Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i18.2769

# THE EFFECT OF ADJUVANT THERAPY OF FOLIC ACID AND METHYLCOBALAMINE ON HOMOCYSTEINE LEVELS AND COGNITIVE FUNCTION IN SCHIZOPHRENIA PATIENTS

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## ABSTRACT

**Background:** Cognitive dysfunction in schizophrenic patients has a very high prevalence. Antipsychotic drugs as the main treatment for patients with schizophrenia, provide a symptom response that is not always optimal. Adjunctive treatment with certain vitamins and minerals may be beneficial for people with psychiatric disorders due to a biological mechanism by which these nutrients may improve the cognitive symptoms of schizophrenia. Providing Folic Acid and Methylcobalamin required for homocysteine methylation to methionine and SAM synthesis (S-adenosylmethionine) causes a decrease in homocysteine levels and repairs cell damage and neuronal injury in the brain and improves psychiatric disorders, such as cognitive disorders.

**Objectives:** Determine the effect of folic acid adjuvant therapy and methylcobalamin on the homocysteine levels and cognitive function of schizophrenic patients receiving risperidone therapy

**Methods:** The experimental analysis research design by measuring pre- and post-tests with non-random group selection was carried out in January-March 2023 at Dadi RSKD South Sulawesi Province. The number of subjects was 48 according to the inclusion and exclusion criteria. Subjects were divided into 4 groups, namely the control group, folic acid, methylcobalamin, and folic acid plus methylcobalamin. To assess cognitive function, MoCA-Ina was used and homocysteine levels were measured Enzyme-Linked Immunosorbent Assay (ELISA). The Wilcoxon, Mann Whitney and Spearman correlation tests were carried out to see the significance.

**Result:** Value change of Montreal Cognitive Assessment-Indonesian version (MoCA-Ina) of schizophrenic patients receiving adjuvant therapy plus folic acid + methylcobalamin compared to groups methylcobalamin showed significant results on 4-8 week ($p<0.05$). Rate change of Homocysteine schizophrenic patients who received adjuvant therapy with folic acid plus

methylcobalamin and the methylcobalamin group were more significant than the control group baseline up to 8 weeks ($p<0,05$)

**Conclusion:** Adjuvant therapy with methylcobalamin and folic acid + methylcobalamin is better at improving cognitive function. Administration of adjuvant therapy with methylcobalamin correlated strongly with improving cognitive function and reducing homocysteine levels, whereas adjuvant therapy with folic acid plus methylcobalamin correlated moderately with increasing cognitive function and reducing homocysteine levels.

**Keywords:** Schizophrenia, Risperidone, MoCA-Ina, Folic Acid, Methylcobalamin, Homocysteine, Cognitive

## INTRODUCTION

Schizophrenia is a severe mental disorder associated with deterioration in daily life and social functioning (American Psychiatric Association, 2013). The global prevalence of schizophrenia is approximately 1% of the population. The psychopathology of schizophrenia can be classified into five domains: positive symptoms, negative symptoms, cognitive symptoms, aggressive symptoms, and affective symptoms (Amir, 2017). Cognitive dysfunction in schizophrenia patients has a very high prevalence, with an estimated 98% of schizophrenia patients showing impaired cognitive function. This impairment is typically identifiable at the early stages of the illness, before receiving antipsychotic therapy, and tends to persist throughout the course of schizophrenia (Bhattacharya, 2015). Cognitive dysfunction in schizophrenia may also be caused by abnormalities in the anatomy and function of neurons in the brain (Roffman, et al., 2013).

