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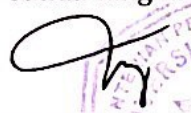
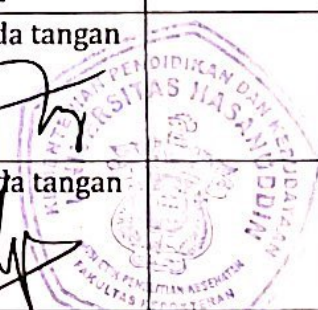

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REKOMENDASI PERSETUJUAN ETIK

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Tanggal: 8 Februari 2021

Dengan ini Menyatakan bahwa Protokol dan Dokumen yang Berhubungan Dengan Protokol berikut ini telah mendapatkan Persetujuan Etik :

No Protokol	UH20110675	No Sponsor Protokol	
Peneliti Utama	dr. Herwina	Sponsor	
Judul Peneliti	Pengaruh Adjuvan Vitamin C Terhadap Kadar Brain Derived Neurotropic Factor (BDNF) dan Perbaikan Gejala Negatif Pasien Skizofrenia		
No Versi Protokol	2	Tanggal Versi	1 Februari 2021
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Tempat Penelitian	RS Universitas Hasanuddin dan RS Jejaring di Makassar		
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Ketua Komisi Etik Penelitian Kesehatan FKUH	Nama Prof.Dr.dr. Suryani As'ad, M.Sc.,Sp.GK (K)	Tanda tangan 	
Sekretaris Komisi Etik Penelitian Kesehatan FKUH	Nama dr. Agussalim Bukhari, M.Med.,Ph.D.,Sp.GK (K)	Tanda tangan 	

Kewajiban Peneliti Utama:

- Menyerahkan Amandemen Protokol untuk persetujuan sebelum di implementasikan
- Menyerahkan Laporan SAE ke Komisi Etik dalam 24 Jam dan dilengkapi dalam 7 hari dan Laporan SUSAR dalam 72 Jam setelah Peneliti Utama menerima laporan
- Menyerahkan Laporan Kemajuan (progress report) setiap 6 bulan untuk penelitian resiko tinggi dan setiap setahun untuk penelitian resiko rendah
- Menyerahkan laporan akhir setelah Penelitian berakhir
- Melaporkan penyimpangan dari prokol yang disetujui (protocol deviation / violation)
- Mematuhi semua peraturan yang ditentukan



Effect of Adjuvant Vitamin C on Brain-Derived Neurotrophic Factor Levels and Improvement of Negative Symptoms in Schizophrenic Patients

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Abstract

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AIM: This study aims to determine the effect of adjuvant Vitamin C on brain-derived neurotrophic factors (BDNF) levels and improvement of negative symptoms in schizophrenic patients.

METHODS: This study was conducted at Hasanuddin University Hospital and its affiliate with 60 schizophrenic patients (30 controls, 27 treatments, and three dropout patients). The ELISA sample examination method was used to examine blood levels of BDNF, and Vitamin C levels before and after administration of Vitamin C. In addition, the negative symptoms were measured using the PANSS score.

RESULTS: There was a significant increase in BDNF levels in treatments group compared the control at 4th–8th weeks with $p = 0.005$ (4th week) and ≤ 0.0001 (<0.05) (8th week). The improvement in PANSS scores for negative symptoms in the treatment groups compared to the controls at the 2nd, 4th, and 8th weeks resulted in $p = 0.042$ (2nd week) and <0.0001 (4th–8th weeks). Furthermore, there was an increase in serum Vitamin C levels in the treatment groups with an initial average value = 4.762 and after 8 weeks = 148.155. Strong correlation between increased BDNF levels and improvement in negative symptoms on the PANSS score was found with $p = 0.001$ (4th week) and ≤ 0.0001 (8th week).

CONCLUSION: The administration of Vitamin C significantly increases BDNF levels and improves the PANSS score for negative symptoms in the treatments compared to the control groups.

