May 2019. Vol. 32. No.1 ISSN 2307-2083
International Journal of Research in Medical and Health Sciences
© 2013- 2019 IJRMHS & K.A.J. All rights reserved
http://www.ijsk.org/ijrmhs.html

The Difference of total Panss Scores between Male's Schizofrenia that Treatment by Risperidon with Addition of Vitamin C and those only gets Risperidon at Prof M. Ildrem Psychiatric Hospital Medan

MUHAMMAD YUSUF[1], ELMEIDA EFFENDY[2], MUSTAFA MAHMUD AMIN[2]

[1] Magister Student Department of Medical Science (Physiciatric) of North Sumatera University Medan and General Hospital Haji Adam Malik Medan-North Sumatera Indonesia.
[2] Lecturer in the Department of Medical Sciences (Physiciatric) of North Sumatra University and General Hospital Haji Adam Malik Medan- North Sumatera Indonesia;
Email: siregar.my88@gmail.com

ABSTRACT

Schizophrenia affecting aproximately about 1% of the population and one of the mental disorders that most often causes paralysis and expensive costs in the long run throughout the world. Vitamin C has been suggested to be useful in treating chronic schizophrenia and is useful in conjunction with other compounds for slow down development disease parkinson's. In part big vitamin deficiency cause symptoms psychiatry in a manner significant on some people large vitamins visible have role in disturbance psychiatric, Vitamins B, C, D, and E are known as important play role in treatment schizophrenia.
Aim of the Research: *To determine the difference in total PANSS scores in men with schizophrenia who received risperidone by adding vitamin C, and those who only received risperidone.*
Method: *The study was a non-randomized experimental pre-post test design study intervention group adding treatment with vitamin C and the control group, by comparing the two groups.*
Research Results*: There were significant differences in PANSS who received risperidone therapy at week 8 with p = 0.033 (p <0.05).*
Conclusion: *this study have reported significant clinical therapy with supplementation therapy with vitamin C in schizophrenia after therapy at week 8.*

Keywords: *Schizophrenia, Vitamin C, total PANSS score*

1.PRELIMINARY

1.1. Background

Schizophrenia affects about 1% of the population and one of the mental disorders that most often causes paralysis and expensive costs in the long run throughout the world. The mainstay of treatment is using antipsychotic drugs. Although usually the patient is in remission 'positive symptoms' (such as hallucinations and delusions) in few first month of treatment, poor long-term outcomes, such as 80% of patients relapse within 5 years. In addition, 'negative symptoms' (eg anhedonia and no motivation) are largely unresponsive to antipsychotic treatment but have a strong influence on functional outcomes. Although interven psychosocial (such as *Cognitive Behavior Therapy)* is effective for reducing residual symptoms in people with schizophrenia, but it is expensive and not accessible to the majority of patients. Thus, new interventions are needed that can provide the additional treatment needed to support and maintain full psychosocial recovery.

It has been suggested that additional treatment with certain vitamins and minerals can be beneficial for people with psychiatric disorders, possibly because there are biological mechanisms by which these nutrients can exert positive effects. Improvements can occur from solving nutritional deficits, because diet quality is increasingly recognized as a risk for many psychiatric disorders, and people with schizophrenia are at greater risk of having a diet bad. Consequently, people with schizophrenia often have a spectrum of vitamin and mineral deficiencies, even before being given antipsychotic treatment.

© 2013- 2019 IJRMHS & K.A.J. All rights reserved

Some researchers have implicated the role of free radical pathology in schizophrenia. Unusual abnormal activity of antioxidant enzymes and other lipid peroxidation indices in plasma and red blood cells has been detected in people with schizophrenia. The brain contains large amounts of unsaturated fatty acids, catecholamines and monoamines, which are the target molecules for lipid peroxidation, contain a lot of iron and produce hydroxyl radicals which are very damaging for lipid peroxidation. Monoamine and oxidation catecholamines also produce superoxide anions in the brain. Ascorbic acid as an antioxidant vitamin also plays an important role in protecting damage from free radicals in the brain. Found in brain tissue and the dominant area of dopamine at high concentrations compared to other organs. An Arvindakshan et al. Study reported a reduction in *Brief Psychiatric Therapy Scale* (BPRS) and *Positive and Negative Syndrome Scale* (PANSS) after supplementation with omega-3 fatty acids, vitamin C, and vitamin E.

