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The effectiveness of risperidone on PANSS score and IL-6 in confirmed COVID-19 schizophrenic patients

Sonny Teddy Lisal,[1] Hawaidah,[1] Dessy Natalia,[1] Arifin Seweng,[2] Yuyun Widaningsih,[3] Erlyn Limoa,[1] Saidah Syamsuddin[1]

[1]Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar; [2]Department of Biostatistics, Faculty of Public Health, Universitas Hasanuddin, Makassar; [3]Department of Clinical Pathology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

Correspondence: Dessy Natalia, Department of Psychiatry, Faculty of Medicine, Hasanuddin Universitas, 90245Makassar, Indonesia.
Tel.: +628114615988
E-mail: dessynatalia.psychiatry@gmail.com

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Abstract

The study aimed to determine the efficacy of risperidone on PANSS scores and Interleukin 6 (IL-6) levels in schizophrenia patients with confirmed COVID-19. The study type was analytical observational, with a prospective cohort design. The subjects included inpatient Schizophrenia patients with and without COVID-19, mild-moderate and asymptomatic COVID-19, and schizophrenic patients without COVID-19 who were hospitalized and met the inclusion and exclusion criteria, for a total of 22 subjects in each group. The Positive and Negative Syndrome Scale (PANSS) and Elisa Interleukin 6 (IL-6) serum were sampled consecutively for this study. In the positive covid-19 group, the Mean IL-6 Post was significantly lower than Pre (23.0 vs. 26.1, $p<0.001$), while in the control group, the Mean IL-6 Post (four weeks) was significantly lower than Pre (baseline), with 19.3 vs. 21.0 ($p<0.001$). Serum IL-6 levels appeared to be an effective prognostic biomarker in COVID-19 patients. The 35 pg/mL cut-off point could distinguish mild-moderate patients from more severe ones. We discovered that schizophrenia patients with verified positive COVID-19 received COVID-19 therapy in the form of a combination of antipsychotic and antivirals had IL-6 levels lower than 35 pg/mL, indicating the role of antipsychotic (risperidone) and antiviral in reducing IL-6 levels.

Introduction

The COVID-19 outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) was detected for the first time in Wuhan, China, spread throughout the country since late December 2019, and has attracted significant attention from all over the world. The first case of COVID-19 in Indonesia was reported on March 2, 2020, with as many as 2 cases, and until now, the number of cases has been increasing. It was reported that until March 23, 2021, in 34 provinces, there were 1,505,775 positive confirmed cases, 142,695 recovered cases, and 40,754 people died from this disease. South Sulawesi was ranked fifth in the number of positive confirmed cases, with 39,703 (4.5%), recovered 33,156 cases (83.5%), and 675 cases died (1.7%).[1]

The most common clinical manifestations of COVID-19 infection are cough and fever; about 8-19% progress to Acute Respiratory Distress Syndrome (ARDS), especially in the elderly and patients with multiple comorbidities. There have also been reports of lymphopenia, elevated C-

Reactive Protein (CRP), proinflammatory cytokines, ferritin, and D-dimer, and histopathological findings show an infiltrate of monocytes, macrophages, lymphocytes, vasculitis, and hypercoagulability in the lung tissue. Diffuse alveolar damage, focal hyperplasia of pneumocytes with infiltration of proinflammatory cells, and intravascular thrombosis lead to impaired pulmonary alveolar gas exchange.[2]

Coronavirus particles can be found in macrophages, but it is still unknown whether it is due to direct infection by the virus or the phagocytosis process.[3] This will activate the NLRP3 inflammasome receptor on monocytes/macrophages, releasing many proinflammatory cytokines (IL-6, GM-CSF, IL-1B, TNF, CXCL-8, CCL-3), causing a cytokine storm.[4]

A study by Gao et al. showed increased levels of cytokines, especially IL-6, which is directly related to the severity of the disease.[5] Another study showed that IL-6 is an effective biomarker of SARS-CoV-2 and may predict respiratory failure with a high degree of accuracy and help clinicians allocate patients correctly at an early stage. Serum IL-6 levels are a valuable prognostic biomarker in patients diagnosed with COVID-19 disease. The 35 pg/mL cut-off point can differentiate patients with more severe conditions.[6]

