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RESEARCH ARTICLE
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EFFECT OF CITICOLINE ADJUVANT THERAPY ON NEGATIVE SYMPTOMS AND INTERLEUKIN 6 (IL -6) LEVELS IN SCHIZOPHRENIC PATIENTS RECEIVING RISPERIDONE THERAPY

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Abstract

Background: Schizophrenia has a variety of debilitating symptoms with most categorized into three groups: positive, negative and cognitive symptoms. Inflammation stated as one mechanism Which underlying symptom negative, especially deficit motivation, through effect cytokine inflammation of the basal ganglia. Anti-inflammatory pathway cholinergic is new neuroimmunomodulatory pathway found. Citicoline as an α7nAChR agonist has a role as an anti-inflammatory which can prevent extreme inflammatory reactions in the brain. On research previously There are significant findings about effect of using citicoline adjuvant therapy on IL-6 levels and negative symptoms in schizophrenic patients. Research involving clinical trials still very limited about administration of citicoline against patient schizophrenia.

Purpose: Analyzing the influence citicoline adjuvants to symptom negative and IL-6 levels in patients with schizophrenia receiving risperidone therapy.

Method: This is study experimental with design *Randomized clinical trials* with double-blind approach. Study performed on 40 patients with schizophrenia treated at Hospital Specifically for Dadi Region, South Sulawesi Province. Patient grouped be 2 in random i.e. 20 patients given risperidone 4-6 mg/ day and therapy adjuvant oral citicoline 2,000 mg/day for 8 weeks (treatment) and 20 patients given risperidone 4-6 mg/ day (control). A total of 20 individuals Healthy used for control of IL-6 levels. Done measurement serum IL-6 levels before therapy (*baseline*) and 8th week. Done measurement symptom SANS clinical before therapy (*baseline*), 4th week and 8th week post therapy. Data analyzed by Chi-Square test, Independent T Test, Paired T test and Spearman's Test.

Results: There is change symptom negative ones significant in patients with schizophrenia that gets risperidone therapy and citicoline adjuvant or alone received risperidone at both in 4th week and 8th

week of therapy, however change more many patients with schizophrenia that gets risperidone and citicoline adjuvant therapy. There is decline group serum IL-6 levels treatment nor group control after 8th week of therapy, however No There is difference significant decline serum IL-6 levels in both groups. There is no significantly correlation in statistics between negative symptoms with serum IL-6 levels in both groups, however in a clinical negative symptom followed with decline serum IL-6 level.

Conclusion: Citicoline adjuvant therapy orally 2,000 mg / day for 8 weeks able repair symptom more negative better than with only risperidone therapy but There is no difference significant in decreased serum IL-6 inter group.

Keywords: Schizophrenia, Risperidone, Citicoline**,** SANS, IL-6.

1. Introduction

Schizophrenia is a serious mental disorder that affects more than 21 million people worldwide. Schizophrenia affects about 7 per thousand of the adult population, mostly in the 15-35 year age group (Maqbool et al., 2019). The incidence of schizophrenia in Indonesia is 6.7 per 1000 households in 2018 (Basic Health Research (Riskesdas), 2018). The incidence of schizophrenia in South Sulawesi in 2018 reached 8.85% (Riskesdas, 2018). Schizophrenia has a variety of debilitating symptoms with most of them categorized into three groups: positive, negative and cognitive symptoms. Negative symptoms include blunted affect, anhedonia, and social withdrawal (Gomes & Grace, 2021). Negative symptoms occur in more than 50% of people with schizophrenia, have a major impact on life functioning, and place a great burden on patients, families and the health care system (Galderisi et al., 2018). The negative symptoms of schizophrenia are debilitating and chronic, difficult to treat and contribute to poor functional outcomes (Goldsmith & Rapaport, 2020).

Motivational deficit is the main negative symptom and is associated with changes in reward processing, which involve subcortical areas such as the basal ganglia. Dopamine-rich areas, such as the ventral striatum, have been implicated in reward processing deficits. Inflammation is stated as one of the mechanisms underlying negative symptoms, especially motivational deficits, through the effect of inflammatory cytokines on the basal ganglia (Goldsmith & Rapaport, 2020). Previous studies have reported that major alterations of the innate immune system are associated with schizophrenia. Interlukin-6 (IL-6) has a role in schizophrenia associated with activated microglia and interferes with neuronal survival by increasing oxidative stress and reducing neurotrophic support (Khandaker et al., 2015). Increased expression of IL-6 in the central nervous system from activated astrocytes and microglia becomes an important mediator of the interaction between the immune system and the central nervous system in schizophrenia (Shahraki et al., 2016).

