Journal of Hainan Medical University

http://www.hnykdxxb.com

Effect of berberine combined with risperidone therapy on endocrine hormones and oxidative stress in patients with schizophrenia

Wei Dong[1], Wei−Xia Gu[2], Xiao−Wei Tang[1], Peng Liu[1], Jin−Tong Zhao[1], Xin Chu[1]✉

[1] *Department of Psychiatry, Wutaishan Hospital Affiliated to Yangzhou University in Jiangsu Province, Yangzhou City, Jiangsu Province, 225000*

[2] *Department of Neurology, Wutaishan Hospital Affiliated to Yangzhou University in Jiangsu Province, Yangzhou City, Jiangsu Province, 225000*

ARTICLE INFO

Article history:
Received 12 Jun 2017
Received in revised form 19 Jun 2017
Accepted 3 Jul 2017
Available online 14 Jul 2017

Keywords:
Schizophrenia
Berberine
Risperidone
Endocrine hormone
Oxidative stress

ABSTRACT

Objective: To study the effect of berberine combined with risperidone therapy on endocrine hormones and oxidative stress in patients with schizophrenia. **Methods:** A total of 90 patients with schizophrenia who were treated in our hospital between May 2014 and May 2016 were collected, reviewed and then divided into the control group (n=47) who received risperidone therapy and the observation group (n=47) who received berberine combined with risperidone therapy. Serum insulin resistance index levels, thyroid hormone and prolactin contents as well as oxidative stress index contents before and after treatment were compared between two groups of patients. **Results:** Before treatment, differences in serum insulin resistance index levels, thyroid hormone and prolactin contents as well as oxidative stress index contents were not statistically significant between two groups of patients. After treatment, serum FINS and HOMA-IR levels in observation group were lower than those in control group; serum T3 content was higher than that in control group while PRL content was lower than that in control group; serum MDA content was lower than that in control group while SOD, GSH-Px and CAT contents were higher than those in control group. **Conclusion:** Berberine combined with risperidone therapy for patients with schizophrenia won't cause severe endocrine hormone level disorder, and helps to reduce the systemic oxidative stress response.

1. Introduction

Schizophrenia belongs to holergasia, it mostly starts in young adults, and patients can show perception, thought, emotion, behavior and other aspects of incoordination, and should be treated early to alleviate disease and prevent its recurrence[1,2]. Risperidone is the most typical drug for treatment of acute or chronic schizophrenia, belongs to the benzisoxazole derivatives, and has been proven to be able to effectively improve the positive and negative symptoms in patients with schizophrenia[3,4]. Current research has pointed out that risperidone treatment alone may cause endocrine disorders, and therefore, adding other drugs is recommended to broaden clinical curative effect and weaken the overall adverse reactions. Berberine is the Chinese patent medicine that regulates glucolipid metabolism and so on, it also has positive anti-inflammatory effect, and there is not much research at present on its role in adjuvant treatment of patients with schizophrenia. In the research, berberine combined with risperidone was applied for the treatment of patients with schizophrenia, and its application value was discussed from endocrine hormone, oxidative stress and other aspects.

✉Corresponding author: Xin Chu, Department of Psychiatry, Wutaishan Hospital Affiliated to Yangzhou University in Jiangsu Province, Yangzhou City, Jiangsu Province, 225000.
Tel: 13705275860

Fund Project: Instructional Scientific Research of Jiangsu Provincial Commission of Health and Family Planning in 2015 No: Z201522.