Introduction

Schizophrenia is a complex, multifactorial, and chronic psychiatric disorder with numerous negative symptoms and impacts on sufferers and the environment [1], [2]. Meanwhile, negative symptoms are a major component of schizophrenia and cause most of the long-term disability and poor prognosis in patients with this disorder. The term negative symptom describes a reduction or loss of normal behavior and function related to motivation and interest, as well as verbal/emotional expression. The negative symptom domain of schizophrenia usually consists of these five signs, namely, lack of emotional expression, avolition (reduction in the number of words spoken), avolition (reduction in goal-directed activities due to decreased motivation), antisociality, and anhedonia (reduced pleasurable activities) [3], [4].

Aside from the negative symptoms, one of the neurotrophins predicted to play a role in the disruption of dopamine activity is BDNFs. Furthermore, BDNF plays a role in neuronal development and plasticity [5], [6]. It regulates aspects of developmental plasticity in the brain

and is involved in cognitive function as well as its related negative symptoms [7]. Similar to other neurotrophins, the role of brain-derived neurotrophic factor (BDNF) was initially identified in neuronal proliferation, neurogenesis, differentiation, and degeneration. Furthermore, BDNF function in regulating activity-dependent neuron modification has been described. For example, it regulates both memory formation and long-term potentiation, as an activity-dependent reinforcement of synaptic efficacy [8].

Ascorbic acid (Vitamin C) is an antioxidant vitamin and plays an important role in protecting against free radical damage in the body. It is found in brain tissue and dopamine dominant areas with higher concentrations compared to other organs [9]. A prospective double-blind placebo-controlled study of 40 outpatients in India examined Vitamin C supplementation (500 mg/day) for 8 weeks in patients with schizophrenia taking second-generation antipsychotics [10]. The previous studies also showed that Vitamin C supplementation improves negative symptoms in schizophrenic patients and reduces free radical-induced brain damage [11], [12].

An observation on the effect of Vitamin C at a dose of 1000 mg/day on schizophrenic patients by assessing the PANSS score observed during weeks 8–16 which showed improvement in negative symptoms and elevated levels of dehydroascorbic acid [11], [12], [13], [14]. Although some studies are controversial, most of the data show an association between ascorbic acid levels and schizophrenia symptoms [10]. Furthermore, the potential use of Vitamin C as a therapeutic adjuvant in the treatment of schizophrenia needs to be exploited.

Therefore, due to the lack of studies on the effect of Vitamin C in improving clinical negative symptoms and changes in BDNF levels in schizophrenia patients, as well as the controversy on the patients' blood before and after Vitamin C administration, this study aims to examine the effect of Vitamin C on the improvement of negative symptoms in schizophrenia patients and BDNF levels.

Subjects and Methods

A total of 60 samples divided into two groups were used in this experimental study with a pre- and post-test control group design, where Group I consisted of 30 respondents given a placebo as a control, and Group II consisted of 30 respondents given Vitamin C at a dose of 1000 mg/day. The inclusion criteria for each group were schizophrenia patients diagnosed based on DSM V aged 18–50 years, using atypical antipsychotic therapy doses (risperidone and clozapine), and initial serum Vitamin C levels of 1–300 ng/ml. Meanwhile, the exclusion criteria include patients with comorbid physical disease disorders, such as impaired liver and kidney function, diabetes, neurological and cardiovascular disease, history of substance, and antioxidant use during the previous 1 week. The respondents were recruited from the Special Regional Hospital of Dadi South Sulawesi Province.

The BDNF and Vitamin C levels were assessed using ELISA through the patient's blood of 3cc obtained from the median cubital vein. Furthermore, the sample was centrifuged and serum was inserted into blank, standard, and sample wells. In the blank wells, blood samples and horseradish peroxidase (HRP) were not added, meanwhile, 50 µl of standard solution was added to the standard well, while 40 µl of special solution and 10 µl of serum were added to the sample well. Furthermore, 50 µl of HRP was added to each except the blank wells and the plate was then covered, lightly shake and incubated for 60 min at 37°C. The BDNF levels and improvement of negative symptoms were measured at the 2nd, 4th, and 8th weeks. Moreover, the measurement of negative symptoms was based on the PANSS score, while Vitamin C levels were measured at the beginning

and end of the study. Statistical analysis was performed using the SPSS version 22.0 for Windows.