Antipsychotic drugs are becoming standard therapy for schizophrenia by blocking dopamine receptors, and targeting not only D2 receptors but also D3 and D4 receptors which are involved in various functions including cognitive processes. Antipsychotics that have properties as receptor antagonists such as D2 receptor antagonists play a role in reducing positive symptoms and can cause decreased cognition in a dose-dependent manner (Bittner et al., 2021). Drug therapy that blocks dopamine-type D2 receptors is beneficial for controlling positive symptoms of the disease, but not negative or cognitive symptoms (Bradford, 2009). Risperidone as an atypical antipsychotic drug exhibits higher affinity for 5-HT2A receptors than D2 receptors and lower affinity for D2 receptors compared to that seen with conventional antipsychotics. The effect of the mechanism of action of this drug is expected to be related to improvements in cognitive and negative symptoms (Horacek et al., 2006). The existence of the role of inflammation in the pathophysiology of schizophrenia which is related to negative symptoms makes the role of anti-inflammatory drugs that can be used in adjuvant therapy of schizophrenia to overcome negative symptoms. The cholinergic anti-inflammatory

pathway (CAP) is a newly discovered neuro-immunomodulator pathway. The alpha-7-acetylcholinenicotinic receptor (α7nAChR) is a fundamental component of this pathway, which interacts with acetylcholine (ACh) and initiates intracellular molecular events. A large number of studies have demonstrated that α7nAChR activation can effectively change the cytokine profile, and consequently exert an inhibitory effect on local and systemic inflammation (Wu et al., 2021).

Citicoline is a complex organic molecule that is produced endogenously as an intermediate molecule in the de novo synthesis of cell membrane phospholipids. Citicoline is rapidly hydrolyzed to choline and cytidine by membrane phosphodiesterase when administered exogenously. Thus, the level of choline in the brain and blood circulation increases. Choline increases the synthesis of acetylcholine and its release into the synaptic cleft. The citicolinemediated increase in the activity of the sympathetic and cholinergic systems causes many pharmacological and physiological effects (Barış et al., 2019). Citicoline has a role as an antiinflammatory which can prevent extreme inflammatory reactions in the brain by inhibiting the release of free fatty acids and reducing damage to the blood-brain barrier. Citicoline also exhibits α7nAChR agonist activity which overall has beneficial therapeutic effects in schizophrenic patients (Ghajar et al., 2018). Citicoline also inhibits neuronal excitotoxicity by weakening glutamine concentrations in the synaptic cleft by increasing glutamate uptake by increasing glutamate transporter expression (Al-kuraishy et al., 2022).

Ghajar et al. (2018) in his research reported that the use of citicoline as adjuvant therapy in schizophrenic patients who received effective risperidone therapy could reduce negative symptoms. Meanwhile, it was reported that increased IL-6 as an inflammatory biomarker underlies the mechanism of negative symptoms of schizophrenia (Goldsmith & Rapaport, 2020). However, there are no studies that directly conduct research related to the effect of using citicoline adjuvant therapy on IL-6 levels in schizophrenic patients.

There are significant findings about the effect of using citicoline adjuvant therapy on IL-6 levels and negative symptoms in schizophrenic patients. The presence of a serum IL-6 biomarker that is comparable to negative symptoms can be a simple and accurate measurement tool in predicting the prognosis of schizophrenia treatment. This study can also provide information regarding optimizing pharmacological management of schizophrenic patients by adding citicoline therapy to improve negative symptoms. Research involving clinical trials is still very limited regarding the administration of citicoline to schizophrenic patients. On this basis, researchers are interested in conducting research on the effect of citicoline adjuvant therapy on negative symptoms and IL-6 levels in schizophrenic patients receiving risperidone therapy. Based on the above background, the formulation of the problem in this study is: What is the effect of citicoline adjuvants on negative symptoms and IL-6 levels in schizophrenic patients receiving risperidone therapy? The general objective of this study was to determine the effect of citicoline adjuvants on negative symptoms and IL-6 levels in schizophrenic patients receiving risperidone therapy. In particular, this study attempted to measure the negative symptoms of schizophrenic patients who only received risperidone therapy at the start of the study (baseline), week 4 and week 8, to measure the negative symptoms of schizophrenic patients who received risperidone and adjuvant citicoline therapy at the start of the study (baseline), week 4 and week 8, measured serum IL-6 levels of schizophrenic patients who only received risperidone therapy at the start of the study (baseline) and week 8, measured serum IL-6 levels of schizophrenic patients who received risperidone therapy and citicoline adjuvant at baseline and week 8. In addition, this study compared changes in negative symptoms in the treatment group and the control group at the beginning of the study (baseline), week 4 and week 8, compared changes in serum IL-6 levels in the treatment group and the control group at the start of the study (baseline) and week 8, and determined the correlation between negative symptoms and IL-6 levels in schizophrenic patients receiving risperidone and citicoline adjuvants. The hypothesis of this study is that citicoline adjuvant therapy

