Research Paper

A Study Exploring the Cognitive Effects of Risperidone and Aripiprazole in Individuals with Schizophrenia

YIYUE DONG[1], TIANLIN ZHANG[1], S. ZHU[1], YANG XU[1] AND SHAXIN LIU[1]*

Department of Rehabilitation Medicine, West China Hospital, [1]West China School of Medicine, Sichuan University, Chengdu, Sichuan 610041, China

The objective of this study was to analyze the cognitive function and capacity of adult patients with schizophrenia who received treatment with risperidone and aripiprazole. 100 adult patients with schizophrenia, aged 30 y or younger, were enrolled in this study at our hospital's psychiatry department from June 2021 to June 2022. The participants were randomly divided into a control group (n=50) treated with risperidone or an observation group (n=50) treated with risperidone assisted by aripiprazole. The study found that the observation group achieved a higher total effective rate of 90.00 % after 8 w of treatment, which was significantly higher than the 72.00 % rate achieved by the control group ($p<0.05$). There was no significant difference in the incidence of adverse drug reactions between the two groups ($p>0.05$). The scores of the matrics consensus cognitive battery were significantly higher in the observation group (90.15±6.62) than in the control group (80.54±6.75) ($p<0.05$). Additionally, the observation group showed significantly higher levels of bone metabolic markers, including bone Gla protein, procollagen type I carboxy-terminal propeptide, vitamin D-total and bone-specific alkaline phosphatase, compared to the control group ($p<0.05$). Moreover, the study showed that the beta-carboxy-terminal telopeptide of type I collagen level was significantly decreased in the observation group compared to the control group ($p<0.05$). Additionally, according to the study results, activities of daily living scores were significantly higher in the observation group compared to the control group ($p<0.05$). According to our study, the administration of both risperidone and aripiprazole appears to be an effective way to improve cognitive function, capacity and bone metabolism in adult patients with schizophrenia. The combined treatment provides further therapeutic efficacy without increasing adverse drug reactions, which has important implications for clinical practice.

Key words: Schizophrenia, aripiprazole, risperidone, cognitive function, adverse drug reaction

Typically, schizophrenia is a severe and chronic mental disorder that tends to impact young adults. Its etiology is not well understood and the symptoms are complex and diverse, including thinking disorders, perceptual abnormalities, affective disturbances, and behavioral changes. Because of its chronic nature and high rate of relapse, the primary treatment for schizophrenia is medication to control symptoms and improve overall function[1,2]. However, individual responses to drugs can vary, and the optimal use of medications remains a critical clinical research topic. Combining different medications for the treatment of schizophrenia has been shown to improve clinical outcomes, without increasing adverse drug reactions and has been identified as a promising treatment approach[3,4]. Risperidone is an atypical antipsychotic medication that exerts strong antagonistic effects on dopamine D2 receptors and effectively improves positive and affective symptoms. Aripiprazole, a medication that regulates both sides of the nervous system, has a preference for Serotonin 1A (5-HT1A) and Serotonin 2A (5-HT2A) receptors, as opposed to other antipsychotic drugs. The effectiveness of using aripiprazole and risperidone concurrently to treat schizophrenia in adult patients under 30 y is not yet fully understood due to the limited studies available. In light of this, the purpose of our investigation was to determine the efficacy of combining aripiprazole and risperidone in the treatment of young adult patients with schizophrenia, whose ages were 30 y or below.

***Address for correspondence**
E-mail: liushaxin@scu.edu.cn

MATERIALS AND METHODS

Research objects:

In this research, 100 adult schizophrenic patients aged <30 y were selected as participants from June 2021 to June 2022 at our hospital and they were randomly assigned into two groups, with the control group consisting of 50 patients (23 males and 27 females) aged between 18-30 y, their average age was (24.02±5.57) y, and the length of their illness ranging from 13-96 mo, averaging (55.18±8.47) mo. Among them, 30 patients were unmarried and 20 were married. The observation group included 50 participants (22 males and 28 females) whose ages ranged from 19-30 y old, with an average age of (24.26±5.83) y and a disease history between 14-97 mo, with an average duration of (55.47±8.89) mo. Among them, 28 patients were unmarried and 22 were married. The demographic data, including age and disease duration, were not significantly different between the two groups ($p>0.05$), and the study received approval from the hospital ethics committee.

