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

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Abstract：

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

[Methods] Use methods of double center,randomized, double blind, self crossover, 22 Parkinson's patients who met the inclusion criteria were randomly divided into A group and B group, then were carried on the curative effect analysis, and were observed therapeutic effect.

[Results] The treatment group of 22 cases, basically cured in 0 cases, markedly effective in 9 cases, effective in 8 cases, ineffective in 5 cases. The total efficiency rate and total effective rate were 40.91% (9/22) or 77.27% (17/22) respectively. The control group of 22 cases, basically cured in 0 cases, markedly effective in 2 cases, effective in 3 cases, ineffective in 17 cases. The total efficiency rate and total effective rate were 9.09% (2/22) or 22.73% (5/22) respectively, the total effective rate and total effective rate in the treatment group were higher than those in the control group, the difference was statistically significant ($P<0.05$). Among them, the main symptoms of resting tremor, rigidity, bradykinesia, evaluation, the treatment group has significant difference ($P<0.01$); There was no significant difference in the control group ($p>0.05$); There was 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 in patients with Parkinson's disease and other symptoms, and the use of safety.

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

Parkinson's disease by the British doctor James Parkinson first described in 1817, is one of the most common in the elderly degenerative disease of the central nervous system, resting tremor, muscle rigidity, bradykinesia, postural abnormalities, loss of balance for clinical features. Parkinson's disease is a worldwide medical problem. With the aging population becoming more and more serious, Parkinson's disease has become one of the most important diseases affecting human health.

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At present, drug treatment can only control the symptoms of Parkinson's disease, but can not cure, and can not stop or improve the development of disease[1] , its increasingly prominent failures and adverse reactions have drawn wide attention from the medical community. The main surgical treatment is destruction, deep brain stimulation and tissue cell transplantation. Because of the irreversible destruction of the cranial nerve, destruction causes many complications, some of which are disabled for life, and now it is not advocated; Deep brain stimulation, that is, the installation of brain pacemaker, because of the risk of implanting foreign bodies in the brain, and high costs, the condition of the operation of the hospital and patients are very limited; Tissue cell transplantation, using stereotaxic techniques, it is still under investigation that brain cells that produce dopamine, such as fetal brain or neural stem cells, are transplanted into the brain[2].

Transcranial magnetoelectric encephalopathy treatment instrument（brand name：AOBO Parkinson's Treatment Instrument[3], TME）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, the patent number is ZL2009I0071875.X[11] .This paper is on the clinical application of TME in the treatment of patients with mild to moderate PD's safety and effectiveness evaluation, the relevant data is approved by the State Drug Administration in 2011 and is partial clinical basis for Transcranial magnetoelectric encephalopathy treatment instrument, TME registration number: hei shi yao jian xie(zhun)zi 2011 No. 226001th.

1 Clinical data and methods

1.1 Clinical general data

(1) Diagnostic criteria

Referring to *Diagnostic criteria and differential diagnosis of Parkinson's disease and Parkinson's syndrome* formulated by National Symposium on extrapyramidal diseases at October 1984. diagnostic criteria：

a. There are at least 4 typical symptoms and signs (static tremor, less movement, muscle rigidity, and positional reflex disorder) in 2;

b. There is the diagnosis of idiopathic Parkinson's disease does not support the atypical symptoms and signs, such as pyramidal sign, apraxia of gait disorder, cerebellar syndrome, intention tremor, gaze palsy, severe autonomic dysfunction was associated with mild dementia, extrapyramidal symptoms.

(2) Total number of cases

According to characteristic of Transcranial magnetoelectric encephalopathy treatment instrument and Parkinson's disease , fewer cases is not easy to obtain a large sample, under the assumption that the treatment group was significantly better than the placebo group in the situation, determine the treatment group of 22 cases, and the control group of 22 cases, because of the cross design, taking the total sample of 22 cases, so the greater the probability that the clinical trial results were statistically significant.

(3) Case selection

Case inclusion criteria:

a. Compliance with Parkinson disease diagnostic criteria;

b. Between the ages of 45~70；

c. Modified Hoehu-Yahr staging in patients with mild to moderate disease (grade 1~3);

d. During the inspection to stop taking drugs benserazide;

e. According to the purpose of clinical trials and the characteristics of the disease, both men and women can;

f. All patients signed informed consent.

