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Folic Acid as the Adjuvant Therapy for Chronic Schizophrenia: A Comprehensive Study on Glutathione Reductase

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Abstract

BACKGROUND: Schizophrenia is a severe mental disorder. Oxidative stress is one of the pathophysiologies or hypotheses of schizophrenia. Folic acid is a vitamin that plays a role in preventing oxidative stress. Oxidative stress will reduce antioxidant enzymes and worsen the symptoms of schizophrenia.

AIM: This study was to determine the effect of folic acid adjuvant therapy on Glutathione reductase levels and PANSS scores in chronic schizophrenic patients.

METHODS: The research design used was a double-blind randomized controlled trial with a pre-test and post-test design. In this study, there were 36 treatment patients and 36 control patients. Research subjects in the treatment group were given antipsychotic therapy and folic acid 2 mg, in the control group were given antipsychotic therapy and placebo. The study was conducted for 3 weeks during hospitalization. PANSS scores and GR levels (pg/ml) were measured on the first day and after the treatment was completed.

RESULTS: In this study, there was a significant increase in glutathione reductase levels in pre and post-test between the control group and the treatment group ($p<0.001$). There was a significant decrease in the total PANSS score on pre and post-test between the control group and the treatment group ($p<0.001$). There was a significant decrease in positive PANSS scores on pre and post-test between the control group and the treatment group ($p=0.015$). There was a significant decrease in negative PANSS scores on pre and post-test between the control group and the treatment group ($p<0.001$). There was a significant decrease in general PANSS scores on pre and post-test between the control group and the treatment group ($p=0.029$).

CONCLUSION: There is an effect of adjuvant folic acid in increasing Glutathione reductase levels and decreasing PANSS scores in chronic schizophrenic patients.

Introduction

Schizophrenia is one of severe mental disorder. It is marked by psychiatric syndromes, such as positive, negative, and cognitive symptoms [1]. The 2018 Basic Health Research (Riskesdas) shows that the prevalence of schizophrenia in Indonesia is 6.7/1,000 households [2].

Oxidative stress is involved in schizophrenia pathophysiology or hypotheses [3]. It is a condition that arises due to excessive free radicals formation, such as reactive oxygen species and reactive nitrogen species, causing an imbalance between the oxidation process and antioxidant availability [4]. Antioxidants take parts in balancing free radicals, leading to oxidative stress reduction and neuron damage prevention [5].

Glutathione (GSH) is the main antioxidant in the brain. It plays a major part in opposing oxidative stress. In its formation process, the glutathione reductase (GR) enzyme is needed [6]. In schizophrenic patients, the GSH level declines as much as 40% in the frontal cortex area and 35% in blood plasma [7], [8], [9]. Studies have found that the declined GSH level worsened the total Positive and Negative Symptom Scale (PANSS) score [10].

Folic acid is a vitamin that prevents the oxidative process through a one-carbon cycle of metabolism by preventing hyperhomocysteinemia, a condition that increases free radicals and decreases GSH levels [7], [8]. Therefore, folate deficiency has been identified as one of schizophrenia's risk factors [11].

To sum up, hyperhomocysteinemia decreases the GSH and GR levels, which will worsen schizophrenia symptoms. On the other hand, folic acid plays a role in preventing hyperhomocysteinemia, which further leads to the GSH and GR levels improvement, and also schizophrenia symptoms as well [6], [9], [10]. Hence, in this study, we aim to determine the effectivity of folic acid as a therapy adjuvant on GR levels and PANSS score improvement in chronic schizophrenic patients.

Methods

This study used a double-blinded study, using randomized controlled trial with a pre-test and post-test study design. It was conducted at Dr. Amino Gondohutomo Regional Mental Hospital Semarang. Blood samples for accessing the GSH level were examined at Central Laboratory, Diponegoro National Teaching Hospital, Semarang. Data collection was carried out from January 1 to March 30, 2021. This research had obtained ethical clearance from the Health Research Ethics Committee of Regional Mental Hospital Dr. Amino Gondohutomo, Central Java Province. The ethical license number is No. 420/15161.

Research subjects were selected using the consecutive sampling method. They must meet the following inclusion criteria: Schizophrenic patients aged 21–50 years old, diagnosed by PPDGJ III, have suffered for at least 2 years, and are receiving standard hospital treatments (psychotropics with or without additional anticholinergics). Patients with a history of comorbid cardiac schizophrenia, hypertension, anemia, diabetes mellitus, cardiovascular disease, alcohol and substance abuse are excluded from the study. Patients who suddenly refuse to follow procedure (given adjuvant therapy or taking blood samples) and patients who went home at their request before the study ends are considered to have dropped out. After selection, the patient's family is asked whether they are willing to participate in the study and sign the informed consent form.

At first, the subjects were asked for their demographic data. Then, after being randomized using the four-blocks randomization method, they are divided into two groups, namely, the control and the treatment group. On the 1 day of treatment, both groups were assessed using a PANSS score and had their serum GR level measured. GR serum was measured using Elabscience ELISA Kit. Catalog No. E-EL-H1339 96T. The control group received standard antipsychotics and a placebo for 3 weeks. The treatment group received standard antipsychotics and folic acid as adjuvants as much as 2 mg/day for 3 weeks. Both groups were monitored and evaluated for adjuvant side effects and clinical conditions daily. In the 3 week, all subjects were assessed for PANSS score and their serum GR level again.

