




The Augmentation Effect of N-Acetyl Cysteine Antioxidant on Superoxide Dismutase Levels in Schizophrenic Patients Treated with Risperidone

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Abstract

BACKGROUND: Schizophrenia affects approximately 1% of the population and in Indonesia, the prevalence is about 400.000 people or as many as 1.7/10,000 individuals of the population. Schizophrenia is characterized by positive symptoms, negative symptoms, and also cognitive, aggressive, and affective symptoms, where negative symptoms reflect loss of function. One important factor that plays a role in the pathophysiology of schizophrenia is the excessive production of free radical substances and the failure of the anti-oxidant defense process.

AIM: The aim of this study is to see how levels of superoxide dismutase change after N-acetylcystein augmentation in schizophrenic patients treated with risperidone.

METHODS: This study is a pre-post experimental test design, where schizophrenic patients meet inclusion and exclusion criteria. At baseline and after 8 weeks of N-acetyl cysteine (NAC) administration, patients were assessed at each of the time points using Positive and Negative Syndrome Scale (PANSS), and SOD was measured in blood at both time points.

RESULTS: The average negative PANSS score in the Risperidone + NAC baseline group was 29.93 (± 1.83); in the risperidone group was 29.83 (± 1.19) ($p = 0.87$). The average negative PANSS score at the end of week 8 was statistically significantly different ($p = 0.001$) in the Risperidone + NAC group (17.40 ± 1.84) and in the risperidone group (21.00 ± 0.74). The average baseline superoxide dismutase (SOD) levels in the Risperidone + NAC group were 63.57 (± 22.44), and in the risperidone group was 85.79 (± 101.05). SOD levels at week 8 in the Risperidone + NAC group were 71.72 (± 31.20) and in the risperidone group 128.27 (± 117.67). Δ SOD in the Risperidone + NAC group was 8.15 (19.54) and Δ SOD in the risperidone group was 42.48 (± 54.30).

CONCLUSION: $p = 0.028$ research data show that NAC augmentation can improve the negative symptoms of schizophrenia through reducing SOD levels in the blood.

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Introduction

Schizophrenia affects approximately 1% of the population and in Indonesia, the prevalence is around 400,000 people or as many as 1.7/1000 population [1]. Schizophrenia is characterized by positive symptoms, negative symptoms, and also cognitive, aggressive, and affective symptoms [2], where negative symptoms reflect loss of function [3]. Negative symptoms are said to be associated with the alteration in central nervous system structure.

Many studies have examined the role of oxidative stress in pathogenesis, progression, and treatment of psychiatric disorders. One important factor that plays a role in the pathophysiology of schizophrenia is the excessive production of free radical substances and the failure of the anti-oxidant defense process [4].

The 2008 Uma *et al.* study showed that malondialdehyde level was increased in schizophrenia with positive symptoms (163%), negative (137%), and cognitive symptoms (132%) compared to the control group. Free radicals, especially reactive oxygen species (ROS), superoxide, and highly reactive hydroxyl radicals have unpaired electrons in molecular or atomic orbits that are arranged in the center and directed under physiological conditions during aerobic metabolism. As hazardous free radicals, they are usually deactivated or sought for antioxidants before causing damage to lipids, proteins, or nucleic acids. Normally ROS is neutralized by an anti-oxidant defense mechanism, namely superoxide dismutase catalase and glutathione peroxidase, it is the primary enzyme involved in the direct disposal of ROS. Glutathione transferase, glucose-6-phosphate dehydrogenase, and copper-binding ceruloplasmin are secondary anti-oxidant enzymes that maintain a stable concentration of glutathione and NADPH for optimal function of the primary antioxidant

enzymes [5]. Superoxide dismutase is an important enzyme that is important in detoxification from superoxide radicals because they are the first substances produced in the majority of reactions that resulted in biological free radicals. Several studies have shown that superoxide dismutase (SOD) levels are increase in patients with chronic schizophrenia. A study with 68 schizophrenic patients (29 males and 39 females), aged between 18 years old and 61 years old (group divided by age <34 years old, and >34 years old) showed that SOD levels in patients with the age group below 34 years were significantly higher than in the older group of patients [6]. Several studies have shown that administration of N-Acetyl Cysteine (NAC) can improve the enhancement of negative symptoms in schizophrenic patients [7]. NAC is a derivative of the amino acid L-cysteine and is rapidly absorbed orally. NAC can modulate several dopamine and glutamate neurotransmission systems. In the pathophysiology of schizophrenia, there is a decrease in glutamate levels in the prefrontal cortex and dysfunction in glutamate metabolism. Oxidative stress is also linked to the severity of symptoms, subtypes of schizophrenia, and oxidative stress [8].

