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The Effectiveness of Meloxicam Adjuvant Therapy to Improve Cognitive Function of Schizophrenic Patients

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A B S T R A C T

Introduction: Schizophrenia is a chronic psychotic disorder triggered by genetic and environmental factors such as an inflammatory response. The inflammatory response in schizophrenic patients increases with cognitive decline. Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) group with Cyclo-oxygenase (COX-2) inhibitory activity and can suppress the production of inflammatory cytokines. This study aimed to determine the efficacy of Meloxicam as an adjuvant therapy to improve cognitive function in schizophrenic patients.

Methods: This was a quasi-experimental study using a single-blind, pretest–post-test design. The sample size in this study was 34 subjects who had met the inclusion and exclusion criteria. All samples were divided into two groups, namely the treatment group, with as many as 17 subjects receiving additional therapy with Meloxicam 15 mg/day for 4 weeks, and the control group, with 17 subjects. The score of the Schizophrenia Cognition Rating Scale (ScoRS) was assessed before and after therapy. Data analysis used SPSS 25.0. In both groups, the SCoRS score was different.

Results: In the treatment group, there was a decrease in the SCoRS score that was greater than in the control group. There was a statistically significant difference with p = 0.002 in decreasing SCoRS scores.

Conclusion: Adjuvant therapy Meloxicam improves cognitive function in schizophrenic patients at Dr. Arif Zainuddin Regional Mental Hospital (RSJD), Surakarta.

Highlights:
1. Schizophrenic patients have cognitive dysfunction.
2. Meloxicam, as an adjuvant therapy, can improve cognitive function in schizophrenic patients.

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Introduction

Schizophrenia is a chronic psychotic disorder that often subsides but comes and goes with various clinical manifestations. The symptoms and course of the disease vary widely.[1] Another opinion says schizophrenia is a chronic psychotic disorder caused by genetic and environmental factors such as infection and the immune response to infection. Activation of the immune system causes behavioral, neuroendocrine, and neuropathological changes in the central nervous system.[2,3] These changes occur due to the interaction of cytokines with their receptors on neurons and glial cells of the brain.[3] Schizophrenic patients can be found in almost all parts of the world. The prevalence of schizophrenic patients in the general population ranges from 1% to 1.3%.[1] Approximately 70% of schizophrenic patients experience cognitive dysfunction in concentration, memory, attention, executive function, and language.[2,4]

Schizophrenia has symptoms such as positive, negative, and cognitive dysfunction. Visual and auditory hallucinations, delusions, disorganized behavior, and speech characterize positive symptoms.[4] Negative symptoms include loss of motivation and poverty of speech. The cognitive dysfunction of schizophrenia involves thought disorganization, impaired concentration, problems with attention, memory- and problem-solving, and psychosocial difficulties such as lack of social relationships and significantly less total productive activity.[5] In other words, schizophrenia is signed by a wide range of behavioral and cognitive deficits that can easily interfere with the basic processes of human cognition and judgment.[6,7]

Inflammation is thought to be one of the factors that cause schizophrenia. Inflammatory markers such as pro-inflammatory cytokines are causal to psychiatric disorders. Schizophrenia is one of them.[7] Inflammation of the Central Nervous System (CNS), which is closely associated with neurodegeneration, plays a role in the proinflammatory cytokines, and microglia play a role in the inflammatory process of the CNS. Increased production of pro-inflammatory cytokines and microglia can trigger schizophrenia.[8,9] Increased inflammatory response in schizophrenic patients is associated with changes in cognitive function. Excessive activation of the immune response causes cognitive changes through the effects of peripheral cytokines, activation of microglia, and neurodegenerative processes.[8,10]

Non-steroidal anti-inflammatory drugs (NSAIDs) are drugs used to relieve inflammation and pain.[11] NSAIDs consist of a non-selective group that works by inhibiting the cyclo-oxygenase enzyme (COX-1 and COX-2), thereby reducing the production of prostaglandins (PG). In contrast, another group of NSAIDs, selective COX-2 inhibitors, works by inhibiting the COX-2 enzyme. NSAID inhibits prostaglandin production by blocking COX activity. This group of drugs has general abilities as analgesic, anti-inflammatory, and antipyretic.[11,12]