COVID-19 is characterized by complexities, including human-to-human transmission, the transmission of asymptomatic carriers, and high transmission efficiency, leading to a worldwide pandemic.[7] Patients with severe mental disorders are more susceptible to infection for various reasons, some related to the presence of an underlying disease and some due to environmental factors, including housing insecurity, smoking, poor access to health facilities, and the effects of medications used to treat the disorder. This increased susceptibility to respiratory tract infections may contribute to the risk of COVID-19 in patients with severe mental illness or who are in inpatient care.[8]

DADI Regional Special Hospital, South Sulawesi Province, reported that 80 patients with Schizophrenia positively exposed to COVID-19 since December 2020 were generally asymptomatic. These patients received typical and atypical antipsychotic therapies, including haloperidol, chlorpromazine, risperidone, and clozapine.

Schizophrenia is a chronic mental disorder characterized by many symptoms, such as hallucinations, delusions, confused thoughts, and impaired cognitive function.[9] The etiology of schizophrenia itself is not well understood. The hypothesis that often arises is that biological mechanisms such as the metabolic system or the immune system are involved in the pathophysiology of schizophrenia. Several processes, such as inflammation, oxidative stress, and complex interactions of neurotransmitters, are concerned with the pathophysiology of schizophrenia.[10]

The release of proinflammatory cytokines and free radicals associated with activated microglia is associated with the pathophysiology of schizophrenia. It is also found in postmortem examination of brain tissue.[11] An increase in several markers of inflammation in serum and CSF, such as Prostaglandin E2 (PGE2), Creative Protein (CRP), and several proinflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, and Tumor Necrosis Factor (TNF)α also observed in schizophrenic patients.[12] Involvement of the immune system is thought to be related to the pathogenesis of schizophrenia, especially in negative symptoms and cognitive dysfunction.[13] This immune system dysregulation can be connected to events, risk factors, or responses to therapy in schizophrenic patients.[14]

Antipsychotic medication is the treatment of choice for schizophrenia. Risperidone is a second-generation antipsychotic drug that is effective for positive and negative symptoms of schizophrenia. Side effects of these drugs are mild and generally do not interfere with cognitive function. There are several mechanisms by which risperidone may decrease IL-6 levels. Accumulating evidence has shown that astrocytes can amplify the CNS's inflammatory response, a phenomenon closely related to the neurobiology and development of neuropsychiatric disorders. Quincozes-Santos et al. observed that risperidone had anti-inflammatory action on C6 astroglia, decreasing IL-6 release.[15] People with schizophrenia and people who have SARS-CoV-2 both have an inflammatory response that includes higher levels of cytokines and inflammatory markers like IL-1β, IL-6, IL-8, and TNF. So, this study aims to explore the relationship between IL-6 levels, the efficacy of risperidone therapy, and the PANSS score in schizophrenia patients diagnosed with COVID-19.

Materials and Methods

Study design

This study was an analytical observational study with a prospective cohort approach. A cohort study examines the relationship between exposure and disease by selecting two or more study groups based on exposure status and then following them for a certain period to identify and calculate the magnitude of the disease.

Population and sample

The population in this study were Schizophrenic subjects with and without COVID-19, mild-moderate and asymptomatic COVID-19, and schizophrenic subjects without COVID-19 who were hospitalized and met the inclusion and exclusion criteria. The research sought individuals aged 20-50 diagnosed with both COVID-19 and Schizophrenia, actively taking risperidone at a daily dosage of 2-6 mg for at least four weeks, confirmed with an RT-PCR swab test to have mild to moderate symptoms or be asymptomatic and have a PANSS total score of less than 95, indicating significant

illness. The control group included individuals with Schizophrenia, negative for COVID-19, also taking Risperidone at a similar dosage for at least four weeks, and a PANSS total score of less than 95. Exclusion criteria involved individuals abusing drugs or alcohol, taking specific medications, or having severe unrelated physical illnesses. Drop-out criteria included individuals leaving the hospital before four weeks or passing away.

