Effect of lamotrigine on cognitive function and serum inflammatory factors in patients with depression of recurrent bipolar disorder

Shaobo Shi, Lu Li, Lina Song and Xinrui Wang
Department of Psychiatry, Mental Health Center of Qingdao, Qingdao, PR China

Abstract: In the present study, an effort was made to investigate the effect of lamotrigine on cognitive function and serum inflammatory factors in patients with depression of recurrent bipolar disorder and to explore its possible mechanism.140 patients with depression of recurrent bipolar disorder, admitted from June 2015 to April 2017, were selected as the research subjects, followed by random division into the research group and the control group with 70 cases (n=70) in each group. The control group was treated with sodium valproate and the research group was treated with lamotrigine. After 2 months of treatment, comparison was made between the two groups for the emotional state, cognitive function and serum inflammatory factors. Results showed that the Hamilton Depression Scale (HAMD) score and Bech-Rafaelsen Mania Rating Scale BRMS score in the research group were significantly lower than in the control group ($P<0.05$). The time of Trail Making Test-A(TMT-A) and Trail Making Test-B(TMT-B) in the research group was significantly shorter than that of the control group, with a statistically significant difference ($P<0.05$). The serum levels of MIF, IL-1β and IL-6 in the research group were significantly lower than those in the control group and the difference was statistically significant ($P<0.05$). Research concluded that lamotrigine may help alleviate the clinical symptoms and improve cognitive function in patients with depression of recurrent bipolar disorder.

Keywords: Bipolar disorder, lamotrigine, cognitive function, inflammatory factors.

INTRODUCTION

Bipolar disorder (BPD) is a serious mental disease, characterized by high prevalence, recurrence rate, disability rate, mortality rate, comorbidity rate and low age (Malhotra *et al*., 2013). Clinical manifestations of BPD are complex including various emotional, psychotic, somatic &cognitive symptoms. BPD frequently happens at the same time with a variety of other diseases, thus making difficulty in its clinical identification and treatment (Price & Marzani-Nissen, 2012). Previous research revealed that inflammatory factors may be a significant mechanism for the pathogenesis of bipolar affective disorder (Vuksan-cusa *et al*., 2010). Lamotrigine with trade name "Lamictal" was used initially to treat epilepsy (Hatch *et al*., 2017) and has also got some efficacy as a mood stabilizer for the treatment of BDD (Green *et al*., 2005). Currently, lamotrigine is used as a mood stabilizer in patients with of BPD however in China the use of this drug is limited. It is reported that lamotrigine has no adverse effect on cognitive function in patients with epilepsy. The effects of lamotrigine on cognitive function in patients with BPD are reported by few researchers (McVearry *et al*., 2009). In this research, the method of randomized controlled trial was implemented to explore the influence of lamotrigine on cognitive function and serum inflammatory factors in patients with recurrent BPD and aimed to analyze its possible mechanism.

**Corresponding author:* e-mail: sci477@aliyun.com

MATERIALS AND METHODS

Sodium valproate sustained release tablets (Hangzhou pharmaceutical company Sanofi synthelabo Minsheng), lamotrigine (Glaxo Smith Kline Pharmaceuticals S.A. (Poland). Study was carried out on 140 patients (research subjects) with depression of recurrent BPD admitted from June 2015 to April 2017. Study had certain inclusion & exclusion criteria in data collection process.Study included only those subjects &/or patients who were in accordance with the diagnostic criteria of depression in "Chinese mental disorders classification and diagnostic criteria third edition (CCMD-3)", having more than 18 years of age with HAMD score ≥ 17 points & specifically those who signed informed consent form. In the same way, the present study excluded all those subjects and/or patients who had severe heart, liver, kidney and other organ dysfunction and individuals with any other type of psychiatric and/or neurological disorders. Drug allergic patients & those who quit or fall off halfway were also not included in the study. Research & control groups were designed from140 cases of patients with 70 cases placed in each group. Gender wise, the research group contained 34 male and 36 female cases. Age of the patients in research group ranged from 44 to 63 years with an average age of 48.4±1.5 years. Course of disease in research group was 1 to 14 months with an average time of 9.7±1.4 months. On the other hand, control group comprised of 35 male and 35 female subjects having 43 to 62 years of age with an average age of 48.7±1.8 years. The course of disease in control group was found 1 to 13 months with an average time of 9.5±1.2 months. The

research data had no any statistically significant difference between research & control group related to the gender, age and course of disease and was comparable.