Results

Demographic characteristics analysis

This study examines demographic variables, including age, gender, occupation, marital status, education, the length of illness, the genetic history of mental disorder in the family, body mass index, smoking, and the rate of hospital admission (s). A total number of 72 people were included in this study.

Table 1: The differences in glutathione reductase level between the control and the treatment groups

Glutathione reductase (pg/ml)	Groups		p-value
	Control	Treatment	
Pre-test	1385.69 ± 948.43	1212.14 ± 907,76	0.362[‡]
Post-test	2287.36 ± 2455.50	6719.75 ± 4712,20	<0.001[†]*
Delta	901.67 ± 2169.73	5507.61 ± 4944,30	<0.001[‡]*
p (pre vs. post)	0.078[†]	<0.001[†]*	

*Significant ($p < 0.05$); [‡]Mann–Whitney; [†]Wilcoxon.

The differences in GR level between the control and the treatment groups

The differences in GR level values between the control and the treatment groups are shown in Table 1.

In this study, glutathione reductase levels before and after intervention were significantly increased (delta) in both control and treatment groups, with delta values as much as 901.67 ± 2169.73 and 5507.61 ± 4944.30, respectively (significantly different, $p < 0.001$).

The differences in total PANSS score between the control and the treatment groups

The differences in total PANSS score between the control and the treatment groups are shown in Table 2.

Table 2: Differences in total PANSS score between the control and the treatment groups

Total PANSS	Groups		p-value
	Treatment	Control	
Pre-test	83.86 ± 17.27	87.69 ± 14.71	0.314[§]
Post-test	49.14 ± 11.02	64.08 ± 11.79	<0.001[§]*
Delta	34.72 ± 13.18	23.61 ± 9.56	<0.001[§]*
p (pre vs. post)	<0.001*	<0.001*	

*Significant ($p < 0.05$); [§]Independent t; Paired t, PANSS: Positive and Negative Symptom Scale.

There is an improvement in the total PANSS score. The mean difference (delta) of the total PANSS score in the treatment group was −34.72 ± 13.18 and in the control group was −23.61 ± 9.56. Statistically, both showed a significant difference ($p < 0.001$).

The differences in positive symptoms of PANSS score between the control and the treatment groups

The difference in positive PANSS score between the control and the treatment groups is shown in Table 3.

Table 3: The difference in positive PANSS score between the control and the treatment groups

Positive PANSS	Groups		p-value
	Treatment	Control	
Pre-test	22.94 ± 4.76	23.56 ± 4.74	0.587[§]
Post-test	12.11 ± 2.96	15.03 ± 2.96	<0.001[§]*
Delta	10.83 ± 4.12	8.53 ± 3.74	0.015[§]*
p (pre vs. post)	<0.001*	<0.001*	

*Significant ($p < 0.05$); [§]Independent t; Paired t, PANSS: Positive and Negative Symptom Scale.

There is an improvement in the positive PANSS score. The difference in the mean (delta) of the positive symptom PANSS score in the treatment was −10.83 ± 4.12 and in the control group was −8.53 ± 3.74. Statistically, both showed a significant difference (p = 0.015).

The difference in negative symptoms of PANSS score between the control and the treatment groups

The difference in the negative PANSS score between the control and the treatment groups is shown in Table 4.

Table 4: Difference in the negative PANSS score between the control and the treatment groups

Negative PANSS	Groups		p-value
	Treatment	Control	
Pre-test	19.28 ± 5.56	19.11 ± 6.48	0.907§
Post-test	10.47 ± 3.65	14.89 ± 5.30	<0.001†*
Delta	−8.81 ± 3.91	4.22 ± 3.13	<0.001†*
p (pre vs. post)	<0.001†*	<0.001*	

*Significant (p < 0.05); §Independent t; †Mann–Whitney; Paired t; ‡Wilcoxon, PANSS: Positive and Negative Symptom Scale.

There is an improvement in the negative PANSS score. The difference in the mean (delta) of the negative symptom PANSS score in the treatment group was −8.81 ± 3.91 and in the control group was −4.22 ± 3.13. Statistically, both showed a significant difference (p < 0.001).

The difference in general symptoms of PANSS score between the control and the treatment groups

The difference in general PANSS score between the control and the treatment groups is shown in Table 5.

Table 5: The difference in general PANSS score between the control and the treatment groups

General PANSS	Groups		p-value
	Treatment	Control	
Pre-test	41.64 ± 11.33	45.03 ± 9.46	0.173§
Post-test	26.56 ± 7.79	34.17 ± 6.78	<0.001§*
Delta	15.08 ± 9.42	10,86 ± 8.42	0.029†*
P (pre vs. post)	<0.001*	<0.001*	

*Significant (p < 0.05); §Independent t; †Mann–Whitney; Paired t, PANSS: Positive and Negative Symptom Scale.

