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Evaluation of serum indexes and electrophysiological characteristics after ziprasidone combined with modified electroconvulsive therapy for schizophrenian

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ABSTRACT

Objective: To study the effect of ziprasidone combined with modified electroconvulsive therapy (MECT) on serum indexes and electrophysiological characteristics of schizophrenia. **Methods:** A total of 44 patients with schizophrenia treated in our hospital between May 2014 and July 2016 were selected and randomly divided into MECT group and control group, MECT group received ziprasidone combined with MECT therapy and control group received ziprasidone therapy. Before treatment as well as 1 month, 2 months and 3 months after treatment, serum nerve cytokine levels and inflammatory factor levels as well as nerve electrophysiology parameters were detected. **Results:** 1 month, 2 months and 3 months after treatment, serum BDNF, GDNF and NGF levels of both groups were significantly higher than those before treatment, IL-1β, IL-6, IL-17 and TNF-α levels were significantly lower than those before treatment, P300 and N2-P3 latency were significantly shorter than those before treatment, and P300 and N2-P3 amplitude were significantly higher than those before treatment; serum BDNF, GDNF and NGF levels of MECT group were significantly higher than those of control group, IL-1β, IL-6, IL-17 and TNF-α levels were significantly lower than those of control group, P300 and N2-P3 latency were significantly shorter than those of control group, and P300 and N2-P3 amplitude were significantly higher than those of control group. **Conclusion:** Ziprasidone combined with modified electroconvulsive therapy can improve neuron function, reduce neuron damage and adjust nerve electrophysiology function.

1. Introduction

Schizophrenia is a kind of mental illness with high incidence, which not only adversely affects the life and health of patients, but also increases the burden of the family and society. Dopaminergic nervous system and 5-hydroxytryptamine nervous system dysfunction in the anterior lobe and mesolimbic system are associated with schizophrenia, and regulating the function of dopamine and 5-hydroxytryptamine is an important target in the treatment of schizophrenia. Ziprasidone is a kind of atypical antipsychotic drug that has antagonism effect on the 5-hydroxytryptamine 2A receptor and 1D receptor as well as dopamine D2 receptor, and can significantly improve the mental symptoms of patients with schizophrenia[1,2]. Modified electroconvulsive therapy (MECT) is a new treatment developed from the traditional electroconvulsive therapy, which is combined with narcotics and muscle relaxants, and then stimulates the brain with current containing certain pulse to cause loss of consciousness, regulate neurotransmitter release and thus improve mental symptoms[3,4]. In the following study, the effect of ziprasidone combined with modified electroconvulsive therapy on serum indexes and electrophysiological characteristics of schizophrenia was analyzed.

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2. Subjects and methods

2.1 Research subjects

A total of 44 patients with schizophrenia treated in our hospital between May 2014 and July 2016 were selected as the research subjects, all patients were in line with the diagnostic criteria for schizophrenia, and they were with PANSS score ⩾60 points and ASA anesthesia 1-2 grade; patients with MECT contraindications, alcohol abusers, pregnant and breast-feeding women as well as the patients who were using large dose of antipsychotics and mood stabilizers were excluded. Random number table was used to divide the patients into the MECT group who received ziprasidone combined with MECT therapy and the control group who received ziprasidone therapy. MECT group included 10 male cases and 12 female cases that were 39-58 years old; control group included 9 male cases and 13 female cases that were 38-59 years old. The two groups of patients were not significantly different in general data (P>0.05).

