Clinical study on Transcranial magnetoelectric encephalopathy treatment instrument treatmenting alzheimer's disease

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Abstract：

[Objective] Evaluate on the treatment efficacy and safety for transcranial magnetoelectric encephalopathy treatment instrument (brand name: AOBO Alzheimer's Treatment Instrument) treatmenting mild to moderate alzheimer's disease.

[Methods] Methods 80 patients with mild to moderate AD [Hachinski ischemia score ≤ 4 cent, degree of dementia（CDR=1.0）or (CDR=2.0)]were double center，randomized，double blind，Parallel，placebo controlled, clinical trial for 8 weeks, including treatment group and control group, each of 40 case. All the patients were given regular basic medical treatment and standardized nursing care, The patients of treatment group were treated with Transcranial magnetoelectric encephalopathy treatment instrument, The patients of control group were simulated treated with Transcranial magnetoelectric encephalopathy treatment instrument.

[Results] Clinical trial results show, after treated for 8 weeks, Compared with the control group, the treatment group's score of MMSE、ADAS-Cog and ADL improved significantly (difference between groups is P<0.001、0.0001、0.05). When treated 4 weeks, the score of MMSE and ADAS has been improved.There was no adverse reaction in the two groups.

[Conclusions] The test statistical results proved, Transcranial magnetoelectric encephalopathy treatment instrument has good therapeutic effect for treatment mild to moderate alzheimer's disease. It can improve the mental state, cognitive behavior and self-care ability of daily life, and it is used safety.

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

Alzheimer's disease is a disease mainly for neuronal degenerative cognitive dysfunction, the ability of daily life and loss of mental and behavioural disorders, there is no development of any kind of really effective drugs can prevent and delay the disease[1], and the prevalence rate of AD increased gradually. The treatment of AD has become the focus of world brain scientists.

The patented product (Patent No.: ZL2009I0071875.X)-Transcranial magnetoelectric encephalopathy treatment instrument（brand name：AOBO Alzheimer's Treatment Instrument[4] , TME）that developed by Harbin Aobo Medical Apparatus co.,ltd. on the basis of the " The theory of brain cell activation [2]" is a non intrusive physical therapy apparatus for rehabilitation treatment for AD that based on the core technology of transcranial electric (TES) brain function rehabilitation therapy instrument[5,6] and integrated transcranial magnetic stimulation (TMS) . By activating the core region neurons and activating the cortical functional areas by TMS, the instrument fully takes into account the fact that the neurotransmitter, the whole brain distribution and the high impedance of the skull can be activated by TES.

TME can also be understood as the endogenous neurotransmitter control technology, this paper is on the clinical application of TME in the treatment of patients with mild to moderate AD's safety and effectiveness evaluation, the relevant data is approved by the State Drug Administration in 2014 and is partial clinical basis for Transcranial magnetoelectric encephalopathy treatment instrument（brand name：AOBO Alzheimer's Treatment Instrument）, TME registration number: hei shi yao jian xie(zhun)zi 2014 No. 2260036th.

1.   Clinical data and methods

1.1   Object of study

(1) AD patient general data：

A double center, randomized, double blind, parallel, placebo-controlled clinical study of 80 patients was conducted. The treatment group (treated by transcranial magnetoelectric encephalopathy treatment instrument) in 40 cases, male 13 cases, female 27 cases, age ranged from 50 to 75 (59.93 + 7.22), mini mental state evaluation (MMSE) score of 10 to 22 (17.35 + 2.89), Alzheimer's assessment (ADAS) score of 19 to 45 (29.53 + 6.72); control group(treated by model of transcranial magnetoelectric encephalopathy treatment instrument)   in 40 cases, male 16 cases, female 24 cases, age ranged from 50 to 78 (62.48 + 7.73), mini mental state evaluation (MMSE) score of 11 to 23 (17.48 + 2.94), Alzheimer's assessment (ADAS) score of 20 to 45 (31.70 + 7.42); There was no significant difference in sex, age and MMSE and ADAS scores between the treatment group and the control group.

(2) Diagnostic criteria：

All AD patients met the AD diagnostic criteria of *neurology*[7], and *the American Manual of diagnostic manual of mental disorders* (Fourth Edition) (DSM- IV) [8].

(3) Standard for admission cases

a. Consistent with Alzheimer's disease, DSM- IV diagnostic criteria;

b. Hachinski ischemia score less than or equal to 4 points;

c. The degree of dementia was mild (CDR=1.0) or moderate (CDR=2.0);

d. Between 50~80 years of age: both sexes were available; all patients signed informed consent.