can improve negative symptoms and reduce IL-6 levels in schizophrenic patients receiving risperidone therapy.

2. Research Methods

This research is an experimental study with a randomized clinical trial design, measuring pre- and post-tests with random group selection. Variable measurements were made before and after treatment. This study also used a double-blind approach. This research was conducted at the Dadi RSKD South Sulawesi and sample testing was carried out at the Research Laboratory of the UNHAS RSPTN in March 2023 - April 2023. This research was conducted at the Dadi RSKD in South Sulawesi Province and at the UNHAS RSPTN Research Laboratory.

The population in this study were all schizophrenic patients who were treated at Dadi Regional Special Hospital, South Sulawesi Province. The sample in this study were all patients with stable phase schizophrenia who were treated at Dadi Special Hospital in South Sulawesi Province who met the inclusion and exclusion criteria. The sample size is determined by the sample formula which performs a paired numerical comparative test of two groups more than one measurement, namely:

$$n = 2\left(\frac{(Z\alpha + Z\beta)S}{x1 - x2}\right)^2 = \left(\frac{(1{,}96 + 0{,}84)\text{x } 23{,}17}{22{,}09}\right)^2$$

$$n = 17{,}25 = 20 \text{ (rounded)}$$

Based on the calculation results, the minimum number of samples for each group is 20 people. This research was conducted in two sample groups so that the total sample was 40 people.
Information:
n = Minimum number of subjects per group
α = Type one error, set at 5%, one-way hypothesis
Zα = The standard value of α is 5%, which is 1.96
β = Type two error, set at 20%
Zβ = Standard value of 20% β, which is 0.84
x1-x2 = The difference in IL-6 levels which is considered significant, is set at 22.09
(Saidah et al., 2021) s = Combined standard deviation = 23.17 (Saidah et al., 2021)

The sampling technique for each group was carried out by means of Consecutive Sampling, namely taking samples from all the subjects observed and meeting the criteria until the required number of samples was met. The inclusion criteria for the treatment group were patients diagnosed with schizophrenia according to PPDGJ-III/ICD-10, patients aged 20-45 years, patients with <5 years of illness, patients who had passed the acute phase (PANSS-EC <15), received risperidone therapy 4 -6 mg/day, and willing to get citicoline adjuvant therapy. The inclusion criteria for the control group included patients diagnosed with schizophrenia according to PPDGJ-III/ICD-10, patients aged 20-45 years, patients with a duration of illness <5 years, patients who had passed the acute phase (PANSS-EC <15) and were receiving risperidone therapy. 4-6 mg/day.

The exclusion criteria were having organic comorbidities and infectious diseases, having a BMI ≥ 25 kg/m2 (obesity criteria), having a history of consuming drugs before being admitted to the hospital, using anti-inflammatory drugs and antibiotics, and having strenuous physical activity 24 hours before the intervention. Lastly, the criteria for Drop Out were not regularly participating in the entire citicoline adjuvant therapy, not regularly taking the drug risperidone, research subjects refused to continue the study and research subjects died.

The type of data used in this study is primary data, data obtained directly from research subjects. Instruments in this study were informed consent sheets, PPDGJ-III instruments, clinical symptom instruments in the form of a Scale for the Assessment of Negative Symptoms (SANS), risperidone drug, citicoline drug, blood sampling kit and IL-6 level examination, and ELISA kit.