2.2 Treatment methods

MECT group received modified electroconvulsive therapy combined with ziprasidone treatment, and modified electroconvulsive therapy was as follows: patients were fasting for solids and liquids for 6h before treatment, took horizontal position and then received intravenous injection of atropine and propofol, they received intravenous injection of suxamethonium chloride after anesthesia took effect and eyelash reflex disappeared, then pressurized mask was used for oxygen supply, the bite block was placed, the breathing was manually controlled, electric convulsion therapy instrument was used for treatment, power (mc) = age×5, current was 800 mA, the pulse width was 1.0 ms, the frequency was 30-70 Hz, and stimulation time was 3-6 s. The treatment lasted for 3 months, three times a week in the first month, 2 times a week in the second month and once a week in the third month. They received ziprasidone treatment during treatment, and the method was as follows: ziprasidone, initial dose 20 mg, oral administration, 2/d, then gradually increasing the dose according to the illness, and maximum dose 160 mg/d. Control group received ziprasidone treatment, and the method was as follows: ziprasidone, initial dose 20 mg, oral administration, 2/d, then gradually increasing the dose according to the disease, and maximum dose 160 mg/d.

2.3 Serum index detection methods

Before treatment as well as 1 month, 2 months and 3 months after treatment, serum samples were collected from the two groups respectively, and enzyme-linked immunosorbent assay kits were used to determine brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), nerve growth factor (NGF), interleukin-1 β (IL-1 β), IL-6, IL-17 and tumor necrosis factor-α (TNF-α) levels.

2.4 Nerve electrophysiology parameter detection methods

Before treatment as well as 1 month, 2 months and 3 months after treatment, the brain evoked potentiometer was used to detect nerve electrophysiology parameters, the recording electrodes were placed on the prefrontal area, central area and parietal region, two eye electrodes were placed 2 cm above two eyes, and specific parameters were as follows: impedance between electrodes was lower than 5 kΩ, sensitivity was 5 μV, detection frequency was 1 time/s, stimulation time was 20 ms, stimulation intensity was 85 dB, frequency was 100 Hz, and the P300 wave latency and amplitude as well as the N2-P3 wave latency and amplitude were recorded respectively.

2.5 Statistical processing methods

SPSS 20.0 software was used to input and statistically process data, measurement data analysis between two groups was by t test and P<0.05 indicated statistical significance in differences.

3. Results

3.1 Serum nerve cytokine levels of two groups of patients before and after treatment

Before treatment as well as 1 month, 2 months and 3 months after treatment, analysis of serum nerve cytokines BDNF (ng/mL), GDNF (pg/mL) and NGF (ng/mL) between two groups of patients was as follows: (1) before treatment, differences in serum BDNF, GDNF and NGF levels were not statistically significant between two groups of patients (P>0.05); (2) 1 month, 2 months and 3 months after treatment, serum BDNF, GDNF and NGF levels of both groups were significantly higher than those before treatment, and differences in serum BDNF, GDNF and NGF levels were statistically significant within same group before and after treatment (P<0.05); (3) 1 month, 2 months and 3 months after treatment, serum BDNF, GDNF and NGF levels of MECT group were significantly higher than those of control group, and differences in serum BDNF, GDNF and NGF levels were statistically significant between two groups after treatment (P<0.05).

Table 1.

Comparison of serum nerve cytokine levels between two groups of patients before and after treatment.

Groups	n	Treatment	BDNF	GDNF	NGF
MECT	22	Before treatment	8.12±0.93	402.67±52.21	18.31±2.32
		1 month after treatment	10.93±1.14^{*a}	495.51±59.28^{*a}	25.48±3.15^{*a}
		2 month after treatment	12.38±1.46^{*ab}	578.59±64.72^{*ab}	30.24±3.89^{*ab}
		3 month after treatment	14.02±1.77^{*abc}	702.12±87.92^{*abc}	39.12±4.65^{*abc}
Control	22	Before treatment	8.20±0.98	405.42±52.18	18.44±2.03
		1 month after treatment	9.41±1.07^{a}	441.24±56.84^{a}	22.11±2.70^{a}
		2 month after treatment	10.78±1.26^{ab}	509.28±62.36^{ab}	25.52±3.23^{ab}
		3 month after treatment	11.49±1.67^{abc}	542.58±71.82^{abc}	28.49±4.21^{abc}

*: compared with control group at the same point in time, P<0.05; ^{a}: compared with same group before treatment, P<0.05; ^{b}: compared with same group 1 month after treatment, P<0.05; ^{c}: compared with same group 2 months after treatment, P<0.05.

