Clinical study on Transcranial magnetoelectric encephalopathy treatment instrument treatmenting vascular dementia

Wei Zou [1] Qiang Tang [2] Zuodong Sun [3*] Yanli Xing [2] Xueping Yu [1] Kang Li [4]
Wuyi Sun [5] Wenhua Wang [5] Bo Liu [2] Li Zhang [2] Xiaohong Dai [1] Yan Hou [4]

[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)
[4] (School of public health,Harbin Medical University，Harbin, 150000, China)
[5] (Harbin Aobo Medical Apparatus Co.,Ltd, Harbin, 150090, China)

Abstract：

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

[Methods] Methods 80 patients with mild to moderate VD [Hachinski ischemia score ≥7 cent, degree of dementia （CDR=1.0） or（CDR=2.0）]were double center，randomized，double blind，Parallel，placebo controlled, clinical trial for 4 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] After treated for 4 weeks, Compared with the control group, the treatment group's score of MMSE、CDR and ADL improved significantly (difference between groups is $P<0.0001$、0.05、0.05). There was no adverse reaction in the two groups.

[Conclusions] Transcranial magnetoelectric encephalopathy treatment instrument has good therapeutic effect for treatment mild to moderate vascular dementia. It can improve the mental state, cognitive behavior and self-care ability of daily life, and it is used safety.

Keywords： Rehabilitation medicine；Transcranial magnetoelectric；Vascular dementia；Cognitive impairment；The theory of brain cell activation

Vascular dementia is a severe impairment of memory, cognition and behavior caused by ischemic stroke and hemorrhagic stroke. It is one of the sequelae of stroke,usually 2 months later. Whether it is ischemia or bleeding, for neurons, the cause of direct damage to neurons is ischemia. With the acceleration of aging in China and the increasing incidence of cerebrovascular disease, the incidence of VD is on the rise, be next only to Alzheimers disease, exploring the treatment of VD has been a focus of attention all over the world.

The patented product (Patent No.: ZL2009I0071875.X)-Transcranial magnetoelectric encephalopathy treatment instrument[3]（TME） that developed by Harbin Aobo Medical Apparatus co.,ltd. on the basis of the " The theory of brain cell activation [1]" is a non intrusive physical therapy apparatus for rehabilitation

* Corresponding author: Zuodong Sun (E-mail: sunzuodong@pai314.com).

treatment for AD that based on the core technology of transcranial electric (TES) brain function rehabilitation therapy instrument[4,5] 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. The efficacy and safety of TME in the treatment of patients with mild to moderate VD are summarized in this paper. 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

1.1 General data

The selected cases were from the First Affiliated Hospital,Heilongjiang University of Chinese Medicine and Second Affiliated Hospital,Heilongjiang University of Chinese Medicine. The 80 patients were randomly divided into treatment group and control group according to the principle of double center, random, double blind, parallel and placebo control. The treatment group(treated by transcranial magnetoelectric encephalopathy treatment instrument) of 40 cases, 18 cases were male, 22 were female, aged from 47 to 75 (61.45 + 7.14), mini mental state evaluation (MMSE) score of 10 to 23 (17.80 + 2.88); the control group(treated by model of transcranial magnetoelectric encephalopathy treatment instrument) of 40 cases, 26 cases were male, 14 were female, aged from 45 to 79 (62.95 + 8.77), MMSE score ranged from 11 to 22 (17.33 + 3.12) points. There was no significant difference in sex, age and MMSE score between the treatment group and the control group.

1.2 Diagnostic criteria

Referring to the diagnostic criteria of NINDS-AIREN vascular dementia (Roman, GC, et, al., Neurology, 1993) and the national "9·5 key diagnostic criteria, namely:

(1) Dementia;

(2) Evidence of cerebrovascular disease (CT or MRI：confirmed multiple cerebral infarcts and lacunar infarcts, single infarcts and focal signs of important sites);

(3) There is a clear cause and effect relationship between the two injuries (dementia within 6 months after a definite stroke, cognitive impairment, or fluctuating, progressive, progressive cognitive impairment).

1.3 Standard for admission cases

(1) Consistent with the diagnostic criteria for vascular dementia NINDS-AIREN; dementia onset within 6 months of stroke, the disease continued for more than 3 months.

(2) Hachinski ischemia score more than 7 cent;

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

(4) Between 40~75 years of age: both sexes were available and all patients signed informed consent.

1.4 Exclusion criteria:

(1) Hachinski ischemia scores (HIS) score of 5 to mixed dementia and no more than 6 points to 4 points in Alzheimer's disease, Cornell Depression Scale score is greater than or equal to 8;

(2) Patients with vascular dementia with severe (CDR=3.0) and suspected vascular dementia (CDR=0.5);

(3) Dementia resulting from Cerebral hemorrhage or extensive cortical infarction;

(4) The neural function defect associated with severe patients, such as aphasia etc.;

(5) Combined with heart, brain, liver, kidney and hematopoietic system and other serious primary diseases, mental patients;

(6) Allergic to aspirin and salicylic acid; stomach and duodenal ulcers; bleeding prone patients;

(7) Persons under 40 or above 75 years of age;

(8) Safety measures were performed before treatment, severe abnormalities (laboratory indicators exceeded normal, on-line or offline 20%);

(9) Intolerant of instrument therapy, severe side effects, allergic;

(10) Take medications to improve vascular dementia within a week.