Selection criteria:

Inclusion criteria: All met the clinical diagnostic criteria of schizophrenia[5]; the course of disease was ≥1 y, and the continuous hospitalization time was more than 3 mo; the patients were not treated with antipsychotic drugs 1 mo before joining the group; the family members knew and signed the informed consent form; there was no other mental illness and the clinical data were complete.

Exclusion criteria: For those who were intolerant to this medication; patients with malignant tumor; women during pregnancy and lactation; severe cardiac and renal insufficiency; the laboratory index was abnormal and those who give up or/are transferred to hospital.

Methods:

Administered twice a day and starting with an initial dose of 1 mg, the control group was treated with oral risperidone tablets (H20052330 Zhejiang Huahai Pharmaceutical Co., Ltd.). In the 1st w, the dose was gradually increased, 2~4 mg/twice a day, and it was appropriate for patients to tolerate. From the 2nd w, according to the patient's condition, maintain the dose, or appropriately increase the dose, 4~6 mg/times, the maximum daily dose do not exceed 10 mg. The observational cohort was prescribed a combination of aripiprazole and risperidone, with the dosage of risperidone tablets being identical to that received by the control group. At the same time, aripiprazole tablets (Chinese medicine H20061305 Zhejiang Otsuka Pharmaceutical Co., Ltd.) were given orally, the initial dose was 10~15 mg/once a day. The dose was maintained within 2 w. From the 3rd w, according to the patient's condition and tolerance, the maintenance dose or appropriate increase of the dose can be increased to a maximum of 30 mg/times. Both groups underwent continuous treatment for a total of 8 w and were then monitored for a follow-up period of 3 mo.

Observation indexes:

Treatment evaluation: The therapeutic effect was assessed according to the guidelines for the treatment of schizophrenia[6]. A significant effect was defined by the disappearance of clinical symptoms, with a reduction of over 70 % in scores on the Positive and Negative Syndrome Scale (PANSS). An effective outcome was defined by the effective control of clinical symptoms, with a reduction of 30 %-69 % in PANSS scores. An ineffective outcome was defined by a decrease of less than 30 % in PANSS scores and a lack of significant improvement in clinical symptoms or even symptom worsening. The efficiency index was determined by adding the success rate of significantly successful and successful treatments, and dividing that figure by the total count of cases, and then multiplying by 100 %. The cognitive capabilities of subjects were appraised using the schizophrenia cognitive function test (consensus version) Matrics Consensus Cognitive Battery (MCCB) both pre and post-treatment[7]. The battery encompasses a total of seven cognitive domains, inclusive of processing speed, attention/vigilance, working memory, verbal and visual learning and memory, reasoning and problem-solving, as well as social cognition, to assess patients' cognitive function.

Daily living: The Activities of Daily Living (ADL) Scale was adopted to assess patients' daily living activities both pre and post-treatment[8]. The scale includes items on physiological, psychological and social function. The liaison automatic Chemiluminescence immunoassay analyzer was used to measure bone metabolism markers in 5 ml of venous blood samples collected prior to and

post-treatment. Bone Metabolic Markers Included Osteocalcin (BGP), Procollagen Type I Collagen Carboxy-Terminal Propeptide (PICP), Vitamin D-Test (VitD-T), the Beta (β)-isomerized Carboxy-Terminal Telopeptides (β-CTx) and Bone-Specific Alkaline Phosphatase (BALP).

Adverse drug reactions: Adverse drug reactions experienced by participants during the treatment were recorded, including insomnia, anxiety, dry mouth, constipation, dizziness, headache, nausea, vomiting, indigestion and others.

Statistical analysis:

The presentation of continuous data was accomplished *via* x±s notation. Intergroup comparison was accomplished employing independent sample t-tests, while paired t-tests were implemented to determine any changes within each group. Results with a $p \leq 0.05$ were recognized as statistically significant. Statistician utilized Statistical Package for the Social Sciences (SPSS) 26.0 software.

RESULTS AND DISCUSSION

The results in Table 1 demonstrate that following 8 w of treatment, the observation group had a significantly higher total effectiveness rate in comparison to the control group ($p<0.05$). There were no notable distinctions in MCCB scores between the two groups before treatment; nevertheless, post-treatment, the scores of the observation group were considerably higher than those of the control group ($p<0.05$) as shown in Table 2.

Prior to treatment, no substantial distinction in ADL scores was observed between the two groups; however, by the end of the follow-up period, the ADL score of the observation group was significantly higher than that of the control group ($p<0.05$) as shown in Table 3.

