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The Effect of Folic Acid Adjuvant on Cognitive Function on Patients with Chronic Schizophrenia

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ABSTRACT

Background: Schizophrenia is a severe mental disorder that associated with daily life and social function deterioration and could be accompanied with cognitive deficits. Meanwhile, hyperhomocysteinemia (HHcy) is the increasing homocysteine (Hcy) level which might be the one of biological factor in schizophrenia. In recent study with healthy subjects, it was known that there was a correlation between total Hcy level and cognitive function. Folic acid is part of water-soluble vitamin B and expected to have important role in oxidative stress by preventing hyperhomocysteinemia
Objective:. This study aimed to elaborate the effect of folic acid adjuvant to improve cognitive function in chronic schizophrenia patients
Methods: This was a double-blinded randomized controlled trial with pre and post-test clinical trial design. This study included 32 patients in control group and 32 patients in treatment group. MOCA-INA score was examined in all subjects on the first day. Then, all subjects were given standard antipsychotic treatment plus folic acid adjuvant / placebo during 3 week of hospitalized treatment and 1 week of outpatient treatment. When the 4-week treatment finished, the subjects were followed by MOCA-INA post-test.
Results: In this study, we had the significant difference of pre and post-test MOCA-INA score in the control group ($p<0.001$), significant difference of pre and post-test MOCA-INA score in the treatment group ($p<0.001$), and significant difference of post-test MOCA-INA score between the control and treatment group ($p<0.001$)
Conclusion: Folic acid adjuvants significantly improved cognitive function in chronic schizophrenic patient

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1. Introduction

Schizophrenia is a severe mental disorder, which can reduce the quality of life that affects 1% of the world's population.1 Indonesian National Health Research in 2018 reported that the prevalence rate of schizophrenia was 0.6% to 1.9%.2 It is estimated that 98% of schizophrenic patients are found to have a deterioration in cognitive function, which is one of the core symptoms of schizophrenia.3 This might be due to anatomical and functional abnormalities of the neuron cells in the brain. Recent research suggests the cause of cognitive dysfunction is due to the abnormalities in neuroplasticity of neuron cells around the prefrontal cortex.4

Hyperhomocysteinemia (HHcy) is an increase of homocysteine (Hcy) level in the blood, which is widely linked with the occurrence of schizophrenia. Recent research shows a relation between total Hcy levels and cognitive function in healthy subjects. The relation of elevated Hcy levels with the psychopathology of schizophrenia provides a basis for adjunctive therapy with vitamin supplements.5 Folic acid is a vitamin that prevents oxidative stress through one-carbon (C1) metabolism.6 Folic acid deficiencies have been identified as a risk factor for schizophrenia, as blood folate level tends to fall in schizophrenic patients.7 The role of folic acid in oxidative stress is to prevent hyperhomocysteinemia and help increase reactive oxygen species (ROS).8

Hyperhomocysteinemia is one of the biological factors occurring in schizophrenia, which may result in cognitive dysfunction. Folic acid plays a role in oxidative stress by preventing the occurrence of hyperhomocysteinemia.3,11,12 Through this study, we aimed to find whether there was an effect of folic acid adjuvant administration on cognitive function as measured by MOCA-INA in chronic schizophrenic patients.