3. Results

3.1 Sociodemographic Characteristics, SANS Scores and Interleukin-6 Baseline

Characteristics of research subjects, SANS and Interleukin-6 Baseline values obtained from primary data can be seen in Table 1.

Table 1. Characteristics of research subjects (n=20)

Variabel	**Treatment**	**Control**	***p***
	n = 20	*n* = 20	
Age (mean ± SD)	34,25 ± 7, 49	33,55 ± 6, 99	0,762*
Gender			
Man	18 (90%)	19 (95%)	0,732**
Woman	2 (10%)	1 (5%)	
Education			
Elementary School	8(40,0%)	7 (35%)	0,106**
Junior high school	6 (30,0%)	7 (35%)	
Senior high school	5 (25,0%)	6 (30%)	
Bachelor	1 (5,0%)	0	
Work			
Work	10 (50,0%)	7 (35%)	0,639**
Doesn't work	10 (50,0%)	13 (65%)	
Marital status			
Marry	8 (40,0%)	2 (10%)	0,761**
Not married yet	12 (60,0%)	18 (90%)	
Baseline total SANS values	57,05 ± 9,21	57,40 ± 7,15	0,894*
Interleukin-6 Serum baseline	63,47 ± 21,69	68,17 ± 20,18	0,486*

**Independent T Test, **Chi-Square Test*

The basic characteristics of the study subjects including age, gender, education, occupation, marital status, total baseline SANS values and baseline serum Interleukin-6 found no significant differences between the treatment and control groups (p>0.05). Thus, the research subjects are homogeneous.

3.2 Comparison of Total SANS Scores in the Treatment and Control Groups

Table 2. Analysis of changes in total SANS values in the treatment group

SANS	**n (20)**	**Average ± S. D**	**Difference (Elementary School)**	**Mark p**
Baseline Week -4	n=20 n=20	57,05 ± 9,21 52,25 ± 8,50	4,80 (2,60)	<0,001
Week -4 Week -8)	n=20 n=20	52,25 ± 8,50 48,30 ± 7,54	3,95 (1,63)	<0,001
Baseline Week ke-8	n=20 n=20	57,05 ± 9,21 48,30 ± 7,54	8,75 (2,89)	<0,001

Paired T Test

From table 2, the total SANS value decreased by an average of 4.80 points from the first week to the 4th week (p <0.001), from the 4th week to the 8th week the total SANS value decreased by an average of 3.95 points (p < 0.001) and from the first week to the 8th week the total SANS value decreased by an average of 8.75 points.

Table 3. Analysis of changes in total SANS values in the control group

SANS	n (20)	Average ± s. d	Difference (Elementary School)	*p*
Baseline Week -4	n=20 n=20	57,40 ±7,15 56,10 ± 6,90	1,30 (0,73)	<0,001
Week -4 Week -8	n=20 n=20	56,10 ± 6,90 54,25 ± 7,01	1,85 (0,93)	<0,001
Baseline Week -8	n=20 n=20	57,40 ± 7,15 54,25 ± 7,01	3,15 (1,26)	<0,001

Paired T Test

From Table 3, the total SANS value decreased by an average of 1.30 points from the first week to the 4th week (p <0.001), from the 4th week to the 8th week the total SANS value decreased by an average of 1.85 points (p<0.001) and from the first week to the 8th week, the total SANS value decreased by an average of 3.15 points. Comparison of the total SANS values in the treatment group and the control group measured at baseline, week 4 and week 8 can be seen in table 4, table 5 and table 6.

Table 4. Comparative analysis of the total SANS values between the treatment group and the control group at baseline and the 2nd week4

	SANS baseline (Mean ±Elementary School)	SANS week 4 (Mean ±Primary School)	Change in total SANS value	The difference in the average decrease (IK95%)	*p*
Treatment	57,05 ±9,21	52,25 ± 8,50	- 4,80	-3,50(-2,27-4,73)	< 0,001
Control	57,40 ±7,15	56,10 ± 6,90	- 1,30		
p	0,894	0,124			

Independent T Test

From Table 4, it was found that the p-value for the difference in the average decrease in the total baseline SANS score - week 4 in the treatment group and the control group was p <0.001, so it can be concluded that there was a significant change in the SANS score in both the control and treatment groups. However, the change in the total SANS score in the treatment group was greater than that of the control group, where the total SANS score was reduced by an average of 3.5 points better than the control group with a 95% confidence interval ranging from -2.27 to -4.73.