3.2. Serum inflammatory factor levels of two groups of patients before and after treatment

Before treatment as well as 1 month, 2 months and 3 months after treatment, analysis of serum inflammatory factors IL-1 β , IL-6, IL-17 and TNF- α between two groups of patients was as follows: (1) before treatment, differences in serum IL-1 β , IL-6, IL-17 and TNF- α levels were not statistically significant between two groups of patients (P>0.05); (2) 1 month, 2 months and 3 months after treatment, serum IL-1 β , IL-6, IL-17 and TNF- α levels of both groups were significantly lower than those before treatmen, and differences in serum IL-1 β , IL-6, IL-17 and TNF- α levels were statistically significant within same group before and after treatment (P<0.05); (3) 1 month, 2 months and 3 months after treatment, serum IL-1 β , IL-6, IL-17 and TNF- α levels of MECT group were significantly lower than those of control group, and differences in serum IL-1 β , IL-6, IL-17 and TNF- α levels were statistically significant between two groups after treatment (P<0.05).

3.3 Nerve electrophysiology parameters of two groups of patients before and after treatment

Before treatment as well as 1 month, 2 months and 3 months after treatment, analysis of nerve electrophysiology parameters P300 latency (ms) and amplitude (mV) as well as N2-P3 latency (ms) and amplitude (mV) between two groups of patients was as follows: (1) before treatment, differences in P300 latency and amplitude as well as N2-P3 latency and amplitude were not statistically significant between two groups of patients (P>0.05); (2) 1 month, 2 months and 3 months after treatment, P300 and N2-P3 latency of both groups were significantly shorter than those before treatment, P300 and N2-P3 amplitude were significantly higher than those before treatment, and differences in P300 latency and amplitude as well as N2-P3 latency and amplitude were statistically significant within same group before and after treatment (P<0.05); (3) 1 month, 2 months and 3 months after treatment, P300 and N2-P3 latency of MECT group were significantly shorter than those of control group, P300 and N2-P3 amplitude were significantly higher than those of control group, and differences in P300 latency and amplitude as well as N2-P3 latency and amplitude were statistically significant between two groups after treatment (P<0.05).

4. Discussion

Schizophrenia is a psychiatric illness with extremely high incidence, and the 5-hydroxytryptamine and dopamine dysfunction in the anterior lobe and mesolimbic system are associated with its occurrence. Ziprasidone is a common clinical atypical

Table 2.

Comparison of serum inflammatory factor levels between two groups of patients before and after treatment (pg/mL).

Groups	n	Treatment	IL-1 β	IL-6	IL-17	TNF- α
MECT	22	Before treatment	29.38±3.41	23.48±3.19	44.21±5.86	34.56±4.21
		1 month after treatment	20.19±2.89^{*a}	16.24±2.16^{*a}	26.68±3.25^{*a}	21.35±2.95^{*a}
		2 month after treatment	16.52±2.03^{*ab}	12.18±1.68^{*ab}	21.15±3.25^{*ab}	16.58±2.14^{*ab}
		3 month after treatment	11.98±1.86^{*abc}	9.39±1.02^{*abc}	16.58±1.98^{*abc}	12.38±1.89^{*abc}
Control	22	Before treatment	30.11±3.89	23.21±3.24	44.78±5.91	35.02±4.46
		1 month after treatment	25.58±3.05^{a}	20.22±2.78^{a}	37.32±4.87^{a}	29.34±3.52^{a}
		2 month after treatment	21.32±2.58^{ab}	16.78±2.15^{ab}	31.46±4.25^{ab}	23.56±3.24^{ab}
		3 month after treatment	17.64±2.14^{abc}	13.22±1.75^{abc}	26.24±3.25^{abc}	18.89±2.21^{abc}

*: compared with control group at the same point in time, P<0.05; ^{a}: compared with same group before treatment, P<0.05; ^{b}: compared with same group 1 month after treatment, P<0.05; ^{c}: compared with same group 2 months after treatment, P<0.05.

Table 3.

Comparison of nerve electrophysiology parameters between two groups of patients before and after treatment.