Prior to treatment, there were no significant differences in bone metabolism indices between the two groups ($p>0.05$). After treatment, the indices of bone metabolism in the observation group were significantly improved compared to those of the control group ($p<0.05$) as shown in Table 4.

Throughout the course of treatment, there were no significant disparities in the occurrence of adverse drug reactions between the observation group and the control group ($p>0.05$), as shown in Table 5.

Schizophrenia is one of the common diseases in psychiatry. Due to its prolonged course and relapsing tendency, schizophrenia can cause mental disorders and have a severe impact on the quality of life as the disease progresses. Drugs are the main means for the treatment of schizophrenia. Antipsychotics are used to treat the clinical symptoms of schizophrenia by influencing dopamine levels, thereby achieving therapeutic goals. Some studies have found that long-term use of a single antipsychotic drug not only increases the risk of adverse drug reactions, but also cannot effectively improve the therapeutic effect[9]. Achieving a balance between efficacy and safety is a major focus of clinical research in the treatment of schizophrenia. Based on this, the present study utilized an aripiprazole plus risperidone regimen, which was found to not only not exacerbate adverse drug reactions, but also further enhance the clinical efficacy of treatment, effectively improving patient's cognitive function and behavioral ability.

TABLE 1: GROUP COMPARISON OF THERAPEUTIC EFFECT

Group	n	Significant effect	Effective	Invalid	Overall efficiency
Observation	50	31 (62.00)	14 (28.00)	5 (10.00)	45 (90.00)
Control	50	15 (30.00)	21 (42.00)	14 (28.00)	36 (72.00)
χ^2					4.159
p					0.041

TABLE 2: COMPARISON OF MCCB SCORES PRE- AND POST-TREATMENT (x±s, POINTS)

Group	n	MCCB		t	p
		Before	After		
Observation	50	55.61±4.23	90.15±6.62	31.089	0.001
Control	50	56.04±4.49	80.54±6.75	21.369	0.001
t		0.493	7.187		
p		0.623	0.001		

TABLE 3: GROUP COMPARISON OF ADL SCORES PRE AND POST TREATMENT (x±s)

Group	n	Time	Physiological function	Psychological function	Social function
Observation	50	Before	65.29±2.64	59.18±2.84	62.91±3.25
		After	86.29±5.84	86.95±5.49	90.16±5.51
t			12.798	27.071	21.072
p			<0.001	<0.001	<0.001
Control	50	Before	65.33±2.62	59.23±2.54	63.05±3.21
		After	76.19±5.74	74.75±5.83	79.51±5.41
t			7.417	17.064	9.503
p			<0.001	<0.001	<0.001
Comparison of t/p before treatment			0.208/0.836	0.416/0.678	0.356/0.722
Comparison of t/p during follow-up			7.269/0.001	10.371/0.001	9.762/0.001

TABLE 4: COMPARISON OF THE CHANGES OF SERUM BONE METABOLISM INDEXES PRE AND POST TREATMENT (x±s)

Group	Time	VitD-T (ng/ml)	BALP (%)	PICP (μg/l)	BGP (μg/l)	β-CTX (mg/l)
Observation (50)	Before	20.42±1.67	3.12±1.51	95.62±25.19	2.15±0.82	0.56±0.15
	After	38.58±3.44	6.01±1.28	160.51±45.22	5.26±1.64	0.29±0.11
t		33.581	10.323	8.864	11.994	10.264
p		0.001	0.001	0.001	0.001	0.001
Control (50)	Before	20.66±1.39	3.13±1.54	96.02±25.74	2.17±0.55	0.55±0.17
	After	28.52±2.81	4.36±1.42	125.39±35.17	3.97±1.43	0.48±0.14
t		17.728	4.152	4.765	8.307	2.248
p		0.001	0.001	0.001	0.001	0.026
Comparison of t/p before treatment		0.781/0.437	0.033/0.974	0.078/0.937	0.143/0.886	0.312/0.756
Comparison of t/p during follow-up		16.015/0.001	6.103/0.001	4.335/0.001	4.192/0.001	7.546/0.001

TABLE 5: GROUP COMPARISON OF THE INCIDENCE OF ADVERSE DRUG REACTIONS (n, %)

Group	n	Dry mouth and constipation	Insomnia and anxiety	Dizziness and headache	Nausea and vomiting	Dyspepsia	Incidence rate
Observation	50	1 (2.00)	1 (2.00)	2 (4.00)	1 (2.00)	2 (4.00)	7 (14.00)
Control	50	2 (4.00)	2 (4.00)	1 (2.00)	0	0	5 (10.00)
χ^2				0.095			
p				0.758			