Vitamin C has been suggested to be useful in treating chronic schizophrenia and is useful in conjunction with other compounds to slow the development of Parkinson's disease. [4] There are several studies that state many factors regarding the etiopathogenesis of schizophrenia, including genetic and biochemical studies. One of the important factors considered to be involved in the pathophysiology of schizophrenia is excessive production of free radical agents and antioxidant failure in defense mechanisms. Although many studies have been conducted in this field, further studies are needed to establish the role of oxidative imbalances in people with schizophrenia. Cellular oxidative damage is generally caused by free radicals and *Reactive Oxygen Species* (ROS). Many of the biochemical processes involved inROS levels are low. Oxidative stress is a disorder of the oxidative mechanism of balance as a result of an increase in oxidant levels and or a decrease in antioxidant levels .

Some studies suggest that the cause of schizophrenia is because dopamine levels are not enough because of the loss of dopamine-producing cells. On the other hand, it has been postulated that schizophrenia has been associated with hyperactivity of the dopaminergic brain system which might reflect the underlying dysfunction of *N-methyl-D-aspartate* (NMDA R) neurotransmission.

A relatively new approach such as the role of vitamin C in the etiology and treatment of schizophrenia was carried out by Sershen et al. According to the researchers, deficits in NMDAR are associated with persistent negative symptoms and cognitive deficits in schizophrenia. This hypothesis is supported by the fact that fl avoprotein *D-amino acid oxidase (DAO) is* shown to reduce the *D-Ser* gliotransmitter, an essential driver of *N-methyl-D-aspartate*- type glutamate receptors, while much evidence suggests that DAO, along with its drivers, G72 protein, can play a key role in the pathophysiology of schizophrenia. Furthermore, in postmortem studies DAO activity was found to be twice as high in schizophrenic subjects. Sershen et al. showed that the dose of acute ascorbic acid (300 mg/kg) inhibited locomotor activity induced by *Phencyclidine* (PCP) and induced in mouse models, which subsequently attenuated in D-serine (600 mg / kg). The authors suggest that this effect can result from changes in vitamin C depending on operator translocation of dopamine membranes and / or modified redox mechanisms that modulate NMDARs.

There is an urgent need for pharmacological care beyond the use of current antipsychotic drugs to overcome these sequelae, which contribute substantially to functional disorders. Many researchers attribute schizophrenia to vitamin deficiency, both after the disease has been diagnosed or during prenatal development. Vitamin supplementation can provide therapeutic benefits through a mechanism of action that is separate from the current treatment regimen, which focuses primarily on monoamine and histamine.

The role of vitamin supplementation has been explained in several psychiatric case studies. Vitamins and minerals are involved in one or more biochemical pathways and / or physiological actions that affect man's age brain function. Vitamins play a major role in a number of vital functions, acting as cofactors or as coenzymes and catalyzing some reactions that occur in the body. Most vitamin deficiencies cause psychiatric symptoms significantly in some people. Most vitamins appear to have a role in psychiatric disorders, Vitamin B, C, D, and E are known to play a role of an important in the treatment of schizophrenia.

Thus, the purpose of this study was to menge tahui whether oral
vitamin supplementation with atypical antipsychotics

© 2013- 2019 IJRMHS & K.A.J. All rights reserved

will increase the improvement of clinical symptoms and can be given as adjunctive therapy in the treatment of schizophrenia.

1.2. Problem Formulation

By looking at the background of the problem above, then you can formulated research problems as follows:

Are there differences PANSS total score on men with schizophrenia who gets risperidone by adding vitamin C, and who only gets risperidone?