Ethical approval

Ethical approval was by taken by Mental Health Center of Qingdao through No.138801.

Therapeutic method

Sodium valproate sustained release tablets were given orally to the control group patients with an initial dose of 0.5g once a day. The dose was increased to 1.0g b.i.d. after 1 to 2 weeks. Research group patients were orally administered with lamotrigine with an initial dose of 25mg o.d for 2 weeks followed by 50mg o.d for next two weeks. The dose was increased every weekly or after 2 weeks with the maximum increase of 50-100mg until the best effect was achieved. The optimized maintenance dose that reached the best effect was 100-200mg per day. Both the groups were treated continuously for 2 months.

Observational index

Depression and mania

Depression and mania were assessed by HAMD & BRMS before treatment and2 months later to the treatment. Higher the score on either of the scales, the more severe the state of depression and mania was observed.

Cognitive function

Prior to treatment and two months after treatment, cognitive function was measured using the TMT of cognitive function, including the digital portion of TMT-A and the letter portion of TMT-B, with less time consuming and better cognitive function.

Serum cytokine

5mL of peripheral venous blood was collected from both groups twice, before treatment & sixty days after treatment respectively and the expression of MIF, IL-1β and IL-6 in macrophages were determined by Elisa kit. MIF is a pro-inflammatory cytokine produced by granulocytes and secretory cells of the hypothalamus-pituitary-adrenal axis, which inhibits the secretion of morning cortisol (Cor) and subsequently causes anxiety and depression symptoms (Bick *et al*., 2015). IL-1β, a member of IL-1 family, can promote the over-activation of the hypothalamic-pituitary-adrenal axis together with IL-6, leading to enhancement of neurotransmitter metabolism, such as dopamine and 5- HT, in the nucleus of the hypothalamus of the brain and the marginal structure of the thalamus (Liège *et al*., 2000).

STATISTICAL ANALYSIS

SPSS 21 software was used for statistical analysis. The measurement data was represented by t test, gender and other counting data was expressed by frequency and/or rate, and they were detected by chi-square test with a significant difference of $P<0.05$.

RESULTS

Comparison of the state of depression and mania

There was no statistically significant difference in HAMD score and BPMS score between the patients of the two groups ($P>0.05$) before treatment. After 2 months of treatment, the HAMD score and the BPMS score of the two groups were significantly lower than those in the corresponding group before treatment and the difference was statistically significant ($P<0.05$). Moreover, the HAMD score and BPMS score in the research group were significantly lower than those in the control group and the difference was statistically significant ($P<0.05$) as given in table 1.

Comparison of cognitive function between the two groups before and after treatment

Before treatment, there was no significant difference in TMT-A and TMT-B time between the two groups ($P>0.05$). After 2 months of treatment, the time of TMT-A and TMT-B in the two groups was significantly shorter than those in the same group before treatment. In addition, the time of TMT-A and TMT-B in the research group was significantly shorter than those in the control group and the difference was statistically significant ($P< 0.05$) as depicted in table 2.

Comparison of serum cytokine content in two groups before and after treatment

The serum levels before treatment of MIF, IL-1β and IL-6 in two groups didn't show statistically significant difference ($P>0.05$). After treatment for 2 months, the serum levels of MIF, IL-1β and IL-6 in the patients of two groups were significantly lower than those in the same group before treatment and the difference was statistically significant ($P<0.05$). The serum levels of MIF, IL-1β and IL-6 in the research group were significantly lower than those in the control group ($P<0.05$). As demonstrated in table 3.