Meloxicam is a COX-1 and COX-2 selective NSAID anti-inflammatory drug and is relatively safe against gastrointestinal side effects. In addition, meloxicam has an anti-inflammatory effect equivalent to other anti-inflammatories. Meloxicam has a selectivity towards COX-2, which is more significant than COX-1.[13]

A study conducted by Müller, *et al.* (2010) in schizophrenic patients showed that the administration of adjuvant NSAIDs combined with risperidone given for 5 weeks showed an improvement in cognitive function assessed from a decrease in the positive scale, negative scale, and general psychopathology scale (PANSS) score (difficulty in abstract thinking and disorientation).[14] Different results showed in a study conducted by Rapaport, *et al*. (2005) that stated in a double-blind, randomized controlled trial (RCT) study, schizophrenic patients with risperidone received 8 weeks of adjuvant NSAIDs.[15] The study concluded that adjuvant NSAIDs in schizophrenic patients did not improve clinical symptoms.

Following the differences from the previously mentioned studies, this study aimed to determine the efficacy of Meloxicam as an adjuvant therapy to improve cognitive function in schizophrenic patients. This study hypothesizes that there is an effective adjuvant treatment, Meloxicam, on cognitive function in schizophrenic patients.

Methods

The study used a quasi-experimental, single-blind, pretest–post-test design conducted in the Inpatient Unit of Dr. Arif Zainuddin Regional Mental Hospital (RSJD), Surakarta, from May to July 2020. Schizophrenic patients were given combination antipsychotic therapy (risperidone-chlorpromazine, and/or haloperidol injection) and underwent hospitalization at RSJD, which met the inclusion and exclusion criteria from May to July 2020. Samples were taken using a purposive sampling technique.

The inclusion criteria were schizophrenic patients who were hospitalized at RSJD from May to July 2020, received treatment with a combination antipsychotic risperidone-chlorpromazine, and/or intramuscular injection of haloperidol, aged 18-40 years old, and got approval from the caregiver. The exclusion criteria were schizophrenic patients with organic disorders such as epilepsy, stroke, mental retardation or head injury with a history of decreased consciousness, substance and alcohol abuse, taken anti-inflammatory drugs or steroids, or taken anti-inflammatory drugs or steroids for less than one month, and gotten electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS).

In experimental research, the sample size of each treatment group should be in the range of 15 to 20 samples.[16] Calculation of research subjects is determined by using a formula.

$(t-1)(n-1) \geq 15$

$(2-1)(n-1) \geq 15$

$(n-1) \geq 15$

$n \geq 15 = 15+10\% = 15+1.5 = 15+2$

$n \geq 17$

Therefore, the minimum number of samples for each group in this study was 17 subjects. The data obtained were then collected and analyzed to determine the difference between Meloxicam adjuvant therapy for improving cognitive function as seen through changes in the Schizophrenia Cognition Rating Scale (ScoRS), through paired t-test analysis if the data distribution was normal, and the Wilcoxon test if the data distribution was abnormal. The difference was significant when $p < 0.05$. All statistical analyses used the Statistical Package for the Social Sciences (SPSS) 25.0.

Results

The sample size in this study was 34 subjects who had met the inclusion and exclusion criteria. All samples were divided into two groups, namely the treatment group, with as many as 17 subjects, and the control group, with as many as 17 subjects. Subjects in the treatment group received additional therapy with Meloxicam 15 mg per day for 4 weeks, in addition to combination antipsychotic therapy of risperidone-chlorpromazine and/or injection of haloperidol, while subjects in the control group only received antipsychotic therapy with the combination of risperidone-chlorpromazine and/or injection of haloperidol.

The research subject data was obtained from the results of the SCoRS score assessment. After all research data had been collected, data analysis was performed using the Statistical Package for the Social Sciences (SPSS) program. From the research conducted, data were obtained about the demographic characteristics of the research subjects and the results of the pre- and post-test SCoRS assessments. The data obtained are presented in tabular form.

