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THE EFFECT OF PIRACETAM SUPPLEMENTATION ON COGNITIVE FUNCTION AND HOMOFANILIC ACID LEVELS IN SCHIZOPHRENIC PATIENTS TREATED WITH RISPERIDONE

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Abstract

Background: Study of the supplementation of piracetam on cognitive function and plasma HVA levels in the treatment of schizophrenia in humans had never been conducted before. Meaningful findings in this study could provide information about optimizing pharmacological management in schizophrenic patients by adding piracetam and ultimately will improve the prognosis of the disorder. One of the simple and accurate tools for predicting the cognitive function and the prognosis of schizophrenia treatment is HVA level.

Objective: to determine the effect of piracetam supplementation on cognitive function and homovanillic acid levels in schizophrenic patients treated with risperidone.

Method: This study was experimental study, using a pre- and post-test study design with random group selection, in which variable measurements were carried out before and after treatment, conducted at RSKD Dadi South Sulawesi Province and the blood testing were send to the Research Laboratory of RSPTN UNHAS. The study subject were hospitalized schizophrenia patients who received a therapeutic dose of risperidone as many as 20 subject in treatment groups and 20 subject in control groups. The Moca-Ina were messure at weeks 0 & 8 eather in treatment group (who received Piracetam 2400 mg / day and risperidone 2-4 mg / day) and the contol group (who received risperidone 2-4 mg / day) for 8 weeks. Two measurements of Homovanilic Acid levels with ELISA were carried out in both groups, namely at the beginning of week 0 and weekend 8.

Results: MoCA-Ina values were significantly high in both grups with $p < 0.05$, where the treatment group was higer than the control group with $p = 0.015$ (<0.05). Plasma homovanilic acid levels was increased in the treatment group, but there was no significant difference between before and after treatment $p = 0.065$ (> 0.05). There was no direct correlation between plasma homovanilic acid levels and cognitive function with $p > 0.05$.

Conclusion: supplementation of oral Piracetam 2400 mg/day and risperidone for 8 weeks, was better to improve cognitive function than risperidone alone, there was also a slight increases homofanilic acid levels.

Keywords: Cognitive Function, Homofanilic Acid, Schizophrenia

1. Introduction

Epidemiological studies of schizophrenia show that the average prevalence of schizophrenia in the world is 0.7% with an incidence ratio between males compared to females, namely 1.4: 1 (Benson & Feinberg, 2017). The incidence of schizophrenia in the world in 2018 reached around 23 million people and in Indonesia it was 6.7 per 1000 households (Basic Health Research (Riskesdas), 2018; World Health Organization, 2017). The incidence of schizophrenia in South Sulawesi in 2018 reached 8.85% (Riskesdas, 2018).

Schizophrenia is a mental illness characterized by positive symptoms of hallucinations, delusions, thought disturbances, and negative symptoms of social behavior (Nguyen, 2015). Study had shown that individuals diagnosed with schizophrenia experience a decline in cognitive function from the premorbid period to the post onset period, with moderate to severe cognitive deficits in several domains, including attention, working memory, learning, verbal memory, and executive function in schizophrenic patients (Bhandari A et al., 2016).

Positive symptoms occur periodically during psychotic exacerbations, negative and cognitive symptoms often appear before the first psychotic episode and persist with poor functional outcome and a poor prognosis. Acute dysregulation of dopaminergic neurotransmission plays a major role in the occurrence of psychotic symptoms. However, increasing evidence also implicates glutamatergic pathomechanisms, particularly N-methylD-aspartate (NMDA) receptor dysfunction in the pathogenesis of schizophrenia and in the emergence of negative symptoms and cognitive dysfunction. In line with this notion, several gene variants that affect the NMDA receptor pathway had been reported to increase in schizophrenia, and have been studied using imaging genetics approaches. Several attempts had been made to develop drugs that modulate the glutamatergic pathway. The most successful approach is one that aims to influence this pathway using compounds that enhance NMDA receptor function (Gruber et al., 2014; Rubio et al., 2012).