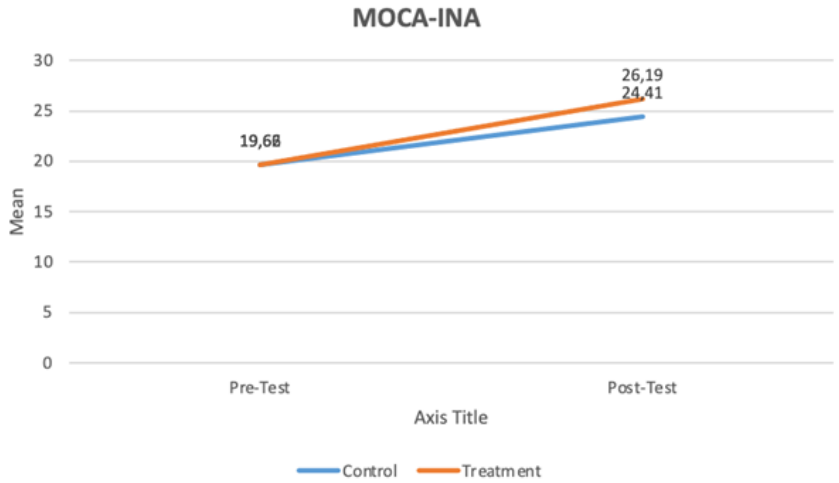

Figure 1. Changes in the MoCA-INA Score from the Pre Test and Post Test of the treatment and control group (n = 64).

Table 1. Demographic Characteristics Description of Research Subjects

Variable	Groups		Total	*p*
	Control	Treatment		
Gender				
Male	21 (65,6%)	23 (71,9%)	44 (68,8%)	0,590¥
Female	11 (34,4%)	9 (28,1%)	20 (31,3%)	
Age	34,41 ± 8,64	34,75 ± 8,45	34,58 ± 8,48	0,873§
Marital status				
Married	16 (50%)	10 (31,3%)	26 (40,6%)	0,240¥
Unmarried	13 (40,6%)	17 (53,1%)	30 (46,9%)	
Divorced	1 (3,1%)	0 (0%)	1 (1,6%)	
Widowed	2 (6,3%)	5 (15,6%)	7 (10,9%)	
Educational status				
Elementary school	2 (6,3%)	8 (25%)	10 (15,6%)	0,117¥
Junior high school	16 (50%)	9 (28,1%)	25 (39,1%) 26 (40,6%)	
High school	13 (40,6%)	13 (40,6%)	3 (4,7%)	
Bachelor degree	1 (3,1%)	2 (6,3%)		
Occupational status				
Employed	20 (62,5%)	17 (53,1%)	37 (57,8%)	0,448¥
Unemployed	12 (37,5%)	15 (46,9%)	27 (42,2%)	
Genetic history of mental disorder				
Present	4 (12,5%)	4 (12,5%)	8 (12,5%)	1,000¥
Absent	28 (87,5%)	28 (87,5%)	56 (87,5%)	

Note : § Independent t; ¥ Chi square

Table 2. Mean Differences of MOCA-INA Pre-test, Post-test, and Delta Score

Moca INA	Groups		p
	Control	Treatment	
Pre-test	19,62 ± 1,95	19,66 ± 2,78	0,819‡
Post-test	24,41 ± 2,42	26,19 ± 2,83	0,001‡*
p	< 0,001¶*	< 0,001¶*	
Delta	4,78 ± 2,34	6,53 ± 3,62	0,002‡*

*Note : * significant (p < 0,05); ‡Mann Whitney; ¶Wilcoxon*

2. Methods

This was a double-blinded randomized controlled trial with pre and post-test clinical trial design. The study was conducted on July 1st to August 30th, 2020. The ethical permission has been approval from the Health Research Ethics Committee of the Ethics Committee of the Faculty of Medicine, Diponegoro University. The study population was patient with chronic schizophrenia treated at Dr. Amino Gondohutomo Regional Psychiatric Hospital, aged 20 - 50 years old, who have been diagnosed as schizophrenia for at least 2 years7, receiving psychotropic medication with or without additional anti-cholinergic, with minimum degree of elementary school, and were given consent by the patient's family. Subjects with general medical disorder and / or other comorbid, history of substance and alcohol abuse known from history taking, and consumption of anti-epileptic drugs were excluded. Subjects were then categorized as drop out if they experience side effects of adjuvant administration or worsening clinical symptoms during treatment.

