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A paired case-control comparison of ziprasidone on visual sustained attention and visual selective attention in patients with paranoid schizophrenia

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Abstract. – OBJECTIVE: Cognitive impairment is one of the main targets of the treatment to schizophrenia.The atypical antipsychotic was proved to improve the cognition function of the patients. There were a few of clinical trials to detect the effect of medicine treatment on attention function. But the respective changes of sustained and selective attention in the patients with treatment of ziprasidone were rarely investigated. This present study was to explore the effect of ziprasidone on visual sustained and selective attention in schizophrenia.

PATIENTS AND METHODS: There were 81 patients who were treated with ziprasidone and matched with 81 healthy controls in this open-label trial. The functions were evaluated by Continuous Performance Test (CPT) and Color Word Test (CWT) at baseline and eight weeks later. Between two groups the functions were compared at the two time points, and in patients group those were compared prior to and post treatment.

RESULTS: As compared with healthy controls, the functions of the patients were worse. But after 8 weeks treatment of ziprasidone the functions improved in some degree, which were indicated by the change of CPT and CWT indexes. Furthermore, those of patients post treatment were better than prior to treatment.

CONCLUSIONS: Patients with paranoid schizophrenia have visual sustained and selective attention deficits. The deficits can be improved partly with ziprasidone treatment.

Key Words:
Paranoid schizophrenia, Sustained attention, Selective attention, Ziprasidone, Case control study.

Introduction

Attention is the regulating mechanism involved in all human mental activities and an essential component of cognitive functions. In general, attention is included in sustained attention, selective attention and divided attention. Sustained attention, or vigilance, as it is more often called, is the basic guarantee of complete selective attention, divided attention and other cognitive functions[1]. There are several neuropsychological tests to examine sustained attention, one of them is the Continuous Performance Test (CPT). With the aid of computers, CPT is more available to examine it in clinical trials widely. Egeland et al[2] and Kahn PV et al[3] found that CPT is better to indicate the function of sustained attention. The indexes of CPT, the mistaken score and the missed score, can represent the inhibition ability of irrespective stimulations, attention-maintaining ability and vigilance level (stability). They are negatively correlated with sustained attention. Selective attention involves selective filtration and processing of information[4], with the neural function area being the frontal lobe[5]. And the most classic test for selective attention function is the Stroop test, which reflects the ability of cerebrum dealing target stimulation prior to non-target stimulation[6,7]. The Color Word Test (CWT) is a typical kind of Stroop test. The reaction speed and accuracy indicates selective attention function. Faster and more correct responding means better condition of that. The completed number of CWT is positive correlated with the

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function, the error number and the time per correct answer are negatively correlated. There are plenty of trails which had found that ziprasidone is beneficial for the rehabilitation of cognition function in schizophrenia[8-10]. But few of them was concerned with the condition of sustained and selective attention. The present study aimed to explore the effect of ziprasidone on visual sustained and selective attention of patients with schizophrenia.

Patients and Methods

Patients

Patients hospitalized with paranoid schizophrenia in Shandong Province Mental Health Center from January 2009 to January 2012 were screened. Subjects were eligible if they met the following criteria: (1) age from 16 to 59 years (2) diagnosis of paranoid schizophrenia based on DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) and total Positive And Negative Syndrome Scale (PANSS) scores ≥60 and positive score ≥20, (3) total disease course ≤3 years, (4) absence of any other antipsychotic drug within 1 week, (5) junior middle school or higher education, and (6) ability to complete the cognitive test themselves. Patients were ineligible if they had received ≥4-weeks of antipsychotic treatment, long-acting antipsychotic drugs within 2 months or electric shock treatment within 1 month, participated in other clinical drug studies, or had serious unstable somatic diseases, vision disorders, color blindness, organic or psychoactive substance-induced mental disorders, mental retardation, significant abnormal findings or serious side effects to ziprasidone. Pregnant or lactating women were also excluded from the study. Subjects were required to withdraw from the study if they experienced and were unable to tolerate serious side effects, had suicide tendency or experienced serious diseases, if the treatment was not effective or the disease worsen, or if the participation of guardians was required.

Healthy volunteers from provincial residential areas served as controls. The inclusion and exclusion criteria were similar to the criteria for the patients. These controls were matched to the patients with regard to sex, age (a difference <1years), education level (junior middle school, senior school or special school, and university or higher).

This study protocol was approved by the Ethics Committee of Shandong Mental Center (Shandong, China) and written informed consent was obtained from every participant.

In both patient and control groups, 81 subjects (each group including 45 males and 36 females) were enrolled, including 41 with junior middle school, 27 with senior school or special school, and 13 with university or higher education. The average age difference was 0.46±0.25 years between the two groups. All subjects were right-handed.