Exclusion criteria：

a. Parkinson's syndrome, etc;

b. Combined with other heart, brain, liver, kidney, endocrine and hematopoietic systems and other serious diseases;

c. Persons under 45 or over 70 years of age;

d. Psychiatric patients;

e. A woman who is pregnant or preparing for pregnancy; a lactating woman.

Case rejection criteria:

a. A person who is forced to discontinue treatment because of adverse effects;

b. Those who fail to make follow-up visits or fail to visit may not be able to judge the efficacy or data, and affect the therapeutic effect;

c. 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

In accordance with the two center, randomized, double-blind, crossover controlled method, 22 patients were randomly divided into A group and B group, A group, treatment group, treatment for 10 days, 2 times a day, each treatment time was 30 minutes, 10 minute break in the middle; then, A group is the control group, for 10 days, with a total of 20 days. The B group was a control group with a duration of 10 days, 2 times a day, with a treatment duration of 30 minutes, with a 10 minute interval. Then, the B group was the treatment group for a period of 10 days, with a total of 20 days.

Before the treatment, 12 hours of anti PD drugs were discontinued, and the anti PD drugs were not taken in the morning. The treatment started at 2 hours after breakfast.

(3) Blind implementation

Each trial was attended by 2 individuals, 1 treated, and 1 evaluated. The patients did not know whether they were receiving experimental instruments or placebo controlled instruments, and the operators who participated in the evaluation did not know the actual grouping situation, and simulated the double blind effect.

(4) Curative effect determination

The unified PD scoring scale UPDRS III.

(5) 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 examination;

c. ECG examination, liver function and kidney function examination.

(6) 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 PPS data set of this experiment is the same as that of the FAS dataset, so the statistical results of the PPS dataset and the FAS data set are listed together.

2.1 Statistical analysis of efficacy of main end points in effectiveness evaluation

The treatment group total effective rate and total effective rate was 40.91% (9/22) and 77.27% (17/22), its 95% confidence interval respectively (20.36 ~ 61.45) and (59.76 ~ 94.78), the control group total effective rate and total effective rate was 9.09% (2/22) and 22.73% (5/22), its 95% interval respectively (0 ~ 21.10) and (5.22 ~ 40.24), there is significant difference of the center effect (P=0.0006); The total efficiency of the test was adjusted to the central adjusted P=0.0003, and the total effective rate and the total effective rate of treatment group was higher than that of control group, the treatment group is better than control group. See Table 1 to table 5.

Table 1 the distribution of clinical efficacy in the two groups after 20 days (PPS and FAS)

Grouping	Cases	Basic control	Excellent	Effective	Invalid	*Z*	*P*
A	22	0	9	8	5	3.5000	0.0005
B	22	0	2	3	17	3.5000	0.0005

Note: P value: up PPS analysis, down FAS analysis

Table 2 After 20 days of treatment, the clinical efficacy, total effective rate and total effective rate of the two groups were compared (PPS and FAS)

Grouping	Cases	Total apparent efficiency(%)	Total effective rate(%)	P_1	P_2
A	22	40.91	77.27	0.0148	0.0003
B	22	9.09	22.73	0.0148	0.0003

Note：P1：Chi square test of total apparent efficiency；P2：Chi square test of total effective rate. The value of P：up PPS analysis, down FAS analysis.

Table 3 After 20 days of treatment, 95% confidence intervals of the clinical efficacy of the two groups were estimated (PPS and FAS)

Grouping		Cases	Total apparent efficiency(%)	Total effective rate(%)
A	Bilateral	22	20.36～61.45	59.76～94.78

	Unilateral	22	23.67～58.15	62.58～91.97
B	Bilateral	22	0.00～21.10	5.22～40.24
	Unilateral	22	0.00～19.17	8.03～37.42
The difference between the two groups	Bilateral	-	8.02～55.62	29.78～79.31
	Unilateral	-	11.85～51.79	33.76～75.33

Table 4 The distribution of clinical efficacy at different stages of treatment in the two groups (PPS and FAS)

Grouping	After 10 days of treatment					After 20 days of treatment					*Z*	*P*
	Cases	Basic control	Excellent	Effective	Invalid	Cases	Basic control	Excellent	Effective	Invalid		
A	11	0	5	3	3	11	0	4	5	2	3.3443	0.0008
B	11	0	0	0	11	11	0	2	3	6	-1.5702	0.1164

Note: # Wilcoxon test; P value: up analysis results after 10 days of treatment, down analysis results after 20 days of treatment.