2 Test method

2.1 Test participation

Research center: 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.

2.2 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.According to grouping of selected cases, All the patients were given regular basic medical treatment (given orally Bayaspirin, 100mg/1 times daily) 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.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 4 courses of treatment.

2.3 Curative effect determination

(1) Main indicators: mini mental status assessment (MMSE);

(2) Secondary indicators: assessment of daily living ability (ADL:Barthel index),Clinical dementia assessment (CDR).

2.4 Safety evaluation

Before the treatment (0 weeks) and at the end of treatment (4 weeks), in each check once before and after treatment, method :

(1) General physical examination;

(2) Blood routine, urine routine, liver function and kidney function examination;

(3) ECG examination

2.5 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 .

3 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.

3.1 Before treatment, in treatment and after treatment, MMSE, CDR and ADL scores.

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

Table 1 Treatment group and control group before treatment scale

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

Group	Cases	MMSE	CDR	ADL
Treatment group	40	17.80±2.88	1.35±0.48	68.38±15.62
Control group	40	17.33±3.12	1.43±0.50	64.88±12.78
Test statistic		0.707	-0.682	1.097
P		0.4814	0.4974	0.2762

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	CDR	ADL
Treatment group	40	20.50±3.65	1.11±0.49	75.63±11.56
Control group	40	18.53±3.46	1.35±0.56	68.75±11.42
Test statistic		2.482	-2.030	2.676
P		0.0152	0.0457	0.0091

Table 3 The treatment group and the control group, treatment for 4 weeks

(before treatment - before treatment) after the difference in the scale

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

Group	Cases	MMSE	CDR	ADL
Treatment group	40	2.70±1.64	-0.24±0.38	7.25±8.91
Control group	40	1.20±1.62	-0.08±0.21	3.88±5.60
Test statistic		4.120	-2.381	2.028
P		0.0001	0.0204	0.0467

3.2 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 3.

3.3 Dementia degree (with CDR score)

After treatment, the treatment group compared with the control group CDR score improved ($P< 0.05$), as shown in Table 3.

3.4 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 3.

3.5 Clinical safety

There were no adverse reactions or adverse events in the two groups during the study. 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 ($P > 0.05$).

4 Discuss

Vascular dementia is a group of intellectual and cognitive dysfunction syndrome caused by cerebrovascular diseases. It is one of the common causes of Alzheimer's disease. Cerebrovascular lesions

are the basis of VD, and hemorrhagic or ischemic lesions can be seen in the brain parenchyma. VD dementia can occur suddenly or step by step, with the course of fluctuation associated with cerebrovascular events. The selected cases in this study are limited to ischemic stroke. In acute phase of stroke, neuron death is mainly necrosis, and secondary death or delayed death after acute stage is mainly apoptosis. The former occurs in the early central area after ischemia, and the latter occurs in the penumbra after ischemia. Autophagy may also be one of the ways of ischemic neuronal death.

The acute phase of stroke is mainly controlled by medicinal chemistry, with the aim of saving life and saving dying neurons[6]. TME stimulation leads to rhythmic bidirectional oscillations in intracellular and extracellular calcium concentrations[7], the aim was to restore homeostasis of extracellular calcium concentration, It does not cause a toxic response in calcium dependent cells, It's different from that in the acute phase of stroke, a series of reactions evoked by the imbalance of internal and external ion homeostasis in neurons cause neuronal damage[8]. Therefore, the content of this article does not involve the pathological process and repair mechanism of ischemic neuronal injury in the acute phase of stroke.

The mechanism of TME on VD may be that it reverses neurons, such as cholinergic neurons and peptidergic neurons, that have entered apoptotic processes. Previous evidence suggests that the loss of acetylcholine (ACh) is associated with cognitive impairment, the death or apoptosis of cholinergic neurons is not only lost in ACh. Neuropeptides and neurotransmitters coexist[9-11]. Compared with neurotransmitters, neuropeptides are more useful for modulating slow and long-lasting functional changes, many neuropeptides also have neurotrophic effects. TME works well for VD, which may activate neurotransmitter neurons, such as cholinergic neurons and peptidergic neurons, and restore the stability of the environment.

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.

This clinical trial shows, Transcranial magnetoelectric encephalopathy treatment instrument（brand name：AOBO Alzheimer’s Treatment Instrument）has good therapeutic effect for treatment mild to moderate vascular dementia. It can improve the mental state, cognitive behavior and self-care ability of daily life, and it is used safety.

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Author contribution statement:

Wei Zou, Qiang Tang: Proposed research ideas, clinical trial program master design;
Zuodong Sun: Put forward the research ideas and clinical trial design participants, transcranial magnetic therapy instrument computer disease inventor, the "preface" and "discussion" part of the main author, responsible for the drafting and revision of the final version;
Wuyi Sun, Wenhua Wang: One of the authors of "preface" and "discussion" in this article;
xueping Yu, Yanli Xing: 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.