: Proposed research ideas and primary designers of the clinical trial protocol;
Sun Zuodong: Proposed research ideas and participant in clinical trial protocol design, inventor of the transcranial magnetoelectric encephalopathy treatment instrument, primary author of the "Introduction" and "Discussion" sections, responsible for drafting and final revision of the manuscript;
Sun Wuyi, Wang Wenhua: Inventors of the transcranial magnetoelectric encephalopathy treatment instrument, co-authors of the "Introduction" and "Discussion" sections;
Xing Yanli, Yu Xueping: Major participants in designing the clinical trial protocol and leaders in implementing the clinical trial;
Liu Bo, Zhang Li, Dai Xiaohong: Implementers of the clinical trial protocol;
Li Kang: Major participant in designing the clinical trial protocol and person in charge of mathematical statistical analysis;
Hou Yan: Statistical analyst for clinical trial data.