Recent studies had focused on the use of pharmacotherapy in the form of atypical antipsychotics (Second Generation Antipsychotic/SGA) to treat patients after the acute phase condition of schizophrenia has been treated. The choice of SGA such as Risperidone is based on the ability of these drugs to improve positive symptoms, negative symptoms, cognitive function and lower neuroleptic side effects compared to First Generation Antipsychotic (FGA) drugs (Azmanova et al., 2018; Stępnicki et al., 2018).

Piracetam is a cyclic derivative of gamma-aminobutyric acid (GABA) showing the effect of piracetam on the regulation of glutamate release observed in the cortex and hippocampus, indicating involvement of NMDA receptors induced by piracetam (Suliman et al., 2016). Piracetam is a nootropic drug that improves one or more aspects of mental function, especially cognitive functions such as working memory, motivation and attention. Piracetam can be used as an oral supplement to relieve negative symptoms of schizophrenia and in improving cognitive function will also improve behavioral function (Nguyen, 2015). Over the past few years, progress has been made in the diagnosis of schizophrenia through standardized systems and structured interviews such as the DSM-V, but the accuracy of these diagnostic methods often exhibits overlapping symptoms similar to those of other psychiatric disorders. Schizophrenia is a heterogeneous disease with various abnormal metabolites involving several biochemical pathways. Recently, studies had focused in finding the bloodbased

biomarkers for schizophrenia. Compared to biomarkers in the central nervous system, plasma biomarkers are much easier and economical to test for and identify in blood samples. In addition, previous studies have provided evidence that peripheral biologic characteristics might reflect corresponding changes in the central nervous system. One of the prognostic biomarkers of schizophrenia is homovilic acid (HVA) (Cao et al., 2020).

Measurement of the plasma concentration of the dopamine metabolite, HVA, is an indirect tool for assessing changes in dopamine turnover in schizophrenic patients (Davidson et al., 1991). The effect of piracetam on dopamine metabolism in rat striatal tissues and on behavioral effects has been studied in mice where piracetam at doses of 600 mg/kg and 1,000 mg/kg increased HVA in the striatum (Rago et al., 1981). Another study reported that piracetam at 5 g/kg, increased plasma HVA levels (Nybfick et al., 1979). Research on the effects of piracetam on cognitive function and plasma HVA levels in the treatment of schizophrenia in humans has never been done before. The existence of significant findings in this study can provide information regarding the optimization of pharmacological treatment in schizophrenic patients by adding piracetam and will ultimately improve the prognosis of the disorder. However, research involving clinical trials is still very limited about the role of piracetam on schizophrenic patients, and currently there is no research conducted in Indonesia.

2. Material and Methods

2.1 Subjects

The population in this study was all schizophrenic patients who were treated at Dadi Regional Special Hospital, South Sulawesi Province. The sample in this study were all patients in stable phase schizophrenia who were treated at the Dadi Regional Special Hospital in South Sulawesi Province who met the inclusion and exclusion criteria.

The inclusion criteria were subjects diagnosed with schizophrenia according to DSMV and PPDGJ III, aged 20-45 years, research subjects with disease onset <5 years, had passed the acute phase, and willing to participate in the study. Exclusion criteria included having organic co-morbidities, having a history of abuse of psychotropic drugs for < 1 year, and using anti-inflammatory drugs and antibiotics. The criteria for dropping out include not regularly following the entire therapy, study subjects refusing to continue the study, and study subjects dying.
Concentration HVA was measured in the subjects plasma using the Enzyme-Linked Immunosorbent Assay (ELISA) method, according to the manufacturer's instructions. Values are expressed as ng/L.

2.2. Procedure

Each subject who met the criteria for schizophrenia according to the ICD-10 criteria and met the inclusion criteria in the study group was recorded and their medical history was taken. The researcher then explained to the family and the subject about the aims and objectives of the study. If agreed, the subject will be involved in the research (informed consent). The study subjects were divided into two groups (the treatment group was given risperidone therapy and supplementation piracetam, and the control group was given risperidone only). MoCA-Ina scores were measured in both groups at study entry, in the 0 and 8 week. HVA level in the blood in both groups was recorded at the start of the study and at week 8.

2.3. Statistical Analysis

Data were analyzed using the SPSS 24.0 computer program and Microsoft Excel to obtain the expected statistical results with homogeneity test, independent t-test, Mann-Whitney test, and Spearman test.