Treatment

This study used an open-label design. Patients took oral ziprasidone twice daily after meals. With ziprasidone 40 mg/d as the initial dosage, the dosage was gradually up-titrated within 7 days according to patients' tolerance and could be adjusted at any time. The dosage range was 80-160 mg/day and the final average dosage was 144.85 ± 26.10 mg. Other antipsychotic drugs, thymoleptics, mood stabilizers and antianxiety drugs were prohibited, with the exception of lorazepam (1-4 mg/day) in the event of somnipathy, trihexyphenidyl (2-6 mg/day) in the event of

Table I. Continuous Performance Test (CPT) and Color Word Test (CWT) results in patients and controls.

		Controls (n=81)	Patients at baseline (n=81)	Patients post treatment (n=81)
CPT	2-figure mistaken scores	1.89 ± 1.76	2.65 ± 2.36[b]	2.19 ± 1.94[ae]
	2-figure missed scores	2.10 ± 1.57	2.42 ± 1.90[a]	2.24 ± 1.83[ad]
	3-figure mistaken scores	2.73 ± 1.80	4.92 ± 3.78[c]	3.39 ± 2.96[bf]
	3-figure missed scores	3.90 ± 4.51	4.83 ± 5.01[b]	4.08 ± 4.69[ae]
CWT	Completed number	42.04 ± 7.50	33.17 ± 11.62[b]	39.75 ± 9.02[ae]
	Error number	2.30 ± 3.08	4.08 ± 8.74[c]	3.11 ± 5.09[be]
	Time per correct answer (s)	1.51 ± 2.22	2.27 ± 2.36[c]	1.93 ± 1.58[be]

Paired t test: vs. controls, [a]$p > 0.05$, [b]$p < 0.05$ and [c]$p < 0.01$; prior to vs. post treatment, [d]$p > 0.05$, [e]$p < 0.05$ and [f]$p < 0.01$.

Table II. Table II. Positive and Negative Syndrome Scale (PANSS) scores at baseline and post treatment.

Patients (n=81)	PSS scores	NSS scores	General psychopathology scores	Total PANSS scores
Baseline	26.42 ± 7.57	25.90 ± 8.22	42.20 ± 10.16	94.52 ± 18.70
Post treatment	14.85 ± 5.62	13.02 ± 8.36	23.40 ± 9.75	51.27 ± 10.80
d ±s	12.02 ± 6.96	12.90 ± 8.18	19.00 ± 10.25	43.25 ± 15.02
t	2.88	2.96	2.84	2.91
p	0.01	0.00	0.01	0.00

mean ± standard deviation.

acute extrapyramidal symptoms (EPS), inderal (20-60 mg/day) in the event of tachycardia and Vitamin B6 (30-60 mg/day) in the event of gastrointestinal reactions.

Efficacy and Side Effects

Efficacy was evaluated using PANSS. Side effects and abnormal examination results were recorded and analyzed by physicians. If abnormal results were not clinically significant, or were clinically significant but guardians provided consent patients could continue the study. Every evaluation was performed by 2 attending psychiatrists and the average was the final score. The consistency check of physicians was r = 0.92.

Visual Sustained and Selective Attention

Sustained attention was evaluated using CPT and selective attention using CWT with the aid of the computer.

During CPT, 2 or 3-figure Arabic numbers in white word 100 Arial bold font continuously emerged in the center of the black 17-inch computer screen at an interval of 800 ms. Every number lasted for 200 ms. The sequence was computer generated at random. When the consecutive numbers were identical, subjects were instructed to press the key as soon as possible. The frequency of pressing keys for nonidentical numbers was the mistaken score and the frequency of not responding to identical numbers was the missed score. This test consisted of 2 panels: 2-figure and 3-figure numbers. Every panel was terminated with 30 key presses. CWT consisted of 100 characters with different colors and meanings. These characters in 10 row*10 column in bold fonts were shown in the 17-inch computer display. The sequence and color was computer generated at random. Subjects were required to correctly identify the color of each character (i.e. red, yellow, green and blue) from left to right as soon as possible within 1 minute. Results were judged by trained investigators. The completed number, error number and time per correct answer [the average time of completion following correct identification, 60 seconds (completed numbers-error number)] of CWT were recorded.

The above tests were conducted in a quiet environment. Before the formal test, subjects received adaptive training to understand the test requirements. Test investigators were trained attending psychiatrists. All tests applied the same instruction and training tests. Prior to the CPT test, subjects were required to perform cross balance of left and right hands and the smartest hand was selected.

Study Procedures

Patients were evaluated using CPT, CWT and PANSS twice, before and 8 weeks after treatment. Conventional tests (e.g. blood routine, blood biochemical test and electrocardiogram) were conducted at baseline, 4 and 8 weeks after treatment. treatment-related side effects were recorded during the 8 week study period. The controls completed the CPT and CWT at baseline and 8 weeks.