Antipsychotic medications, the main treatment for patients with schizophrenia, do not always provide optimal symptom relief, often come with side effects, and treatment adherence is often poor. Consequently, a significant amount of research is being conducted to identify new drugs from different classes that may be effective in treating schizophrenia (Ballon & Stroup, 2013; Priebe, et al., 2016). In a study conducted by Li et al. in 2015, Olanzapine and risperidone were the two most commonly prescribed second-generation antipsychotics (SGA) in various countries. While first- and second-generation antipsychotic drugs are effective in reducing positive symptoms, they are mostly neutral in relation to the cognitive features of the disorder. An observational study of first-episode psychotic disorders showed no significant change in homocysteine (Hcy) levels during antipsychotic pharmacotherapy (Vuksan-Ćusa, et al., 2011). Additional treatment with specific vitamins and minerals can benefit individuals with mental disorders, possibly due to biological mechanisms through which these nutrients can improve clinical and cognitive symptoms of schizophrenia, as patients with schizophrenia are at risk of poor diet. Consequently, individuals with schizophrenia often have a spectrum of vitamin and mineral deficiencies, even before receiving antipsychotic treatment (Firth, et al., 2017).

Folic Acid (Vitamin B9) and Methylcobalamin (Vitamin B12) are required for homocysteine methylation into methionine and for the synthesis of SAM (S-adenosylmethionine). Folate deficiency specifically affects central monoamine metabolism and one-carbon metabolism, leading to increased homocysteine levels and cell damage and neuronal injury in the brain due to oxidative stress (Crespo & Gonzalez, 2017), exacerbating psychiatric disorders such as cognitive impairment (Hill, et al., 2011). Filipa Pedro dos Reis' 2021 retrospective cohort study revealed significantly lower serum folate levels ($p=0.01$) in children and young adults hospitalized for psychiatric disorders with psychotic symptoms compared to patients of the same age with acute mental illnesses without psychotic symptoms. Meta-analysis studies have shown a significant relationship between serum folate and the risk of schizophrenia, and decreased serum folate levels are associated with schizophrenia risk factors ($p=0.001$) (Wang, et al., 2016).

Homocysteine (Hcy) is an amino acid that participates in the methionine cycle, affecting brain development through various cellular pathways. Elevated blood homocysteine levels have been

associated with several psychiatric and neurodegenerative disorders, including depression, schizophrenia, Alzheimer's disease, and Parkinson's disease, which are related to folate and vitamin B12 deficiencies (Stahl, 2013).

Chen et al. (2019) assessed the relationship between Hcy levels and cognitive deficits in schizophrenia patients across all age groups, showing a significant relationship between higher Hcy concentrations and worse cognitive performance in schizophrenia patients. There were significant differences in cognitive test scores for five MCCB indices between schizophrenia patients and healthy controls ($p<0.05$). A study conducted by Tomioka et al. (2020) compared two groups and examined folate and homocysteine levels. Serum folate concentration was higher in women than in men. Lower serum folate levels were observed in male and female patients with schizophrenia ($p<0.001$).

However, a study conducted by Adam Wysokiÿski, (2017) contradicted previous findings, not finding differences in folate or homocysteine levels between schizophrenia patients and patients who have recovered. Hyperhomocysteinemia may be more closely associated with obesity or other metabolic disorders than with schizophrenia itself. Limitations of the study included a small sample size and lack of behavioral data (such as dietary intake records). Given the significant impact of folic acid and methylcobalamin, as well as homocysteine, on cognitive function, and the absence of research on the effectiveness of adjunct therapy with Folic Acid and Methylcobalamin on Homocysteine levels and cognitive function in schizophrenia patients receiving risperidone therapy, the researchers are interested in examining the effects of adjunct therapy with Folic Acid and Methylcobalamin on Homocysteine levels and cognitive function in schizophrenia patients at the South Sulawesi Provincial Special Hospital. The general objective of this study is to test the effects of adjunct therapy with Folic Acid and Methylcobalamin on Homocysteine levels and cognitive function in schizophrenia patients receiving risperidone therapy.

## RESEARCH METHODS

This research is an experimental analysis study, measuring pre-test and post-test with non-randomized group selection, where variable measurements are taken before and after the intervention. The research is planned to be conducted from January 2023 to March 2023. This study is intended to take place at the South Sulawesi Provincial Special Hospital, Dadi.