2. Information and methods

2.1 Case information

90 patients with schizophrenia who were treated in our hospital between May 2014 and May 2016 were enrolled as research subjects, and families of patients signed informed consent. After the therapies were reviewed, the enrolled patients were divided into the control group (n=47) who received risperidone therapy and the observation group (n=47) who received berberine combined with risperidone therapy. Control group included 25 men and 22 women that were 16-58 years old; observation group included 22 men and 21 women that were 18-59 years old. The gender and age distribution of the two groups are similar (P>0.05), and the study was approved by the hospital ethics committee.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) in accordance with the diagnostic criteria for schizophrenia in Classification and Diagnostic Criteria of Mental Disorders CCMD-3; (2) diagnosed for the first time, and not receiving systematic treatment before; (3) completing the whole treatment and examination, and with complete clinical data. Exclusion criteria: (1) associated with anxiety, depression and other mood disorders; (2) associated with berberine and risperidone allergy; (3) with systemic infectious diseases; (4) with endocrine diseases such as diabetes, hyperthyroidism, thyroidism and primary hyperaldosteronism.

2.3 Therapy

Control group of patients were treated with risperidone, specifically as follows: risperidone (Xi'an Janssen Pharmaceutical Co., Ltd., approved by the H20010309), starting dose 1 mg/d, adjusting the dose according to patients′ condition, maximum dose 6 mg/d, for 2 months of continuous treatment.

Observation group of patients received berberine combined with risperidone therapy, specifically as follows: berberine (Nanjing Baijingyu Pharmaceutical Co., Ltd., approved by H32023081) 300 mg/time, 3 times/d, for 2 months of continuous treatment. Risperidone usage and dosage were the same as those of control group.

2.4 Observation indexes

Before and after treatment, 3-5 mL of fasting cubital venous blood was collected from two groups of patients, anti-coagulated and then centrifuged for 15 min at 3 000-3 500 r/min, and upper serum was kept and cryopreserved in deep cryogenic refrigerator for test. Radioimmunoassay was used to determine serum fasting insulin (FINS) levels, and insulin resistance index (HOMA-IR) was calculated. The serum triiodothyronine (T3) and prolactin (PRL) levels were determined by enzyme-linked immunosorption assay (ELISA). ELISA was used to detect serum oxidative stress indicators malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) levels.

2.5 Statistical processing

Data in the study were recorded and analyzed by specially-assigned person, and statistical software was SPSS 20.0. Insulin resistance indexes, thyroid hormone, prolactin, oxidative stress indexes and other measurement data were in terms of mean ± standard deviation, and comparison between groups was by t test. $P<0.05$ was the standard of statistical differences in differences.

3. Results

3.1 Serum insulin resistance indexes

Before treatment and 2 months after treatment, comparison of serum insulin resistance indexes FINS (μU/mL) and HOMA-IR between two groups of patients was as follows: before treatment, serum FINS content and HOMA-IR level were not significantly different between two groups of patients ($P>0.05$). Compared with those before treatment, serum FINS content and HOMA-IR level in control group increased significantly after treatment ($P<0.05$) while serum FINS content and HOMA-IR level in observation group didn′t change significantly after treatment ($P>0.05$); Compared with those in control group, serum FINS content and HOMA-IR level in observation group decreased significantly after treatment ($P<0.05$), shown in Table 1.

3.2 Serum thyroid hormone and prolactin contents

Before treatment and 2 months after treatment, comparison of serum T3 (nmol/L) and PRL (IU/L) contents between two groups of patients was as follows: before treatment, serum T3 and PRL contents were not significantly different between two groups of

Table 1.
Comparison of insulin resistance index levels between two groups of patients before and after treatment.

Groups	*n*	FINS		HOMA-IR	
		Before treatment	After treatment	Before treatment	After treatment
Control group	47	14.38±1.76	21.75±2.96*	1.21±0.14	1.46±0.18*
Observation group	43	14.29±1.68	14.71±1.85	1.22±0.15	1.25±0.16
t		0.173	9.281	0.261	7.593
P		>0.05	<0.05	>0.05	<0.05

Note: compared with same group before treatment, *$P<0.05$.

Table 2.
Comparison of thyroid hormone and prolactin contents between two groups of patients before and after treatment.