Statistical Analysis

SPSS 14.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Data were displayed mean ± SD and compared using the Pearson correlation analysis and paired *t*-test. Significance was set at $p < 0.05$.

Results

A total of 66 controls completed the self-control test and no statistical differences in CPT and CWT-related indexes were noted ($p < 0.05$).

The Result of CPT Indexes and Comparison

As showed in the upper part of Table I, there was the result of CPT indexes.

At baseline, 2-figure mistaken scores ($t = 2.51$, $p = 0.02$), 3-figure mistaken scores ($t = 3.1$, $p = 0.00$) and 3-figure missed scores ($t = 2.19$, $p = 0.03$) were statistically higher in patients than controls. But the 2-figure missed scores ($t = 1.58$, $p = 0.12$) were not statistically different between patients and controls.

After treatment, 3-figure mistaken scores ($t = 2.20$, $p = 0.03$) were statistically higher in patients than controls. However 2-figure mistaken scores ($t = 1.45$, $p = 0.15$), 2-figure missed scores ($t = 0.83$, $p = 0.42$) and 3-figure missed scores ($t = 0.84$, $p = 0.40$) were not statistically different.

Between prior to and post treatment in patients, 2-figure mistaken scores ($t = 2.01$, $p = 0.04$), 3-figure mistaken scores ($t = 2.97$, $p = 0.00$) and missed scores ($t = 2.29$, $p = 0.03$) significantly decreased post treatment. The 2-figure mistaken scores were not statistically different prior to and post treatment ($t = 1.12$, $p = 0.23$).

The Result of CWT Indexes and Comparison

As showed in the under part of Table II, there was the result of CWT indexes.

At baseline, the completed numbers ($t = 2.02$, $p = 0.04$) were statistically lower in patients; the error number ($t = 3.20$, $p = 0.00$) and time per correct answer ($t = 2.89$, $p = 0.00$) were statistically higher in patients compared with controls.

After treatment, the error number ($t = 2.37$, $p = 0.02$) and time per correct answer ($t = 2.25$, $p = 0.03$) were still remarkably higher in patients than controls. But completed numbers ($t = 1.68$, $p = 0.09$) was not statistically different.

Between prior to and post treatment in patients, completed numbers ($t = 2.00$, $p = 0.04$) significantly increased, error number ($t = 2.53$, $p = 0.02$) and time per correct answer ($t = 2.16$, $p = 0.03$) significantly decreased.

Comparison of PANSS Score Prior to and Post treatment in Patients

Scores of every PANSS item statistically decreased following 8-week treatment ($p < 0.05$) (Table II).

Discussion

Comparison of two tests of healthy controls proved that CPT and CWT exhibited excellent stability and could avoid learning bias. Comparison between controls and patients showed that patients with paranoid schizophrenia had visual sustained and selective attention deficits, consistent with other studies[11]. Theses result may be related to the frontal lobe functional impairment, as indicated by functional imaging[12,13], Moreover, several indices regarding sustained attention were not statistically different between controls and patients prior to treatment, suggesting that sustained attention was less impaired as compared with selective attention, in accordance with reports by Luck and Gold[11].

In addition, patients' sustained and selective attention can be plastic[14,15]. Ziprasidone may have some beneficial effect, as reported by previous studies[16,17]. Notably, simple items of sustained attention and reaction speed of selective attention returned to normal following short-term ziprasidone treatment. However, despite some improvements the accuracy of selective attention remained worse than that in the normal population; a finding that is inconsistent with reports by Grootens et al[18]. A possible explanation for this maybe the different medical treatment methods, relative short course of disease, and perhaps the methods used to evaluate attention.

The beneficial effect of ziprasidone on sustained and selective attention is attributed to the pathological mechanism. Ziprasidone blocks the dopamine (D) 2 receptors in the limbic system to dramatically improve positive symptoms. It also has strong antagonistic effects on serotonin (5-HT) 2A receptors in the presynaptic membrane of mesocortical pathway, inducing dopamine release to activate D2 receptors in the anterior frontal lobe to improve negative symptoms. Meanwhile, it activates D1 and 5-HT1A receptors in the anterior frontal lobe and blocks norepinephrine recovery to activate $\alpha 2$- and $\beta 2$-adrenergic receptors[19]. Thus, continuity, speed and accuracy of brain response to external information can be maintained at a high level.

Conclusions

Sustained and selective attention is still not ideal in spite of significant improvement following short-term ziprasidone treatment. The correlation between the improvement and change in psychiatric symptom remains unclear. Therefore, larger long-term studies are needed.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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