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Effectiveness of Adjuvant Treatment of N-Acetylcysteine on Negative Symptoms and Neutrophil-Lymphocyte Ratio (NLR) in Schizophrenic Patients

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A B S T R A C T

Introduction: Schizophrenia is a mental disorder that has a negative symptom domain. Negative symptoms are commonly referred to as the essence of schizophrenia. Treatment of negative symptoms is still considered less than optimal. The ratio of neutrophils and lymphocytes is one of the markers of inflammation. This study aimed to analyze the effectiveness of N-acetylcysteine as adjuvant therapy for improving negative symptoms and changes in the neutrophil-lymphocyte ratio (NLR) in schizophrenic patients.

Methods: This was a quasi-experimental study using a single-blind, pretest–post-test design. The subjects were 34 schizophrenic patients who were inpatients at Dr. Arif Zainuddin Regional Mental Hospital (RSJD), Surakarta, from May to July 2020. The subjects were assigned using a purposive sampling technique based on inclusion criteria and received adjuvant N-acetylcysteine therapy at 400 mg/day for 4 weeks. Data collection was obtained from medical records, interviews, field notes, positive scale, negative scale, and general psychopathology scale (PANSS) assessment sheets, and blood NLR examinations. Data analysis used SPSS 25.0.

Results: There was a significant difference between the treatment and control groups in reducing negative PANSS subscale measurement after adjuvant N-acetylcysteine treatment. However, there was no significant difference between the control and treatment groups after N-acetylcysteine administration for NLR.

Conclusion: The dose of adjuvant therapy N-acetylcysteine given to patients in this study had an effect on decreasing the negative subscale PANSS score.

Highlights:
1. The essence of schizophrenia is the negative symptoms.
2. Adding meloxicam can improve the negative symptoms and changes in the NLR in schizophrenic patients.

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Introduction

Schizophrenia is a severe and complex brain disorder. The median incidence reported of schizophrenia was 15.2 per 100,000 persons, and a pooled lifetime prevalence was reported as 0.40%.[1] Other works suggest that the lifetime prevalence of schizophrenic patients was 0.48%.[2] Another study conducted in China showed that the lifetime prevalence of schizophrenia patients was 1.25% of the total 2.47% of psychotic disorders.[3] Schizophrenia disorders have several overlapping areas, such as negative, positive, and cognitive symptoms. The deciphering of positive symptoms is paranoia, delusions, visual and/or auditory hallucinations, etc., usually resulting from the disorder. Negative symptoms are associated with the disorder or the consequences of taking medications, such as social withdrawal, anhedonia, apathy, and alogia.[4]

Negative symptoms of schizophrenia include reduced affective response, social withdrawal, poor social drive, and reduced interest. Negative symptoms last longer than positive symptoms. Based on previous studies, it has been shown that disturbances in the ventral striatum and smooth tissue degeneration in the frontal lobes are associated with the development of negative symptoms of schizophrenia Negative symptoms of schizophrenia are starting to get more attention. It seems that the increasing research associated with antipsychotic therapy still shows limited results in managing negative symptoms. In addition, negative symptoms have a poorer prognosis and greater social and family burden. Persistent negative symptoms associated with a long duration of untreated psychosis are very strong predictors of poor treatment response.[5,6] Adding meloxicam can improve the negative symptoms and changes in the neutrophil-lymphocyte ratio (NLR) in schizophrenic patients.

A single-blind randomized controlled trial (RCT) aimed at confirming the effect of N-acetylcysteine on C-reactive protein high-sensitivity (hs-CRP) levels compared to the control group showed that patients with ST-segment elevation acute myocardial infarction who received fibrinolytic therapy were compared with patients with ST-segment elevation acute myocardial infarction who received adjuvant therapy with N-acetylcysteine 600 mg three times daily for 3 days. It showed that the patient's hs-CRP level was elevated. Adjuvant therapy could not reduce N-acetylcysteine therapy.[7] An experimental double-blind RCT study showed that patients receiving N-acetylcysteine in the low hs-CRP group did not significantly prevent major adverse cardiac events (MACE). However, in the high hs-CRP group, the incidence of MACE decreased significantly with N-acetylcysteine. A double-blind RCT study assessing the effects of N-acetylcysteine on the symptoms and cognition of schizophrenia range disorders showed that N-acetylcysteine significantly improved overall positive scale, negative scale, and general psychopathology scale (PANSS), negative symptoms, and symptom scores of disorganized thoughts.