1 .3. Hypothesis

PANSS score a total difference on men with schizophrenia who get risperidone by adding vitamin C, and who only get risperidone.

1 . 4 The purpose Research

1.4.1. General purpose

There is a difference in the total PANSS score on men with schizophrenia who get risperidone with the addition of vitamin C, and those who only get risperidone .

1.4.2. Special purpose

1. To find out the demographic characteristics of the research subject; age , level of education, second job, marital status , duration of illness , Body Mass Index (BMI), onset, number of attacks, andtotal PANSS score of week 0 .
2. To know the difference total P ANSS score on men with schizophrenia who get risperidone by adding Vitamin C , at the beginning and at the end of the week VIII.
3. To determine the per distinctions total score PANSS on men with schizophrenia those who only get risperidon, at the beginning and at the end of week VIII.
4. To determine the per distinctions t otal score PANSS on men with schizophrenia who get risperidone by adding Vitamin C , and those who only get risperidone at the end of week VIII.

1 . 5 . Benefits of Research

1. The results of this study are expected to provide information about the benefits of adding v itamin C to total changes score PANSS .
2. The results of this study are expected to be a consideration in providing vitamin C as an adjunct therapy to men with schizophrenia.
3. The results of this study can also be continued for further similar research material or this research is used as an ingredient .

2.LITERATURE

2.1. Schizophrenia

2. 1 . 1. History

Kraepelin translates *Morel's demence precoce* into precocious dementia, a term that emphasizes changes in cognition (dementia) and early (precocious) onset of this disorder. Patients with precocious dementia are described as experiencing worsening clinical symptoms of hallucinations and delusions. Kraepelin distinguishes these patients from people who experience different episodes of disease with periods of normal functioning, so this is classified as having manic-depressive psychosis.

Bleuler coined the term schizophrenia, which replaced precocious dementia. Bleuler chose this term to express the existence of cracks in the mind, emotions and behavior in patients with this disorder.Bleuler identifies the specific basic symptoms of schizophrenia to develop his theory of the separation of internal souls from patients. These symptoms include mind association disorders, especially loose associations, affective, autistic disorders, and ambivalence summarized as *the four As* : associations, affect, autistic and ambivalence.

2. 1 .2. Definition

Schizophrenia is a psychotic disorder that is generally characterized by a distinctive and distinctive distortion of thoughts and perceptions, and by the affect unnatural *(Inappropriate)* or blunt *(blunted).* Clear awareness and intellectual abilities are usually maintained, although certain cognitive deficits can develop later. This disorder involves the most basic functions that give a normal person a feeling of personality (*individuality)* , uniqueness and *self-direction* . The most intimate / deep thoughts, feelings and actions are often felt to be known by or shared with other people, and understandings can arise, which explains that natural and supernatural powers are working to influence the

© 2013- 2019 IJRMHS & K.A.J. All rights reserved

mind and deeds of sufferers in ways that often do not enter sense or *bizarre.*

2. 1 .3. Epidemiology

In the United States, the prevalence during a person's life to experience schizophrenia is around 1%, which means that about 1 person out of 100 people will experience schizophrenia during their lifetime. Based on the *Epidemologic Catchment Area* study sponsored by the *National Institute of Mental Health, the* prevalence during a person's life to experience schizophrenia is around 0.6-1.9%. In the United States, about 0.05% of the total population is treated with a diagnosis of schizophrenia each year and only half of all patients with schizophrenia received treatment, despite experiencing severe disorders.

The prevalence between men and women is the same, but both sexes show differences in the onset and travel of patients. Men have an early onset than women . Age the peak for the onset of men is 10 to 25 years, for women peak age is 25 to 35 years. The onset of schizophrenia before the age of 10 years or after 60 years is very rare. Ninety percent of patients who received the treatment of schizophrenia air between the ages of 15 to 55 years. In general, women with schizophrenia have better *outcomes* than men .