Results

Based on the statistical tests, the data obtained include the characteristics and distribution of the subject, as well as the relationship of various variables with the PANSS value of negative symptoms and the samples' BDNF. The samples were between 20 and 50 years old. Table 1 shows the demographic characteristics of subjects.

Table 1: Demographic characteristics of subjects

Characteristics	Control (n = 30)	Treatment (n = 27)	p-value
Age (Mean ± SD)	35.81 ± 7.00	35.68 ± 7.644	0.904
Gender			
Male	25 (83.3%)	23 (85.2%)	0.849
Female	5 (16.7%)	4 (14.8%)	
Education			
Elementary school	18 (60%)	9 (33.3%)	0.015*
Junior high school	8 (26.7%)	7 (25.9%)	
Senior high school	4 (13.3%)	9 (33.3%)	
Bachelor	0 (0%)	2 (7.4%)	
Types of schizophrenia			
Paranoid	5 (16.7%)	13 (48.1%)	0.358
Non-paranoid	25 (83.3%)	14 (51.9%)	
Length of treatment (Mean ± SD)	2.37 ± 1.145	2.70 ± 1.263	0.298
IMT (Mean ± SD)	19.50 ± 3.693	20.74 ± 2.569	0.263
Initial PANSS (Mean ± SD)	39.07 ± 5.199	38.74 ± 5.281	0.773
Initial BDNF (Mean ± SD)	0.795 ± 0.341	1.0595 ± 0.417	0.014**
Initial Vitamin C (Mean ± SD)	5.501 ± 6.499	4.761 ± 5.635	0.749

Significance test: *Chi-square, **Mann–Whitney U-test.

Based on the Mann–Whitney U-test as shown in Table 2, there were no significant differences in age, gender, occupation, marital status, body mass index, and type of schizophrenia in the treatment and control groups ($p > 0.05$). Therefore, it was concluded that the data above are homogeneous. Moreover, to examine the comparison of PANSS values for negative symptoms was conducted in the control and the treatment groups. The demographic characteristics are in line with a previous study which stated that the most common age for schizophrenia is in the productive range or young adults [1]. The schizophrenia diagnosis generally occurs in young adults (or in late adolescence) with onset ranging from 18 to 25 and 25 to 35 years in males and females, respectively [13]. However, rare onset occurs at an early age below 10 years (early-onset schizophrenia) and an advanced age over 50 years (late-onset schizophrenia) [14].

Table 2: Comparison of PANSS values for negative symptoms in the control and treatment groups

Comparison	Mean ± SD		p-value
	Control (n = 30)	Treatment (n = 27)	
Initial PANSS	39.07 ± 5.199	38.74 ± 5.281	0.773
PANSS 2 nd week	32.67 ± 4.950	35.67 ± 6.239	0.042
PANSS 4 th week	29.23 ± 4.569	23.07 ± 5.690	0.0001
PANSS 8 th week	27.20 ± 4.773	13.19 ± 4.860	0.0001

*Significant at 0.05 (Mann–Whitney U-test).

The comparison of PANSS values for negative symptoms in the control and treatment groups measured at 0, 2nd, 4th, and 8th weeks is presented in Table 2.