N-acetylcysteine was unable to improve cognitive symptoms and positive symptoms.[8] A meta-analysis conducted by Yolland, *et al*. (2019) indicated that both PANSS score and total scores experienced valuable improvements, with the cognitive area of working memory in the N-acetylcysteine group after treatment for 24 weeks.[9] Non-pharmacological therapies such as cognitive behavioral therapy (CBT) and motivation and engagement training (MOVE) could optimize the treatment efficacy. Other therapies, such as cognitive enhancement therapy (CET), could improve the quality of life of schizophrenic patients which can also be achieved with pharmacotherapy combinations.[10] Family models could also be applied in schizophrenia management. The concept aids families in managing their stress by reducing burden and stigma. Hence, the patients can survive, rise, become stronger, and provide better care for schizophrenic patients.[11] There needs to be a long-term cure for schizophrenia. High treatment adherence may reduce the symptoms of schizophrenia and guard against relapse. Family support is essential to ensure that the patients continue to take their medication regularly.[12] Spirituality also plays an important role for schizophrenic patients, including helping recovery and hope.[13]

This study aimed to analyze the effectiveness of N-acetylcysteine as adjuvant therapy for improving negative symptoms and changes in the NLR in schizophrenic patients.

Methods

This was a cross-sectional retrospective study using secondary data collected from medical records. This study was conducted on 34 schizophrenic patients who were inpatients at Dr. Arif Zainuddin Regional Mental Hospital (RSJD), Surakarta, from May to July 2020. Subjects who met the inclusion criteria received combination antipsychotic therapy of risperidone–chlorpromazine and/or haloperidol injection. Research subjects were taken by purposive sampling and classified into two groups, the treatment group (N-acetylcysteine 400 mg/day for four weeks) and the control group.

Chlorpromazine is a typical (first-generation) antipsychotic that works specifically to reduce positive symptoms in schizophrenic patients. Risperidone is an atypical antipsychotic (second class) that can reduce negative symptoms in schizophrenic patients. Using a combination of these two drugs in clinical practice to treat schizophrenic patients has been shown to be effective in reducing positive and negative symptoms of schizophrenia compared to the beneficial effects achieved with monotherapy of both drugs.

The research subjects grouped into the treatment group received additional therapy of meloxicam 15 mg per day for 4 weeks, in addition to antipsychotic therapy with risperidone-chlorpromazine combination, while subjects in the control group received antipsychotic therapy with the combination of risperidone-chlorpromazine. The research subject data was obtained from the results of the examination of NLR levels and the results of the negative subscale PANSS score assessment. After all research data had been collected, then data analysis was performed using the Statistical Package for the Social Sciences

(SPSS) 25.0 program. From the study, data were obtained about the demographic characteristics of the research subjects and the results of the NLR examination and the PANSS negative subscale pre- and post-test assessment.

Results

The 34 research subjects who were inpatients at RSJD were then classified into two groups consisting of a control group and a treatment group. Demographic results for schizophrenia patients were 15 males (14.1%) and 2 females (5.9%) in both the treatment and control groups. The statistical analysis examined the relationship between gender and schizophrenia using Fisher's Exact test, p = 1.000. This showed that there was no sex difference in schizophrenia incidence between the control and treatment groups. This means that both groups were in the same state and in the same position. Gender is also a risk factor for other mental illness diseases, such as anxiety.[14]

Based on the statistical analysis results using the Chi-Square test to investigate the relationship between age and schizophrenia (p = 0.492), there was no difference in age between the control group and the treatment group. Both groups were in the same state and were equal. Based on the educational characteristics, there were 13 middle school equivalent patients, consisting of one subject in the treatment group (2.9%) and 12 subjects in the control group (35.3%). The high school equivalent group included 21 people. It consisted of 16 subjects in the treatment group (47.1%) and 5 subjects in the control group (14.7%). The statistical analysis results using the Chi-Square test to investigate the relationship between schizophrenia and age obtained a p-value of 0.000. This indicates that there was an educational association between the schizophrenia treatment group and the control group, and the two groups were not in the same and equal position.

The characteristics of the samples of the two groups were performed by a comparative test as seen in Table 3. There was no significant difference between the two groups in gender (p = 1.00), age (p = 0.40), or pre-test NLR value (p = 0.59). There was a significant difference between the treatment group and the control group at the level of education (p = 0.00) and the PANSS pre-test score (p = 0.013). Age used an independent T-test, gender used Fisher's Exact test, education used the Chi-Square test, and the PANSS and NLR pre-test values used the Mann-Whitney test. Suicidal thoughts were more prevalent in those who were younger in age, had illnesses that lasted longer, scored lower on the Global Assessment of Functioning (GAF) scale, were largely female, were unemployed, made less money, and had less education.[15]

The PANSS score before being given N-acetylcysteine 2x400 mg in the treatment group had an average value of 37.35; in the control group was 32.35. The statistical test results were p-value = 0.013, indicating a significant difference between the control and treatment groups. The difference in PANSS scores before and after being treated with N-acetylcysteine 2x400 mg, the treatment group had an average of 19.70 and the control group was 11.88. The statistical test results obtained p-value = 0.000 (p > 0.05), meaning there was a significant difference between the treatment and control groups.

