Clinical Study of Transcranial Magnetic-Electrical Encephalopathy Treatment Device for Vascular Dementia

Authors: Zou Wei, Tang Qiang, Sun Zuodong, Xing Yanli, Yu Xueping, Li Kang, Sun Wuyi, Wang Wenhua, Liu Bo, Zhang Li, Dai Xiaohong, Hou Yan, Sun Zuodong

Date: 2017-02-13T00:00:00+00:00

Abstract

[Objective] To evaluate the efficacy and safety of the transcranial magnetic and electrical brain disease therapy device (trade name: Aobo Alzheimer' s Therapy Device) for the treatment of mild to moderate vascular dementia (VD).

[Methods] A randomized, placebo-controlled, multicenter 4-week clinical trial was conducted in 80 patients with mild to moderate AD [Hachinski Ischemic Scale score 7, 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 medical treatment and nursing care. The treatment group was treated with the transcranial magnetic and electrical brain disease therapy device, while the control group received sham treatment with a simulated device.

[Results] At 4 weeks of treatment, the treatment group showed significant improvement compared with the control group in Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and Activities of Daily Living (ADL) scores (between-group differences $P<0.0001$, $P<0.05$, and $P<0.05$, respectively). No adverse reactions occurred in either group.

[Conclusion] The transcranial magnetic and electrical brain disease therapy device is effective in treating mild to moderate vascular dementia, demonstrates favorable improvement in patients' mental status, cognitive function, and activities of daily living, and is safe to use.

Full Text

Clinical Study on Transcranial Magnetoelectric Encephalopathy Treatment Instrument for Vascular Dementia

**Zou Wei[1], Tang Qiang[2], Sun Zuodong[3]*, Xing Yanli[2], Yu Xueping[1], Li Kang , Sun Wuyi , Wang Wenhua , Liu Bo[2], Zhang Li[2], Dai Xiaohong[1], Hou Yan **

[1]First Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin 150000, China
[2]Second Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin 150000, China
[3]Ya' ou Brain Science Institute of Heilongjiang Province, Harbin 150090, China
School of Public Health, Harbin Medical University, Harbin 150000, China
Harbin Aobo Medical Apparatus Co., Ltd, Harbin 150090, China

Corresponding author: Sun Zuodong. E-mail: szd1966512@163.com

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 vascular dementia (VD).

[**Methods**] Eighty patients with mild to moderate VD [Hachinski Ischemia Scale score 7 points, dementia severity (CDR=1.0) or (CDR=2.0)] were enrolled in a randomized, placebo-controlled, multicenter 4-week clinical trial, with 40 cases each in the treatment group and control group. All enrolled patients received standard internal medicine basic 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 sham device.

[**Results**] After 4 weeks of treatment, the treatment group showed significant improvement compared with the control group in Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and Activities of Daily Living (ADL) scores (inter-group differences $P<0.0001$, $P<0.05$, and $P<0.05$, respectively). No adverse reactions occurred in either group.

[**Conclusions**] The transcranial magnetoelectric encephalopathy treatment instrument demonstrates therapeutic efficacy for mild to moderate vascular dementia, showing favorable effects on patients' mental status, cognitive behavior, and daily living self-care ability, with a favorable safety profile.

Keywords: Rehabilitation medicine; Transcranial magnetoelectric; Vascular dementia; Cognitive impairment; Brain cell activation theory

Classification Number: R454

Vascular dementia (VD) refers to severe functional disorders of memory, cognition, and behavior caused by ischemic or hemorrhagic stroke, representing one of the sequelae of cerebrovascular events, typically occurring two months post-stroke. Whether ischemic or hemorrhagic, the direct cause of neuronal injury is ischemia. With accelerated population aging and increasing incidence of cerebrovascular diseases in China, the incidence of VD continues to rise, ranking second only to Alzheimer's disease (AD). The search for effective VD treatments remains a global concern.

Harbin Aobo Medical Apparatus Co., Ltd. has developed a patented product based on the "Brain Cell Activation Theory" [1] (Invention Patent No.: ZL200910071875.X)—the transcranial magnetoelectric encephalopathy treatment instrument [3] (TME). This non-invasive physical therapy device integrates transcranial magnetic stimulation (TMS) technology for VD rehabilitation, building upon the core technology of transcranial electrical brain function rehabilitation therapy instruments [4,5]. The instrument simultaneously activates core regional neuronal populations through transcranial electrical stimulation (TES) while stimulating cerebral cortical functional areas through TMS, fully considering both the whole-brain distribution of transmitter neurons and the high impedance of the skull. This article summarizes the clinical study results on the efficacy and safety of TME in treating mild to moderate VD patients. These data were recognized by national regulatory authorities in 2014 and served as partial clinical evidence for certification and registration of the transcranial magnetoelectric encephalopathy treatment instrument (Medical Device Registration No.: Hei Food and Drug Administration Medical Device (Approval) No. 2014 2260036).

