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EFFECT OF FOLIC ACID AND METHYLCOBALAMIN ADJUVANT THERAPY ON IMPROVEMENT OF CLINICAL SYMPTOMS AND BDNF LEVELS OF IN SCHIZOPHRENIA PATIENTS

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Abstract

Background : Schizophrenia is a mental disorder characterized by delusions, hallucinations, cognitive and affective impairments that impact various aspects of life and society. Schizophrenia patients often have a spectrum of vitamin and mineral deficiencies. Folic acid and methylcobalamin as adjuvant therapy in schizophrenia patients are considered to improve clinical symptoms, maximize the quality of life of schizophrenia patients, and increase BDNF levels, which have been widely studied as a cognitive marker in schizophrenia patients.

Objective: Determine the effect of folic acid and methylcobalamin adjuvant therapy on improving clinical symptoms and BDNF levels in schizophrenic patients receiving risperidone therapy.

Method: We used experimental analysis in our study by measuring pre- and post-tests with non-random group selection. This study was carried out at the Dadi Special Regional Hospital in South Sulawesi Province of Indonesia in February–March 2023, and sample testing was carried out to the HUMRC Research Laboratory of Hasanuddin University. A total of 46 subjects were divided into a treatment group of 23 subjects who received risperidone therapy of 4-6 mg/day plus adjuvant therapy of folic acid and methylcobalamin for 8 weeks and a control group of 23 subjects who only received risperidone therapy of 4-6 mg/day. PANSS was used to assess clinical symptoms, and serum BDNF levels were measured using enzyme-linked immunosorbent assays (ELISA). The Wilcoxon, Mann-Withney, and Spearman correlation tests were carried out to see the significance.

Results: There was a decrease in PANSS both in the treatment group and in the control group after receiving a significant therapeutic dose of antipsychotic risperidone with a p value (< 0,001). The treatment group with risperidone antipsychotic therapy with adjuvants of folic acid and methylcobalamin showed an improvement in clinic symptoms of 63.33 percent, with the clinical interpretation of symptoms showing very much improvement, compared to the control group with a clinical improvement of the symptoms of 46.19 percent, with the clinical manifestation interpretation showing much improvement. There was an increase in the level of BDNF in the treatment group receiving risperidone

antipsychotic therapy with adjuvant therapy of folic acid and methylcobalamin, with a significant p value (<0,001) compared to the control group that received only risperidone antipsychotic therapy.
Conclusion: Effects of Folic Acid and Methylcobalamin Adjuvant Therapy and Standard Therapy Risperidone 4-6 mg/day can improve clinical symptoms and increase serum BDNF levels.

Keywords: Schizophrenia, Folic acid, Methylcobalamin, Risperidone, Clinical Symptoms, BDNF Serum

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a secretory growth factor (neurotrophin) that promotes the proliferation and survival of neurons, synaptic plasticity, and long-term potentiation in the central nervous system. Due to its complex role, BDNF has been extensively studied and is believed to play a key role in regulating cognitive functions in individuals. BDNF has been widely investigated based on the hypothesis of neuronal development in schizophrenia, given its role in the development and physiology of the central nervous system (Di Carlo and Ursini, 2019). Some evidence indicates a significant role for BDNF in schizophrenia. Post-mortem studies have found reduced expression of BDNF mRNA and protein in the prefrontal cortex and hippocampus of the brains of individuals with schizophrenia. However, the relationship between serum BDNF levels and schizophrenia psychopathology is less clear (Durany et al., 2001; Weickert et al., 2003; Hashimoto et al., 2005; Nieto et al., 2013).