The population in this study comprises all schizophrenia patients being treated at the South Sulawesi Provincial Special Hospital, Dadi. The sample for this research includes all stable phase schizophrenia patients being treated at the South Sulawesi Provincial Special Hospital, Dadi, who meet the inclusion and exclusion criteria. The sampling is done using consecutive sampling. The sample size is determined using the formula*:*

$$n1=n2 = Y\left[2\left(\frac{(Z\alpha+Z\beta)S}{(x1-x2)}\right)^2\right]$$

$$= 0{,}411\left[2\left(\frac{(1.64+0.84)15}{10}\right)^2\right]$$

$$= 11,\ 37 = 11$$

n1=n2 : Number of samples
Zα : Type 1 error
Zβ : Type 2 error
Y : Correction factor Due to repeated measurements
S : Standard intersection
X1-X2: The difference that is considered meaningful

According to Sastoasmoro & Ismael (2010) stated that to anticipate respondents who are likely to decrease, the following formula is used:

$$n' = \frac{n}{1-f}$$

$$= \frac{11}{1-0{,}1}$$

= 12,2 = 12

Description of the formula above:
n' = Number of samples after revision
n = Original sample count
1 – f = Estimated proportion of drop outs, which is estimated at 10 % (f = 0.1)
Based on the calculation above, the minimum sample size for each group is 11, plus 10% of the sample for the risk of dropping out during the study.
The sampling technique for each group was carried out by means of Consecutive Sampling, namely all patients who met the Selection Criteria. Inclusion criteria included patients diagnosed with schizophrenia according to ICD-10, patients aged 20-45 years, patients with disease onset <3 years, PANSS score 60-80, willing to participate in the study, last education at least junior high school, receiving risperidone therapy 4-6 mg/day, have blood pressure <120/80. Whereas the exclusion criteria were having organic comorbidities (Organic Mental Disorders), having a history of consuming drugs <1 year, not being willing to participate in the study, and using anti-inflammatory drugs and antibiotics. Criteria for Drop Out were irregular consumption of risperidone, adjuvant folic acid and methylcobalamin, research subjects refused to continue the study, and research subjects died. Data processing was carried out after recording the research instruments using the program.

## RESULTS

Data on the characteristics of research subjects obtained from medical records were analyzed descriptively using Chi Square which can be seen in Table 1.

**Table 1** Sociodemographic Characteristics of Research Subjects

| Characteristics | | | Group | | | | Amount | Mark p |
|---|---|---|---|---|---|---|---|---|
| | | | Folic Acid + Methylcobalamin | Folic acid | Methylcobalamin | Control | | |
| Work | Work | n | 8 | 9 | 8 | 7 | 32 | 0.861 |
| | | % | 66.7% | 75.0% | 66.7% | 58.3% | 66.7% | |
| | Doesn't work | n | 4 | 3 | 4 | 5 | 16 | |
| | | % | 33.3% | 25.0% | 33.3% | 41.7% | 33.3% | |
| Education | Junior high school | n | 6 | 7 | 7 | 7 | 27 | 0.97 |
| | | % | 50.0% | 58.3% | 58.3% | 58.3% | 56.3% | |
| | Senior high school | n | 5 | 4 | 4 | 5 | 18 | |
| | | % | 41.7% | 33.3% | 33.3% | 41.7% | 37.5% | |
| | PT | n | 1 | 1 | 1 | 0 | 3 | |
| | | % | 8.3% | 8.3% | 8.3% | 0.0% | 6.3% | |
| Sick Period | < 1 year | n | 2 | 1 | 1 | 2 | 6 | 0.375 |
| | | % | 16.7% | 8.3% | 8.3% | 16.7% | 12.5% | |
| | 1 year | n | 5 | 2 | 1 | 1 | 9 | |
| | | % | 41.7% | 16.7% | 8.3% | 8.3% | 18.8% | |
| | 2 years | n | 3 | 3 | 5 | 2 | 13 | |
| | | % | 25.0% | 25.0% | 41.7% | 16.7% | 27.1% | |
| | 3 years | n | 2 | 6 | 5 | 7 | 20 | |
| | | % | 16.7% | 50.0% | 41.7% | 58.3% | 41.7% | |
| Marital Status | Not married yet | n | 6 | 4 | 5 | 5 | 20 | 0.922 |
| | | % | 50.0% | 33.3% | 41.7% | 41.7% | 41.7% | |
| | Marry | n | 4 | 7 | 5 | 6 | 22 | |
| | | % | 33.3% | 58.3% | 41.7% | 50.0% | 45.8% | |
| | Divorced | n | 2 | 1 | 2 | 1 | 6 | |
| | | % | 16.7% | 8.3% | 16.7% | 8.3% | 12.5% | |
| Amount | | n | 12 | 12 | 12 | 12 | 48 | |
| | | % | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | |

The basic characteristics of the research subjects including occupation, education, length of illness, marital status found no significant differences between the treatment and control groups (p>0.05). Thus, the research subjects are homogeneous. Changes in the value of the MoCA-Ina scale in each group were carried out using the Wilcoxon (scores not normally distributed) and the T-test paired test (scores normally distributed) with the following results:

**Table 2**. Changes in the control group's MoCA-Ina scale score

| Moca-Ina (Control) | N (n=12) | Median (Minimum-maximum) | *p* |
|---|---|---|---|
| Week 0<br>Week 4 | n=12<br>n= 12 | 18,83 (17-20)<br>20,33 (19-22) | 0.002 |
| Week 4<br>Week 8 | n=12<br>n= 12 | 20,33 (19-22)<br>22,16 (19-24) | 0.007 |
| Week 0<br>Week 8 | n=12<br>n= 12 | 18,83 (17-20)<br>22,16 (19-24) | 0.002 |

Wilcoxon test (p<0.05)

In Table 2, the p values for changes in the MoCA-Ina score weeks 0-4, weeks 4-8, and weeks 0-8 were 0.002, 0.007 and 0.002 or p <0.05 so it can be concluded that there was an increase in the MoCA-Ina score which statistically significant in the control group at 4 and 8 weeks.

**Table 3**. Changes in the MoCA-Ina scale scores of the Folic Acid Treatment Group

| Moca-Ina (Folic acid) | N (n=12) | Means (Sb) | *Difference (Sb)* | *p* |
|---|---|---|---|---|
| Week 0<br>Week 4 | n=12<br>n= 12 | 19.33 (1.30)<br>20.50 (1.31) | 1.16<br>(0.39) | < 0.001 |
| Week 4<br>Week 8 | n=12<br>n= 12 | 20.50 (1.31)<br>22.41 (1.62) | 1.91<br>(1.67) | 0.002 |
| Week 0<br>Week 8 | n=12<br>n= 12 | 19.33 (1.30)<br>22.41 (1.62) | 3.08<br>(150) | < 0.001 |

*Paired sampel test (p<0.05)*

In Table 3, the p values for changes in MoCA-Ina scores weeks 0-4, weeks 4-8, and weeks 0-8 were 0.000, 0.002, 0.002 or p <0.05 so it can be concluded that there was an increase in the MoCA-Ina score which statistically significant in the Folic Acid treatment group at 4 and 8 weeks.

**Table 4.** Changes in MoCA-Ina scale scores for the Methylcobalamin treatment group

| Moca-Ina (Methylcobalamin) | N (n=12) | Mean (Sb) | *Difference (Sb)* | *p* |
|---|---|---|---|---|
| Week 0<br>Week 4 | n=12<br>n= 12 | 18.58 (1.24)<br>19.91 (1.56) | 1.33<br>(0.78) | <<br>0.001 |
| Week 4<br>Week 8 | n=12<br>n= 12 | 19.91 (1.56)<br>22.66 (1.82) | 2.75<br>(1.81) | <<br>0.001 |
| Week 0<br>Week 8 | n=12<br>n= 12 | 18.58 (1.24)<br>22.66 (1.82) | 4.08<br>(2.02) | <<br>0.001 |

Paired sample test (p<0.05)

In Table 4, the p value for changes in MoCA-Ina scores weeks 0-4, weeks 4-8, and weeks 0-8 was 0.000 or p <0.05 so it can be concluded that there was a statistically significant increase in MoCA-Ina scores in Folic Acid treatment group at 4 and 8 weeks.