(4) Exclusion criteria：

a. Hachinski ischemia scores (HIS) score of 5 to 6 mixed dementia and Hachinski ischemia scores (HIS) score of 7 vascular dementia, Cornell Depression Scale score is greater than or equal to 8;

b. Patients with severe (CDR=3.0) and suspected dementia (CDR=0.5);

c. Patients with heart, brain, liver, kidney, hematopoietic system and other serious primary diseases；

d. Persons under 50 or above 80 years of age;

e. Patients taking part in other clinical trials；

f. Patients with safety index severely abnormal (laboratory indicators exceeded normal-line 20%);

g. Intolerant of instrument therapy, severe side effects, allergic;

h. Patients who does not comply with the design proposal.

1.2 Test method

(1) Test participation

Clinical research **participation** 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.

(2) Test method

Transcranial magnetoelectric encephalopathy treatment instrument and model of transcranial magnetoelectric encephalopathy treatment instrument are similar in appearance and treatment, provided by Harbin Aobo Medical Apparatus co.,ltd.

Operated by specially trained medical personnel. In strict accordance with the *research manual* of product, select the treatment site, fixed treatment terminal, set the treatment parameters. Patients were treated with standard treatment modalities (with normal therapeutic dose output) or an analog treatment model (which did not actually have therapeutic dose output). Treat 2 times a day, 30 minutes each，The interval between the two treatments is over 10min. Continuous treatment for 7 days for 1 courses，a total of 8 courses of treatment.

(3) Curative effect determination

a. Main outcome measures: mini mental status assessment (MMSE), clinical dementia evaluation (CDR), and Alzheimer's assessment (ADAS-Cog);

b. Secondary indicators: assessment of daily living ability (ADL:Barthel index).

(4) Safety evaluation

Before the treatment (0 weeks) and at the end of treatment (8 weeks), in each check once before and after treatment, method :

a. General physical examination;

b. Blood routine, urine routine, liver function and kidney function examination;

c. ECG examination.

(5) Statistical analysis

SAS9.1.3 statistical analysis software was adopted to evaluate the main curative effects. At the same time, the two data sets of FAS and PPS were calculated, and the safety evaluation was carried out to analyze the SAS data .

2. Result

The results of PPS analysis in this experiment are close to that of FAS analysis, so the statistical results of FAS analysis are listed only.

2.1 Before treatment, in treatment and after treatment, MMSE, ADAS, CDR and ADL scores.

As shown in Table Table 1, table 2 and table 3.

Table 1 treatment group and control group before treatment scale
Score ($x \pm s$, point), test statistic (t value) and P value

Group	Cases	MMSE	ADAS	CDR	ADL
Treatment group	40	17.35±2.89	29.53±6.72	1.33±0.47	77.63±14.50
Control group	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

		P	0.8482	0.1731	0.8159	0.3637

Table 2 treatment group and control group, after 4 weeks of treatment scale

Score (x ± s , point), test statistic (t value) and P value

Group	Cases	MMSE	ADAS	CDR	ADL
Treatment group	40	17.95±3.01	28.73±6.56	1.29±0.48	78.25±14.30
Control group	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
P		0.6506	0.0687	0.6486	0.2428

Table 3 treatment group and control group, after 8 weeks of treatment scale

Score (x ± s , point), test statistic (t value) and P value

Group	Cases	MMSE	ADAS	CDR	ADL
Treatment group	40	18.93±3.37	27.78±7.35	1.19±0.46	79.25±14.08
Control group	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
P		0.1062	0.0237	0.2440	0.1423

2.2 Cognitive function (scored by MMSE)

The curative effect observation showed that the MMSE score of the treatment group was significantly higher than that of the control group (P < 0.001) after treatment, as shown in Table 5, and the MMSE score improved significantly at 4 weeks after treatment (P< 0.05), as shown in table 4.