Based on Table 1, the characteristic variables that are quantitative with ratio data (numeric) are age and SCoRS value. Age in the treatment group averaged 34.76 ± 5.14 years old, and the control group averaged 32.29 ± 4.91 years old, with statistical results showing $p = 0.097$ ($p > 0.05$), indicating that there was no significant difference in the characteristics of subjects based on age between the treatment group and the control group. The average SCoRS value in the treatment group was 2.36 ± 0.25, and the control group averaged 2.87 ± 0.69, with statistical results showing $p = 0.177$ ($p > 0.05$), indicating that there was no significant difference in the characteristics of subjects based on the pretest SCoRS value between the treatment and control group.

Characteristic variables that are qualitative with nominal data (categorical) are gender and level of education. By gender, it is known that most patients were males, namely 11 patients (32.4%) in the treatment group and 15 patients (44.1%) in the control group. Meanwhile, education below junior high school equivalent was 14 patients (41.2%) in the treatment group and 12 patients (35.3%) in the control group. Education above the high school equivalent was 3 patients (8.8%) in the treatment group and 5 patients (14.7%) in the control group. The results obtained statistically showed that there was no significant difference between the treatment group and the control group in gender ($p = 0.225$), age ($p = 0.097$), and education ($p = 0.668$) because the p-value > 0.05. The characteristics of the research subjects between the treatment and control groups were homogeneous.

Table 1. Characteristics of research subjects

Characteristic	Group		p-value
	Treatment (n = 17)	Control (n = 17)	
Gender			
Male	11 (32.4%)	15 (44.1%)	0.225
Female	6 (17.6%)	2 (5.9%)	
Age			0.097
Mean ± SD	34.76 ± 5.14	32.29 ± 4.91	
Score of SCoRS Pretest			
Mean ± SD	2.36 ± 0.25	2.87 ± 0.69	0.177
Education			
≤ JHS	14 (41.2%)	12 (35.3%)	0.668
≥ SHS	3 (8.8%)	5 (14.7%)	

JHS: junior high school; SHS: senior high school

Discussion

Table 2 presents data on differences in SCoRS scores before and after treatment in the treatment and control groups and data on the decline in SCoRS scores. The data had been tested for normality and homogeneity and was normally distributed. In the treatment group with adjuvant Meloxicam 15 mg/day, statistical calculations showed the mean pre-test SCoRS score was 2.36, and the post-test SCoRS score average was 1.39. The mean results in the control group showed that the mean score of the pre-test SCoRS was 2.87, and the mean score of the SCoRS post-test was 1.47. The data on decreasing SCoRS score significantly affected the administration of adjuvant Meloxicam on improving the SCoRS score ($p = 0.01$) because the p-value was <0.05.

The data assessment started with assessing the subject characteristics of age, gender, initial SCoRS score, and education level.

Table 2. The mean score of the pretest, post-test, and the decrease in SCORS scores in the treatment and control groups

	Mean	SD	Min – Max	95% CI	p
SCoRS pretest					
Treatment	2.36	0.21	2.10 – 3.10	2.25 – 2.47	0.177
Control	2.87	0.69	2.00 – 3.90	2.51 – 3.23	
SCoRS post-test					
Treatment	1.39	0.14	1.20 – 1.70	1.32 – 1.46	0.037
Control	1.47	0.51	1.00 – 2.75	1.21 – 1.73	
Decrease in SCoRS					
Treatment	0.96	0.25	0.55 – 1.70	0.83 – 1.09	0.01
Control	1.40	0.76	0.01 – 2.35	1.00 – 1.79	

Source: Research data, processed

The treatment and the control group in this study were equivalent in terms of characteristics, including age, gender, initial SCoRS score, and education level, as shown in Table 1. Therefore, it can be said that the sample of this study was homogeneous. The treatment group and the control group had the same initial data. This can be seen from the results of statistical calculations, which show no significant difference in the initial SCoRS scores in the two groups. Thus, it can be said that the sample of this study was homogeneous. This study found that both groups experienced a decrease in SCoRS scores. This could be because both groups received the same standard antipsychotic therapy and benefited from the antipsychotic therapy.