Groups	n	Treatment	P300		N2-P3	
			Latency	Amplitude	Latency	Amplitude
MECT	22	Before treatment	375.21±43.75	5.27±0.66	92.12±10.24	6.89±0.92
		1 month after treatment	336.52±36.16^{*a}	7.95±0.93^{*a}	83.32±10.63^{*a}	7.97±0.94^{*a}
		2 month after treatment	317.67±34.95^{*ab}	8.46±0.92^{*ab}	80.12±8.91^{*ab}	8.45±0.91^{*ab}
		3 month after treatment	297.32±33.51^{*abc}	9.12±1.02^{*abc}	76.65±8.78^{*abc}	8.93±1.02^{*abc}
Control	22	Before treatment	374.61±39.47	5.31±0.59	92.48±10.77	6.94±0.98
		1 month after treatment	359.31±40.34^{a}	6.09±0.78^{a}	87.41±9.45^{a}	7.35±0.89^{a}
		2 month after treatment	342.18±39.35^{ab}	6.98±0.79^{ab}	85.52±9.22^{ab}	7.55±0.92^{ab}
		3 month after treatment	338.55±41.28^{abc}	7.58±0.93^{abc}	82.15±9.72^{abc}	7.93±0.94^{abc}

*: compared with control group at the same point in time, P<0.05; ^{a}: compared with same group before treatment, P<0.05; ^{b}: compared with same group 1 month after treatment, P<0.05; ^{c}: compared with same group 2 months after treatment, P<0.05.

antipsychotic drug for the treatment of schizophrenia, has the effect of antagonizing 5-hydroxytryptamine 2A receptor and 1D receptor as well as dopamine D2 receptor in central nervous system, can significantly improve mental symptoms and has less adverse reactions and high security[5]. However, the effect of single drug treatment on controlling the mental symptoms in patients with schizophrenia is not ideal, and combined medication does no have definite effect on improving the mental symptoms and will increase the occurrence risk of adverse reactions. Modified electroconvulsive therapy (MECT) is the new treatment means for schizophrenia developed in recent years, and after general anesthesia, it causes extensive cerebral cortex discharge through electrical stimulation to adjust the release of dopamine, 5-hydroxytryptamine and γ-aminobutyric acid, norepinephrine and other neurotransmitters in the brain, thus correct the disorganized neurotransmitter effect and improve mental symptoms[6,7]. Because intravenous anesthetics and muscle relaxants are used together during treatment, the convulsion and other extreme therapeutic reactions won't occur in patients, which greatly increase the treatment compliance and tolerance[8]. It has been reported that MECT combined with antipsychotic drugs improves the schizophrenia treatment effect, but there is no report about the effect of ziprasidone combined with MECT treatment of schizophrenia.

The weakened and lost protective effect of neurotrophic factor, nerve growth factor and other nerve cytokines on dopaminergic neurons and serotonergic neurons have played an important role in the occurrence and development of schizophrenia. BDNF and GDNF are important neurotrophic factors that have important regulating effect on the survival of dopaminergic neurons and serotonergic neurons in the central nervous system[9,10]; NGF is a nerve cytokine that can both nourish the nerves and promote the axon growth, and it has important regulating effect on the growth of dopaminergic neuron and serotonergic neuron axon[11]. Studies have shown that BDNF, GDNF and NGF levels decrease significantly in patients with schizophrenia, the dopaminergic neurons and serotonergic neurons lose the protection from above nerve cytokines and are damaged, thus leading to the neurotransmitter effect disorder and causing mental symptoms[12,13]. In order to define the effect of MECT combined with ziprasidone therapy on above nerve cytokines, serum BDNF, GDNF and NGF were analyzed before and after treatment in the study, and the results showed that serum BDNF, GDNF and NGF levels of both groups after treatment were significantly higher than those before treatment, and serum BDNF, GDNF and NGF levels of MECT group were significantly higher than those of control group. This means that both ziprasidone monotherapy and MECT combined with ziprasidone therapy can increase the contents of nerve cytokines and improve the dopaminergic neuron and serotonergic neuron function, and MECT combined with ziprasidone therapy has better improving effect on neuron function than ziprasidone monotherapy.