Risperidone is widely used drug in treating schizophrenia, which can improve positive symptoms and stabilize emotional symptoms by antagonizing 5-HT2 receptor and dopamine receptor. However, studies have found that long-term risperidone treatment for schizophrenia is easy to cause dizziness, headache, insomnia and other adverse drug reactions and the efficacy is not very satisfactory[10]. In this study, aripiprazole was used as adjuvant therapy. Compared to the control group, the observation group exhibited a notably greater effective treatment rate ($p<0.05$), but the two groups had similar incidences of adverse drug reactions ($p>0.05$). The combined use of aripiprazole and risperidone did not result in a significant increase in the incidence of adverse drug reactions, while also proving to be more clinically effective. Therefore, this drug regimen is considered a safe and effective option for the treatment of adult schizophrenia patients under the age of 30 y. Aripiprazole is known to exhibit its therapeutic effect by inhibiting the physiological activity of dopamine receptors, while concurrently stimulating neuronal synaptic cells. This action has been shown to improve the negative symptoms as well as accompanying emotional symptoms in schizophrenia patients. A combined treatment regimen of aripiprazole and risperidone has demonstrated significant improvements in treating positive and emotional symptoms in schizophrenia patients, while also minimizing the adverse side effects associated with medication. Results from studies indicate that the combined approach to treating schizophrenia with medication can improve efficacy, despite the possibility of a slightly higher incidence of adverse reactions than single-drug therapies[11]. There are some differences with the results of this study and the reason may be the small sample size of this study, which leads to the bias of the conclusion. Therefore, future research should focus on increasing the sample size in order to improve the accuracy of the study findings.

In patients with schizophrenia, those with positive symptoms are easy to reduce bone mineral density due to long-term agitation and excitement, large body consumption and those with negative symptoms are easy to reduce bone mineral density due to unhealthy lifestyle and lack of outdoor exercise. The findings of this study showed that treatment for a period of 8 w led to significantly higher levels of bone metabolism parameters such as BGP, VitD-T, PICP and BALP in the observation group as compared to the control group ($p<0.05$). Furthermore, the levels of β-CTX were significantly lower in the observation group than in the control group ($p<0.05$). The findings of the study demonstrate that the combination of aripiprazole and risperidone is an effective treatment for adult schizophrenia in terms of improving bone metabolism, promoting patient recovery and enhancing overall patient quality of life. The presence of biochemical markers such as BGP, VitD-T, PICP, BALP and β-CTX are an important means of measuring bone metabolism and their levels are useful in diagnosing conditions such as osteoporosis and abnormal calcium metabolism. Among the biochemical indicators of bone metabolism, VitD-T includes both endogenous and exogenous. Due to the lack of outdoor activities in patients with schizophrenia, the skin absorbs less sunlight and ultraviolet rays and reduces the formation of bone matrix, thus leading to abnormal bone metabolism. BALP can reflect the activity of bone cells, while β-CTX has a high sensitivity to bone resorption and is the main index of high bone resorption. Bone metabolism indexes can reflect bone turnover status in time and are of great value for osteoporosis diagnosis, fracture risk prediction and treatment in patients with schizophrenia. Numerous studies have indicated that the combination therapy involving aripiprazole and risperidone plays a significant role in improving bone metabolism among patients diagnosed with schizophrenia[12,13]. The results of this study confirm earlier findings that the combined use of aripiprazole and risperidone provides significant improvements in bone metabolism among patients with schizophrenia. Moreover, the study revealed that the observation group had notably higher scores on measures of cognitive function and daily behavior ability than the control group ($p<0.05$). The results indicate that aripiprazole, when used in conjunction with risperidone, is an effective treatment for adult schizophrenia in patients under 30 y old. This therapy can significantly enhance cognitive function among patients and promote the improvement of daily behavior ability, leading to better health outcomes. Risperidone inhibits adrenaline secretion by inhibiting dopamine D2 receptor and binding it to the serotonin receptor, thereby improving positive symptoms in patients. At the same time, aripiprazole combined adjuvant can stimulate neuronal synaptic cells, inhibit receptor factors, nervous system, stabilize the internal environment, improve the negative symptoms of patients. The

integration of pharmacological compounds has shown to augment the attenuation of both positive and negative symptoms in individuals diagnosed with schizophrenia, leading to advancements in cognitive function and daily functioning abilities. Lin *et al.*[14] confirmed in the study on the treatment of schizophrenia that risperidone combined with aripiprazole could effectively reduce nerve function damage, improve patients' memory function and social function, and achieve significant therapeutic effects. Chen *et al.*[15] found in their study on patients with schizophrenia that aripiprazole combined with risperidone could improve patient's violent behavior, improve cognitive function, and further improve clinical efficacy. Our findings are congruent with the aforementioned research conclusions.