Table 5 The distribution of clinical efficacy at different stages of treatment in the two groups (PPS and FAS)

Grouping	After 10 days of treatment			After 20 days of treatment			P_1	P_2
	Cases	Total apparent efficiency (%)	Total effective rate (%)	Cases	Total apparent efficiency (%)	Total effective rate (%)		
A	11	45.45	72.73	11	36.36	81.82	0.0351	0.0010
B	11	0.00	0.00	11	18.18	45.45	0.6351	0.1827

Note：P1：Chi square test of total apparent efficiency；P2：Chi square test of total effective rate. up analysis results after 10 days of treatment, down analysis results after 20 days of treatment.

2.2 Effectiveness evaluation, statistical analysis of the main individual indicators

In the evaluation of the main symptoms of resting tremor, muscle rigidity, bradykinesia, the patients in the treatment group had significant difference (P<0.01); the control group were not obviously improved (p>0.05); there were significant differences between the treatment group and control group (p<0.05). From the two groups of patients with Parkinson disease rating scale, a total of 36 individual indicators in the overall situation, three representative symptoms of individual symptoms, see table 6.

Table 6 Two groups of patients with Parkinson disease rating scale of the individual indicators of the general situation (PPS and FAS)

Item	Curative effect	Experimental group	Control group	Test statistic	The value of P
Static tremor	Effective	11	1	11.4583 (chi-square)	0.0007
	Invalid	11	21		
Muscle rigidity	Effective	11	4	4.9563 (chi-square)	0.0260
	Invalid	11	18		
Leg flexibility	Effective	6	1	Exact propability	0.0931
	Invalid	15	20		

2.3 Statistical analysis of clinical safety

The treatment group and the control group have no adverse reactions or adverse events in the clinical trials.

In summary, the experimental statistics show that, Transcranial magnetoelectric encephalopathy treatment instrument（brand name：AOBO Parkinson's Treatment Instrument） treatment of mild and moderate Parkinson disease has a short-term effect, especially can improve the patients with Parkinson's disease of static tremor, muscle rigidity, bradykinesia and other symptoms, and safe to use.

3 Discuss

The clinical symptoms of PD are mainly static tremor, muscle rigidity, bradykinesia. The main pathological changes were degeneration of dopaminergic neurons in substantia nigra and death, resulting in the decrease of DA content in striatum. The process of DA formation: tyrosine, which is obtained directly or indirectly from food, produces DOPA under the action of tyrosine hydroxylase in neurons, and DA is formed after dopa decarboxylase decarboxylase.

DA is surrounded by dopaminergic neurons axon terminals synaptic vesicles, and the release of dopamine in the vesicles is accomplished by Ca2+ dependent rapid regulation of vesicular exocytosis[13,14]. When the intracellular Ca2+ concentration increases to a certain extent in the cell, it triggers the release of dopamine by vesicles. Ca2+ influx is caused by the opening of voltage gated Ca2+ channels when they are depolarized in the cell membrane. Vesicular exocytosis is divided into Ca2+ dependent rapid regulation exocytosis and basal exocytosis, the basal exocytosis is not regulated by action potential and Ca2+[15], In addition to the extracellular Ca2+ influx, the Ca2+ of axon cytoplasm also comes from the intracellular calcium storage stores of synapses[16]. The internal flow Ca2+ plays a role after stacking with basic calcium ions.

