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THE EFFECT OF DONEPEZIL ON THE IMPROVEMENT OF COGNITIVE FUNCTION AND PLASMA *BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF)* LEVELS IN SCHIZOPHRENIA

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Abstract

Background: Donepezil administration as adjuvant therapy in schizophrenic patients is considered to improve cognitive function and is associated with increased levels of *BDNF* which has been widely studied as a cognitive marker for schizophrenia. The purpose of this study was to determine the effect of Donepezil on the improvement of cognitive function and plasma *BDNF* levels in patients with schizophrenia.

Objective: To determine the effect of adjuvant therapy of donepezil in improving cognitive function and *BDNF* levels in schizophrenic patients receiving risperidone.

Method: Forty-four (44) schizophrenia inpatient were divided into two groups, the research group, and the control group. Both groups received Risperidone 4 mg/day, and only the treatment group was received 5 mg donepezil for 6 weeks. To assess cognitive function, the SCoRS v BI scale was used and plasma *BDNF* levels were measured. Independent tests, Wilcoxon, Friedman and Spearman correlation tests were performed to assess the difference means between groups.

Results: There was a significant improvement in cognitive function in both groups ($p<0.05$). Although there was an increase in plasma BDNF levels in both groups, only research group was statistically significant at ($p<0.05$). The comparison of changes in the SCoRS v BI scores, plasma *BDNF* levels and in the correlation in both group was significant ($p <0.05$).

Conclusion The addition of adjuvant therapy donepezil to standard therapy Risperidone 4 mg/day was associated with improved cognitive function and also associated with increased plasma *BDNF* levels.

Keywords: Schizophrenia, Donepezil, Risperidone, Cognitive Function, *BDNF*

Introduction

Schizophrenia is a complex and severe psychiatric disorder with a lifelong etiology with a prevalence of at least 1% of the population in Indonesia and the world. It is characterized by signs of psychotic symptoms, affective disorders and cognitive dysfunction. It is one of the leading causes of disability in the world. (Murray and Lopez, 1996-World Health Organization, 2001).

Data for 2018 from the World Health Organization (WHO) stated that around 23 million people worldwide suffer from schizophrenia (WHO, 2018). The prevalence of schizophrenia in Indonesia is increasing every year. The prevalence of schizophrenia in South Sulawesi especially increases every year. Based on Riskesda 2018 data of 5.73% per mil in urban areas and 11.10% per mil in rural areas where Pangkep district ranks first as urban districts with many psychosis/schizophrenia patients then Wajo districts, North Luwu and Pare-pare. (Riskesdas, 2018).

In addition to psychotic symptoms, cognitive dysfunction is one of the core symptoms of schizophrenia. According to Keefe et al (2011), relative neurocognitive deficits occur in schizophrenia. One influential study noted that 90% of patients had significant deficits in one domain and 75% had deficits in at least two domains.

Although approximately 27% of schizophrenic patients are considered to have no cognitive deficits based on clinical neuropsychological assessment, these patients tend to have the highest level of premorbid cognitive function and show lower levels of premorbid functioning and the education level of their parents. 98% of schizophrenic patients show a lower cognitive level when compared to the level of education of their parents. It is very likely that almost all schizophrenic patients show levels below what is expected in the absence of the disease. Pharmacogenetic studies of the cognitive effects of antipsychotics that are currently available, although in a relatively early stage, suggest that the treatment of cognitive deficits in schizophrenia could be improved by focusing on genetic variants associated with specific cognitive dysfunctions in the general population and using them to match most pharmacological interventions and and/or psychologically relevant to the genetic and cognitive profile of the target population. Such a strategy would drive advances in drug development and provide a platform for the individualized treatment of cognitive deficits in schizophrenia. suggested that the treatment of cognitive deficits in schizophrenia could be improved by focusing on the genetic variants associated with specific cognitive dysfunctions in the general population and using these to match the most relevant pharmacological and/or psychological interventions to the genetic and cognitive profiles of the target population.