Table 5. Comparative analysis of total SANS values between the treatment group and the control group at week 4 and week 8.

	Week 4 of SANS (Mean ± Elementary School)	SANS Week 8 (Mean ± Primary School)	Change in total SANS value	The difference in the average decrease (IK95%)	*p*
Treatment	52,25±8,50	48,30 ± 7,54	-3,95	-2,10(-1,25-2,95)	< 0,001
Control	56,10±6,90	54,25 ± 7,01	-1,85		
p	0,124	0,014			

Independent T Test

From Table 5, it was found that the p-value for the mean difference in the total SANS score for the 4th – 8th week in the treatment group and the control group was p <0.001, so it can be concluded that there was a significant change in the total SANS score in both the control and treatment groups. However, the change in SANS score in the treatment group was greater than that in the control group, where the total SANS score was reduced by an average of 2.10 points better than the control group with 95% confidence intervals ranging from -1.25 to -2.95.

Table 6. Comparative analysis of total SANS values between the treatment group and the control group at baseline and week 8.

	SANS baseline (Mean ±Elementary School)	SANS week 8 (Mean±Primary School)	Change in total SANS value	% Reduction in total SANS baseline – week 8	The difference in the average decrease (IK95%)	*p*
Treatment	57,05±9,21	48,30 ± 7,54	-8,75	15,3 %		< 0,001

Control	57,40±7,15	54,25 ± 7,01	-3,15	5,5 %	-5,60 (-4,17-7,03)	
p	0,894	0,014				

Independent T Test

From table 6, it was found that the p value for the mean difference in the decrease in the total SANS score at the beginning - the 8th week in the treatment group and the control group was p <0.001, so it can be concluded that there was a significant change in the total SANS score in both the control and treatment groups. However, the change in the total SANS score in the treatment group was greater than that of the control group, where the total SANS score decreased by an average of 5.60 points better than the control group with a 95% confidence interval ranging from -4.17 to -7.03. Changes in total SANS values from baseline to week 8 were found in the treatment group at -8.75 and in the control group at -3.15, so it can be said that administration of citicoline adjuvant provided better negative symptom improvement than without citicoline administration.

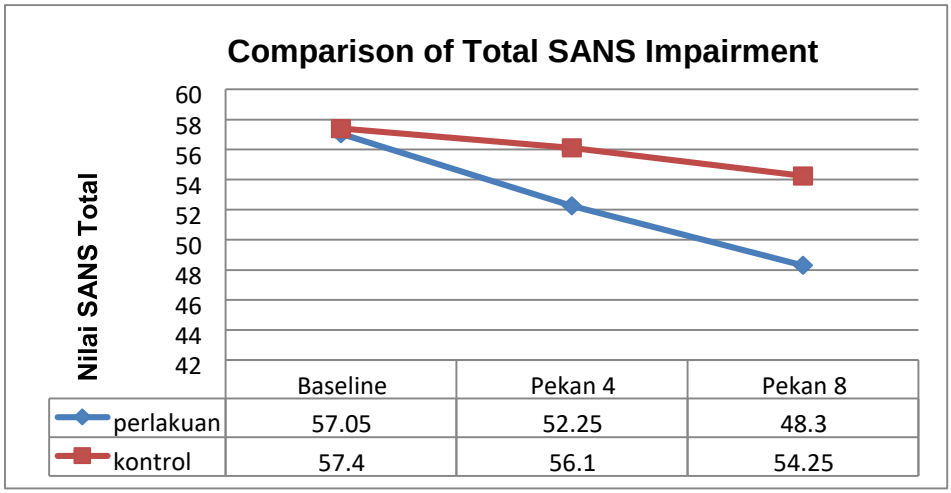

Figure 1. Graph of a comparison of the reduction in the total SANS score in the treatment group and the control group.

The difference in the steepness of the decrease in SANS scores can be said to be a contribution from the citicoline adjuvant, where it appears that the administration of citicoline adjuvant causes better improvement of negative symptoms (SANS) than without the addition of citicoline adjuvant.

3.3 Comparison of Serum Interleukin-6 Levels in the Treatment and Control Groups

A total of 40 research subjects who received Risperidone in both the treatment group and the control group were measured for serum IL-6 levels at the baseline (baseline) and at the end of the 8th week. The measurement results are shown in table 7 and table 8.