In summary, the combination regimen of aripiprazole and risperidone for adult schizophrenia ≤30 y old can effectively improve bone metabolism indexes, improve cognitive function and behavioral ability of patients, which is conducive to promoting clinical efficacy and has important research value. However, this study has some limitations, such as a small sample size and short study time, and further research should be continued to enlarge the sample size in the upcoming researches, in order to provide more ideas for the treatment of schizophrenia.

Conflict of interests:

The authors declared no conflict of interests.

REFERENCES

1. Liu WS, Zhang X, Qi DD. Research progress of oral drug therapy for schizophrenia. Inner Mongolia Med J 2019;53(12):1473-4.
2. Hermans RA, Ringeling LT, Liang K, Kloosterboer SM, de Winter B, Hillegers MH *et al.* The effect of therapeutic drug monitoring of risperidone and aripiprazole on weight gain in children and adolescents: The SPACe 2: STAR (trial) protocol of an international multicentre randomised controlled trial. BMC Psychiatry 2022;22(1):1-8.
3. Xia H, Liu C, Huang SY. Effect of combination therapy with two drugs on NSE and S100β in patients with first-episode schizophrenia. Shenzhen J Integr Chin Western Med 2021;31(4):21-3.
4. Soria-Chacartegui P, Villapalos-García G, Zubiaur P, Abad-Santos F, Koller D. Genetic polymorphisms associated with the pharmacokinetics, pharmacodynamics and adverse effects of olanzapine, aripiprazole and risperidone. Front Pharmacol 2021;12(17):711940.
5. Branch of Psychiatry, Chinese Medical Association. CCMD-3 Classification and Diagnostic Criteria of Mental Disorders in China. Shandong Sci Technol Press; 2001.
6. Ding Q. Treatment guidelines for schizophrenia. Chin J Clin 2002;30(2):21-2.
7. Zou Y, Cui J, Wang J. Study on the clinical reliability and validity of the Chinese version of cognitive function test for schizophrenia. Chin J Psychiatry 2009;42(1):29-33.
8. Zhou J, Liu F, Zhou Mi. Comparison of the characteristics of a new activity of daily living scale and Barthel Index-5 items in the rehabilitation department. Chin J Rehabil Med 202;136(12):1529-34.
9. Liu XM. Comparison of efficacy, medication compliance and adverse reactions of different antipsychotics in treatment of newly diagnosed schizophrenia patients. Chin J Mod Appl Pharm 2022;16(13):152-4.
10. Ren Z, He Y, Xue H. Research progress of risperidone in the treatment of schizophrenia. Tianjin Pharm 2019;32(2):73-8.
11. Wang Q, Zhao L, Wang S. Efficacy and adverse reactions of aripiprazole combined with risperidone in patients with schizophrenia. Int J Psychiatry 2002;49(1):45-52.
12. Lai G, Zhou Xi, Jin G. Effects of risperidone combined with metformin on bone metabolism insulin and renal function in patients with type 2 diabetes mellitus. J Oriental Med 2019;40(17):2507-10.
13. Dong R, Yuan L, Yang Y, Du XD, Jia Q, Dillon BA, *et al.* Differential effects of different antipsychotic drugs on cognitive function in patients with chronic schizophrenia. Hum Psychopharmacol 2020;35(6):1-8.
14. Lin L, Huang Xi, Su M. Clinical efficacy of risperidone combined with aripiprazole in the treatment of schizophrenia and its effect on memory function and neural function. J Clin Rational Use Med 2019;15(30):74-7.
15. Chen Y, Huang S, Zhou Y. Effect of aripiprazole combined with risperidone on violent behavior in schizophrenia and its effect on cognitive function. Shanghai J Med 2019;42(24):33-6

This article was originally published in a special issue, "New Research Outcomes in Drug and Health Sciences" Indian J Pharm Sci 2023:85(6) Spl Issue "184-189"