Table 1. Characteristics of research subjects

Characteristics	Group		p-value
	Treatment (n = 17)	Control (n = 17)	
Age (years old) Mean ± SD	31.47 ± 4.85	32.29 ± 4.91	0.626*
Gender Man Woman	 15 (44.1%) 2 (5.9%)	 15 (44.1%) 2 (5.9%)	 1.000**
Education Middle school equivalent High school equivalent	 1 (2.9%) 16 (47.1%)	 12 (35.3%) 5 (14.7%)	 0.000***
PANSS pretest score negative subscale	37.3529 (100%)	32.3529 (100%)	0.013****
NLR Pretest Score	2.47 (100%)	2.75 (100%)	0.595****

*Independent T-test; **Fisher's Exact test; ***Chi-Square test; ****Mann-Whitney test

Table 2. Effect of N-acetylcysteine on changes in PANSS scores on the negative subscale and the control group

Parameter	Mean		p-value
	Treatment (n = 17)	Control (n = 17)	
PANSS pre-test1	37.35	32.35	0.013
PANSS post-test2	17.64	20.47	0.012
PANSS drop	19.70	11.88	0.000

(1) PANSS pre-test and PANSS reduction using independent T-test (normal distribution)
(2) PANSS post-test using Mann-Whitney test (not normal distribution)

Table 3. Effect of N-acetylcysteine on changes in PANSS scores on the negative subscale and the control group

Parameter	Mean		p-value
	Treatment (n = 17)	Control (n = 17)	
PANSS pre-test1	37.35	32.35	0.013
PANSS post-test2	17.64	20.47	0.012
PANSS drop	19.70	11.88	0.000

(1) PANSS pre-test and PANSS reduction using independent T-test (normal distribution)
(2) PANSS post-test using Mann-Whitney test (not normal distribution)

Discussion

Schizophrenia is a chronic disease that is usually found in adolescents to adults. In men, it mainly appears at the age of 15-25 years old, while in women at 25-35 years old. Schizophrenia is more common in men as much as 72% than in women. A demographic study showed that 85% of schizophrenic patients are unemployed.[16,17] Negative symptoms of schizophrenia include reduced affective response, social withdrawal, poor social drive, and reduced interest. Negative symptoms last longer than positive symptoms. Negative symptoms of schizophrenia are starting to get more attention. It seems that the increasing research associated with antipsychotic therapy still shows limited results in managing negative symptoms.[5,18]

The occurrence of aggressive behavior indicates to some extent the severity of this disorder. NLR could be used as a biomarker to evaluate the aggression risk in patients.[19] A report revealed that the level of NLR was high in the schizophrenia group, regardless of metabolic parameters. Therefore, it can be assumed that the etiology of this disease was also triggered by the inflammatory process.[20] NLR was increased in the dementia group, alcoholism group, bipolar affective disorder, schizophrenia, depression group, anxiety disorder group, and mild intellectual disability.[21]

Behavioral dysfunction, which is considered a negative symptom, reflects hypoactivity or dysfunction of mesocortical dopamine projections that may be due to neurodevelopmental abnormalities of the system of N-methyl-d-aspartate (NMDA) glutamate. However, there is a hypothetical excess of dopamine elsewhere in the brain–in the mesolimbic dopamine pathway–the resulting increase in dopamine in that pathway will exacerbate positive symptoms. Disorders of the glutamate system are known to be due to an inflammatory process that can be caused by an imbalance of antioxidants in the body.[22,23]

Oxidative stress induces various reactive oxygen species (ROS) that cause cell damage. It explains the causes of various kinds of mental illness and disorders. Not only schizophrenia, many are caused by one of them being oxidative stress, the infectious process which is one of the triggering factors for schizophrenia is widely stated.[24,25] A 12-week double-blind RCT study to evaluate the efficacy of 1200 mg N-acetylcysteine as an additional treatment to conventional antipsychotics in 84 patients with chronic schizophrenia indicated that N-acetylcysteine treatment improved the psychopathology of negative, positive, and cognitive symptoms. N-acetylcysteine is also well tolerated, easy, and safe to use as an effective therapeutic strategy to improve the treatment progress for schizophrenia.[26]

The difference in NLR values after being treated with N-acetylcysteine 2x400mg in the treatment group had a mean of -0.19 and the control group was -0.20 with statistical test results p = 0.990. From the statistical test results, there was no significant difference. This can be related to the duration of administration and the dose of N-acetylcysteine used. Sugiarto, *et al*. (2017) examined the effectiveness of N-acetylcysteine in reducing proinflammatory cytokines for 20 weeks.[27] He found that there was a decrease in proinflammatory cytokines with the administration of N-acetylcysteine 1800 mg/day.