This study used consecutive sampling and randomization with 4 blocks randomization. Minimum sample size with a drop out correction of 10% as many as 33 subjects/group. The independent variable was folic acid, the dependent variable was social and personal function. Sociodemographic questionnaire and the Indonesian version of the Montreal Cognitive Assessment questionnaire (MoCA-Ina) were used as research instruments. MoCA assesses different cognitive domains: attention and concentration, executive functioning, memory, attention, language, abstraction, and orientation. A total score of 30 with a cut-off point of 26.49 The MoCA-INA score was assessed in all subjects on the first day of treatment. Subjects were randomly divided into treatment and control groups. The treatment group was given folic acid adjuvant 2 mg / day9 for 4 weeks and standard anti-psychotic. The control group was given placebo for 4 weeks and standard anti-psychotics. Subjects were monitored and evaluated for adjuvant side effects and clinical conditions daily. In the fourth week, the cognitive function of all subjects was assessed in the ward before going home. This study has acquired ethical clearance by the Health Research Ethics Committee (KEPK) of Dr. Amino Gondohutomo Regional Psychiatric Hospital with Decree No. 420/6043 dated June 26th 2020.

3. Results

There were 66 subjects who met the inclusion criteria. Among these, 2 subjects were categorized as Drop Out due to seizures and Malignant Neuroleptic Syndrome. There were no side effects during the drug intervention. At the end of the study, the number of subjects in the treatment and control groups each remained 32 patients.

Demographic Characteristics of Study Population

In the demographic characteristics analysis of the subjects, there was no significant difference between the demographic variables (table 1). This study examines demographic variables including gender, age, education level, marriage status, occupational status, and genetic history of mental disorder in the family. There was 71.9% male in the treatment group, while there was 65.6% male in the control group ($p = 0.590$). The average age of the subjects in the treatment group was 34.75 ± 8.45 years old, while the control group was 34.41 ± 8.64 years old ($p = 0.873$). The marital status analysis in the treatment group was 53.1% unmarried, while 50% were married in the control group ($p = 0.240$). Among the treatment group, 40.6% graduated from high school, while 50% of the control group graduated from junior high school ($p = 0.117$). The number of working subjects in the treatment group was 53.1% and the control group was 62.5% ($p = 0.440$). Both groups reported 12.5% of subjects to have genetic history of mental disorder in the family ($p = 1$).

MOCA-INA Score Analysis for Treatment and Control Groups.

The MoCA-INA score of the treatment group showed a significant rise between pre and post test score ($p<0.001$). The control group's MoCA-INA score also showed a statistically significant rise between the pre and post test score as well ($p <0.001$). The difference (delta) in the MoCA-INA score of the treatment group was higher than control group ($p = 0.002$) (table 2). Figure 1 showed a rise in the MoCA-INA score between the pre and post-test in both groups. The mean MoCA-INA pre-test score for the two groups was 19.6. The MoCA-INA post-test score graphic shows the mean score of the treatment group was 26.19, while the control group was 24.41.

4. Discussions

The result shows that there were differences between patients' cognitive function who received adjuvant folic acid and those who received anti-psychotic only based on the MoCA-INA score.

Demographic Characteristics of Study Population

Subjects in the two groups did not differ significantly in the gender, age, marital status, occupational status, education level and genetic history variables (table 1). There were more male subjects (68.8%) than women, with a mean age of 34.58 ± 8.48 years old. This is in accordance with previous epidemiological study which indicates that schizophrenia is more common in men.[10] As much as 46.9% of the subjects were unmarried. The same thing was also found in research conducted by Yeqing Wu, et al., (2018) about schizophrenic patients in Fengtai District of Beijing City in 2011 - 2015, where 82.1% of the subjects were not married.[11]

The research variables in this study were dominated by high school/equivalent graduates, namely 40.6% of the total subjects. The number of subjects who have a job were as much as 57.8%. This result was quite different from a previous study conducted by Christian Hakulinen et al., (2019) on 2,390,127 patients in Denmark, where schizophrenia was significantly associated with lower levels of education (does not receive secondary education or higher), unemployment, and low-income level.[12] Most of the subjects did not have a genetic history of mental disorders in the family (87.5%). This result was inconsistent with previous study by Mao Sheng Ran, et al.(2017) that stated family history of mental disorders, especially those who have diagnosed with schizophrenia, is a strong determinant of the risk of developing schizophrenia.[13.14]