Groups	*n*	T3		PRL	
		Before treatment	After treatment	Before treatment	After treatment
Control group	47	2.14±0.25	1.65±0.18*	0.73±0.08	1.78±0.24*
Observation group	43	2.15±0.26	2.07±0.21	0.74±0.09	0.79±0.08
t		0.261	6.394	0.158	9.271
P		>0.05	<0.05	>0.05	<0.05

Note: compared with same group before treatment, *$P<0.05$.

Table 3.
Comparison of serum oxidative stress index contents between two groups of patients before and after treatment.

Groups	*n*	MDA		SOD		GSH-Px		CAT	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	47	4.18±0.53	3.07±0.42*	16.28±2.11	20.17±2.56*	61.28±7.09	75.69±8.53*	6.28±0.79	7.91±0.85*
Observation group	43	4.15±0.49	2.11±0.27*	16.19±2.07	23.51±2.89*	61.53±7.15	88.51±0.97*	6.31±0.75	8.66±0.97*
t		0.173	6.983	0.157	8.092	0.251	10.163	0.253	7.281
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before treatment, *$P<0.05$.

patients ($P>0.05$). Compared with those before treatment, serum T3 content in control group decreased significantly while PRL content increased significantly after treatment ($P<0.05$), and serum T3 and PRL contents in observation group didn't change significantly after treatment ($P>0.05$); compared with those in control group, serum T3 content in observation group increased significantly while PRL content decreased significantly after treatment ($P<0.05$), shown in Table 2.

3.3 Serum oxidative stress index contents

Before treatment and 2 months after treatment, comparison of serum oxidative stress indexes MDA (nmol/L), SOD (U/mL), GSH-Px (U/mL) and CAT (U/mL) contents between two groups of patients was as follows: before treatment, serum MDA, SOD, GSH-Px and CAT contents were not significantly different between two groups of patients ($P>0.05$). Compared with those before treatment, serum MDA contents in both groups decreased significantly while SOD, GSH-Px and CAT contents increased significantly after treatment ($P<0.05$); compared with those in control group, serum SOD, GSH-Px and CAT contents in observation group increased significantly while MDA content decreased significantly after treatment ($P<0.05$), shown in Table 3.

4. Discussion

Risperidone belongs to atypical antipsychotics, has been widely used in the treatment of patients with schizophrenia in recent years, and has better than efficacy than traditional antipsychotics[5,6]. But foreign studies in recent years have shown that the long-term use of risperidone can increase the long-term risk of stroke, coronary heart disease and other cardiovascular and cerebrovascular diseases in patients with schizophrenia, which is closely related to the drug effect on endocrine hormone levels in patients[7,8]. Given the status quo that risperidone is efficient and affects the endocrine system function, some scholars have proposed to join other mechanisms of drugs to resist the side effects of risperidone, and expand the overall effect. Berberine is the alkaloid extracted from rhizoma coptidis, golden cypress, berberis poiretii schneid and other plants, which has a variety of actions such as resisting pathogenic microorganisms, improving insulin resistance and anti-inflammation, and has also been successfully applied in nervous system diseases at present[9,10]. In the research, berberine combined with risperidone was used for the treatment of patients with schizophrenia, and its therapeutic effect was discussed from the endocrine hormone levels, oxidative stress extent and other aspects.

The effect of risperidone in the treatment of schizophrenia is mainly achieved by blocking dopamine D2 receptor and 5-HT2A receptor, and thus increases patients' appetite through the reward pathway mediated by dopamine, and with the extension of drug action cycle, patients can gradually develop lipid accumulation and insulin resistance[11,12]. Insulin resistance can follow the weight gain caused by risperidone, or be from the direct damage of risperidone to the islet and certain glycosin transporters. Berberine can regulate the body's blood lipid metabolism, inhibit the over-expression of the insulin genes directly and protect the islet B cells[13]. In the study, serum insulin resistance levels were compared between the two groups before and after treatment, and it was found that compared with those before treatment, serum FINS and HOMA-IR levels in control group were higher after treatment, indicating that risperidone treatment alone can cause insulin resistance in patients with schizophrenia; and serum FINS and HOMA-IR levels in observation group after treatment were not significantly different from those before treatment, explaining that adding berberine therapy can effectively reverse the risperidone-induced insulin resistance, and help maintain the body's sugar metabolism balance.