Table 4　The treatment group and the control group, the difference between the scales after 4 weeks treatment(in treatment-before treatment)

Score (x ± s , point), test statistic (t value) and P value

Group	Cases	MMSE	ADAS	CDR	ADL
Treatment group	40	0.60±0.96	-0.80±0.99	0.00±0.00	0.63±2.82
Control group	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
P		0.0382	0.0038		0.2239

Table 5 The treatment group and the control group, the difference between the scales after 8 weeks treatment(after treatment-before treatment)

Score (x ± s , point), test statistic (t value) and P value

Group	Cases	MMSE	ADAS	CDR	ADL
Treatment group	40	1.58±1.53	-1.78±1.68	-0.14±0.32	1.63±3.47
Control group	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
P		0.0002	< 0.0001	0.0880	0.0278

2.3 Alzheimer's rating (using the ADAS score)

After treatment, the ADAS score of the treatment group was significantly higher than that of the control group (P < 0.0001), as shown in Table 5, and the ADAS score was significantly improved (P< 0.005) at 4 weeks of treatment, as shown in table 4.

2.4 Dementia degree (with CDR score)

After treatment, the treatment group compared with the control group CDR score improved (P= 0.0880), as shown in Table 5; and in the treatment of 4 weeks, CDR score did not improve, as shown in Table 4. Treatment with a therapeutic device continued to improve the level of dementia even more dramatically.

2.5 Self-care ability (ADL score)

After treatment, the ADL score of the treatment group was significantly higher than that of the control group (P < 0.05), as shown in Table 5, and there was no significant improvement in the ADL score at 4 weeks (P > 0.05), as shown in table 4.

2.6 Clinical safety

There were no adverse reactions or adverse events in 40 cases treatment group and 40 cases control group. During the use of Transcranial magnetoelectric encephalopathy treatment instrument, all patients had stable vital signs, and no significant changes in examination of blood or urine routine and blood biochemical tests (P > 0.05).

This experiment showed that Transcranial magnetoelectric encephalopathy treatment instrument can improve the light, moderate cognitive impairment, The cognitive function of MMSE and ADAS showed some improvement in the treatment of 4 weeks. There was a marked improvement at 8 weeks, the patient's word recall, attention, memory and computational power were improved, compared with the control group, there was statistical difference.Transcranial magnetoelectric encephalopathy treatment instrument can also improve the self-care ability of patients with AD and reduce the degree of dementia. Transcranial magnetoelectric encephalopathy treatment instrument conducted a two center, randomized, double-blind, parallel, placebo-controlled trial of AD patients, and the results showed that 8 weeks of treatment resulted in significant treatment effects. Statistical analysis showed significant difference, the clinical safety was high without any side effects.

In summary, The test statistical results proved, Transcranial magnetoelectric encephalopathy treatment instrument has good therapeutic effect for treatment mild to moderate alzheimer's disease. It can improve the mental state, cognitive behavior and self-care ability of daily life, and it is used safety[4].

3 Discuss

Alzheimer's disease, plagued the world nearly 35.6 million people, and an annual increase of 4.6 million, only 10 million in China, 80 years of age the elderly prevalence rate of 30%. Unfortunately, so far there is no clear cause of AD, there is no medicine for really effective[9], so there are all kinds of hypothesis, such as β- amyloid hypothesis, Tau protein hypothesis (Tau protein lesions and is thought to occur in the Aβ downstream) and inflammatory hypothesis, cholinergic hypothesis etc, the research on AD mainly concentrated in the mainstream of Aβ[10]. But since 1984, Glenner and Wong have gotten Aβ from Isolation and purification of senile plaques, and They have read their protein sequences, So far 30 years, all drugs based on Aβ have failed all over the world. The existing AD drugs such as cholinesterase inhibitors, NMDA receptor antagonist, are unable to treat cholinergic neurons that have undergone degenerative changes, Perhaps this is why such drugs do not prevent or delay the progression of the disease.Drugs that are being developed for treatment of AD disease are also mostly treatment of upstream and downstream of cholinergic neurons that have undergone degenerative changes.The β-amyloid hypothesis may mislead mainstream research.

The TME, that has been developed based on the theory of brain cell activation, The clinical validity of TME proved the cholinergic hypothesis[10].The cholinergic hypothesis, which is a decrease in basal cholinergic neurons, leads to a decrease in the synthesis, storage, and release of acetylcholine (ACh), leading to a series of clinical manifestations of memory and recognition dysfunction. There has been

evidence that ACh deletion is the primary cause of memory impairment, although it may not be the only cause.

Cholinergic neuronal death, loss of Ach may not be a neurotransmitter, neuropeptides are coexisting with neurotransmitters [11-13], neuropeptide is adapted to adjust a slow and sustained functional changes have neurotrophic effects. The main cause of TME's effect may be the activation of the corresponding neurotransmitter neurons, such as cholinergic neurons and peptidergic neurons.