There were different SCoRS scores in the two groups. In the treatment group, there was a decrease in the SCoRS score that was greater than in the control group. After analyzing with statistical calculations, there was a significant difference in the decrease in SCoRS scores. Hence, it can be said that the addition of Meloxicam 15 mg/day had an effect on reducing SCoRS scores in schizophrenic patients who were hospitalized at RSJD.

These results are in accordance with the study conducted by Müller, *et al.* (2010), which showed that the administration of NSAID adjuvant therapy improved cognitive function.[14] The same results showed in the study of Sil, *et al*. (2016), which stated that the administration of NSAID therapy gave promising results and showed a more beneficial treatment effect when standard antipsychotic therapy was given together with anti-inflammatory drugs compared to the results of treatment using only antipsychotics in terms of improving cognitive function.[17] These results are in accordance with the study conducted by Purwono (2018) that adding Meloxicam therapy effectively reduced Hs-CRP levels and improved PANSS scores. This is in accordance with the results of this study. There were no side effects in this study, especially gastrointestinal side effects, during the adjunctive anti-inflammatory therapy of Meloxicam.[18]

Different results suggest that in a study by Rapaport, *et al*. (2005), who reported that in a double-blind RCT, schizophrenic patients treated with risperidone received an additional 8 weeks of NSAIDs.[15] The study concluded that NSAID adjuvants in schizophrenic patients did not show improvement in clinical symptoms.

Meloxicam is a COX-1 and COX-2 selective anti-inflammatory NSAID and is relatively safe for gastrointestinal side effects. In addition, meloxicam has anti-inflammatory effects comparable to other anti-inflammatory drugs.[10,13] COX-2 inhibitors are selective for COX-2 and help reduce pain and inflammation while reducing the risk of stomach lining damage and not affecting platelet function.[17] Meloxicam absorption has a half-life of up to 20 hours. Meloxicam 7.5-15 mg/day has a lower ulcerogenic side effect than other NSAIDs.[19] The bioavailability of Meloxicam orally is 89%, and maximum plasma concentrations occur within 4-5 hours. Meloxicam can be given regardless of the time of administration or concurrent administration of antacids.[19,20]

Giving adjuvant meloxicam 15 mg/day for 4 weeks can improve cognitive function in schizophrenic patients, as seen from the patient's independence in activities, improved social function, and the patient's encouragement to socialize with other patients in the hospital. Giving Meloxicam 15 mg/day for 4 weeks is expected to provide maximum therapeutic effect. This study collaborated with the doctor in charge of the room, laboratory health analysts in taking blood samples of research subjects in both the control and treatment groups, and with room nurses to supervise additional therapy and side effects.

The results obtained from this study are expected to add insight into psychiatry, especially regarding the effectiveness of giving Meloxicam as adjuvant therapy in improving cognitive function in schizophrenic patients. It can provide benefits in terms of better treatment in schizophrenic patients with cognitive dysfunction. This study is also expected to be the basis for further research to provide benefits in managing schizophrenic patients.

Strength and Limitations

The limitations of this study were the small sample size and the short research period (4 weeks). This study can contribute data for future studies, especially in experimental studies that evaluate the relationship between anti-inflammatory drugs and cognitive function in schizophrenic patients.

Conclusion

There was a difference in the decrease in the SCoRS score between the treatment and the control group. The treatment group experienced a greater decrease in SCoRS scores. Adjuvant therapy Meloxicam 15 mg/day for 4 weeks

had an effect on improving cognitive function, as seen from the decrease in SCoRS scores of schizophrenic patients at RSJD.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Ethical Clearance

This study had received ethical clearance from the Ethics Committee for Health Research, Dr. Moewardi General Academic Hospital, Surakarta (no. 1.410/XI/HERC/2020) on 14 April 2020.

Authors' Contributions

Concepting and designing, data acquisition, analyzing and interpreting data: NNBI. Drafting the manuscript and revising: IGIN. Giving final approval of the manuscript to be published: AH.

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