2.4. Study *Ethics*

This study, was approved by the Ethics Committee for Biomedical Research in

Humans, Faculty of Medicine, Hasanuddin University, Number: **75 / UN4.6.4.5.31/ PP36 / 2023**. Informed consent was provided from the subject the confidentiality was kept.

3. Results

3.1. Characteristics of study subjects

Subject were randomly divided into two groups (20 subjects in the treatment group and 20 subjects in the control group). The Characteristics of study subjects were 17 male (85% in both group) and 3 women (15% in both group group). Most of the education levels were 15 senior high school (75% for the treatment group), and 13 (65% for the control group). Occupation, 14 were employess (70% for the treatment group) and 11 (55% for the control group) and for the unemployed 6 (30% for the treatment group) and 13 (45% for the control group), for marital status, 8 married (40% for the treatment group) and 12 (60% for the control group) and 12 unmarried (60% for the treatment group) and 8 (40% for the control group).

Table 1. Characteristics of *study* subjects

Characteristics	Treatment	Control	Total	P
	n (%)	n (%)		
Age (years)	53,10± 3,65*	35,75 ± 3,14*	35,42 ± 3,38*	0,550[a]
Gender:				
Male	17 (85,0)	17 (85,0)	34 (85,0)	1,000[b]
Female	3 (15,0)	3 (15,0)	6 (15,0)	
Education:				
Junior high school	5 (25,0)	7 (35,0)	12 (30,0)	0,490[b]
Senior high school	15 (75,0)	13 (65,0)	28 (70,0)	
Working status:				
Employed	14 (70,0)	11 (55,0)	25 (62,5)	0,327[b]
Unemployed	6 (30,0)	13 (45,0)	15 (37,5)	
Marital status:				
Married	8 (40,0)	12 (60,0)	20 (50,0)	0,206[b]
Single	12 (60,0)	8 (40,0)	20 (50,0)	

*Data shown with mean ± standard deviation, Independent sample t test, chi square test

Table 1 shows that all the characteristics of the study subjects, namely age, gender, education, occupation, and marital status, did not differ significantly between the treatment and control groups with a $p > 0.05$. These results indicate that the characteristics of the study subjects of the two groups were homogeneous.

3.2 Comparison of MoCA-Ina values.

The comparison of the MoCA-Ina values in schizophrenic patients between baseline and weeks 8 therapy were presented in Table 2.

Table 2. Comparison of MoCA-Ina in schizophrenic patients between baseline and weeks 8 therapy

Group	MoCA-Ina Value				P
	Baseline		Weeks 8		
	Mean	Information	Mean	Information	
Treatment	17,60	Disturbance	20,30	Disturbance	0,000**
Control	18,80	Disturbance	19,70	Disturbance	0,001*

*Data is shown with the mean; Wilcoxon test; *Significant at $p < 0.05$; **Significant at $p < 0.001$.

Table 2 showed that there was a significant increase in the MoCA-Ina value between baseline and weeks 8 of therapy in the treatment group with $p = 0.000$ (<0.05) and in the control group with $p = 0.001$ (<0.05). This means that both treatment and control group were improve in the cognitive function of schizophrenic patients.