1.1 General Data

Enrolled cases were sourced from the First and Second Affiliated Hospitals of Heilongjiang University of Chinese Medicine, totaling 80 cases. According to multicenter, randomized, placebo-controlled principles, patients were randomly divided into treatment and control groups. The treatment group (using the transcranial magnetoelectric encephalopathy treatment instrument) comprised 40 cases (18 males, 22 females), aged 47-75 years (61.45±7.14), with Mini-Mental State Examination (MMSE) scores of 10-23 (17.80±2.88). The control group (using the sham device) comprised 40 cases (26 males, 14 females), aged 45-79 years (62.95±8.77), with MMSE scores of 11-22 (17.33±3.12). No significant differences existed between groups in gender, age, or baseline MMSE scores.

Diagnostic criteria followed the NINDS-AIREN criteria for vascular dementia (Roman GC, et al. Neurology 1993) and relevant diagnostic criteria from the national "Ninth Five-Year Plan" key project: (1) Dementia; (2) Evidence of cerebrovascular disease (CT or MRI confirmation: multiple cerebral infarctions and

lacunar infarctions, single infarction in critical locations, focal signs); (3) Clear causal relationship between the above two types of damage (dementia occurring within 6 months after definite stroke; cognitive decline, or fluctuating/stepwise progressive cognitive impairment). Specific inclusion criteria were: (1) Meeting NINDS-AIREN diagnostic criteria for vascular dementia; dementia onset within 6 months post-stroke with duration exceeding 3 months; (2) Hachinski Ischemia Scale score 7; (3) Mild (CDR=1.0) or moderate (CDR=2.0) dementia severity; (4) Age 40-75 years, both genders eligible, with signed informed consent from all patients.

1.4 Exclusion Criteria

(1) Mixed dementia with Hachinski Ischemia Scale scores of 5-6 or Alzheimer's disease with scores 4, and Cornell Depression Scale score 8; (2) Severe vascular dementia (CDR=3.0) or questionable vascular dementia (CDR=0.5); (3) Dementia following cerebral hemorrhage or large cortical infarction; (4) Patients with severe neurological deficits such as various types of aphasia or agnosia; (5) Patients with severe primary diseases of the heart, brain, liver, kidneys, or hematopoietic system, or psychiatric disorders; (6) Aspirin or salicylate allergy; gastric or duodenal ulcers; bleeding tendencies; (7) Age under 40 or over 75; (8) Patients with severely abnormal safety indicators before treatment (laboratory indicators exceeding normal upper or lower limits by 20%); (9) Patients intolerant to instrument treatment, experiencing severe side effects, or with allergic constitution; (10) Patients taking medications for vascular dementia improvement within one week.

2 Research Methods

Study Centers: First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Second Affiliated Hospital of Heilongjiang University of Chinese Medicine. **Statistical Analysis Unit:** School of Public Health, Harbin Medical University.

2.2 Trial Methods

Both the transcranial magnetoelectric encephalopathy treatment instrument and the sham device had identical appearance and treatment methods, provided by Harbin Aobo Medical Apparatus Co., Ltd. Specially trained medical staff operated the devices according to the methods specified in the product Investigator' s Manual, selecting treatment sites, fixing treatment terminals, and setting treatment parameters. Based on group assignment, all enrolled patients received standard internal medicine basic treatment (oral Bayer Aspirin, 100mg once daily) and standardized nursing care. The treatment group received treatment with the transcranial magnetoelectric encephalopathy treatment instrument, while the control group received simulated treatment with the sham device. Treatment was administered twice daily, 30 minutes each session, with

intervals of at least 10 minutes between sessions. Seven consecutive days constituted one treatment course, with a total of 4 courses.

2.3 Efficacy Evaluation

(1) Primary outcome measure: Mini-Mental State Examination (MMSE); (2) Secondary outcome measures: Activities of Daily Living assessment (ADL: Barthel Index) and Clinical Dementia Rating (CDR).