In addition to being related to the weakened protective effect of nerve cytokines, the dopaminergic neuron and serotonergic neuron damage in patients with schizophrenia are also associated with the inflammatory injury caused by inflammatory response activation and increased inflammatory factor secretion. IL-1β, IL-6, IL-17 and TNF-α are the inflammatory factors that play an important role in the development and change of schizophrenia[14]. IL-1β is an important pro-inflammatory factor in interleukin family, and it can mediate cascade amplification activation of the inflammatory response; IL-6 is secreted by mononuclear macrophages, lymphocytes and epithelial cells, and it has promoting effect on the infiltration of inflammatory cells and the secretion of inflammatory mediators; IL-17 is secreted by Th17 cells, and it has regulating effect on inflammatory response and immune response; TNF-α is mainly secreted by the activated mononuclear macrophages, it is massively synthesized and secreted in the early inflammatory reaction, and it can mediate the inflammatory injury of local tissue[15,16]. In order to define the effect of MECT combined with ziprasidone therapy on neuron injury caused by inflammation, the changes in serum levels of above inflammatory cytokines before and after treatment were analyzed in the study, and the results show that serum IL-1β, IL-6, IL-17 and TNF-α levels of both groups after treatment were significantly lower than those before treatment, and serum IL-1β, IL-6, IL-17 and TNF-α levels of MECT group were significantly lower than those of control group. This means that both ziprasidone monotherapy and MECT combined with ziprasidone therapy can reduce the levels of inflammatory cytokines and relieve the dopaminergic neuron and serotonergic neuron damage caused by inflammation, and MECT combined with ziprasidone therapy has better inhibiting effect on inflammatory response than ziprasidone monotherapy.

The dopaminergic neuron and serotonergic neuron damage in patients with schizophrenia will cause the changes of corresponding nerve electrophysiology characteristics, which are characterized by the reduced amplitude and extended latency. P300 is the most commonly studied part in the mental event-related potential, it is closely related to psychological factors, and the P300 amplitude reduces and the latency is extended in violent people and those with schizophrenia; N2-P3 is another potential associated with schizophrenia-related events, the amplitude reduces and the latency is extended during the development and change of disease[17,18]. In the study, further analysis of above nerve electrophysiology parameters showed that P300 and N2-P3 latency of both groups after treatment were significantly shorter than those before treatment, P300 and N2-P3 amplitude were significantly higher than those before treatment, P300 and N2-P3 latency of MECT group were significantly shorter than those of control group, and P300 and N2-

P3 amplitude were significantly higher than those of control group.. This means that both ziprasidone monotherapy and MECT combined with ziprasidone therapy can adjust the nerve electrophysiology function, increase the amplitude and shorten the latency, and MECT combined with ziprasidone therapy has better improving effect on nerve electrophysiology function than ziprasidone monotherapy.

To sum up, it can be concluded that ziprasidone combined with modified electroconvulsive therapy can improve neuron function, reduce neuron damage and adjust nerve electrophysiology function.

References

[1] Wang HH, Cai M, Wang HN, Chen YC, Zhang RG, Wang Y, et al. An assessor-blinded, randomized comparison of efficacy and tolerability of switching from olanzapine to ziprasidone and the combination of both in schizophrenia spectrum disorders. *J Psychiatr Res* 2016; **4**(85): 59-65.

[2] Miao Y, Chen G, Ren L, Ouyang P. Preparation and evaluation of ziprasidone-phospholipid complex from sustained-release pellet formulation with enhanced bioavailability and no food effect. *J Pharm Pharmacol* 2016; **68**(2): 185-194.

[3] Yang Y, Cheng X, Xu Q, Li R, Liu Z, Wang L, et al. The maintenance of modified electroconvulsive therapy combined with risperidone is better than risperidone alone in preventing relapse of schizophrenia and improving cognitive function. *Arq Neuropsiquiatr* 2016; **74**(10): 823-828.