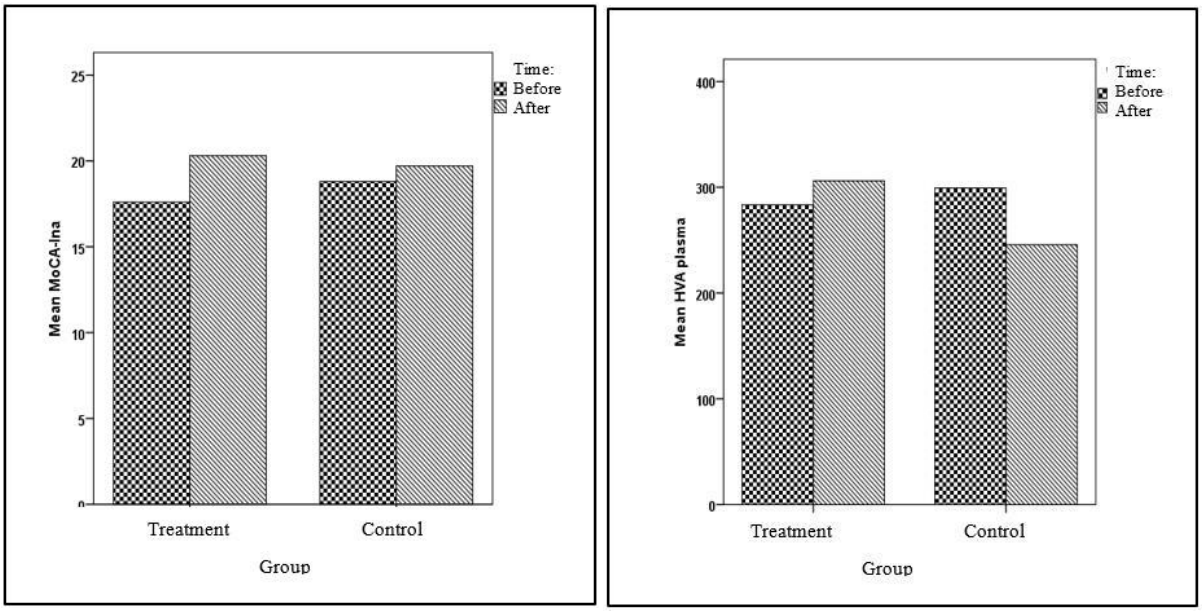

Figure 1(a). Comparison of MoCA-Ina score before and after therapy; (b). comparison of plasma homovanilic acid levels before and after therapy.

Figure 1 (a) showed that the MoCA-Ina score increased in both the treatment and control groups, although the increase in the MoCA-Ina score was greater in the treatment group. Figure 1(b) shows that plasma homovanilic acid levels increased slightly in the treatment group, whereas in the control group plasma homovanilic acid levels decreased after therapy.

3.3 Comparison of plasma homovanilic acid levels

The results of comparison of plasma homovanilic acid levels in schizophrenic patients between baseline and weeks 8 therapy in the treatment and control groups are presented in Table 3.

Table 3. Comparison of plasma homovanilic acid levels in schizophrenic patients between baseline and weeks 8

Group	Baseline	Weeks 8	p
	Homovanilic acid level		
Treatment	283,42 ± 24,88	306,17 ± 52,94	0,065[a]
Control	299,24 ± 110,84	245,74 ± 94,66	0,040[b]*

Data are presented with mean ± standard deviation, aPaired t test, Wilcoxon bTest, *Significant at $p < 0.05$.

In Table 3, the homovanilic acid level of schizophrenic patients in treatment group at the 8th week of therapy was higher than the plasma homovanilic acid level at baseline of therapy, but that there was no statistical significant difference with $p = 0.065$ (> 0.05). In control group, the level of homovanilic acid in the 8th week of therapy was lower than the baseline therapy and there was a statistical significant difference $p = 0.040$ (<0.05), it indicated that risperidone therapy in schizophrenic patients for 8 weeks significantly reduced homovanilic acid levels.

3.4 Comparison of changes of MoCA-Ina between treatment and control groups

The results of a comparison of changes in cognitive function (MoCA-Ina value) between before and after therapy in patients who were given risperidone and piracetam therapy (treatment) and subject who were only given risperidone therapy (control) are presented in Table 4.

Table 4. Comparison of changes of MoCA-Ina between the treatment and control groups

Group	MoCA-Ina score changes	p
	Mean ± SD	
Treatment	2,70 ± 1,08	0,015*
Control	0,90 ± 0,72	

Test Independent sample t test; *Significant at $p < 0.05$.

Table 4 shows that there was an increase in the MoCA-Ina score between the control and treatment groups where the treatment group experienced a greater increase in MoCA-Ina scores than the control group, with p velue = 0.015 (<0.05) which indicated that there was a significant difference in the changed in the MoCA-Ina score between the treatment and control groups. These results indicate that risperidone and piracetam therapy in schizophrenic patients for 8 weeks can improve cognitive function better than risperidone therapy alone.

3.5 Comparison of changes in plasma homovanilic acid levels between treatment and control groups

The results of comparison of changes in plasma homovanilic acid levels between before and after therapy in subject treatment and control groups are presented in table 5.