**Table 5.** Changes in MoCA-Ina scale scores for the Folic Acid + Methylcobalamin Treatment Group

| Moca-Ina<br>(Folic Acid + Methylcobalamin ) | N<br>(n=12) | Median<br>(Minimum-Maximum) | *p* |
|---|---|---|---|
| Week 0<br>Week 4 | n=12<br>n= 12 | 18.5 (16 – 20)<br>21.16 (19-24) | 0.002 |
| Week 4<br>Week 8 | n=12<br>n= 12 | 21.16 (19-24)<br>22.58 (20-26) | 0.003 |
| Week 0<br>Week 8 | n=12<br>n= 12 | 19 (16 – 20)<br>22.58 (20-26) | 0.002 |

Wilcoxon test ($p<0.05$)

In Table 5, the p values for changes in the MoCA-Ina score weeks 0-4, weeks 4-8, and weeks 0-8 were 0.002, 0.003 and 0.002 or $p < 0.05$ so it can be concluded that there was an increase in the MoCA-Ina score which statistically significant in the Folic Acid + Methylcobalamin treatment group at 4 and 8 weeks. The median value of the Moca-Ina scale in the baseline week control group was 18.83, the median value of 4 weeks was 20.33, and 8 weeks was 22.16. for the folic acid + methylcobalamin treatment group, the median values for the baseline week were 18.5, 4 weeks 21.16 and 8 weeks 22.58. In the folic acid group, the median week baseline was 19.33, 4 weeks was 20.5 and 8 weeks was 22.41. In the methylcobalamin group, the median week baseline score was 18.58, 4 week score 19.91 and 8 week score 22.66. Graph values of changes in Moca-Ina scale values in each group can be seen in Figure 1.

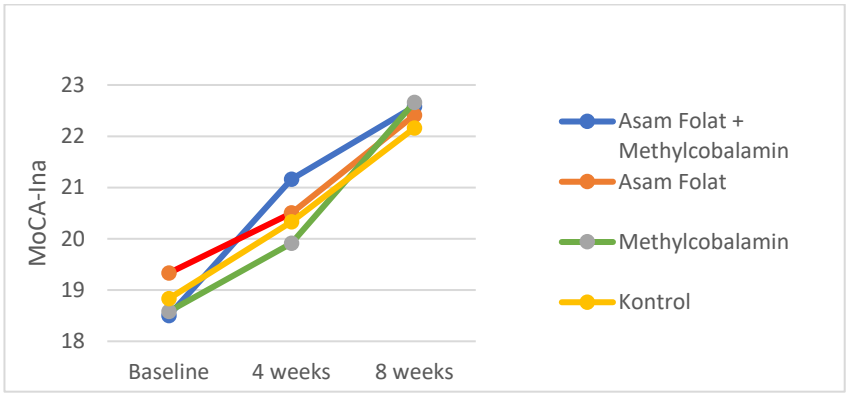


**Figure.1** MoCA-Ina Score change

To find out if there is a comparison of the average homocysteine values of the four paired sample groups which shows that there is an effect of giving treatment to the treatment group and the control group at baseline, and 8 weeks, a paired t test is performed if the data is normally distributed. If the data is not normally distributed, then the Wilcoxon test is performed. The following is a comparison of the average homocysteine values in research subjects which can be seen in Table.

**Table 6.** Changes in serum homocysteine levels for the control group

| Homocysteine<br>(Control) | N<br>(n=12) | Means<br>(Sb) | *Difference (Sb)* | *p* |
|---|---|---|---|---|
| baseline week<br>8 weeks | n=12<br>n= 12 | 29.00 (11.64)<br>26.27 (16.87) | 2.73<br>(10.53) | 0.388 |

Paired sample test ($p<0.05$)

In Table 6, the p-value for changes in hcy levels at baseline and 8 weeks was 0.388 ($p>0.05$) so it can be concluded that there was a decrease in hcy levels that was not statistically significant in the control group at 8 weeks.