The statistical results of the Mann–Whitney U-test in Table 2 showed a significant difference ($p < 0.05$) after the 8th week in PANSS values of the control and treatment groups. In addition, the mean PANSS value in the initial week was greater than the 2nd week in the two groups, and there was a significant decrease in the PANSS value. The PANSS scores of the 8th week showed a significant decrease in the atypical antipsychotic and Vitamin C adjuvant group (median rank 13.19) compared to the atypical antipsychotic group (median rank 27.20), therefore, there was a larger significant difference ($p < 0.0001$). This proves that Vitamin C provides improvements to the negative symptoms of schizophrenic patients. A study [10] showed that in an 8-week double-blind study on 40 controlled schizophrenia patients in India showed that the administration of atypical antipsychotics and Vitamin C at a dose of 500 mg/day significantly decreased serum malondialdehyde indicative of oxidative stress and increased plasma ascorbate levels (20.41 ± 2.84 at baseline vs. 22.79 ± 2.27 after 8 weeks of treatment) [5]. In the same study, concomitant administration of ascorbic acid (500 mg/day) and atypical antipsychotics had similar results, but plasma ascorbate levels were higher (21.51 ± 2.84 M/L at baseline and 33.54 ± 2.84 M/L after 8 weeks of treatment). Ascorbic acid inhibits binding at the site of dopamine receptor agonists. In this study, the high concentration of ascorbic acid reduced the action of dopamine and simultaneously potentiated the effect of drugs acting on the antagonist pathway. Furthermore, it plays an important role in anti-superoxide radicals by blocking the Colamin autoxidation, thereby inhibiting the formation of potentially toxic by-products such as 6-hydroxy dopamine (6-OHDA), semi-quinone, hydrogen peroxide, and hydroxyl radicals. This resultantly inhibits nerve damage in the brain and symptoms of developmental disability [15].

In addition, the test showed the changes in serum Vitamin C levels in the treatment group. The results showed the changes in serum vitamin C level in the initial week and week 8 on the treatment group (Table 3).

Table 3: Changes in serum Vitamin C levels in the treatment group

Comparison	Median (Min-Max)	Mean	p-value
Vitamin C in 0 week	0.842 (0.05–18.96)	4.762	0.0001
Vitamin C at 8 th week	153.459 (93.8–225.17)	148.155	

*Significant at 0.05 (Wilcoxon test); (n = 27).

Table 3 demonstrates that there were changes in Vitamin C blood levels in the treatment group from the initial to week 8 which indicated that there was an increase in ascorbic acid levels in the treatment group. This is in line with the previous studies which reported that schizophrenic patients experience a deficiency of ascorbic acid levels in the blood [16], [17]. Meanwhile, increased levels of Vitamin C in the blood inhibit brain damage due to oxidative stress and increase NMDA levels, which resultantly elevate serum BDNF levels in the brain, especially the prefrontal cortex [18].

The findings also showed that there was a significant difference in Vitamin C levels in the initial and 8th week in the treatment groups ($p < 0.05$). To compare serum BDNF levels in the treatment and control groups, a total of 57 schizophrenic patients that received atypical antipsychotic therapy at therapeutic doses were measured for serum BDNF levels at the 0 and 8th weeks. The results are shown in Table 4.

Table 4: Comparison and changes of serum BDNF levels in the treatment and the control groups

Item	Mean \pm SD		p-value
	Control (n = 30)	Treatment (n = 27)	
BDNF in 0 week	0.795 \pm 0.341	1.0595 \pm 0.417	0.014
BDNF in 4 th week	1.152 \pm 0.366	1.514 \pm 0.452	0.005
BDNF in 8 th week	1.519 \pm 0.400	2.553 \pm 0.649	0.0001
BDNF difference between 0 and 4 th week	1.951 \pm 0.6483	2.574 \pm 0.755	0.003
BDNF difference between 0 and 8 th week	2.313 \pm 0.635	3.613 \pm 0.920	0.0001
BDNF difference between 4 th and 8 th week	2.664 \pm 0.701	4.067 \pm 1.043	0.0001

*Significant at 0.05 (unpaired t-test).