Folic acid and methylcobalamin provide substrates for intracellular methylation reactions that are important for normal brain development and function. Methylation is crucial for DNA synthesis and repair, gene expression, neurotransmitter synthesis and degradation, and homocysteine metabolism (Frankenburg, 2007). Abnormal folate metabolism has been implicated in schizophrenia. Low blood folate levels have been reported in patients with schizophrenia and are associated with clinical manifestations, especially in the negative symptom domain (Goff et al., 2004; Roffman et al., 2013). Folate deficiency specifically affects central monoamine metabolism and worsens psychiatric disorders. Elevated blood homocysteine levels have been linked to several psychiatric and neurodegenerative disorders, including depression, schizophrenia, Alzheimer's disease, and Parkinson's disease, which are associated with folate and methylcobalamin deficiency (Garca-Miss et al., 2010). A recent study conducted by Hidayati et al. (2017) in Surakarta with a total of 60 study subjects showed significant differences in the improvement of positive symptoms, negative symptoms, general psychopathology, and total PANSS score between the group of chronic schizophrenia patients receiving additional folic acid and methylcobalamin therapy and the control group (Hidayati et al., 2017).

Based on the above research, adjuvant therapy with folic acid and methylcobalamin has been shown to be effective, as both play a role in homocysteine metabolism. Given this background, the researchers are interested in further investigating the effects of adjuvant therapy with folic acid and methylcobalamin on PANSS scores and plasma Brain-Derived Neurotrophic Factor (BDNF) levels in patients with schizophrenia, considering that study on the use of folic acid and methylcobalamin as adjuvant therapy for schizophrenia patients is still limited. Based on this background, the researcher were interested to study is the influence of adjuvant therapy of folic acid and methylcobalamin for the improvement of clinical symptoms and BDNF levels in patients with schizophrenia receiving risperidone therapy.

2. Material and Methods

The subjects in this study were all male subjects with schizophrenia who were admitted to
Dadi Regional Special Hospital, South Sulawesi Province, fulfilled the inclusion criteria. The inclusion criteria were Male subjects diagnosed with schizophrenia according to ICD-10 criteria, aged 20–45 years, and willing to participate in the study. Exclusion criteria included having a serious physical illness and a history of psychotropic abuse. Subjects drop-out if could not continue the study due to discharge from hospitalization, and the research subjects had hypersensitivity to drugs. Blood samples were taken from as much as 3 cc (3/5 teaspoon) in the mediana cubiti vein by phlebotomy technique using vacuum

and put into a red cap tube. Blood samples were centrifuged to obtain liquid blood serum, which was stored at -70°C until ELISA examination. BDNF concentration was measured in the serum of the samples using Enzyme Linked Immunosorbent Assay (ELISA), according to the manufacturer's instructions.

Each subject who met the criteria for schizophrenia according to ICD-10 criteria and met the inclusion criteria in the research group was recorded, and their medical history data was taken. The researcher then explained to the family and the subject the purpose and objectives of the study. If they agree, then the subject will be involved in the study (with informed consent). The subjects were divided into two groups, namely the treatment group, which was given folic acid adjuvant therapy at a dose of 2 mg and methylcobalamin at a dose of 400 mcg for 8 weeks, and the control group, which was only given risperidone therapy. PANSS scores were measured in both groups at baseline, week 4, and week 8. BDNF blood levels were measured in both groups at baseline and week 8. Data were analyzed using the SPSS 24.0 computer program and Microsoft Excel to obtain the expected statistical results with the homogeneity test, independent t-test, and Mann-Whitney test, Friedman test, and Spearman test. This research was approved by the Ethics Committee for Biomedical Research in Humans, Faculty of Medicine, Hasanuddin University, Number: 94/UN4.6.4.5.31/PP36/2023. Informed consent was obtained from the subject, and confidentiality was maintained.

3. Results

In this study, 46 subjects was enrolled, which was divided into 2 groups: the treatment group with 23 subjects and the control group with 23 subjects, all of whom met the inclusion criteria. To provide descriptive data related to the frequency distribution of research subjects, statistical descriptive analysis was carried out. All subjects in this study were male. The average age of the treatment subjects was 32.96 ± 7.52 years, while in the control group, the average age was 34.87 ± 9.04 years. Data on the level of education of the study subjects showed that the highest level of high school education in the treatment group was 52.2%, while in the control group, the highest level of high school education was 56.5%. In the treatment group, most subjects (60.9%) were unemployed, while in the control group, most were unemployed (65.2%). Marital status in the treatment group was mostly unmarried (60.9%), and in the control group, the majority were unmarried (52.2%). After the homogeneity test was carried out, the p values for all variables were greater than 0.05 (p>0.05), so it could be concluded that the subjects in this study were homogeneous or not significantly different from the T-Independent test in the age group and the chi square test in the marital status group, education, and employment (Table 1).