Research instruments

The data collection tools and study instruments utilized in this research included a demographic questionnaire sheet and the Positive and Negative Syndrome Scale (PANSS), a psychometric tool used to evaluate positive and negative symptoms as well as general psychopathology. Each item on the scale is scored from 1 (no symptoms) to 7 (very severe symptoms). In addition, serum Elisa Interleukin 6 (IL-6) was used as a proinflammatory cytokine marker of inflammation with a limit point for serum IL-6 levels set at 35 pg/mL. The normal range of IL-6 concentrations is between 0-7 pg/mL, and the blood plasma IL-6 levels were measured using the ELISA method.

Data analysis

Data analysis was carried out after the primary data had been collected using the Statistical Package for Social Sciences (SPSS) Program. If the data was normally distributed, an unpaired T-test was applied, and if it was not, Mann-Whitney.

Result

This study was conducted on schizophrenic patients who confirmed positive COVID-19 and had been screened; these patients were inpatients at the Dadi Special Hospital from July to August 2021. A total of 41 patients diagnosed with Schizophrenia with COVID-19 were screened and 22 subjects (53.65%) met the inclusion criteria. Similarly, 22 subjects with negative COVID-19 were screened for a control group.

Data analysis was conducted on 44 subjects aged 18 – 53 years with a mean of 35.9±9.2 years. Table 1 shows the data Normality Testing (n=44), which highlights the distribution of PANSS (Positive and Negative Syndrome Scale) scores and IL-6 levels before and after treatment. It reveals that while PANSS scores exhibited a non-normal distribution in both pre-and post-treatment, IL-6 levels were normally distributed after treatment. This table uses the Kolmogorov-Smirnov test to assess data normality.

The data in Table 2 presents the demographic statistics of the survey's 44 respondents, encompassing gender, age, education, employment, and PCR COVID-19 test results. The analysis reveals that 77.3% of the respondents are male, with the most significant portion falling within the

30-39 age bracket, constituting 43.2% of the sample. Moreover, the majority of participants, totaling 56.8%, have attained a primary school education, while 79.5% reported being unemployed. Comparison of PANSS and IL-6 Pre-Post demonstrates the significant reduction in both PANSS scores and IL-6 levels following the treatment, with respective p-values indicating statistical significance. This suggests improvements in the participants' psychiatric symptoms and inflammatory status (Table 3).

Table 4 shows that the comparison of PANSS and IL-6 Pre-Post (by gender) shows the impact of treatment on PANSS scores and IL-6 levels, categorized by gender. Both men and women showed significant improvements post-treatment, underscoring risperidone's effectiveness across genders.

In Table 5, the data comparing PANSS and IL-6 Pre-Post by age groups shows that there were significant reductions in PANSS scores and IL-6 levels across all age categories. This suggests that the treatment has broad applicability across different age groups.

In Table 6, the comparison of PANSS and IL-6 pre-post (by PCR testing) distinguishes between participants with positive and negative COVID-19 PCR tests. Both groups showed significant decreases in PANSS scores and IL-6 levels, underscoring the potential advantages of risperidone for schizophrenia patients, irrespective of their COVID-19 status.

Discussion

This study was conducted to see the effectiveness of risperidone administration on PANSS scores and Interleukin 6 levels in Schizophrenia patients with confirmed COVID-19 for four weeks, from July to August 2021, with a total sample of 44 people, divided into two groups, namely the COVID-19 POSITIVE group and control groups. Both groups received Risperidone therapy of 2-6 mg per day; the COVID-19 POSITIVE group was the Schizophrenia group with COVID-19, and the control group was the schizophrenia group without COVID-19. Patients who met the inclusion criteria were recorded based on gender, age category, education, occupation, and PCR results.