Table 7. Analysis of changes in serum IL-6 values in the treatment group

Interleukins -6	**Rerata ± s.d**	**Difference ± s.d**	**IK (95%)**	**Mark p**
Baseline (n=20) Week -8 (n=20)	63,47 ± 21,69 41,54 ± 22,31	21,92 ± 15,43	29,14-14,70	<0,001

Paired T Test

Table 8. Analysis of changes in serum IL-6 values in the control group

Interlukin-6	**Average ± s.d**	**Difference ± s.d**	**IK (95%)**	**Mark p**
*Baseline (*n=20*)* Week ke-8 (n=20)	68,17 ± 20,18 49,76 ±19,50	18,41±14,01	24,97-11,85	<0,001

Paired T Test

Table 9. Comparative analysis of serum IL-6 levels between the treatment group and the control group at baseline and week 8.

	IL-6 *Baseline* (Average ± SD)	**IL-6 week -8 (Average ± SD)**	**Rate change IL-6**	**% Decrease in baseline serum IL -6 levels – week 8**	**The difference in the Average decrease (IK95%)**	***p***
Treatment	63,47 ± 21,69	41,54 ± 22,31	-21,92	34,5 %	-3,5 (-5,9212,94)	0,456
Control	68,17 ± 20,18	49,76 ±19,50	-18,41	27 %		
p	0,482	0,223				

Independent T Test

Table 9 shows that the p value for the mean difference in the decrease in baseline IL-6 values - week 8 in the treatment group and the control group was p> 0.05, there was no significant change in serum IL-6 in either the treatment group or the control group. However, changes in IL-6 levels in the treatment group were greater than in the control group, where IL6 levels decreased by an average of 3.5 points better than the control group with 95% confidence intervals ranging from -5-92 to -12, 94. So it can be said that administration of citicoline adjuvant provides a better decrease in serum IL-6 than without citicoline administration.

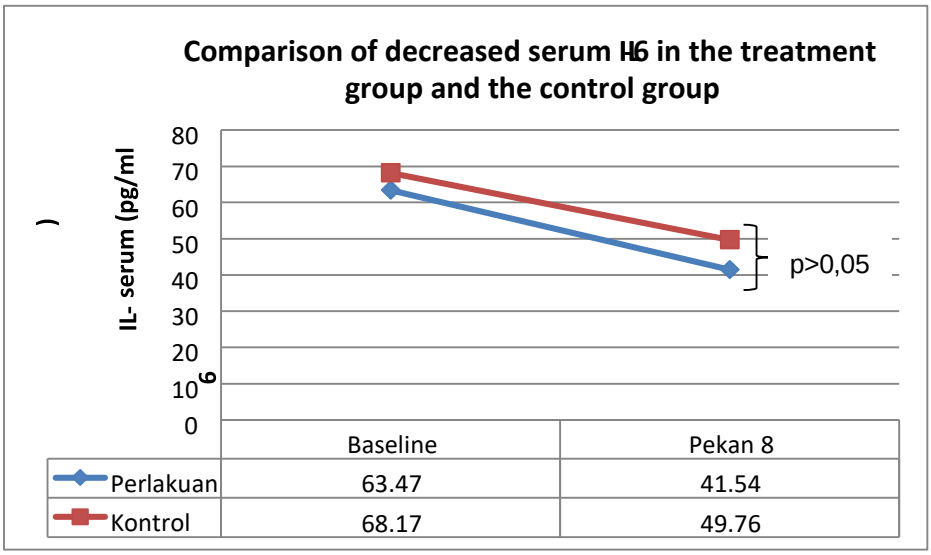

Figure 2. Comparison of decreased serum IL-6 in the treatment and control groups

3.4 Correlation between total SANS values and serum IL-6 levels in the treatment and control groups

Table 10. Correlation between total SANS values (baseline and week 8) with serum nterleukin-6 levels (baseline and week 8) in the treatment group and the control group.