Characteristics of the MOCA-INA score in the control and treatment groups

In this study, there was an improvement of cognitive function in the control group who received anti-psychotic and placebo as well as the treatment group who received anti-psychotic and folic acid therapy. This was indicated by an increase in the MOCA-INA score which is statistically significant between the pre-test and post test score of both groups ($p < 0.001$). In addition, there is also a significant difference in MOCA-INA score ($p = 0.002$) in the control and treatment groups. The post-test MOCA-INA mean score of the treatment group was found to be higher than the control group, which was 26.19 ± 2.83 in the treatment group and 24.41 ± 2.42 in the control group. Based on Husein N, et al., The cut off value of MOCA-INA is 26, which means a score of 26 or above can be interpreted as normal cognitive function.[15]

Cognitive disorders are thought to be caused by various genetic, epigenetic, developmental, and environmental factors. Abnormalities have been found in many areas of a schizophrenic patient's brain; most consistent brain changes are in areas such as the prefrontal cortex, inferior parietal lobule, amygdala, superior temporal gyrus, medial temporal lobe, basal ganglia, thalamus, corpus callosum, and cerebellum.[16,17]

In a study conducted by Fei Ma, et al., (2016), daily administration of folic acid for 12 months was found to magnify positive improvement on cognitive function in patients with mild cognitive impairment by lowering homocysteine concentrations in the blood plasma.[18,19] Homocysteine and its oxidative metabolite, homocysteic acid, are NMDA (N-methyl-D-aspartate) receptor agonists, which may stimulate an increase in calcium influx that causes neurotoxic effects.[19] Other study also showed that mice with hyperhomocysteinemia had lower cortical dopamine and serotonin levels. In addition, homocysteine is also thought to play a role in synaptic plasticity in the hippocampus.[20,21]

In this study, subjects in the control group who received anti-psychotic therapy and placebo also recorded to show improvement in cognitive function even though it has not reached the level of normal cognitive function as with the treatment group ($p < 0.005$). This may be due to the patient receiving atypical anti-psychotic therapy that is also known to improve cognitive function. Several previous studies have proven that some atypical anti-psychotics such as risperidone, paliperidone, lurasidone, ziprasidone, and aripiprazole can improve cognitive function in schizophrenia patients.[20,21,22]

In addition, oxidative stress also affects schizophrenia and cognitive deficits. The brain requires high level of oxygen to function normally, the brain is known as the main storage of free radicals (ROS) as well as areas of high

risk for cognitive deficits. Oxidative stress occurs when there is an imbalance between antioxidants and oxidants.[23] However, this study did not examine inflammatory markers and oxidative stress.

This study was limited as we did not analyze the socioeconomic and family education factors, which can affect the patient's cognitive function. In addition, this study also did not examine the level of homocysteine, folate, and oxidative stress, so it could not further explain the mechanism by which folic acid adjuvant could improve patients' cognitive function.

5. Conclusion

In this study, we revealed that folic acid adjuvant administration improved cognitive function in chronic schizophrenia patients. The MoCA-INA scores were escalated between before and after intervention in both treatment and control group. Meanwhile, the increase of the MoCA-INA scores were greater in the group with folic acid adjuvant administration intervention.

Ethical Approval

This study has acquired ethical clearance by the Health Research Ethics Committee (KEPK) of Dr. Amino Gondohutomo Regional Psychiatric Hospital with Decree No. 420/6043 dated June 26th, 2020

Conflicts of Interest

The authors declare that there was no conflict of interest.

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Author Contributions

Conceptualization, NDW, YRS, LK; Methodology NDW, YRS, LK; Investigation NDW, TH, YRS, LK, M; Formal analysis NDW, YRS, LK; Manuscript drafting NDW, TH, YRS, LK,

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