Table 1. Demographic Characteristics of Research Subjects

Variabel	Treatment (n=23)	Control (n=23)	p
Age (*mean* ± SD)	32,96 ± 7,52	34.87 ± 9,04	0,439*
Education			1,000**
Junior High School	11 (47,8%)	10 (43,5%)	
Senior High School	12 (52,2%)	13 (56,5%)	
Occupation			1,000**
Employed	9 (39,1%)	8 (34,8%)	
Unemployed	14 (60,9%)	15 (65,2%)	
Marital Status			0,766**
Married	9 (39,1%)	11 (47,8%)	
Single	14 (60,9%)	12 (52,2%)	

Mean ± SD, *Independent t-test, **Chi Square Test

Table 2. Results of clinical symptom measurements based on total PANSS values, positive symptoms, negative symptoms, general psychopathology, and baseline week BDNF levels in the treatment and control groups

Variabel	Group		
	Treatment (n=23)	Control (n=23)	p
PANSS Total Baseline	90,83 ± 8,58	88,35 ± 9,22	0,351*
Positive Symptoms Baseline	27,47± 4,20	23,43 ± 4,81	0,006**
Baseline Negative Symptoms	17,83 ± 2,44	17,57 ± 2,06	0,698*
General Psychopathology Baseline	45,52 ± 4,47	47,39 ± 4,31	0,148
BDNF Baseline	1,20 ± 0,63	1,04 ± 0,42	0,652**

Mean ± SD, PANSS (Positive and Negative Syndrome Scale), BDNF (Brain Derived Neurotrophic Factor) *Independent t test, **Mann Whitney test

Table 3. Comparison of Clinical Symptoms Based on PANSS Values, Positive and Negative Symptoms, and General Psychopathology in the Treatment Group and Control Group at Baseline Week, 4th Week, and 8th Week

Variabel	Group			
	Treatment (*Mean* ± SD)	p	Control (*Mean* ± SD)	p
PANSS baseline week	90,83 ± 8,58		88,35 ± 9,22	
PANSS 4th week	68,30 ± 9,53	0.001*	74,17 ± 9,36	0.001**
PANSS 8th week	52,30 ± 7,59		61,39 ± 8,71	
Positive Symptoms baseline week	27,48 ± 4,20		23,43 ± 4,81	
Positive Symptoms 4th week	21,26 ± 2,94	0.001*	21,48 ± 4,45	0.001**
Positive Symptoms 8th week	16,87 ± 2,18		19,09 ± 4,37	
Negative Symptoms baseline week	17,83 ± 2,44		17,57 ± 2,06	
Negative Symptoms 4th week	14,00 ± 2,04	0.001**	15,87 ± 1,71	0.001*
Negative Symptoms 8th week	10,87 ± 1,66		13,70 ±1,79	
General Psychopathology baseline	45,52 ± 4,47		47,39 ± 4,13	
General Psychopathology 4th week	33,39 ± 6,40	0.001**	36,39 ± 6,18	0.001**
General Psychopathology 8th week	24,52 ± 5,53		28,61 ± 7,65	

Mean ± SD, PANSS (Positive and Negative Syndrome Scale)
*Repeated ANOVA test
**Friedman's test

In the treatment group that received folic acid and methylcobalamin adjuvant therapy, the mean difference in PANSS values from the baseline week to the 8th week was 38.52. Whereas in the control group that only received risperidone antipsychotic therapy, the mean difference in the PANSS value from baseline to the 8th week was 26.96. The difference between the treatment and control groups was 11.56. Changes in these values can be seen in Table 4.