The findings showed that there was a significant difference in serum BDNF levels from the initial to 8th week between the treatment and control groups ($p < 0.05$). Moreover, Table 4 shows that there was a significant difference in the BDNF levels for the 8th week between the treatment and the control groups ($p < 0.05$). Table 4 shows the changes in BDNF levels from the initial week before Vitamin C administration, where the 4th week has a $p < 0.005$ and 8th week has $p < 0.0001$. This indicates that Vitamin C affects changes in BDNF levels compared to the control group due to its characteristic as an antioxidant in increasing BDNF levels, while BDNF functions in neuroplasticity and other neurotransmitter regulators [19], [21]. Finally, the test was conducted to test the relationship between PANSS values and initial week serum BDNF levels and the relationship between PANSS values and serum BDNF levels at the 8th week in the treatment and the control groups. Furthermore, BDNF is strongly associated with negative symptoms as empirically evidenced in Table 5.

Table 5: The relationship between PANSS values and serum BDNF levels in the initial week on the treatment and control groups

PANSS	BDNF (n = 57)
0 week	$r = -0.722$; $P < 0.0001$
8 th week	$r = -0.722$; $P < 0.0001$

*Spearman test; r=strength of correlation; 0.1–0.3 weak; 0.4–0.6 moderate; 0.7–0.9 strong.

The results as presented in Table 5 showed that the correlation between PANSS values for negative symptoms and serum BDNF levels in the initial week was insignificant ($p > 0.05$) and has weak correlation strength with negative direction. In examining the relationship between PANSS values and serum BDNF levels at the 8th week in the treatment and the control groups, the results showed that the correlation between PANSS values for negative symptoms and serum BDNF levels at the 8th week was significant ($p < 0.05$), and shows a strong correlation with negative direction.

The close relationship between BDNF levels and improvement in negative symptoms is closely

related to decrease BDNF levels compared to patients with positive symptoms through a glutamatergic mechanism [20], [21], [22], [23], [24]. Moreover, an increase in BDNF levels through Vitamin C administration to active people [25] is expected to improve the negative symptoms of schizophrenic patients. The previous studies implicate brain glutamatergic abnormalities in the pathophysiology of schizophrenia which found variable changes in glutamate receptors and their modulators in schizophrenia [26], [27], [28], [29]. This is also supported by a previous study which reported that the application of antioxidants in clinical trials prevents or reduces disease progression [30].

Conclusion

The results of this study showed that administration of Vitamin C significantly increases BDNF levels and improves the negative symptoms in schizophrenic patients. More specifically, there was a significant increase in BDNF levels in treatments group compared the control at the 4th and 8th weeks with $p = 0.005$ (4th week) and ≤ 0.0001 (<0.05) (8th week). The improvement in PANSS scores for negative symptoms in the treatment groups compared to the controls at the 2nd, 4th, and 8th weeks resulted in $p = 0.042$ (2nd week) and <0.0001 (4th and 8th weeks). Furthermore, there was an increase in serum Vitamin C levels in the treatment groups with an initial average value = 4.762 and after 8 weeks = 148.155. Strong correlation between increased BDNF levels and improvement in negative symptoms on the PANSS score was found with $p = 0.001$ (4th week) and ≤ 0.0001 (8th week). The administration of Vitamin C significantly increases BDNF levels and improves the PANSS score for negative symptoms in the treatments compared to the control groups.

Overall, the findings found that statistically Vitamin C has a potential effect on changes in BDNF levels and improvement of negative symptoms in schizophrenic patients at a dose of 1000 mg/day for the 8th weeks of administration. The findings revealed that there is increasing evidence that oxidative stress contributes to the pathophysiology of schizophrenia as indicated by an increase in lipid peroxidation products in plasma and cerebrospinal fluid and an increase in enzymatic and non-enzymatic oxidants in schizophrenia. Due to the large lipid contents and the high oxidative metabolism in the myelin sheath, the brain is a target for free radicals which cause damage. Therefore, oral antioxidant supplementation is given as a secondary therapy to prevent oxidative as well as nerve tissue damage and improve clinical symptoms.

The limitation of this study lies in empirical testing to limit the effect of Vitamin C on the amelioration

of negative symptoms in schizophrenic patients and BDNF levels, and did not examine side effects and mechanisms. Hence, further studies are needed to test side effects and mechanisms of glutamatergic mechanism affecting symptoms of schizophrenia.

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