Treatment	Interleukin-6 Serum
Total SANS score	r = 0,289 p = 0,071 n = 40
Control	Interleukin-6 Serum
Total SANS score	r = 0,232 p = 0,149 n = 40

spearman test, p<0.05 significance r = correlation strength; 0.1 - 0.3 weak; 0.4 - 0.6 medium; 0.7 - 0.9 strong

The relationship between the levels of SANS values in the treatment group and the control group can be seen in Table 10. The results of the correlation analysis using the Spearman correlation test showed that the correlation between the total SANS values (baseline and week 8) and serum Interlukin-6 levels (baseline and week 8) -8) in the treatment group was not significant (p> 0.05) with a weak correlation strength and a positive direction of the correlation. The correlation between total SANS values (baseline and week 8) and serum Interlukin-6 levels (baseline and week 8) in the control group

was not significant (p>0.05) with weak correlation strength and a positive direction. The correlation between total SANS values and serum IL-6 levels was not statistically significant, but clinically there was a decrease in total SANS values followed by a decrease in serum IL-6 levels in the treatment and control groups.

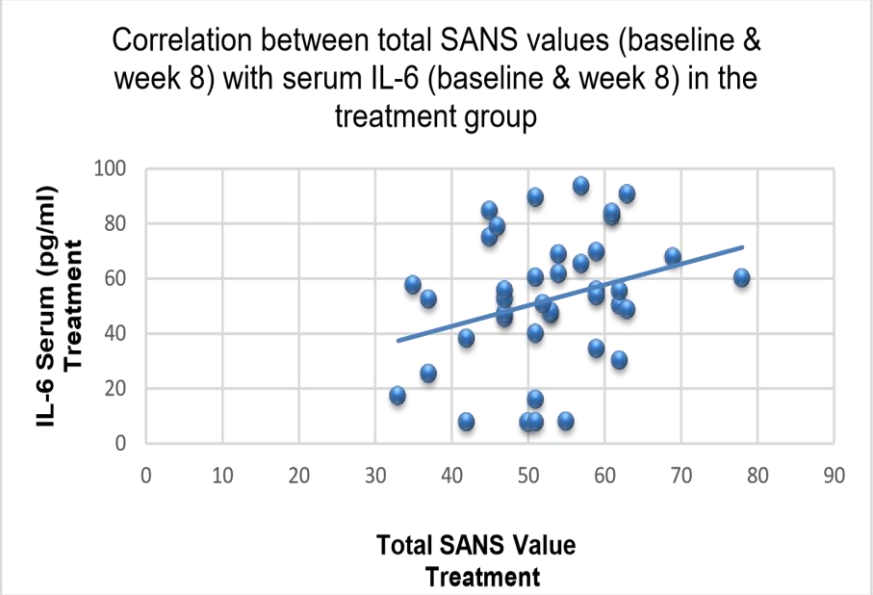

Figure 3. Graph of correlation between total SANS values (baseline and week 8) and serum interleukin-6 (baseline and week 8) in the treatment group

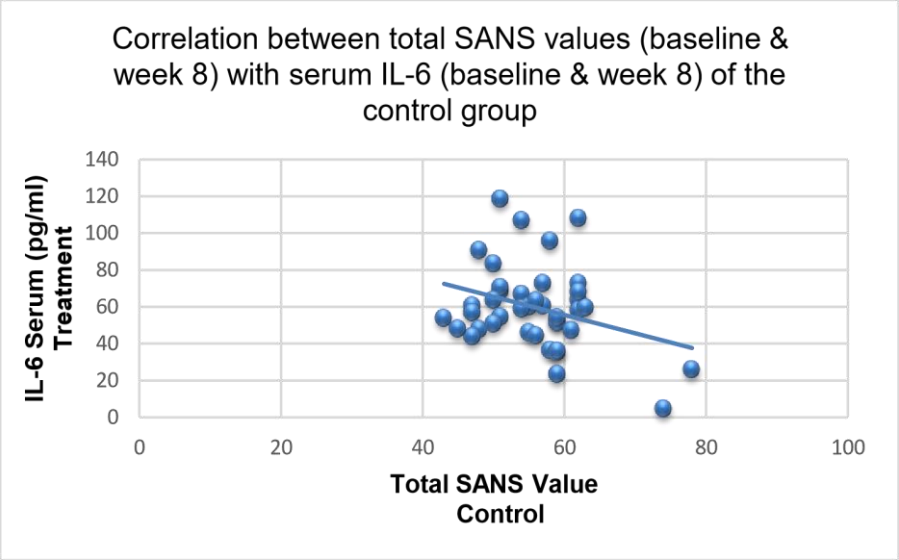

Figure 4. Graph of correlation between total SANS values (baseline and week 8) and serum interleukin-6 (baseline and week 8) of the control group

For improvement in negative symptoms in the treatment group and control group as measured by the total SANS score based on the decrease in the total SANS score from baseline to the 8th week in both groups there was a significant decrease (p <0.001). In both treatment and control groups, a therapeutic dose of antipsychotics was given in this study using risperidone 4-6 mg/day. Risperidone as a second-generation antipsychotic, which appears to be more efficacious than first generation antipsychotics in treating primary negative symptoms, then from the meta-analysis conducted showed that its efficacy is also in improving secondary negative symptoms.