DISCUSSION

Bipolar effective disorder is a common disease in the department of psychiatry. Its clinical treatment is more difficult and recurrence is serious. In the development process of BPD, the alternation of depression and mania will not only affect the emotional state of patients but also causes cognitive dysfunction and affects daily work and life (Robinson *et al*., 2015; Benedetti *et al*., 2016). At present, mood stabilizers are mainly used to treat depressive episodes of bipolar disorder (Viguera *et al*., 2007). More commonly accepted mood stabilizers include lamotrigine and sodium valproate (Altamura *et al*., 2008). Lamotrigine is safe, with mild side effects and self-remission (Mitchell *et al*., 2013). The findings of this

Table 1: Comparison of the scores of depression and mania in the two groups of patients before and after treatment (x±s)

Groups	HAMD score/points		BPMS score/points	
	Prior treatment	After 2 months of treatment	Prior treatment	After 2 months of treatment
Control group (n=70)	37.34±4.15	30.72±3.21	28.06±3.13	21.85±2.76
Research group (n=70)	37.52±4.23	21.68±3.71	28.11±3.24	16.49±2.13
T	0.56	5.91	0.42	6.83
P	>0.05	<0.05	>0.05	<0.05

Table 2: Comparison of cognitive function between the two groups of patients before and after treatment (x ± s)

Groups	TMT-A/s		TMT-B/s	
	Before treatment	2 months after treatment	Before treatment	2 months after treatment
Control group (n=70)	74.56±7.63	63.24±6.68	98.67±9.36	84.35±7.04
Research group (n=70)	74.48±7.57	55.35±6.51	98.52±9.27	77.16±7.12
T	0.94	6.14	0.72	7.05
P	>0.05	<0.05	>0.05	<0.05

Table 3: Comparison of serum cytokine content in two groups of patients before and after treatment (x ± s)

Groups	MIF/（ng·L^{-1}）		IL-1β/（ng·L^{-1}）		IL-6/（ng·L^{-1}）	
	Prior to treatment	2 months after treatment	Prior treatment	2 months after treatment	Prior to treatment	2 months after treatment
Control (n=70)	59.26±6.2	45.07±5.58	0.48±0.13	0.28±0.08	106.35±9.6	87.82±9.1
Research (n=70)	59.45±6.3	35.23±4.61	0.47±0.11	0.19±0.07	105.28±9.4	71.29±8.4
T	0.26	4.36	0.34	5.02	0.38	6.17
P	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

study are with the agreement of the study conducted by Michell et al., 2013. As per this study, the time of TMT-A and TMT-B in the research group was significantly shorter than that in the control group with a statistically significant difference (P<0.05). The serum levels of MIF, IL-1β and IL-6 in the research group were significantly lower than those in the control group and the difference was statistically significant (P<0.05).

The conclusions also supported the views of the Mitchell *et al*., 2013 which confirmed that lamotrigine can improve cognitive function in patients. In previous studies, the study of patients with BPD was mainly focused on monoamine neurotransmitters (Lin *et al*., 2001). Recently, with the deepening of cell and molecular research, more and more scholars believe that the changes of emotional state and cognitive function are closely related to inflammatory reaction (Panou *et al*., 2012). The excessive secretion of inflammatory factors such as MIF, IL-1β and IL-6 is the characteristic of over activation of inflammation. In the present study, the serum levels of MIF, IL-1β, and IL-6 in the research group were significantly lower than those in the control group, suggesting that lamotrigine has an inhibitory effect on the expression of inflammatory cytokines.

CONCLUSION

Lamotrigine can help alleviate the clinical symptoms and improve cognitive function in patients with depression of recurrent bipolar disorder. The mechanism of its action may be related to the inhibition of the expression of serum inflammatory cytokines.

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