**Table 7.** Changes in serum homocysteine levels in the Folic Acid Treatment Group

| Homocysteine (Folic acid) | N (n=12) | Means (Sb) | *Difference (SD)* | *p* |
|---|---|---|---|---|
| Week 0<br>Week 8 | n=12<br>n= 12 | 25.81 (13.25)<br>23.48 (14.55) | 2.32<br>(7.99) | 0.335 |

Paired sample test (p<0.05)

In Table 7, the p value for changes in hcy levels at baseline and 8 weeks was 0.335 (p>0.05) so it can be concluded that there was a decrease in hcy levels that were not statistically significant in the Folic Acid treatment group at 8 weeks.

**Table 8.** Changes in serum homocysteine levels in the Methylcobalamin Treatment Group

| Homocysteine (Methyl cobalamin) | N (n=12) | Mean (Sb) | *Difference (Sb)* | *p* |
|---|---|---|---|---|
| baseline week<br>8 weeks | n=12<br>n= 12 | 26.43 (15.36)<br>23.42 (16.45) | 3.00<br>(12.34) | 0.036 |

Paired sample test (p<0.05)

In Table 8, the p value for changes in hcy levels at baseline and 8 weeks was 0.036 (p <0.05) so it can be concluded that there was a statistically significant decrease in hay levels in the Methyl cobalamin treatment group at 8 weeks.

**Table 9.** Changes in serum homocysteine levels in the Folic Acid + Methylcobalamin Treatment Group

| Homocysteine (Asam Float + Methyl cobalamin) | N (n=12) | Mean (Sb) | *difference (Sb)* | *p* |
|---|---|---|---|---|
| Week 0<br>Week 8 | n=12<br>n= 12 | 28.01 (7.81)<br>18.55 (11.5) | 9.46<br>(10.37) | 0.009 |

*Paired difference test (p<0.05)

In Table 9, the p value for changes in hcy levels at baseline and 8 weeks was 0.009 (p <0.05) so it can be concluded that there was a statistically significant decrease in hcy levels in the Folic Acid + Methylcobalamin treatment group at 8 weeks. The mean value of hcy levels in the control group at baseline was 29 weeks, the mean at 8 weeks was 26.27. For the folic acid + methylcobalamin treatment group, the mean week baseline was 28.01 and 8 weeks was 18.55. In the folic acid group, the mean week baseline was 25.81 and 8 weeks was 23.48. In the methylcobalamin group, the baseline week's mean was 26.43, 8 weeks' mean was 23.42. Graph values of changes in serum hcy levels in each group can be seen in Figure 2.

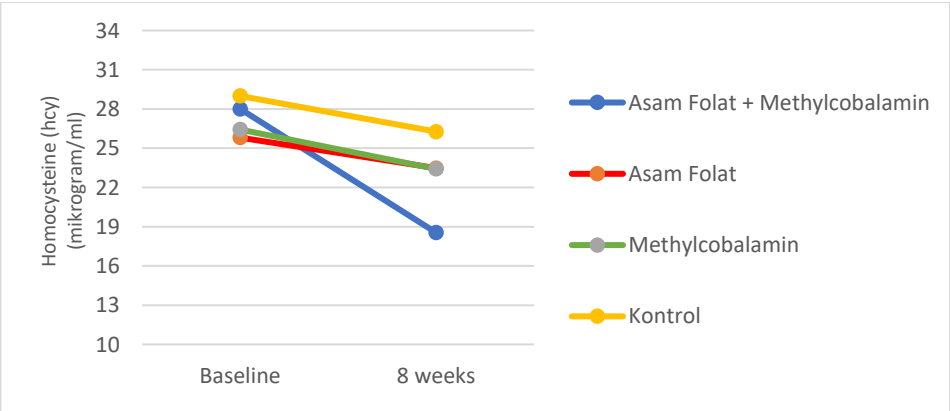


**Figure 2.** Changes in Serum Homocysteine Levels

To find out that there is a comparison of the average difference in MoCA-ina scale scores which shows the effect of adjuvant therapy in the treatment group and the control group at baseline, 4 weeks and 8 weeks, the Mann Whitney test was performed.