Table 4. Improvement in Clinical Symptoms Based on the Difference in PANSS Values in the Treatment and Control Groups at the Baseline Week, Week 4th, and Week 8th

Group	PANSS Total Score						
	Mean Difference Week 0-4	p	Mean Difference Week 4-8	p	Mean Difference Week 0-8	P	Difference between treatment and control groups
Treatment	22,52±10,24	0.014**	16,00±7,08	0.008**	38,52±10,82	0.001*	11,56
Control	14,87±5,32		12,78±5,78		26,96±8,86		

Mean ± SD, PANSS (Positive and Negative Syndrome Scale)
*Independent t test, **Mann Whitney test

There was a decrease in PANSS both in the treatment group and in the control group after receiving a significant therapeutic dose of antipsychotic risperidone with a p value (< 0,001). In the treatment group with risperidone antipsychotic therapy with adjuvants of folic acid and methylcobalamin showed an improvement in clinic symptoms of 63.33 percent, with the clinical interpretation of symptoms showing very much improvement, compared to the control group with a clinical improvement of the symptoms of 46.19 percent, with the clinical manifestation interpretation showing much improvement. Calculation of the percentage for each domain was also carried out, as can be seen in Table 5.

Table 5. Improvement of Clinical Symptoms Based on Percentage Decrease in PANSS Score in Treatment and Control Groups at Baseline Week, 4th Week, and 8th Week

Variabel	Treatment (n=23)						Control (n=23)					
	Mean ± SD	% decrease Baseline-4th Week	% decrease 4th-8th Week	% decrease Baseline -8th Week	Interpretation	p	Mean ± SD	% decrease Baseline-4th Week	% decrease 4th-8th Week	% decrease Baseline -8th Week	Interpretation	p
PANSS Total baseline week	90,83 ± 8,58	37,03%		63,33%	Very much improvement	0.001*	88,35 ± 9,22	24,92%		46,19%	Much improvement	0.001**
PANSS Total 4th week	68,30 ± 9,53		41,78%				74,17 ± 9,36		28,93%			
PANSS Total 8th week	52,30 ± 7,59						61,39 ± 8,71					
Positive Symptoms baseline week	27,48 ± 4,20	30,36%		51,80%		0.001*	23,43 ± 4,81	11,90%		26,45%		0.001**
Positive Symptoms 4th week	21,26 ± 2,94		30,79%				21,48 ± 4,45		16,51%			
Positive Symptoms 8th week	16,87 ± 2,18						19,09 ± 4,37					
Negative Symptoms baseline week	17,83 ± 2,44	35,34%		64,25%		0.001**	17,57 ± 2,06	16,04%		36,62%		0.001*
Negative Symptoms 4th week	14,00 ± 2,04		44,72%				15,87 ± 1,71		24,50%			
Negative Symptoms 8th week	10,87 ± 1,66						13,70 ±1,79					
General Psychopathology baseline	45,52 ± 4,47	41,08%		71,13%		0.001**	47,39 ± 4,13	35,04%		59,83%		0.001**
General Psychopathology 4th Week	33,39 ± 6,40		51%				36,39 ± 6,18		38,16%			
General Psychopathology 8th Week	24,52 ± 5,53						28,61 ± 7,65					

Mean ± SD, PANSS (Positive and Negative Syndrome Scale), *Uji Repeated Anova, ** Uji Friedman