Risperidone has high affinity for D2 receptors and 5-hydroxytryptamine receptor, which can make DA neuron function decline, directly inhibit thyroid hormone production and hinder the prolactin receptor function, and eventually lead to the decrease of thyroid hormone content and the increase of prolactin content in the circulating blood[14,15]. In the study, were serum thyroid hormone and prolactin contents were compared between two groups of patients before and after treatment, and it was found that compared with those before treatment, T3 level in control group decreased while PRL content increased after treatment, indicating that risperidone treatment alone can lead to the abnormal secretion of T3 and PRL; serum T3 and PRL levels in observation group after treatment were not significantly different from those before treatment, indicating that adding berberine therapy can effectively balance the T3 and PRL metabolism levels and maintain the endocrine system steady-state in patients with schizophrenia.

Recent researches have indicated that patients with schizophrenia have different degrees of systemic oxidative stress, it is mainly associated with the changes in antioxidant enzyme activity, and the specific level of oxidative stress is directly related to the severity of schizophrenia[16,17]. MDA is the most commonly studied clinical oxidative metabolite, SOD, GSH-Px and CAT are the antioxidant

substances, and their expression imbalance is the direct cause of oxidative stress reaction[18,19]. In the study, were serum contents of above oxidative stress indexes were compared between two groups of patients before and after treatment, and it was found that compared with those before treatment, serum MDA contents in both groups decreased while SOD, GSH-Px and CAT contents increased after treatment, showing that both treatments can reduce the body′s oxidative stress response; further compared with the control group after treatment, the observation group were with lower serum MDA content, and higher SOD, GSH-Px and CAT contents after treatment, explaining that joining berberine therapy can further inhibit the oxidative stress reaction, this is mainly associated with the anti-inflammation, anti-pathogenic bacteria and other effects of berberine, and it is one of the important mechanisms for combination therapy to exert curative effect.

Berberine combined risperidone therapy for patients with schizophrenia can improve the endocrine hormone level disorder caused by risperidone therapy alone and also enhance the anti-oxidative stress capacity, has positive clinical significance, and is worth popularization and application in clinical practice in the future.

References

[1] Thiebes S, Leicht G, Curic S, Steinmann S, Polomac N, Andreou C, et al. Glutamatergic deficit and schizophrenia-like negative symptoms: new evidence from ketamine-induced mismatch negativity alterations in healthy male humans. *J Psychiatry Neurosci* 2017; **42**(4): 160187.

[2] Vistoli D, Lavoie MA, Sutliff S, Jackson PL, Achim AM. Functional MRI examination of empathy for pain in people with schizophrenia reveals abnormal activation related to cognitive perspective-taking but typical activation linked to affective sharing. *J Psychiatry Neurosci* 2017; **42**(4): 160136.

[3] Suzuki H, Hibino H, Inoue Y, Takaya A. Treatment retention of risperidone long-acting injection in patients with early-onset schizophrenia in Japan. *Asian J Psychiatr* 2017; **27**: 137-138.

[4] Sahni S, Chavan BS, Sidana A, Kalra P, Kaur G. Comparative study of clozapine versus risperidone in treatment-naive, first-episodeschizophrenia: A pilot study. *Indian J Med Res* 2016; **144**(5): 697-703.

[5] Yoshimura Y, Takeda T, Kishi Y, Harada T, Nomura A, Washida K, et al. Optimal dosing of risperidone and olanzapine in the maintenance treatment for patients withschizophrenia and related psychotic disorders: a retrospective multicenter study. *J Clin Psychopharmacol* 2017; **37**(3): 296-301.