Based on the results of previous studies, this research aims to see how much changes of the level of the enzyme SOD in the serum of schizophrenic patients treated with risperidone who received additional NAC and who only received risperidone treatment.

Methods

This study is a pre- and post-test design experimental study, in which 27 samples were patients in the Mental Institution "RS Jiwa Provinsi Sumatera Utara" that met the inclusion criteria, who had been diagnosed according to ICD-10 to rule out other mental problems. Subjects have gone through structured interviews using MINI ICD-10 to evaluate the severity of negative symptoms. Patients were examined with a Positive and Negative Syndrome Scale (PANSS)-Negative scale where all subjects have a score ≥ 21 . All schizophrenic patients received risperidone 4 mg/day in the stabilization phase. Exclusion criteria were subjects who had organic mental disorders and had a history of common medical conditions, especially hypertension, stroke, diabetes mellitus, cholesterol, and infectious diseases. The 27 samples are divided into 2 groups according to age, number of cigarettes, body mass index (BMI), and duration of illness and the severity levels measured by PANSS. Group one comprised 15 individuals and group two comprised 12 individuals. Group one was the group that received additional NAC, NAC was given at baseline of 1000 mg/day, and increased in week 2 up to 2000 mg/day and was maintained until week 8. SOD levels were measured at baseline and in week 8, and compared with group 2 that only received risperidone 4 mg/day.

Superoxide dismutase serum was measured by ELISA method, using the Human Super Oxidase Dismutase kit (Bioassay Technology Laboratory) in accordance with the factory protocol [9].

Results

In Table 1, it shows the average age of the sample is 36.25 (± 6.76); with an average duration of illness 5.3(± 1.75) years, with an average BMI was 21, 24 (1.82), the average positive-PANSS score was 11.11 (± 2.22); negative-PANSS score was 30.02 (± 1.66), average general psychopathology-PANSS score was 31.05 (± 3.72), and an average total-PANSS score was 72.16 (± 5.74). Average SOD score was 88, 79 (± 132.31) with level ranges from 0.00 to 574.

Table 1: Demographic characteristic of research subject

Variable	Risperidone + NAC (n =15)	Risperidone (n =12)	p
Age	35.27(6.34)	38.58(7.86)	0.34 ^a
Education			
Junior high school n(%)	5(33.33)	6(50)	
Public high school n(%)	10(66.67)	6(50)	
Marital status			
Married n(%)	7(46.67)	6(50)	
Not married n(%)	8(53.33)	6(50)	
Duration of illness	4.73(1.49)	6.17(1.99)	0.59 ^b
Smoking	2.07(1.49)	2.83(1.53)	0.18 ^b
BMI	21.02(1.74)	22.06(1.72)	0.13 ^a
Dose	NAC 2000 mg/day + Risperidone 4 mg	Risperidone 4 mg	

^at-test, ^b Mann-Whitney U.

Table 2 shows the mean of positive-PANSS score in \pm the group receiving risperidone with NAC was 10.80 (± 2.34), in risperidone group was 11.58 (± 2.19) at baseline. After 8 weeks, the mean score was 7.93 (± 1.28) at the risperidone with NAC group and 7.17 (± 0.58) in risperidone group. The negative-PANSS scale score at the baseline was 29.93 (± 1.83) in risperidone with NAC group and 29.83 (± 1.19) in risperidone group at the baseline. After week 8, it was found at 17.40 (± 1.84) risperidone with NAC group, 21.00 (± 0.74) in risperidone group. In general, psychopathology PANSS score at baseline was 31.33 (± 3.66) in risperidone with NAC group and 29.92 (± 3.78) in risperidone group. After 8 weeks, it was found 22.73 (± 3.56) in risperidone with NAC group and 23.58 (± 3.23) in risperidone group. The total PANSS score at baseline, 71.80 (± 6.13) in risperidone with NAC group and 71.33 (± 5.76) in risperidone group. After 8 weeks, it was found 48.07 (± 4.96) in risperidone with NAC group, 52.67 (± 5.16) in risperidone group.