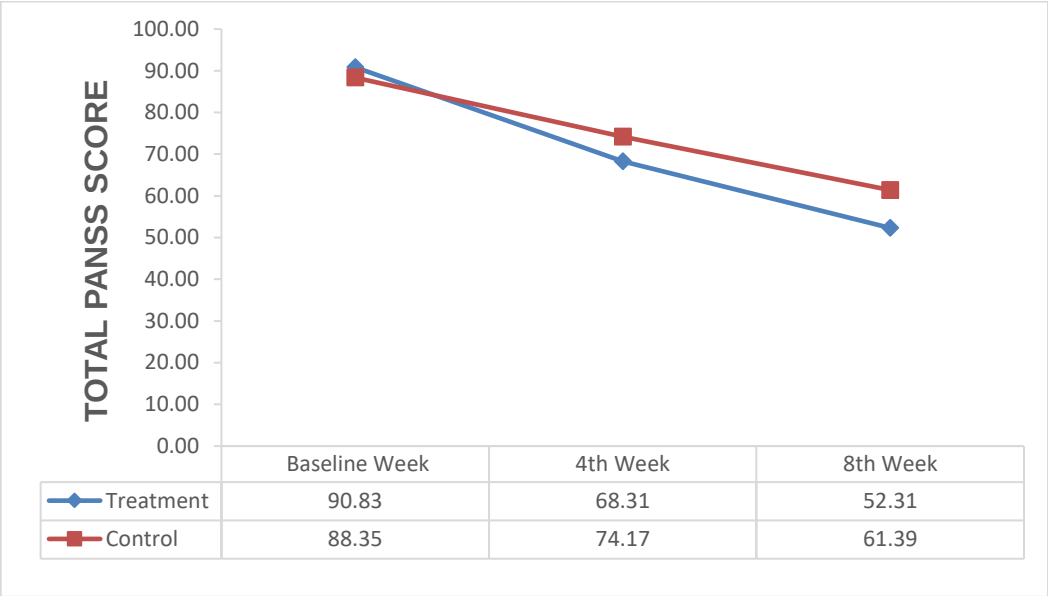

Figure 1. Comparison of Total PANSS Reduction in the Treatment Group and the Control Group

There was a decrease in the total PANSS score, which illustrates the improvement of clinical symptoms in the treatment group after receiving therapeutic doses of antipsychotics and folic acid and methylcobalamin adjuvant therapy, as well as in the control group that received therapeutic doses of antipsychotics. However, the decrease in PANSS total score in the treatment group after receiving risperidone antipsychotic and folic acid and methylcobalamin adjuvant therapy was greatly improved compared to the group that did not receive folic acid and methylcobalamin tablets.

Table 6. Comparison of the increase in serum BDNF in the treatment group and the control group

Variabel	Group			
	Treatment (n=23)	P	Control (n=23)	p
BDNF baseline week	1,20 ± 0,63	0.001*	1,04 ± 0,42	0.412*
BDNF 8th week	1,81 ± 0,93		1,05 ± 0,43	

Mean ± SD
*Uji Wilcoxon

Based on Table 6, it was found that there was an increase in baseline BDNF levels in the treatment group from 1.20 ng/ml to 1.81 ng/ml after 8 weeks, with a difference of 0.61 ng/ml. The p value for changes in plasma BDNF levels in the treatment group was $p < 0.001$ ($p<0.05$), so it can be concluded that statistically there was a significant increase in serum BDNF levels at week 8 or after administration of antipsychotic doses of therapy and adjuvant therapy of folic acid and methylcobalamin. While the control group had a baseline BDNF of 1.04 ng/ml to 1.05 ng/ml after 8 weeks with a difference of 0.01 ng/ml, the p value for changes in plasma BDNF levels in the control group was 0.412 ($p > 0.05$), so it was concluded that statistically there was no significant increase in serum BDNF levels at week 8 in the group that did not receive folic acid and methylcobalamin adjuvant therapy.