Schizophrenia is a chronic mental disorder characterized by many symptoms, such as hallucinations, delusions, confused thoughts, and impaired cognitive function.[9] Several processes, such as inflammation, oxidative stress, and complex interactions of neurotransmitters, are involved with the pathophysiology of schizophrenia.[10]

The release of proinflammatory cytokines and free radicals associated with activated microglia is associated with the pathophysiology of schizophrenia. It is also found in postmortem examination of brain tissue.[11] An increase in several markers of inflammation in serum and CSF, such as Prostaglandin E2 (PGE2), C-Reactive Protein (CRP), and several proinflammatory cytokines such as Interleukin (IL)-1β, IL-6, IL-8, and Tumor Necrosis Factor (TNF) α also observed in schizophrenic patients.[12] Involvement of the immune system is related to the pathogenesis of

schizophrenia, especially negative symptoms and cognitive dysfunction.[13] This immune system dysregulation can be connected to events, risk factors, or responses to therapy in schizophrenic patients.[14]

National patient databases in the UK[16] and South Korea[17] found that patients with psychotic disorders are at increased risk of severe complications of COVID-19. Patients with severe mental illnesses are more susceptible to infection for various reasons, some related to the presence of an underlying disease and some due to environmental factors, including housing insecurity, smoking, poor access to health facilities, and the effects of medications used to treat the disorder. This increased susceptibility to respiratory tract infections may contribute to the risk of COVID-19 in patients with severe mental illness or who are in inpatient care.[8]

Schizophrenia subjects in the COVID-19 POSITIVE group and control groups were more male than female; male subjects were 34 subjects (77.3%), and female subjects were 10 subjects (22.7%). Based on the age, 18-29 years was 12 subjects (27.3%), 30-39 years was 19 subjects (43.2%), 40-53 years was 13 subjects (29.5%) (Table 2). Schizophrenia is more common in men than women.[10] Men have an earlier onset of schizophrenia than women; the peak age is 25 to 35 years, approximately 15-55 years of age for patients on schizophrenia treatment.[9] In this study, the samples were 30-39 years old (43.2%).

The education level in this study was 56.8% elementary school. A deficit in social functioning mode made it difficult for subjects with schizophrenia to continue their education to a higher level. This deficit was in the form of social isolation, often indicated by inadequate and inappropriate emotional responses, poor interpersonal relationships, feelings of threat in social situations, difficulty communicating verbally, and reactions to excessive stimuli.[18]

The subject's initial PANSS scores varied between 68–81, with a mean of 72.4±3.4. The distribution of pre-PANSS data was not Normal. Post-subject PANSS scores ranged between 43–69, with a mean of 56.9±6.3. The distribution of PANSS post data was not Normal. The difference scores of PANSS (pre-post) subjects varied between 7–34, with a mean of 15.6±5.9 (Table 1). The difference in PANSS scores showed a decrease in the post-measurement compared to pre-measurement. The distribution of PANSS difference data was not normal, possibly due to clinical improvement before and after risperidone antipsychotic therapy.

There are several mechanisms by which risperidone may decrease IL-6 levels. The study conducted by De Souza et al. found that risperidone inhibited IL-6-induced S100B secretion, reducing the rate of secretion below the basal level.[19] Circulating levels of IL-6 and IL-10 may regulate the expression of the AKT1, DROSHA, NDEL1, DISC1, and MBP genes.[20] Thus, risperidone treatment may modulate gene expression during the treatment of schizophrenia. In recent years, scientists have discovered in biochemical studies of the central nervous system that IL-6 is