Brain-derived neurotrophic factor *(BDNF)* is a secretory growth factor (neurotropin) that promotes neuronal proliferation and survival, synaptic plasticity and long term potentiation in the central nervous system (Di Carlo et al., 2019). Because of its very complex role, *BDNF* has been extensively researched to play a key role that underlies the regulation of cognitive function in each individual. *BDNF* has been extensively investigated under the neurodevelopmental hypothesis of schizophrenia, given its role in CNS development and physiology. Examination of plasma *BDNF* levels has now been extensively examined in studies of cognitive function of schizophrenic patients and previous studies have also reported a significant positive correlation between plasma *BDNF* levels and cerebrospinal fluid (CSF) in human subjects (Di Carlo et al., 2019; R. Nieto et al., 2013; R. R. Nieto et al., 2021).
Previous studies have shown that donepezil can improve PCP-induced schizophrenic behavioral dysfunction in rats. Donepezil treatment also increased neurotrophic factor content in the hippocampus and cortex of PCP-treated rats. Furthermore, donepezil exhibits an attenuating effect on cognitive dysfunction by inhibiting neuronal apoptosis and regulating synaptic plasticity through the mediation of the p-Akt/Akt, p-GSK-3β/GSK-3β, Bcl-2/Bax and Caspase-3 proteins. The results may be conducive to further study of the mechanisms and clinical applications of donepezil in the treatment of cognitive deficits in schizophrenia.

Research on the effect of donepezil adjuvant therapy on cognitive function in patients with schizophrenia and its relationship with blood BDNF levels has never been carried out in Indonesia, especially Makassar. The significant findings in this regard can provide information regarding diagnostic biomarkers of schizophrenia, good management of schizophrenic patients and will

ultimately improve the prognosis of the disorder. On this basis the researcher is interested in conducting this research.

Materials and Method Materials Subjects

The subjects in this study were all schizophrenic female subjects treated at the Dadi Regional Special Hospital, South Sulawesi Province who met the inclusion criteria.

Inclusion criteria were female subjects diagnosed with schizophrenia according to ICD10 criteria, aged 20-45 years, able and willing to participate, treated_with risperidone 4 mg/day. Exclusion criteria: including having organic comorbidities, history of drug abussed and using anti-inflammatory drugs and antibiotics. Samples were dropped out when not regularly attending, irregularly taking risperidone, the families refused to continue the study or the subject died. Blood samples were obtained from subjects in the morning (around 09.00 AM). Serum was separated, collected and stored at -70^{o}C before use. The concentration of *BDNF* was measured in the serum of subjects using the Enzyme-Linked Immunosorbent Assay (ELISA) method, according to the manufacturer's instructions. Values are expressed as ng/mL.

Results

Characteristics of Patients

This study was carried out in the Kenanga room at Dadi Hospital, South Sulawesi Province in August 2022-September 2022 and the blood serum was analyzed at the Hasanuddin University Medical Research Center (HUMRC). 50 subjects who were referred to the Kenanga room at Dadi Hospital, South Sulawesi Province for screening and assessing the subjects interest in the types of adjuvant therapy available. Six patients were drop out so only 44 subjects participated in the study.
The 44 subjects in this study which were divided into 2 groups (22 subjects for treatment group and 22 subjects for control group).

The demographic characteristics of the research and control subject (N=22) were all female (100%). Mostly age of the research subject was 20-45 years. The level of education, mostly elementary school (36.4% for the treatment group, 22.7% for the control group). The onset of disease was varied <5 years, 57.1% in the treatment group and 78.6% in the control group. For occupation who had 90.9% of the research subject did not work either in the treatment or control groups. Likewise, married (59.1%), unmarried(31.8%) and widow (9.1%) .The mean age of the subjects at the time of the study were 33.82 ± 8.03 in the and 31.23 ± 7.51 in the control group with a *p* 0.274 (Mean SD, Independent t Test).

Table 1 Sociodemographic Characteristics by Frequency (N=22)

Variables	Treatment n = 22 (%)	Control n = 22 (%)	P
Age			
Mean±SD	33.82±8.03	31.23±7.51	0.274
Education Level			
Not school	0 (0%)	2 (8.7%)	
Elementary	8(36.4%)	8 (22.7%)	0.163
Secondary	4(14.2%)	8 (22.7%)	
Senior	7(31.8%)	12 (54.5%)	
Working			
Farmer	1(4.5%)	3(13.6%)	
Entepreneur	2(13.6%)	1(4.5%)	
Employee	2(9.1%)	1(4.5%)	
Laborer	0(0.0%)	1(4.5%)	0.357
Housewife	3(13.6%)	6(31.8%)	
Teacher	1 (4.5%)	0(0.0%)	