[4] Vera I, Sanz-Fuentenebro J, Urretavizcaya M, Verdura E, Soria V, Martinez-Amoros E, et al. Electroconvulsive therapy practice in spain: a national survey. *J ECT* 2016; **32**(1): 55-61.

[5] Chen X, Zhang ZH, Song Y, Yuan W, Liu ZX, Tang MQ. A paired case-control comparison of ziprasidone on visual sustained attention and visual selective attention in patients with paranoid schizophrenia. *Eur Rev Med Pharmacol Sci* 2015; **19**(16): 2952-2956.

[6] Jiang Y, Zhang H, Wang Z, Zhao L, Lv L. Effects of modified electroconvulsive therapy on the cognitive function and blood parameters in female patients with schizophrenia. *Int J Clin Exp Med* 2015; **8**(1): 1349-1355.

[7] Lõokene M, Kisuro A, Ma iulis V, Banaitis V, Ungvari GS, Gazdag G. Use of electroconvulsive therapy in the Baltic states. *World J Biol Psychiatr* 2014; **15**(5): 419-424.

[8] Watanabe T, Yoshinaga K, Suzuki Y, Someya T, Baba H. The effectiveness of combining remifentanil with propofol to achieve seizure adequacy in a patient undergoing modified electroconvulsive therapy. *Masui* 2015; **64**(10): 1072-1075.

[9] Nuernberg GL, Aguiar B, Bristot G, Fleck MP, Rocha NS. Brain-derived neurotrophic factor increase during treatment in severe mental illness inpatients. *Transl Psychiatr* 2016; **6**(12): e985.

[10] Tunca Z, Kivircik Akdede B, Ozerdem A, Alkın T, Polat S, Ceylan D, et al. Diverse glial cell line-derived neurotrophic factor (GDNF) support between mania and schizophrenia: a comparative study in four major psychiatric disorders. *Eur Psychiatry* 2015; **30**(2): 198-204.

[11] Dong Z, Sun X, Pan C, Lu T, Han Y, Wang L, et al. Association of DISC1, BDNF, and COMT polymorphisms with exploratory eye movement of schizophrenia in a Chinese Han population. *Psychiatr Genet* 2016; **26**(6): 258-265.

[12] Niitsu T, Shirayama Y, Matsuzawa D, Shimizu E, Hashimoto K, Iyo M. Association between serum levels of glial cell-line derived neurotrophic factor and attention deficits in schizophrenia. *Neurosci Lett* 2014; **11**(575): 37-41.

[13] Martinez-Cengotitabengoa M, MacDowell KS, Alberich S, Diaz FJ, Garcia-Bueno B, Rodriguez-Jimenez R, et al. BDNF and NGF signalling in early phases of psychosis: relationship with inflammation and response to antipsychotics after 1 year. *Schizophr Bull* 2016; **42**(1): 142-151.

[14] CHEN Li-yong, CHEN Zhong, LI Xue-jing. Serum cytokine contents in schizophrenia patient with metabolic syndrome and their correlation with nerve electrophysiology. *J Hainan Med Univ* 2016; **22**(13): 1422-1425.

[15] Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Mol Psychiatr* 2016; **21**(12): 1696-1709.

[16] Peroza LR, Schaffer LF, De Freitas CM, Leal CQ, Ferrari MC, Duarte MM, et al. Alteration of cytokines levels in the striatum of rats: possible participation in vacuous chewing movements induced by antipsycotics. *Neurochem Res* 2016; **41**(9): 2481-2489.

[17] Dutta M, Nath K, Baruah A, Naskar S. A clinical study of neurological soft signs in patients with schizophrenia. *J Neurosci Rural Pract* 2016; **7**(3): 393-399.

[18] Chan RC, Xie W, Geng FL, Wang Y, Lui SS, Wang CY, et al. Clinical Utility and Lifespan Profiling of Neurological Soft Signs in Schizophrenia Spectrum Disorders. *Schizophr Bull* 2016; **42**(3): 560-570.