2. 1 .4. Etiology
2. 1 .4.1. Genetic factors

There is a genetic contribution to perhaps even all forms of schizophrenia, and a high proportion of variance in the propensity for schizophrenia is due to genetic influences, for example, schizophrenia and schizophrenia-related disorders (such as schizotypal, schizophrenia and paranoid personality disorders) where this arose in the value of the relationship that increased among biological relatives of patients with schizophrenia.

2. 1 .4.2. Biochemical factors
2. 1 .4.2.1. Dopamine hypothesis

The simplest formulation of the dopamine hypothesis is based on that schizophrenia is the result of too much dopaminergic activity. This theory evolved from two observations. First, the efficacy and potential of antipsychotic drugs (for example, dopamine receptor antagonists related to their ability to act as antagonists of Dopamine D2 receptors. Second, drugs that increase dopaminergic activity are*psychotomimetic.*

2. 1 .4.2.2. Serotonin

At present some hypotheses state that excessive serotonin is the cause of positive symptoms and negative symptoms of schizophrenia. Serotonin antagonists from clozapine and other second generation antipsychotics have the effectiveness of clozapine to reduce positive symptoms in chronic patients.

2. 1 .4.2.3. Norepinephrine

Anhedonia has long been considered as an important feature of schizophrenia. Selective neuronal degeneration in the nervous system norepinephrine can explain the symptomatological aspects of schizophrenia. However, the biochemical and pharmacological data related to this are still not convincing.

2. 1 .4.2.4. GABA hypothesis

Neurotransmit er *Gamma - aminobutyric acid* (GABA) has an influence on the pathophysiology of schizophrenia based on the discovery that some people with schizophrenia experience a reduction in GABAergic neurons in the hippocampus.

2. 1 .4.2.5. Neuropeptide

Neuropeptides such as P substances and neurotensin are located in the same location as catecholamines and indolamine neurotransmitters and affect the action of these neurotransmitters. Changes in the mechanism of the neuropeptide can facilitate, inhibit, or change the pattern of goals of the nervous system.

2. 1. 4.2.6. Glutamate

Glutamate has been involved because of the digestive process of *phenyciclidine* , a glutamate antagonist that can result in an acute syndrome similar to schizophrenia.

2. 1 .4.2.7. Acetylcholine and nicotine

Some postmortem studies in schizophrenia have shown a decrease in caudal muscarinic and nicotine receptors from putamen, hippocampus and

© 2013- 2019 IJRMHS & K.A.J. All rights reserved

some parts of the prefrontal cortex, where these receptors play a role in sus unans in the neurotransmitter system involved in cognitive, where schizophrenia occurs.

2. 1 .4.3. Neuropathology

In the 19th century, a neuropathologist failed to find basic neuropathology of schizophrenia, and therefore they classify schizophrenia as a disorder fungsio nal. By the end of the 20th century, researchers had made significant steps in uncovering the neuropathological basis of schizophrenia, especially in the limbic system and basal ganglia, including neuropathological or neurochemical abnormalities in the *cerebral* cortex , *thalamus* and brain stem.

2. 1 .4.4. Neural circuit

The gradual evolution of the conceptualization of schizophrenia as a disorder that covers different areas of the brain as a perspective view of schizophrenia as a disruption of the brain's neural circuits.For example, basal ganglia and *cerebellum* are reciprocally related to the frontal lobes, and abnormalities in frontal lobe function are seen in brain imaging studies. It also hypothesizes that early developmental lesions from the dopaminergic pathway to the prefrontal cortex produce disorders of prefrontal function and the limbic system and cause positive and negative symptoms and cognitive impairment observed in people with schizophrenia.

2. 1 .4.5. Brain metabolism

Studies using *magnetic resonance spectroscopy* (a technique for measuring the concentration of specific molecules in the brain) found that people with schizophrenia had *lower* levels of *phosphomonoester* and inorganic phosphate and higher *phosphodiester* levels than the control group. Furthermore, the concentration of *N-acethyl aspartate* is lower in the hippocampus and frontal lobe in people with schizophrenia.