produced by neurons, astrocytes, and microglia and acts as a neurotrophic factor in the central nervous system. However, recent studies suggest that risperidone can attenuate microglia activation in the brain, reducing IL-6 levels and suggesting risperidone may improve brain disease.21
A meta-analysis study that found a decrease in IL-6 levels after short-term risperidone treatment saw a significant reduction after four weeks of antipsychotic administration.[22] In another study that observed a decrease in IL-6 levels within nine days of antipsychotic treatment and at eight weeks showed no significant symptoms, there was no difference between patients and control subjects.[23] Overall, IL-6 levels were normalized to some extent immediately after risperidone treatment. Evidence that cytokines can be affected by antipsychotic treatment, possibly in a dual mode (short-term and long-term), anti-inflammatory in antipsychotics may contribute to the treatment of schizophrenia. Anti-inflammatory effects of antipsychotics may play a role in treating psychotic symptoms.[24,25] In a recent meta-analysis of 12 studies (961 patients with schizophrenia and 729 controls) on the effect of antipsychotics on serum production of interleukin-6 (IL-6), a proinflammatory cytokine, they found that antipsychotic treatment was associated with a decrease in IL-6 on the patient. In contrast, trifluoperazine, a conventional antipsychotic, has been identified as a potential treatment option for microbial-induced septic shock after it reduced the inflammatory response by suppressing proinflammatory cytokines in mice.[26] Recently, Crespo-Facorro *et al.* suggested that aripiprazole, an atypical antipsychotic, could also be reused as a treatment for COVID-19 after transcriptomic analysis revealed that it could reverse the effects caused by COVID-19 on gene expression in patients.27
In this study, in the COVID-19 POSITIVE group, the Mean of IL-6 Post was significantly lower than Pre, which was 23.0 compared to 26.1 ($p<0.001$). While in the control group, the Mean of IL-6 Post was considerably lower than Pre, which was 19.3 versus 21.0 ($p<0.001$) (Table 6). The COVID-19-positive group and control groups might had lower IL-6 values below the cut-off (35pg/mL) even before in treatment antiviral. The phenomena could be the effect of risperidone and antivirals made The COVID-19 positive group asymptomatic and the IL-6 value below the cut-off. Serum IL-6 levels appeared to be a useful prognostic biomarker in patients with a diagnosis of COVID-19 disease. The 35 pg/mL cut-off point could clearly distinguish the patients with more severe disease. Serum IL-6 levels in patients with COVID-19: and non-COVID-19, COVID-19: 7.56, Non-COVID: 0.03, Other diseases 9.12.[28] A study in Shanghai, China, found that in hospitalized COVID-19 patients, the normal concentration ranges for IL-1β, IL-8, IL-10, and tumor necrosis factor-alpha (TNFα) were below 5, 62, 9.1, respectively, and 8.1 pg/mL.[29] The normal concentration range of IL-6 is between 0-7 pg/mL, and the normal IL-2 receptor (IL-2R) ranges from 223 to 710 U/mL.

The lower limit of detection of the kit was 1.5 pg/mL, and the upper limit of detection was 5000 pg/mL without dilution. The upper limit of normal is 7 pg/mL. Baseline IL-6 concentrations are highly predictive of in-hospital mortality for COVID-19 patients. The mean concentration of IL-6 was < 0.001. Serum IL-6 remains high in critically ill patients even after recovery. An IL-6 concentration higher than 37.65 pg/mL was predictive of in-hospital mortality (AUC 0.97 [95% CI 0.95–0.99], P < 0.001) with a sensitivity of 91.7% and a specificity of 91.7%. 95.7%.[30] A study mentions the effect of antipsychotic therapy on disease progression and the correlation between cytokine levels and clinical characteristics.[31] Later the results of this study showed that the cytokine changes in schizophrenia may differ from the clinical status. In this study, schizophrenic patients with confirmed COVID-19 received COVID-19 therapy with an administration of antivirals.

Conclusions

The PANSS scores in both the COVID-19 positive group and control groups at the end of the study were significantly lower than at the initial treatment, and the same trend was observed for the IL-6 scores in both groups. The decreases in PANSS and IL-6 scores were not affected by gender, age, or PCR results. Notably, both the COVID-19 positive group and control groups had a lower value of IL-6 (35pg/mL) at the beginning of the study, suggesting that risperidone may have influenced the IL-6 levels before the COVID-19 diagnosis was confirmed. Additionally, a combination of the antipsychotic risperidone and antivirals was found to lower the IL-6 levels below the cutoff point.