In addition, the targets of TME are not limited to the voltage-gated Ca2+ channels, such as the role of AD, may also be reflected in the specific field of applied polypeptide on senile plaque main component of amyloid beta (A beta) to achieve nuclear charge and Tau protein to acidification, eliminate inflammation, remove A beta or A beta blocking polymerization, protection of and axonal transport system of microtubule assembly[1].

The above is TME's explanation of the validity of AD.

About the security of TME. New advances in biological magnetoelectric can on the central nervous system (CNS) without damage activation, reflecting the possibility of research and treatment, this method is based on the application of external pulse electromagnetic field, it with the exponential decay of the way through the skin, can make the CNS specific area of excitement. The human brain is very arrogant and expensive. In principle, it can not be directly given to high intensity electromagnetic stimulation. High intensity deep brain stimulation or high intensity transcranial magnetic stimulation, equivalent to electroshock therapy or magnetic shock therapy, may cause long-term injury to the brain which is uncertain, The inappropriate consequences of using deep brain stimulation can damage the brain. The magnetic field strength of TME is no more than 50mT. Compared with the high voltage low frequency pulsed magnetic field, the purpose, mechanism, strength and safety of the magnetic field are different, TME uses multi turn magnetic field generator, multi position low frequency and low intensity alternating magnetic field. The direct action is "head" rather than "brain", and the stimulation of target in brain is flexible. The target is superficial cortical layer of brain. The transcranial direct current of TME is a non intrusive transcranial electrical, the brain through the core area of neurons is the micro current. In this way, it can avoid the high intensity pulsed electromagnetic fields on the human brain may cause harm, but also can achieve the desired therapeutic effect. It is not affected by the treatment conditions, safety and no side effects, can be used in family and hospital.

Reference：

1. Ge Ge. Research progress of Alzheimer's disease . Chinese and foreign medical research, 2014,12 (9): 155-157.

2. Sun Zuodong. The theory of brain cell activation . Harbin: Heilongjiang science and Technology Press, 2016.

3. Sun Zuodong. Transcranial computed tomography apparatus [P], China, ZL200910071875.X, 2012-08-22.

4. The world's first Alzheimer's treatment apparatus developed successfully. Technology and publishing, 2014,6:143.

5. Jiao Mingde, Sun Zuodong. Effects of Aobo brain function rehabilitation instrument on cerebral circulation and brain function. Medical health care appliance, 1998,03:251-252.

6. Tian Ningning. Application of Aobo brain rehabilitation therapy instrument in stroke hemiplegia patients. Medical equipment, 2009,09:68.

7. Jia Jianping, Cui Liying, Wang Wei, et al. Neurology. People's Medical Publishing House, 2008, sixth, 217.

8. Xu Xianhao. Neural immunology. Hubei science and Technology Press, 2000, 327-333.

9. Yin Ming. Full-scale setback and thinking in R&D of Alzheimer's disease drug.Acta Pharmaceutica Sinica.2014;49 (6):

757-63.

10. Han Jisheng. Neuroscience. Third Edition. Beijing: Peking University medical press, 2009:195-519.

11. Dong Xinwen. Coexistence of neuropeptide and proposed neurotransmitter in neurons. Progress in Physiological Sciences. 1983; 14(4):328-33.

12. 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. Neuroscience.1978; 3:517-38.

13. Bigon E, Boarato E, Bruni A, et al.: Pharmacological effects of phosphatidylserine liposomes:The role of lysophosphatidylserine. Br.J.Pharmac.1979; 67:611-16.

Author contribution statement:

Qiang Tang, Wei Zou: Proposed research ideas, clinical trial program master design;

Zuodong Sun: Put forward the research ideas and clinical trial design participants, inventor of transcranial magnetoelectric encephalopathy treatment instrument, the "preface" and "discussion" part of the main author, responsible for the drafting and revision of the final version;

Wuyi Sun, Wenhua Wang: Inventor of transcranial magnetoelectric encephalopathy treatment instrument , one of the authors of "preface" and "discussion" in this article;

Yanli Xing , Xueping Yu: Clinical trial design: the main participants and the implementation of clinical trials led;

Bo Liu, Li Zhang, Xiaohong Dai: Clinical trial program implementer;

Kang Li: Principal participant in the design of clinical trial programs and head of mathematical statistical analysis;

Yan Hou: Statistical analysis of clinical trial data.