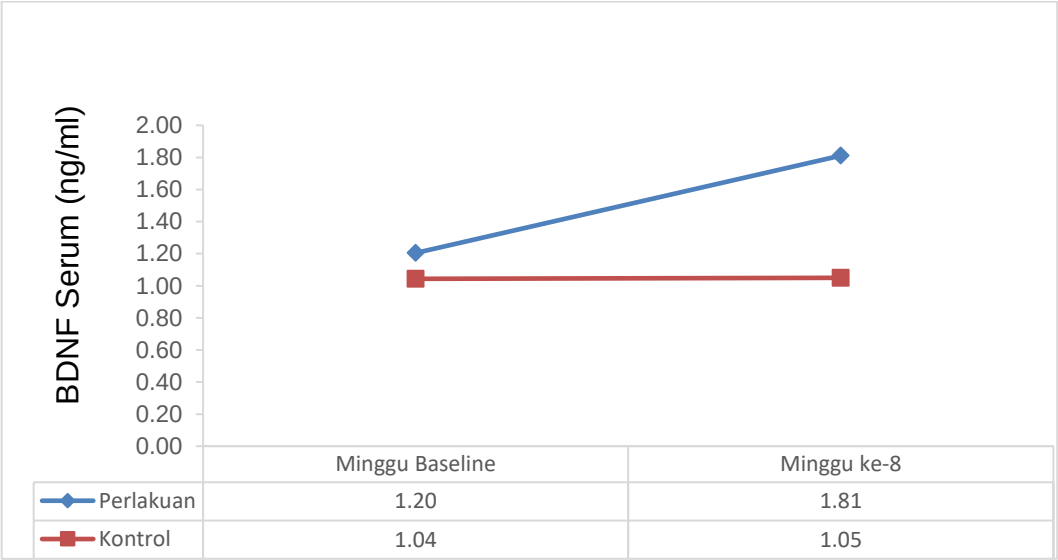

Figure 2. Comparison of the increase in blood serum BDNF in the treatment group and the control group

Table 7. Relationship between Serum BDNF Levels and Total PANSS Values, Domains of Positive Symptoms, Negative Symptoms, and General Psychopathology in the Treatment Group and the Control Group

		BDNF	
		r	**p**
Treatment	PANSS Total	-0,262	0.078
	Positive Symptoms	-0,301	0.042
	Negative Symptoms	-0,260	0.081
	General Psychopathology	-0,262	0.079
Control	PANSS Total	0,025	0.870
	Positive Symptoms	0,010	0.947
	Negative Symptoms	-0,042	0.781
	General Psychopathology	-0,001	0.995

*Spearman Correlation Test

4. Discussion

The total PANSS score based on the treatment group and control group showed a significant difference ($p<0.05$) at weeks 4 and 8 in this study. The treatment group with risperidone antipsychotic therapy with folic acid and methylcobalamin adjuvant showed improvement in clinical symptoms by 63.33 percent, with the interpretation of clinical symptoms showing very much improvement, compared to the control group with improvement in clinical symptoms by 46.19 percent, with the interpretation of clinical symptoms showing much improvement.

In this study, not only negative symptoms but also positive symptoms and general psychopathology improved. This was also influenced by the atypical antipsychotics used by the subjects. The addition of folic acid and methylcobalamin greatly improved clinical symptoms in total PANSS. The same results were also reported in the study of Betty H. et al. (2017), who provided additional folic acid and methylcobalamin therapy in accordance with the research of Levine et al. in 2006. Folic acid therapy is actually more associated with improvements in negative symptoms. In an RCT (randomized controlled trial) study by Roffman et al. (2013), 140 schizophrenia patients received additional therapy of 2 mg folic acid and 400 mcg methylcobalamin. Based on the literature, the response rate of individuals with schizophrenia disorders to clinical symptom improvement after being given folic acid and methylcobalamin is influenced by genetic variations that affect absorption. The MTHFR-677C>T and FOLHI-484T genes have been associated with negative symptom improvement