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Table 1. Data normality testing (n=44)

Variables	Minimum	Maximum	Median	Mean	SD	Data Distribution*
PANSS Pre	68	81	71.0	72.4	3.4	Not Normal
PANSS Post	43	69	58.0	56.9	6.3	Not Normal
Difference PANSS	7	34	13.5	15.6	5.9	Not Normal
IL-6 Pre (pg/mL)	16.1	31.0	24.1	23.6	4.1	Normal
IL-6 Post (pg/mL)	14.3	27.5	21.5	21.1	3.4	Normal
Difference IL-6 (pg/mL)	0.2	4.9	2.3	2.5	1.2	Normal

*Kolmogorov-Smirnov test

Table 2. Characteristics of respondents (n=44).

Category	Variables	n	Percent (%)
Gender	Men	34	77.3

	Women	10	22.7
Age	18-29 years	12	27.3
	30-39 years	19	43.2
	40-53 years	13	29.5
Education	Primary school	25	56.8
	Junior high school	6	13.6
	Senior High School	11	25.0
	College	2	4.5
Employment	Employee	2	4.5
	Farmer	3	6.8
	Entrepreneur	4	9.1
	Not work	35	79.5
PCR	Positive	22	50.0
	Negative	22	50.0

Table 3. Comparison Positive and Negative Syndrome Scale (PANSS) dan IL-6 pre-post.

Category	n	Mean	SD	Decrease (%)	p
PANSS Pre	44	72.4	3.4	21.4	0.000*
PANSS Post	44	56.9	6.3		
IL-6 Pre (pg/mL)	44	23.6	4.1	10.6	0.000**
IL-6 Post (pg/mL)	44	21.1	3.4		

*Wilcoxon Signed Rank test; **Paired t-test

Table 4. Comparison Positive and Negative Syndrome Scale (PANSS) dan IL-6 pre-post (by gender).

Category	Variables	n	Mean	SD	p
Man	PANSS Pre	34	72.1	3.2	0.000*

	PANSS Post	34	56.5	5.9	
	IL-6 Pre (pg/mL)	34	23.6	4.4	0.000**
	IL-6 Post (pg/mL)	34	21.1	3.6	
Women	PANSS Pre	10	73.6	4.0	0.000*
	PANSS Post	10	58.2	7.7	
	IL-6 Pre (pg/mL)	10	23.4	3.3	0.000**
	IL-6 Post (pg/mL)	10	21.0	3.0	

*Wilcoxon Signed Rank test; **Paired t-test

Table 5. Comparison Positive and Negative Syndrome Scale (PANSS) dan IL-6 pre-post (by age).

Category	**Variables**	**n**	**Mean**	**SD**	**p**
18-29 years	PANSS Pre	12	72.3	3.6	0.000*
	PANSS Post	12	56.9	6.2	
	IL-6 Pre (pg/mL)	12	24.5	3.7	0.000**
	IL-6 Post (pg/mL)	12	21.9	3.2	
30-39 years	PANSS Pre	19	71.3	2.6	0.000*
	PANSS Post	19	56.4	6.4	
	IL-6 Pre (pg/mL)	19	23.0	4.7	0.000**
	IL-6 Post (pg/mL)	19	20.8	3.9	
40-53 years	PANSS Pre	13	74.2	3.9	0.000*
	PANSS Post	13	57.5	6.8	
	IL-6 Pre (pg/mL)	13	23.5	3.8	0.000**
	IL-6 Post (pg/mL)	13	20.9	2.9	

*Wilcoxon Signed Rank test; **Paired t-test

Table 6. Comparison Positive and Negative Syndrome Scale (PANSS) dan IL-6 pre-post (by PCR testing).

PCR	Variables	n	Mean	SD	Decrease (%)	p
Positive	PANSS Pre	22	73.5	3.9	22.4	0.000*
	PANSS Post	22	57.0	6.9		
	IL-6 Pre (pg/mL)	22	26.1	2.4	11.8	0.000**
	IL-6 Post (pg/mL)	22	23.0	2.1		
Negative	PANSS - Beginning	22	71.4	2.6	20.6	0.000*
	PANSS - End	22	56.7	5.9		
	IL-6 Pre (pg/mL)	22	21.0	3.9	8.1	0.000**
	IL-6 Post (pg/mL)	22	19.3	3.4		

*Wilcoxon Signed Rank test; **Paired t-test