[6] Samadi R, Soluti S, Daneshmand R, Assari S, Manteghi AA. Efficacy of risperidone augmentation with ondansetron in the treatment of negative and depressive symptoms in schizophrenia: a randomized clinical trial. *Iran J Med Sci* 2017; **42**(1): 14-23.

[7] Liang Y, Yu X. The effectiveness and safety of amisulpride in Chinese patients with schizophrenia who switch from risperidone or olanzapine: a subgroup analysis of the ESCAPE study. *Neuropsychiatr Dis Treat* 2017; **21**(13): 1163-1173.

[8] Suresh Kumar PN, Anish PK, Rajmohan V. Olanzapine has better efficacy compared to risperidone for treatment of negative symptoms in schizophrenia. *Indian J Psychiatry* 2016; **58**(3): 311-316.

[9] Li Jiangong, Zhao Yongping, Liu Ying, Qiu Yuying, Li Meijuan, Jia Qiong, et al. The impact of berberine on insulin resistance and cytokines in patients with schizophrenia. *Tianjin Medical J* 2016; **44**(9): 1143-1146.

[10]Zhang Jing, Zhao Yong-ping, Jia Qiong, Liu Ying, Li Mei-juan, Li Jian-gong, et al. The effect of berberine on the symptoms and glycolipid metabolism in patients with schizophrenia treated by risperidone. *J Tianjin Med Univ* 2016; **22**(4): 338-341.

[11]Sapra M, Lawson D, Iranmanesh A, Varma A. Adiposity-independent hypoadiponectinemia as a potential marker of insulin resistance and inflammation in schizophrenia patients treated with second generation antipsychotics. *Schizophr Res* 2016; **174**(1-3): 132-136.

[12]Gao Shuai, Zhang Yu-liang, Cai Li-li. Investigation of effect of combination of aripiprazole with olanzapine on weight and glucolipid metabolism of patients with schizophrenia. *Sichuan Mental Health* 2015; **28**(2): 127-130.

[13]Chen Fangbin, Sun Jian, Yan Tongjun, Xu Leping, Wang Huanlin. The liver fat content and its relationships with insulin resistance in schizophrenia patients receiving olan-zapine or aripiprazol: a randomized comparative study. *Chin J Nervous Mental Dis* 2015; **41**(11): 646-649.

[14]Chen Ying, Zhu Jianhong, Shen Dehua, Duan Xia-xia, Yu Yan-jun. Changes of thyroid function parameters and sex hormone levels and response to the drug in schizophrenic patients. *J Int Psychiatr* 2015; **42**(2): 32-35.

[15]Su Ben-zhong, Yao Zi-ying, Meng Yan, Zhang Lei, Bai Song-lin. Study of risperidone effect on endocrine in women with schizophrenia. *J Pract Gynecol Endocrinol* 2014; **1**(2): 49-52.

[16]Hardingham GE, Do KQ. Linking early-life NMDAR hypofunction and oxidative stress in schizophrenia pathogenesis. *Nat Rev Neurosci* 2016; **17**(2): 125-134.

[17]Bahceci B, Kokacya MH, Copoglu US, Bahceci I, Sahin K, Bagcioglu E, et al. Elevated nucleosome level and oxidative stress in schizophrenia patients. *Bratisl Lek Listy* 2015; **116**(10): 587-590.

[18]Li Dan, Xu Ahong, Yi Zhenghui, Wang Zuowei, Xue Zhiqiang, Lin Ping. Preliminary study of the relationship between chronic schizophrenia and oxidative stress. *Int J Lab Med* 2015; **36**(18): 2650-2653.

[19]Chao Yangyang, Sheng Weiyong, Zhao Jin, Shi Yuzhong. Alteration of oxidative stress in peripheral blood of first-episode schizophrenia. *Chin J Nervous Mental Dis* 2016; **42**(8): 449-452.