In Table 3, while SOD scores did vary at baseline between the group receiving NAC and the group not receiving NAC, there was a substantial change in SOD levels observed after 8 weeks with a delta of 42 Units /L in the group without receiving SOD compared to a delta of only 8 U/L in the group receiving the addition of NAC

Table 2: PANSS score

	Risperidone + NAC(mean SD)	Risperidone	p
PANSS positive scale score			
Baseline	10.80(2.34)	11.58(2.19)	0.38 ^a
Week 8	7.93(1.28)	7.17(0.58)	0.15 ^b
PANSS negative scale score			
Baseline	29.93(1.83)	29.83(1.19)	0.87
Week 8	17.40(1.84)	21.00(0.74)	0.001 ^a
PANSS general psychopathology scale score			
Baseline	31.33(3.66)	29.92(3.78)	0.33 ^a
Week 8	22.73(3.56)	23.58(3.23)	0.53
Total PANSS score			
Baseline	71.80(6.13)	71.33(5.76)	0.54 ^a
Week 8	48.07(4.96)	52.67(5.16)	0.03 ^a

^at-test ; ^bMann-Whitney U.

In Table 4, it shows the delta SOD level in the risperidone administration added with NAC is 8.15 (19.54), while the one who only received risperidone was 42.48 (54.30).

Table 3: Level of SOD(U/L) in serum

Levels of SOD(U/L):	Risperidone + NAC	Risperidone	p
Baseline	63.57(22.44)	85.79(101.05)	<0.05
Week 8	71.72(31.20)	128.27(117.67)	

Discussion

This study shows that NAC augmentation in schizophrenic patients treated with risperidone can reduce the level of SOD increase. NAC is able to reduce the level of free radicals in the blood in schizophrenic patients. According to Berk *et al.*, NAC is a precursor of glutathione which has a neurotropic antioxidant effect and has a modulation effect on dopaminergic and glutamatergic systems. Along with this study, it was shown that there is a negative symptom improvement in the group receiving NAC [8]. According to Farokhnia *et al.*, NAC shows an effective and safe augmentation strategy, reducing negative symptoms in schizophrenic patients [7].

Table 4: Changes in level of SOD(U/L) in serum

SOD(U/L)	Risperidone+NAC	Risperidone	p
Δ SOD	8.15(19.54)	42.48(54.30)	0.028 ^b

^bMann-Whitney U.

A double-blind placebo-controlled trial adding 1000 mg/day NAC for 6 months in 140 participants shows a decrease in negative symptoms. According to Pazvantoglu *et al.*, the severity of symptoms may correspond to antioxidant levels. Various antioxidants are linked to negative symptoms, poor premorbid function, and abnormalities of computed tomography (CT) [10]. However, there is no correlation between the duration of the disease and the levels of antioxidants found. Gunnes *et al.* state that oxidative stress is higher in schizophrenic patients than controls in which an increase in negative symptom severity coincided with damage to oxidative balance [4]. Oxidative stress was lower in patients using atypical antipsychotics than the one with typical antipsychotics and antipsychotics combination. This suggests that the mechanism of atypical antipsychotics has a positive effect on oxidative

stress, thus it indicates improvement in negative symptoms better than typical.

This study shows that the administration of single risperidone continues to increase the SOD levels, which shows that oxidative stress continues to increase during risperidone administration. NAC is a candidate drug that may be suggested in the administration of atypical antipsychotics to reduce the increase in oxidative stress.

The strength of this study is that it has controlled the duration of illness, BMI, smoking status, age, gender, severity of negative symptoms before administration of NAC, and measurement of SOD level. However, the limitation of this study is that the number of samples is quite limited. Further research is needed to examine SOD levels in schizophrenic patients with long-term treatment or stable phases.

Conclusions

NAC is able to improve negative symptoms, most likely through alleviating oxidative stress in schizophrenic patients treated with risperidone. Therefore, NAC is a potential augmentation therapy in schizophrenia with negative symptoms.

Declarations

Authors' contributions

All authors contributed to the study and writing of the article. All authors have read and approved the final version of the manuscript. DH and EE contribute in finding sample for this study, VC and MSH contribute in monitoring the clinical conditions of the sample, MI and K contribute in medicine preparation and making sure the sample took medicine every day, R contribute in measuring the level of SOD serum.

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Ethics approval and consent to participate

Written informed consent was obtained from all participants. This study was approved by ethic committee of Medical Faculty of Universitas Sumatera Utara.

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