2. 1 .4.6. Electrophysiology

St -study *electroencephalographic* shows that many people with schizophrenia have abnormal electrophysiologic recordings, increased sensitivity to activation procedures (frequent *spike* activity after lack of sleep, decreased alpha activity, increased theta and delta activity.

2. 1 .5. Diagnostic Criteria

The diagnostic criteria for schizophrenia based on PP DGJI-III are as follows :

Schizophrenia disorder based PPDGJI-III are characterized by distorted thinking and perception of the fundamental and distinctive, and therefore affect the unnatural *(Inappropriate)* or blunt *(blunted).*Clear awareness and intellectual abilities are maintained, although certain cognitive deficits can develop later.

Although there are no specific pathognomonic symptoms, in practice it is useful to divide the symptoms into groups that are often found together, for example:

(a) " *Thought echo"* , " *thought insertion* " or " *withdrawal* " and " *thought broadcasting* "
(b) Delusion *of control* , *delusions of influence* or *passivity* , which clearly refers to body movements or movements of limbs, or thoughts, special actions or *sensations* ; delusional perception;
(c) Hallucinations that continually comment on a patient's behavior, or discuss about patients among themselves, or other types of hallucinatory sounds coming from one part of the body;
(d) Other types of sedentary understandings which according to their culture are considered unnatural and are totally impossible, such as regarding religious or political identity, or the strength and ability of " super age man " (for example being able to control the weather, or communicating with aliens from other worlds);
(e) Hallucinations that persist in each modality, if accompanied by either floating / floating ideals or half-shaped without clear affective content, or *over-valued ideas* that persist, or if they occur every day for weeks or months continuously;
(f) The flow of thoughts that are interrupted or which experience interpolations that result in incoherence or irrelevant speech, or neologism;
(g) Catatonic behavior, such as a state of *excitement* (*excitement*), certain posture (*posturing*), or flexibility of Serea, negativism, mutism, and stupor;
(h) "Negative" symptoms such as a very bodily attitude (apathy), stalled speech, and a collapsing or unnatural emotional response, usually resulting in withdrawal from social interaction and a decrease in social performance, but it must be clear that all of

May 2019. Vol. 32. No.1 ISSN 2307-2083
International Journal of Research in Medical and Health Sciences
© 2013- 2019 IJRMHS & K.A.J. All rights reserved
http://www.ijsk.org/ijrmhs.html

these things are not caused by depression or neuroleptic medication;

(i) A change that is consistent and meaningful in the overall quality of some aspects of individual behavior, manifests as loss of interest, not purpose, laziness, *self-absorbed attitude* and social withdrawal.

Diagnostic Guidelines

The normal requirement for a diagnosis of schizophrenia is that there should be very few of the symptoms above that are very clear (and usually two or more symptoms if the symptoms are less sharp or unclear) of symptoms that are included in the symptom group (a) to (d) above, or at least two symptoms from groups (e) to (h), which must always be clearly present for a period of one month or more.Conditions that meet the requirements of the symptom but which are less than one month old (either treated or not) must be diagnosed first as an acute psychotic-schizophrenic disorder (F23.2) and newly reclassified if the symptoms decrease over a period of time longer time.

2.2 . Vitamin C
2.2.1. Definition

Vitamin C (ascorbic acid) is included in the group of water-soluble vitamins. In organisms, Vitamin C can be in two forms: derivatives - ascorbic acid (AA) which in physiological pH occur in the form of anions from ascorbate, and are oxidized - *Dehydroascorbic Acid* (DHA), which is a two e electron AA oxidation product .