2.4 Safety Evaluation

Evaluations were conducted once before treatment (0 weeks) and once at treatment completion (4 weeks), including: (1) General physical examination; (2) Blood routine, urine routine, liver function, and kidney function tests; (3) Electrocardiogram examination.

2.5 Statistical Analysis

SAS 9.1.3 statistical analysis software was used. Primary efficacy evaluation was calculated for both Full Analysis Set (FAS) and Per Protocol Set (PPS) datasets, while safety evaluation was analyzed using the Safety Analysis Set (SAS) dataset.

3 Results

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

3.1 Before, During, and After Treatment

See Table 1 , Table 2 , and Table 3 .

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

Group	n	MMSE	CDR	ADL
Treatment	40	17.80±2.88	1.35±0.48	68.38±15.62
Control	40	17.33±3.12	1.43±0.50	64.88±12.78
Test statistic		0.707	-0.682	1.097

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

Group	n	MMSE	CDR	ADL
Treatment	40	20.50±3.65	1.11±0.49	75.63±11.56

Group	n	MMSE	CDR	ADL
Control	40	18.53±3.46	1.35±0.56	68.75±11.42
Test statistic		2.482	-2.030	2.676

Table 3 Comparison of score changes (post-treatment minus pre-treatment) between treatment and control groups after 4 weeks ($\bar{x}\pm s$, points), test statistics (t-value) and P-value

Group	n	MMSE	CDR	ADL
Treatment	40	2.70±1.64	-0.24±0.38	7.25±8.91
Control	40	1.20±1.62	-0.08±0.21	3.88±5.60
Test statistic		4.120	-2.381	2.028

3.2 Cognitive Function

As measured by MMSE scores, efficacy observation showed that MMSE scores improved significantly in the treatment group compared with the control group after treatment ($P<0.001$), see Table 3.

3.3 Dementia Severity

As measured by CDR scores, the treatment group showed certain improvement compared with the control group after treatment ($P<0.05$), see Table 3.

3.5 Clinical Safety

As measured by ADL scores, the treatment group showed significant improvement compared with the control group after treatment ($P<0.05$), see Table 3. No adverse reactions or events occurred in either group during the study. All patients maintained stable vital signs during treatment with the transcranial magnetoelectric encephalopathy treatment instrument, with no significant changes in blood routine, urine routine, or blood biochemical tests before and after treatment ($P>0.05$).

4 Discussion

Vascular dementia (VaD or VD) is a syndrome of intellectual and cognitive dysfunction caused by cerebrovascular disease, representing one of the common causes of senile dementia. Cerebrovascular lesions constitute the basis of VD, with hemorrhagic or ischemic damage visible in brain parenchyma, predominantly ischemic. VD can occur suddenly or progress stepwise, with a fluctuating course accompanying cerebrovascular events. This study limited enrollment to patients with ischemic stroke. During the acute phase of stroke, neuronal death is primarily necrotic, while secondary or delayed death occurring after the acute

phase is mainly apoptotic. The former occurs early in the central ischemic area, while the latter occurs predominantly in the ischemic penumbra. Autophagy may also represent one mode of ischemic neuronal death.

Acute stroke treatment primarily employs pharmacological and chemical means aimed at saving lives and rescuing dying neurons [6]. TME targets patients in the post-stroke sequelae period. The rhythmic bidirectional oscillation of intracellular and extracellular calcium ion concentrations induced by TME stimulation [7] aims to restore homeostatic balance of calcium concentration without inducing toxic reactions in calcium ion-dependent cells, fundamentally differing from the ion balance disruption and subsequent neuronal damage occurring during acute stroke [8]. Therefore, this discussion does not address the pathophysiological processes and repair mechanisms of acute ischemic neuronal injury.

The mechanism of TME action on VD may involve activating transmitter neurons, prompting reversal of cholinergic neurons, peptidergic neurons, and other neurons that have entered apoptotic programs. Evidence indicates that acetylcholine (ACh) deficiency is closely related to cognitive dysfunction. The death or apoptosis of cholinergic neurons involves more than just loss of ACh. Neuropeptides and neurotransmitters coexist [9-11]. Compared with neurotransmitters, neuropeptides are more suited for regulating slow and persistent functional changes, with many neuropeptides also exerting neurotrophic effects. The efficacy of TME on VD may correspondingly involve activation of transmitter neurons such as cholinergic and peptidergic neurons, restoring the internal environment.