Honorer	0 (0.0%)	0(4.5%)	
Not Working	12 (54.5%)	8 (36.4%)	
Marital Status			
Not Merried	6(31.8%)	10 (45.5%)	
Merried	13 (59.1%)	12 (54.5%)	0.277
Widow	2 (9.1%)	0 (0.0%)	
Disease Onset			
<1 year	12 (54.5%)	14 (68.2%)	0.536
>1 year	10 (45.5%)	7 (31.8%)	

Chi Square test

Comparison The Median Values of SCoRS v BI

Comparison the median values of SCoRS v BI in both the research subject and the control group at baseline, at the 2th week, 4th week and at the 6th week

Table 2 Comparison The Median Values of SCoRS v BI

Group	N	Baseline	2th week	4th week	6th week	p Value
Research	n=22	6.81 (3.75-10.00)	6.00 (2.88-8.63)	5.13 (2.75-7.13)	4.25 (2.25-5.75)	0.000*
Control		6.94 (3.50-9.75)	6.19 (3.88-8.50)	4.88 (3.50-6.75)	3.25 (2.50-5.38)	0.000**

Median (Min-Max)
Friedman Test

In this study, the SCoRS v BI values at baseline, at the 2thz week, at the 4th week and at the 6th week either in the treatment or control group were normally distributed with $p = 0.000$ in both groups. This indicates that the medidan values of SCoRS v BI in both group had statistical significance. More specifically, the comparison of the median SCoRS v BI at baseline, at the 2th week, at the 4th week and at the 6th week for both group as followed :

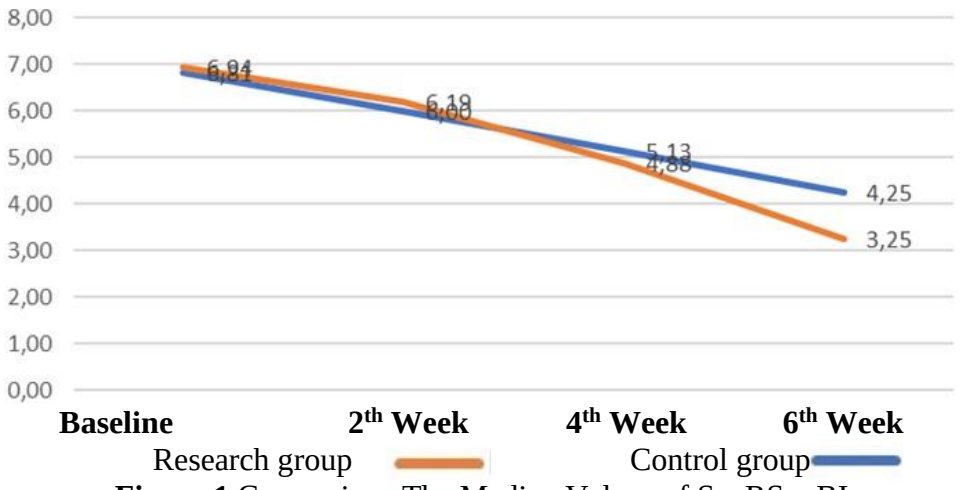

Figure 1 Comparison The Median Values of ScoRS v BI

In this graph, it could be seen that both group had a decreased SCoRS v BI values from at the 2th week, 4th to at the 6th week but the treatment group was higher with $p = 0.000$ (friedman test).

Comparison The Median Levels of *BDNF*

Comparison the median levels of *BDNF* in both group at baseline and at the 6th week.

Tabel 3 Comparison The Median Levels of *BDNF*

Group			*P*
	Baseline	**6th Week**	
Research (22)	0.27 (0.25-0.93)	0.87 (0.27-2.74)	0.000
Control (22)	0.70 (0.25-4.16)	0.73 (0.26-3.64)	0.485

Median (Min-Max)
*Significant $p<0.05$ (wilcoxon test)

In this study, the levels of *BDNF* at baseline and at the 6th week in both group were normally distributed. This indicated that the median levels of *BDNF* in both group have statistical significance especially in research group.
More specifically, the comparison of the median levels of *BDNF* at baseline and at the 6th week in the study subjects for both group as followed:

Figure2 Comp arison The Median Levels of *BDNF*

In this graph it could be seen that both the research group and the control group had an increased levels of *BDNF* at the 6th week. However, the increased levels of *BDNF* in the research group was higher than the control group.