(Roffman, 2013). Improvement in negative symptoms was also associated with increased folic acid levels after folic acid and methylcobalamin supplementation therapy. Folic acid is essential for brain function and plays an important role in mental and emotional health. Folic acid also works together with methylcobalamin to help make red blood cells and help iron work properly in the body. Folic acid deficiency is closely associated with the clinical symptoms of schizophrenia. The literature shows that there are various theories that suggest this, including the following: One piece of literature describes how the role of GCPII (Glutamic Carbonpeptidase II) regulates folate uptake and the activation of N-Methyl-D-Aspartic acid receptors. Low GCPII activity in the brain causes hypoactivity of N-Methyl-D-Aspartic Acid (NMDA) receptors. GCPII then converts the NMDA antagonist N-acetyl-aspartyl glutamate into N-acetyl aspartate and glutamate. Thus, there is activation of glutamate neurons that innervate specific dopamine neurons, which then results in hyperactivity of dopamine neurons in the mesolimbic and can also cause hypoactivity of mesocortical dopamine neurons. If both occur, it can be associated with positive and negative symptoms of schizophrenia. GCPII is also found in the epithelial brush border of the intestinal membrane, where it cleaves the glutamate portion of dietary folyl-polyglutamate to facilitate folate absorption. This dual role for GCPII suggests that hypofolateemia and clinical symptoms of NMDA hypofunction may reflect low GCPII activity (Kennedy DO, 2016, Kirsch et al., 2013, Goff DC, 2004 & Stahl's, 2013).

In this study, there were 46 research subjects who received Risperidone both in the treatment group and the control group and measured serum BDNF levels at baseline and at the end of week 8. From the results of the study, it was found that there was an increase in BDNF levels to the baseline week in the treatment group from 1.20 ng/ml to 1.81 ng/ml after 8 weeks, with a difference of 0.61 ng/ml. The p value in the change in BDNF serum levels in the treatment group was 0.000 ($p < 0.05$), so it can be concluded that there was a statistically significant increase in serum BDNF levels at week 8 or after administering therapeutic doses of antipsychotics and adjuvant therapy of folic acid and methylcobalamin. While the control group's baseline BDNF went from 1.04 ng/ml to 1.05 ng/ml after 8 weeks with a difference of 0.01 ng/ml, the p value on changes in BDNF serum levels in the control group was 0.412 ($p > 0.05$), so it can be concluded that statistically there was no significant increase in serum BDNF levels at week 8 in the group that did not received folic acid and methylcobalamin adjuvant therapy.

In previous studies, folic acid and methylcobalamin have been implicated in the maintenance of a balance between neurotrophic and neurotoxic factors in the central nervous system. Neurotrophins are growth factors that affect the proliferation, differentiation, survival, and death of neural and non-neural cells. A series of animal studies have shown decreased levels of neurotrophins such as NGF (Nerve Growth Factor) and BDNF in the brain as a consequence of vitamin deficiency. Decreased neurotrophin levels may be associated with increased oxidative stress and decreased DHA levels. Decreased levels of BDNF have been widely implicated in the pathophysiology of various psychiatric disorders, such as schizophrenia. Studies have also reported lower levels of BDNF in schizophrenia patients, which have been associated with cognitive impairment. It has been suggested that high expression of neurotrophins in the brain may act as neuroprotection against neurological diseases. Experimental evidence suggests that folic acid and methylcobalamin act as neuroprotective agents against neurological disorders through the BDNF signaling pathway. A recently reported study has shown that combined supplementation of both methylcobalamin and omega-3 fatty acids increased BDNF levels in the cortex and hippocampus regions of the brain. So, based on all of the above facts, changes in neurotrophins and signaling pathways could be one of the possible mechanisms by which BDNF levels are increased (Sable et al., 2012, Rathod et al., 2016)

5. Conclusion

1. There was a decrease in PANSS both in the treatment group and in the control group after receiving a significant therapeutic dose of antipsychotic risperidone. Improvement of clinical symptoms in schizophrenia patients who received adjuvant therapy of folic acid and methylcobalamin showed very much improvement compared to schizophrenia patients who only received risperidone

antipsychotics.
2. There was an increase in BDNF levels in the treatment group and control group at the end of week 8. The increase in BDNF levels in the treatment group was higher than in the control group.
3. Improvement of clinical symptoms with positive symptom domains in schizophrenia patients who received adjuvant therapy of folic acid and methylcobalamin had a significant relationship with an increase in BDNF levels compared to schizophrenia patients who only received risperidone antipsychotics.

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Conflict of Interest
None

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