**Table 10.** Comparison of the average difference in MoCA-Ina scale scores in the treatment group and the control group

| | | Folic acid | Methyl cobalamin | Control |
|---|---|---|---|---|
| MoCA-Ina 0-4 Weeks | Folic Acid + Methyl cobalamin | 0.053* | 0.164* | 0.341* |
| | Folic acid | | 0.563* | 0.167* |
| | Methyl cobalamin | | | 0.556* |
| MoCA-Ina 4-8 Weeks | Folic Acid + Methyl cobalamin | 0.438* | 0.045* | 0.388* |
| | Folic acid | | 0.253* | 0.976* |
| | Methyl cobalamin | | | 0.207* |
| MoCA-Ina 0-8 Weeks | Folic Acid + ethyl cobalamin | 0.475* | 0.725* | 0.699* |
| | Folic acid | | 0.178* | 0.678* |
| | Methyl cobalamin | | | 0.290* |

**Mann Whitney test(p<0.05)*

In Table 10 there is a significant difference in the MoCA-Ina score at 4-8 weeks between the folic acid + methylcobalamin group and the methylcobalamin group with a p value of 0.045 (p <0.05).

**Table 11.** Comparison of the average difference in homocysteine levels in the treatment group and the control group

| | | Folic acid | Methyl cobalamin | Control |
|---|---|---|---|---|
| Chy 0-8 weeks | Folic Acid + Methyl cobalamin | 0.773* | 0.356* | 0.045* |
| | Folic acid | | 0.312* | 0.686* |
| | Methyl cobalamin | | | 0.033* |

* Mann Whitney test(p<0.05)

In Table 11 there is a significant difference in homocysteine levels after 8 weeks of therapy between the folic acid + methylcobalamin group and the control group with a p value of 0.045 (p <0.05), and there is also a significant difference in homocysteine levels between the methylcobalamin group and the control group with p 0.033 (p<0.05)

To see the correlation of the mean difference between MoCA-Ina and Homocysteine in the research subjects, the Spearman test was performed for abnormal data distribution and the Pearson test for normal data distribution. The results of the data correlation analysis are presented in Table 12 as follows:

**Table 12.** MoCA-Ina Correlation and Serum Homocysteine Levels

| Mocha Ina And Chy | Folic acid + Methyl cobalamin | | Folic acid | | Methylcarbylamine | | Control | |
|---|---|---|---|---|---|---|---|---|
| | p value | r value | p value | r value | p value | r value | p value | r value |
| Difference 0-8 Weeks (Delta) | 0.022* | -0,524 | 0,965** | 0.014 | 0.011** | -0,700 | 0,263** | 0,352** |

*Spearman test (significant, p <0.05)

**Pearson's test

r = correlation strength; 0.1 - 0.3 weak; 0.4 - 0.6 medium; 0.7 - 0.9 strong

The results of the correlation analysis using the Spearman correlation test showed that the correlation between the difference in mean MoCA-Ina values and Hcy levels in the folic acid + methylcobalamin group showed a significant relationship (p<0.05) with the strength of the relationship being towards negative. The correlation between the difference in mean MoCA-Ina values and Hcy levels in the

methylcobalamin group showed a significant relationship ($p<0.05$) with a strong negative relationship. The correlation between the difference in mean MoCA Ina values and Hcy levels in the folic acid and control groups showed no significant relationship ($p>0.05$).