If sustained release of DA dopaminergic neurons in high frequency, with the release of DA, into the presynaptic Ca2+ increase, which will increase the catalytic activity of tyrosine hydroxylase expression, and it can also increase the transcription of mRNA synthase gene and tyrosine hydroxylase[17]. On the contrary, dopaminergic neurons if not timely release of dopamine in the normal rate, there will be degenerative disease, and axoplasm increased dopamine, can inhibit the activity of tyrosine hydroxylase, this feedback regulation can lead to dopamine synthesis time dependent inhibition, perhaps with the clinical use of levodopa in treatment of Parkinson's disease "off" the effect of the. Dopaminergic neurons, which undergo degenerative changes, gradually lose function, and apoptosis is the basal state before

apoptosis, and exocytosis is the essential metabolism that maintains it.

Exogenous dopamine, to alleviate the patient's symptoms and further reduces the activity of tyrosine hydroxylase, It reduced the rate of vesicle fusion in the basal state exocytosis, which was originally absent from action potential and Ca2+ regulation, this alternative therapy is equivalent to giving up the rescue of degenerative dopaminergic neurons. The dopaminergic neuron death signaling pathway is upregulated and the apoptotic program is initiated[19]. The death of dopaminergic neurons is probably not just dopamine. This may be the cause of severe dysfunction in PD patients after 2~5 years of levodopa use. A large number of experiments have indirectly proved that TME is related to the production of endogenous dopamine, The effect of TME is much better than that of simple transcranial magnetic or transcranial electrotherapy.

The best target of TME is voltage gated Ca2 + channel, the improvement in clinical symptoms of PD may be due to activation of neurotransmitter neurons, especially dopaminergic neurons. Approximately 80% of dopaminergic neurons in the midbrain are located in substantia nigra of the midbrain, and 20% remain in other parts of the brain[2].Stimulate the calcium channel of the shortest way is non intrusive TME, mainly in the form of voltage, the TMS of TME generates a micro current through the energy of magneto electricity, and the micro current acts on calcium channels. The effectiveness of TME in the treatment of Parkinson's disease is based on the theory of brain cell activation.

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. Because the cerebral cortex and the medulla of the brain do not have pain nerves, that is, pure nociceptive stimulation of these two tissues is not painful, such as using tweezers.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. Although pacemakers are widely used, brain pacemakers are rarely encouraged. The reason is that the heart is a simple organ, and there is only one main reaction: contraction to eject blood, and the brain is much more complex. Electricity is a monotonous, nonspecific stimulus that stimulates existing functions, but does not build these functions. The high intensity transcranial magnetic stimulation magnetic field strength of 1 to 3T, although there is no real electrode in the brain, but this high intensity magnetic field can be one yuan coins hit 1 ~ 2m. Through the skin and skull, it can stimulate the depth of about 2.5cm of the cerebral cortex region. It stimulates the brain area and causes the thumb to respond, because of the unclear mechanism and safety problems, the application range is limited to clinical hospitals, under the operation of professionals, and the disease is limited to serious mental illness.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. Monkey studies have shown that the cortical magnetic stimulation of the brain reaches 1 to 2G, which increases the hippocampus and reduces the threshold of the motor cortex;The transcranial direct current of TME is a non intrusive transcranial electrical, the brain through the core area of neurons is the micro current. Three pairs of electrodes are symmetrically distributed on the upper edge of the ear, the strength in the premise of scalp

nerve pain perception tolerance, a small part of the current path of the substantia nigra. The conventional version is incorrect because of the presence of the skull and the fact that the current cannot pass through or through the skull.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.

Brain cell activation theory and the safety and efficacy of TME in the treatment of mild to moderate PD suggest a reorientation of clinical experts for the treatment of Parkinson's disease, The patients with mild to moderate Parkinson's disease treatment principle of choice should be non intrusive physical means (such as TME, also known as the in vitro brain pacemaker) instead of l-dopa, When using a non intrusive physical means (such as TME) still can not completely control the symptoms when supplemented by l-dopa, With the increase of the course of treatment, levodopa should be reduced until stop. When PD patients are treated with physical therapy alone (such as TME) or take levodopa or two drugs, the use of deep brain stimulation (DBS, the installation of brain pacemakers) will certainly not produce results. At this point, brain damage may be the last of the most helpless options.

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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, 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;
Yanli Xing , XuepingYu: Clinical trial design the main participants and the implementation of clinical trials led;
jing Bai, xiuying Teng: 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.