Comparison of the decrease in serum IL-6 between the treatment group and the control group showed a greater decrease in the treatment group, when seen from the difference in decrease from the baseline to the 8th week. This could be the effect of adding citicoline to the treatment group. The role of citicoline as an alpha7-acetylcholine-nicotinic receptor agonist

(α7nAChR) participates in the negative regulation of adaptive immunity by inhibiting the synthesis and release of many pro-inflammatory cytokines (TNF-α, IL-6, and IFN-γ) in splenic B cells and simultaneously inhibit Ig-G1 production. Collectively, α7nAChR activation is beneficial for B-cell development by promoting their proliferation. revealed that α7nAChR is mainly expressed by microglia in the brain. Thus, cholinergic anti-inflammatory pathway (CAP) signaling there is largely initiated by microglia. Like its effect on macrophages, α7nAChR activation on microglia can also ameliorate inflammation and neuro-oxidative stress and thus is believed to be a viable therapeutic strategy for neuro inflammatory diseases (Wu et al., 2021).

The relationship between total SANS values and serum IL-6 levels in this study was not significant and there was a weak correlation strength in each measurement with a positive direction of correlation. Although the correlation was not statistically significant, clinically there was an improvement in negative symptoms accompanied by an improvement in serum IL-6 levels which could be seen by a decrease in the total SANS value accompanied by a decrease in serum IL-6 levels which was seen after 8 weeks. There is no previous study that has directly assessed the correlation between SANS scores and serum IL-6 levels in schizophrenic patients. But when viewed from the results of research by Goldsmith et al. (2016) who reported increased TNF-α and IL-6 in patients with deficit schizophrenia (with primary negative symptoms) compared to non-deficit patients and healthy controls. TNF-α correlated with the severity of PANSS negative symptoms, particularly with items on the PANSS included in the deficit schizophrenia categorization and no association was found between IL6 concentrations and the PANSS negative sub-scale. In accordance with research conducted by Feng et al. (2002) examined the relationship of several inflammatory biomarkers, one of which was IL-6 and found no association between serum IL-6 and psychopathological parameters (Feng et al., 2002).

4. Conclusion

Based on the results of this study, it can be concluded that there were significant changes in negative symptoms in schizophrenic patients who received risperidone and adjuvant citicoline therapy or who only received risperidone both at week 4 and week 8 of therapy, but the changes were more in schizophrenic patients who receiving risperidone and citicoline adjuvant therapy. There was a decrease in serum IL-6 levels in schizophrenic patients who received risperidone and citicoline adjuvant therapy or who only received risperidone after the 8th week of therapy, with a decrease in IL-6 levels more in the group given citicoline adjuvants but there was no significant difference in decreased IL levels -6 serum in both groups. The findings showed that there was no correlation between the magnitude of changes in negative symptoms and the magnitude of the decrease in serum IL-6 levels in both schizophrenic patients who received risperidone and citicoline adjuvant and those who only received risperidone.

The practical benefit of this research is as a reference material for Psychiatrists/Psychiatrists in the management of schizophrenic patients. While the theoretical benefit is to increase knowledge and understanding regarding the effect of citicoline adjuvant therapy on negative symptoms and IL-6 levels in schizophrenia patients, and to make a scientific contribution, especially in the psychosocial approach regarding the effect of citicoline adjuvant therapy on negative symptoms and IL-6 levels in schizophrenic patients. The methodological benefit is the basis for further research on citicoline adjuvant therapy in schizophrenic patients.

The limitation of this study is that this study did not examine other factors that affect IL-6 levels in schizophrenic patients. As a suggestion, further research can study the factors that influence serum IL-6 levels in schizophrenic patients. Further research with a longer duration can be carried out to see if the decline in SANS values can be sustained like the research that has been done. Further research can examine cognitive function and positive symptoms in schizophrenic patients receiving citicoline adjuvant therapy.

Reference

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