Based on the immunological contribution to the pathophysiology of schizophrenia, a number of studies have recently calculated NLR in schizophrenic patients, examining the utility of this easy and inexpensive blood count marker in disease management. The meta-analysis conducted by Karageorgiou, *et al*. (2019) which examined the relationship between NLR and schizophrenia found ten studies (804 schizophrenic patients and 671 controls).[28] In schizophrenic patients, the NLR increased by 0.65. Medium- and high-quality studies showed a significant increase in NLR in schizophrenic patients (heterogeneity = 0%). N-acetylcysteine is being studied as a new treatment for various mental disorders. Studies show that N-acetylcysteine responds differently to the treatment of several mental disorders. This difference in response may be due to the different metabolic pathways underlying the pathophysiology of different psychiatric disorders and the different effects of the N-acetylcysteine pathway. The proposed mechanism of action of N-acetylcysteine is clinically possible when used in psychiatric disorders, namely oxidative stress, inflammatory mediators, neurotransduction, and multiple signaling pathways involved in neuroplasticity.[29]

There is an association between the presence of inflammation and the process of schizophrenia in schizophrenic patients. Several studies associated with increased production of free radicals, an imbalance towards a pro-oxidant state is formed, an imbalance that lasts a long time can lead to neuropsychiatric diseases.[30,31] A series of studies suggest an abnormal pattern of immune activation shown to be elevated in schizophrenic patients and may contribute to the psychopathology of this disorder.[15,31] Inflammation that continues to occur, according to Jaehne, *et al*. (2015), can decrease the inflammatory response in schizophrenic patients, especially in periods of remission receiving antipsychotic treatment.[32] Ongoing chronic inflammation in schizophrenia will cause biological markers of inflammation such as NLR not to return to normal in the remission phase. The inflammatory process will continue, even during periods of remission.[33] However, it has also been found that in patients taking clozapine therapy, inflammatory markers such as NLR cannot be used because of the agranulocytosis effect.[34]

N-acetylcysteine additional therapy has proven effective and safe as a strategy to alleviate the negative symptoms of schizophrenia.[35] In the same study, N-acetylcysteine was able to mitigate the rising of liver enzymes, cytokine storms, and C-reactive proteins in patients infected with COVID-19.[36] In schizophrenia insight, N-acetylcysteine raises the level of glutathione in the brain and it is being used as an additive for schizophrenic patients.[37] A study identified the effects of N-acetylcysteine therapy on schizophrenic patients.[38] It showed that N-acetylcysteine could improve the negative symptoms and reduce the superoxide level in patients' blood. N-acetylcysteine treatment has been proven to improve cognitive function through neurotransmitter systems.[39] N-acetylcysteine was also proven to improve neural dysfunction.[40] In an animal model (rat), the induction of L-buthionine-(S, R)-sulfoximine (BSO) as an inductor of schizophrenia, N-acetylcysteine treatment could differently modulated the level of the brain-derived neurotrophic factor (BDNF) in the hippocampus and prefrontal cortex.[41]

Strength and Limitations

The strength of this study provides evidence that a new treatment for mental disorders (N-acetylcysteine) is effective as adjuvant therapy to reduce negative symptoms and NLR ratio in schizophrenic patients that can help doctors manage schizophrenic patients. The limitation of this study was that it only used one dose and the number of samples in the study was still lacking. Therefore, further studies are needed to study with a larger sample size and various doses of N-acetylcysteine.

Conclusion

There was effectiveness in the mean score of the PANSS subscale negative post-test in the N-acetylcysteine adjuvant group compared to the control group. No statistically significant difference in the mean NLR results in the N-acetylcysteine adjuvant group compared to the control group. There was an effectiveness of adjuvant treatment of N-acetylcysteine dose in this study to improve negative symptoms but not significant in decreasing the NLR value statistically in schizophrenic patients hospitalized 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 Committee for Health Research, Dr. Moewardi General Academic Hospital, Surakarta (no. 1.410/XI/HERC/2020) on 8 April 2020.

Authors' Contributions

Designing and implementing the research, analyzing the results, writing of the manuscript: IR, AH, WK.

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