## DISCUSSION

In this study, the significant decrease in hcy values was only in the methylcobalamin group and the folic acid plus methylcobalamin group. In the folic acid plus methylcobalamin group there was a significant decrease due to methylcobalamin(B12) functions directly in the cell, where it is responsible for reactivation of folic acid. Without methylcobalamin, folic acid is present in a form that the body cannot use and therefore cannot develop its full effects. The consequences can be anemia, nerve damage, and genetic errors in cell division. Methylcobalamin can be used directly by the body and does not need to be converted first, it has clear advantages over its synthetic form. In one reaction, the methylcobalamin acts together in three ways to reactivate folic acid, Make harmless the harmful substance homocysteine, Producing SAM precursors. The resulting methionine is the precursor S-adenosylmethionine (SAM). SAM is the most important methyl group donor in the human body and provides methyl groups for more than 100 methylation reactions. SAM thus plays an important role in detoxification, regulation of enzymes and genes, neuroprotection, and synthesis of neurotransmitters. SAM deficiency leads to underproduction of the neurotransmitters acetylcholine, dopamine, serotonin, and adrenaline/epinephrine and a general disturbance of the biochemical balance in the brain. A significant increase in homocysteine levels can result in a decrease in antioxidants and an increase in oxidative stress, resulting in cell damage resulting in cognitive symptoms, namely poor concentration, impaired*working memory* and neurological disorders.Reduction of total Hcy with folic acid adjuvant therapy has shown inconsistent results for cognitive function and reduced systemic inflammation.

This is in line with research conducted by Bryan J et al (2002) who conducted a randomized double-blind and placebo-controlled experimental study that there was an increase in the mean value of MoCA-Ina in both the control and treatment groups with risperidone administration, which means that there was a change in cognitive function of research subjects. In the folic acid and control groups there were no significant changes in hcy values which could be caused by the duration of the study subject's illness. Disease onset in the folic acid group, which was at most 50% of research subjects with a 3-year illness duration, and methylcobalamin also affects cognitive function, especially through its role as a cofactor in the formation and maintenance of the central nervous system through two mechanistic processes. First, it is called a hypothesis *hypomethyllation* that vitamin B deficiency directly affects the inhibition of the provision of methyl which is needed in the reactions of components of the central nervous system such as proteins, phospholipids, DNA; metabolism of neurotransmitters such as monoamines (depamin, norepinephrine, and serotonin), which play an important role in neurological and psychological status. Second, the homocysteine hypothesis, that methylcobalamin indirectly and may in a long time affect the brain through the cerebrovascular and function to maintain the integrity of the central nervous system through its role in preventing vascular disease which is very important in cognitive function.

Correlation statistical test between MoCA-Ina scale values and *homocysteine* levels serum in the 8-week treatment and control groups showed a significant relationship in the treatment group that received adjuvant therapy with methylcobalamin and the folic acid plus methylcobalamin group, while in the folic acid and control groups there was no significant relationship. This is in line with the study of Lewerin C et al (2005) in the elderly group in Sweden, showing that plasma homocysteine levels and serum*Methyl Malonic Acid* (MMA) is inversely correlated with cognitive abilities. Giving Methylcobalamin orally can normalize plasma homocysteine levels and serum MMA (Timothy K, 2016). Hcy can also be influenced by stress, genetics, as well as consumption of caffeine and cigarettes and in this study, these factors were not tested, so this is a limitation of this study. In the literature, it is stated that there is a relationship between folate levels and clinical symptoms found in schizophrenia and first episode psychosis. Administration of folic acid adjuvant therapy is more

associated with improvement of positive and negative symptoms of schizophrenia. One of the literature describes how the role of GCPII (*Glutamate Carbonpeptidase II*) regulates folate uptake and acid receptor activation*N-Methyl-D-Aspartate*. The presence of low GCPII activity in the brain causes receptor hypoactivity*N-Methyl-D-Aspartic Acid* (NMDAs). GCPII then converts the NMDA antagonist N-acetyl-aspartyl glutamate to 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 these two things occur, it can be associated with positive or negative symptoms of schizophrenia. Management of negative symptoms will affect the functional prognosis and cognitive function.

## CONCLUSION

Adjuvant therapy with methylcobalamin and folic acid + methylcobalamin is better at improving cognitive function. Administration of adjuvant therapy with methylcobalamin correlated strongly with improving cognitive function and reducing homocysteine levels, whereas adjuvant therapy with folic acid plus methylcobalamin correlated moderately with increasing cognitive function and reducing homocysteine levels. As a suggestion, for psychiatric specialist clinicians, the results of this study can be considered to provide methylcobalamin, as well as folic acid + methylcobalamin as adjuvants in standard therapy for schizophrenic patients using risperidone to improve cognitive function.

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