Recent advances in biomagnetoelectricity permit non-invasive activation of the central nervous system (CNS), demonstrating research and therapeutic possibilities based on external application of pulsating electromagnetic fields that penetrate skin to excite specific CNS regions in an exponentially decaying manner. The human brain is extremely delicate and should not, in principle, receive direct high-intensity electromagnetic stimulation. High-intensity deep brain electrical stimulation or high-intensity transcranial magnetic stimulation is equivalent to electroconvulsive or magnetoconvulsive therapy, with uncertain long-term brain damage risks; improper application of deep brain electrical stimulation may produce consequences equivalent to brain lesioning. Compared with high-voltage low-frequency pulsed magnetic fields, TME' s transcranial magnetic component differs in purpose, mechanism, intensity, and safety profile. TME employs multiturn magnetic field generators with multi-point low-frequency low-intensity alternating magnetic fields, directly acting on the "head" rather than the "brain," providing gentle stimulation to intracerebral targets located in the superficial cortical layers. TME' s transcranial electrical component is also non-invasive, with microcurrents crossing core regional neuronal populations in the brain. This approach avoids potential brain damage from high-intensity pulsed electromagnetic fields while achieving expected therapeutic effects, without environmental restrictions, and is safe for use in both home and hospital settings without side effects.

This clinical trial demonstrates that the transcranial magnetoelectric encephalopathy treatment instrument (brand name: AOBO Alzheimer' s Treatment Instrument) has therapeutic efficacy for mild to moderate vascular dementia, showing favorable effects on patients' mental status, cognitive behavior, and daily living self-care ability, with a favorable safety profile.

References

[1] Sun Zuodong. The theory of brain cell activation [M]. Harbin: Heilongjiang Science & Technology Press, 2016.
[2] Sun Zuodong. Transcranial magnetoelectric encephalopathy therapeutic instrument [P]. China: ZL200910071875.X, 2012-08-22.
[3] Successful development of the first therapeutic instrument for Alzheimer disease in the world [J]. Science-Technology & Publication, 2014, 6: 143.
[4] Jiao Mingde, Sun Zuodong. Effects of Aobo brain function rehabilitation instrument on cerebral circulation and brain function [J]. Medicine Healthcare Apparatus, 1998, 03: 251-252.
[5] Tian Ningning. Application of Aobo brain function rehabilitation instrument in post-stroke hemiplegia patients [J]. Chinese Journal of Medical Device, 2009, 9: 68.
[6] Sun Zuodong. Activate the Sleeping Brain [M]. Harbin: Heilongjiang People' s Publishing House, 2003.
[7] Zhang S, Cui J, Shen PP. The regulation of calcium signaling in apoptosis [J]. Chinese Journal of Cell Biology, 2007, 29: 785-790.
[8] Han JS. Neuro Science (The third edition) [M]. Beijing: Peking University Medical Press, 2009: 1040-1063.
[9] Dong XW. Coexistence of neuropeptide and proposed neurotransmitter in neurons [J]. Progress in Physiological Sciences, 1983, 14(4): 328-333.
[10] Hökfelt T, Ljungdahl A, Steinbusch H, et al. Immunohistochemical evidence of substance P-Like immunoreactivity in some 5-Hydroxytryptamine-containing neurons in the rat central nervous system [J]. Neuroscience, 1978, 3: 517-538.
[11] Bigon E, Boarato E, Bruni A, et al. Pharmacological effects of phosphatidylserine liposomes: The role of lysophosphatidylserine [J]. Br. J. Pharmac, 1979, 67: 611-616.

Corresponding author: Sun Zuodong. E-mail: szd1966512@163.com

Author Contributions Statement

Zou Wei, Tang Qiang: Proposed research ideas and primary designers of the clinical trial protocol;
Sun Zuodong: Proposed research ideas and participated in clinical trial protocol design, inventor of the transcranial magnetoelectric encephalopathy treatment instrument, primary author of the "Introduction" and "Discussion" sections, responsible for manuscript drafting and final version revision;
Sun Wuyi, Wang Wenhua: Inventors of the transcranial magnetoelectric encephalopathy treatment instrument, co-authors of the "Introduction" and "Dis-

cussion" sections;
Yu Xueping, Xing Yanli: Major participants in clinical trial protocol design and implementation leaders;
Liu Bo, Zhang Li, Dai Xiaohong: Clinical trial protocol implementers;
Li Kang: Major participant in clinical trial protocol design and person in charge of mathematical statistical analysis;
Hou Yan: Clinical trial data statistical analyst.

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