Correlation of Cognitive Function (SCoRS v BI) and *BDNF* Levels
Correlation of cognitive function (SCoRS v BI) and *BDNF* levels in both group at baseline and at the 6th week.

Table 4 Correlation of Cognitive Function (SCoRS v BI) and *BDNF* Levels

Research	**Control SCoRS v BI and BDNF**			
Value	***p* Value**	***r* Value**	***p* Value**	***r***
Baseline	0,564	0,13	0,542	0,137
6th Week	0,128	-0,335	0,35	-0,209

Significant $p<0.05$ (spearman test)

In the table above, there was a statistically insignificant correlation between SCoRS v BI and *BDNF* levels with the improvement of cognitive function in schizophrenic subjects after being given adjuvant therapy of donepezil. However the r value, had a tendency for better correlation in treatment group compared to control group (-0.335).

Discussion

The levels of SCoRS v BI were 6.81 at baseline, 6.00 at the 2^{th} week, 5.13 at the 4^{th} week and 4.25 at the 6^{th} week in the treatment group. Where in the control group, the levels of SCoRS v BI were 6.94 at baseline, 6.19 at the 2^{th} week, 4.88 at the 4^{th} week and 3.25 at the 6^{th} week. The decrease values of SCoRS v BI in both group were statistically significant with $p = 0.000$ ($p<0.05$). Although there was an decrease values of SCoRS v BI in both groups, the treatment group was better at the 6^{th} week. The data above showed that there was a better improvement of cognitive function in schizophrenia subjects who were treated with risperidone 2-6 mg with combination of 6 week of adjuvant therapy of donepezil than in subjects only treated with risperidone.

Improvement of cognitive function in control group was also seen where the control group only had risperidone treatment. It was obvious, that risperidone therapy could improve cognitive function by occupaying 5HT2A receptor in mesocortical pathway (Jelena Barkic et al., 2003, Barkic et al., 2003). The study also measured *BDNF* level of schizophrenic subjects who were treated with adjuvant therapy therapy of donepezil for 6 weeks.

In this study was found an increased at *BDNF* levels either in the research group or in the control group at the 6^{th} week where it started to increase from baseline to the 6^{th} week.

This findings was in accordance with studies by Favalli et al., 2012; Nurjono et al., 2012 where The stimulated dopaminergic system from routine administration of donepezil adjuvant therapy could theoretically increase *BDNF* expression through intracellular calcium mobilization which in turn would then accelerate morphological maturation and neuronal differentiation. It is also known that dopamine neuron cells were essential for BDNF mRNA synthesis (Favalli et al., 2012; Nurjono et al., 2012).

Correlation between cognitive fuction which were measured by SCoRS v BI and BDNF level in the treatment group was found statistically significant. This finding was the same with the study by R. R. Nieto et al., 2021, where there was a significant correlation between cognitive function and *BDNF* level (R. R. Nieto et al., 2021) In this study, the result was also the same with the finding of R. R. Nieto et al., 2021,

The limitation of this study was only 6 weeks observation, where other studies did the observation until 12 weeks.

Conclusion

1. There was an improvement of cognitive function in schizophrenic subjects in both group, but the research group showed a higher decreased of SCoRS v BI compared to control group.
2. A significant increase of *BDNF* in schizophrenic subjects in both group, but the research group showed a higher increased of plasma *BDNF* levels compared to control group.
3. There was a positive correelation between changes in plasma *BDNF* levels and cognitive function in both th research and control groups..

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Author Contributions

Conceptualization: Aulya Fadillah Lompi, Sonny T. Lisal. Data curation: Hawaidah, Burhanuddin Bahar. Formal analysis: Aulya Fadillah Lompi, Sonny T. Lisal, Hawaidah. Funding acquisition: Aulya Fadillah Lompi, Sonny T. Lisal. Investigation: Aulya Fadillah Lompi, Sonny T. Lisal, Hawaidah, Burhanuddin Bahar, Jumraini Tammasse, Erlyn Limoa.
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Conflict of Interest

None

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Independent

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