Table 5. Comparison of changes in plasma homovanilic acid levels between the treatment and control groups

Group	Changes in homovanilic acid levels	p
	Mean ± SD	
Treatment	22,75 ± 51,87	0,008*
Control	-53,49 ± 108,21	

Mann Whitney Test; *Significant at $p < 0.05$.

Table 5 showed that in the treatment group there was an increase in plasma homovanilic acid levels, while in the control group there was a decrease in plasma homovanilic acid levels with p = 0.008 (<0.05) which indicated that there was a significant difference in changes in plasma homovanilic acid levels between the treatment and control groups. These results indicate that piracetam increases plasma homovanilic acid levels in schizophrenic patients.

3.6 Correlation of plasma homovanilic acid levels and changes in cognitive function

The correlation between plasma homovanilic acid levels and changes in cognitive function in schizophrenic patients treatment and control groups, the results of which are presented in Table 6.

Table 6. Correlation of plasma homovanilic acid levels and changes in cognitive function after risperidone and piracetam therapy (Spearman test)

Correlation	R	p
Week 0	-0,345	0,136
Week 8	-0,336	0,148
Change	-0,415	0,069

Table 6 showed the correlation between plasma homovanilic acid levels and cognitive function of schizophrenic patients who receiving risperidone and piracetam, between 8th week and baseline of therapy with $p > 0.05$. These results indicated that there was no correlation between plasma homovanilic acid levels and cognitive function in schizophrenic patients receiving risperidone and piracetam.

4. Discussion

The results of this study indicated that the addition of piracetam therapy for 8 weeks in schizophrenic patients receiving risperidone significantly improves the cognitive function of schizophrenic patients. The use of risperidone and piracetam as therapy for schizophrenic patients provides better cognitive function improvements compared to therapy using only risperidone. This result is in line with the previous study by Kabes et al. (1979) that additional piracetam therapy at a fixed dose of 2400 mg/day for 8 weeks in schizophrenic patients who had received psychotropic drugs could increase rapid and significant improvements in cognitive function after co-supplementation of piracetam. The results are similar to other studies that use piracetam 2400 mg compared to placebo for 12 weeks showed improvements in cognitive function and behavioral improvements in schizophrenic patients. The use of piracetam at a dose of 3200 mg as an addition to regular antipsychotic treatment for 8 weeks for schizophrenic patients has also been reported to improve cognitive function (Noorbala et al., 1999). it relates to to how piracetam works on cholinergics and the glutamatergic neurotransmitter system, and restore membrane fluidity (Winblad B., 2005)

In this study, showed that risperidone alone can reduced plasma homovanilic acid levels, while supplementation of piracetam could increased plasma homovanilic acid levels. The decrease in plasma HVA levels in schizophrenic patients after risperidone treatment is in line with previous study that schizophrenic patients undergoing antipsychotic treatment tended to show a decrease in homovanillic acid (Takase et al., 2020). Human studies show that antipsychotics induce a decrease in cerebrospinal fluid HVA (Gasnier et al., 2021). The increase in plasma HVA levels after piracetam supplementation in schizophrenia in this study is in line with the study of Rago, Allikmets and Zarkowsky (1981) that the use of piracetam at a dose of 600 mg/kg and 1,000 mg/kg in rats increased HVA levels but did not significantly increase dopamine levels in the striatum. Similar results were also reported by Nybfick, Wiesel and Skett (1979) that piracetam at a dose of 5 g/kg can increase HVA levels.

The results of this study indicate that plasma homovanilic acid levels in schizophrenic patients are not associated with cognitive function. In previous studies stated that increase HVA plasma concentrations is beneficial for cognitive function in healthy individuals (IberoBaraibar et al., 2016).

5. Conclusion

There was a higher improvement in cognitive function (MoCA-Ina) of schizophrenic patients after supplementation of piracetam therapy for 8 weeks compared to patients who were only given risperidone. There was an increase in homovanilic acid levels in the treatment group and a decrease in homovanilic acid levels in the control group after receiving therapy for 8 weeks. The findings also showed that changes in the MoCA-Ina score did not correlate with plasma homovanilic acid levels in schizophrenic patients who were treated with risperidone and piracetam.

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Conflict of Interest

None

Reference

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