There is an improvement in the general PANSS score. The difference in the mean (delta) of the general symptomatic PANSS score in the treatment group was 15.08 ± 9.42 and in the control group was 10.86 ± 8.42. Statistically, both showed significant differences (p = 0.029).

Discussion

The description of subjects' demographic characteristics

In this study, the mean age of all subjects was 33.78 ± 7.70 years. This result is in accordance with epidemiological studies in schizophrenic patients, declaring that schizophrenia prevalence is high at the age range of 30–40 years old in both males and females [12]. The subjects in this study mainly were males (69.4%). This result is in line with previous epidemiological studies, showing that schizophrenia is more common in men [13], [14].

Most subjects were unemployed (61.1%). This result is in line with another study on 172 schizophrenic patients in Nigeria, where more people were unemployed (51.2%) [15]. Based on marital status, the majority of the research subjects were single (50%), and as many as 13.9% experienced a divorce. This result is similar to a study, finding that schizophrenia patients are more likely to be single [12]. In terms of education-level, research subjects mainly were junior high and high school graduates, as much as 31.9%. This result is in accordance with the previous studies [12], [16].

The average rate of hospital admissions in this study was 3.40 ± 1.96. This result is in conjunction with the previous studies, stating that the onset of illness is proportional to hospital admission rates [16]. The length of illness in this study was 2–21 years, with a mean value as much as 4.67 ± 2.97 years. Another study stated that earlier onset of the illness, meaning a longer duration of illness, the patient's output will get decreased [17].

In genetic variables, most research subjects did not have a genetic history of mental disorders in the family (86.1%). This result is not in accordance with the previous research [18]. Most subjects had normal BMI, as much as 75%. This result is not in line with previous research, which states that schizophrenic women suffer more from obesity, which may be caused by long-term treatment with antipsychotics [18]. Most research subjects (69.4%) are smoking. One hypothesis is plausible to explain; it is that smoking can reduce the symptoms of schizophrenia [19].

Differences in glutathione reductase levels in schizophrenic patients

This study aligns with previous theory, proclaiming that folic acid supplementation as an adjuvant therapy helps in in GSH formation, especially in the one-carbon cycle. GSH is a key liver antioxidant and acts as a cellular redox buffer. Besides, GSH also functioned as a cofactor for GPx family of antioxidant enzymes. GPx enzymes degrade H_2O_2 and alkyl hydroperoxides, yielding GSSG. This condition is also supported by another study, stating that there is a significant relationship between serum folic acid deficiency with lowered GR level, glutathione level, and an increase in homocysteinemia (HHcy) in patients with hypertension [20]. Another study, which was conducted on chronic schizophrenia patients, found a significant difference in terms of blood folic acid levels between the control group. This folic acid level increment was started at week 2 [21].

The differences in total PANSS score before and after folic acid adjuvant therapy

The results of the study are in accordance with research conducted by Xueqin Song *et al*. (2014) which state that folic acid supplementation can significantly reduce the total PANSS score [22]. This result is also aligned with research, where a significant relationship was found between the declined level of the GSH enzyme, an antioxidant, in schizophrenic patients, and an increase in the total PANSS score [10]. This study supports the pathophysiology of antioxidant imbalance affecting the symptoms of schizophrenia. Folic acid can prevent hyperhomocysteinemia by converting homocysteine into methionine in the one-carbon cycle [23], [24].

The differences in positive PANSS score before and after folic acid adjuvant therapy

Another study supports the results of this study, stating that there is a significant relationship between decreased GSH antioxidant enzymes in schizophrenic patients with an increase in positive [10]. The role of antioxidants in positive symptoms of schizophrenia is shown through this mechanism, whereas the low level of glutathione in schizophrenic patients leads to GABA neurotransmitter dysfunction and NMDA receptors disturbance in the prefrontal cortex. Dysfunction of this neurotransmitter affects the feedback loop of the dopamine neurotransmitter. Positive symptoms in schizophrenic patients are assumed to be due to dopamine neurotransmitter escalation in the prefrontal cortex [25].

The differences in negative PANSS score before and after folic acid adjuvant therapy

The results of this study are in accordance with research conducted by Song *et al*., which state that folic acid supplementation can reduce negative PANSS scores [22].

Langbein *et al*. also supports this (2017), declaring that there is a significant relationship between decreased plasma GR levels and an increase in a negative PANSS score. This occurs because there is a decrease in gray matter density in the orbitofrontal cortex, a center for motivation, reward, and decision-making in schizophrenic patients [26].

The differences in general PANSS score before and after folic acid adjuvant therapy

The present study results are supported by Roffman *et al*. (2017), who provided a L-methylfolate intervention for 12 weeks. This intervention was able to reduce the general PANSS score [27].

Conclusion

The use of folic acid as adjuvant therapy improves the psychiatric symptoms of chronic schizophrenic patients and increases serum GR levels. The demographic characteristics of chronic schizophrenic patients based on age, gender, occupation, marital status, education level, the length of illness, genetic history of mental disorder in the family, body mass index, smoking habit, and rate of hospital admissions are varied.

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