In the metabolic process a ascorbate free radical can be produced as a result of one electron oxidation. This variety can then undergo dismutation to form ascorbate and DHA. Vitamins are organic compounds commonly used in food; many of which cannot be synthesized in sufficient quantities by the human body . Vitamins are classified as water soluble and fat soluble.Most of the nine vitamins that are water-soluble as coenzymes in the metabolic process, only one (vitamin K) of the four fat-soluble vitamins that have a role coenzyme. Fat-soluble vitamins are absorbed and stored in the liver and adipose tissue. To prevent various medical ailments caused by vitamin deficiencies, food and drugs have issued specific recommendations for daily vitamin intake. The plasma concentration in healthy age is around 200 µM and the brain part has the highest concentration compared to other tissues.

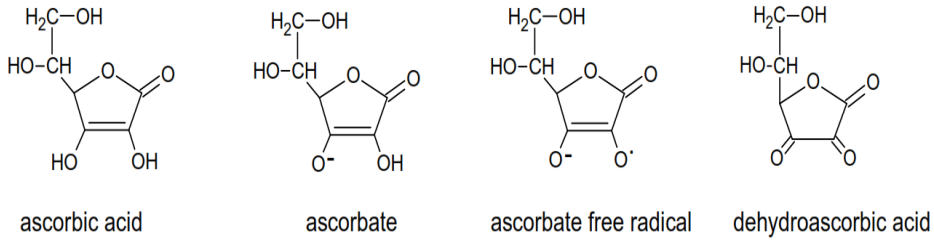


Figure 1. Structure of ascorbic acid
S ource: Kocot J, Kocot DL, Kielczykowska M, Music I, Kurzepa J. Influence Does Vitamin C Neurodegenerative Diseases and Psychiatric Disorders? Nutrients 2017, 9, 659: 1-29.

Vitamin C is a nutrient that is very important for the functioning of the nervous system and its main role in the brain in antioxidant defense. Apart from this role, it is involved in many non-oxidant processes such as collagen biosynthesis, carnitine, tyrosine and peptide hormones and myelin. It plays an important role in neurotransmission and neuronal maturation and function. For example, its ability to reduce the severity of seizures and to reduce damage from seizures has been proven. On the other hand, impaired transport of vitamin C has been shown to contribute to brain damage in premature infants.Furthermore, vitamin C treatment has been reported to improve neuropathological changes as well as memory disorders and neurodegenerative changes in mice exposed to neurotoxic substances such as aluminum or colchicine. As a result, many are interested in the problem of vitamin C deficiency, as well as the treatment of vitamin C in nervous system diseases, which have been observed for years.

Table 1 Vitamins

May 2019. Vol. 32. No.1 ISSN 2307-2083
International Journal of Research in Medical and Health Sciences
© 2013- 2019 IJRMHS & K.A.J. All rights reserved
http://www.ijsk.org/ijrmhs.html

Vitamin	Source	Function	Deficiencies	Daily recommended values (based on 2000 calorie diet)
Water Soluble				
Thiamine (Vitamin B1)	Cereals, bread, grains, legumes, seeds	Coenzyme in formation/ degradation of a-ketols and oxidative decarboxylation of a keto acids	Beriberi; Wernicke-Korsakoff syndrome	1.5 mg
Riboflavin (Vitamin B2)	Dairy, cereals, legumes	Coenzyme in oxidation/reduction reactions	Dermatitis, cheilosis, glossitis	1.7 mg
Niacin (Vitamin B3)	Meats, cereals, whole grains	Coenzyme in oxidation/reduction reactions	Pellagra	20 mg
Pyridoxine (Vitamin B6)	Chicken, fish, pork, eggs, starchy vegetables	Acts as coenzyme for amino acid reactions	Microcytic anemia, dermatitis with cheilosis and glossitis	2 mg
Folate (Vitamin B9)	Liver, leafy vegetables; fortified grain products	Key in one-carbon metabolism	Megaloblastic anemia; neural tube defects	400 µg
Cobalamin (Vitamin B12)	Animal products (meat, dairy)	Key for remethylation of homocysteine to methionine; isomerization to form succinyl coA; DNA synthesis	Megaloblastic anemia; pernicious anemia; neuropsychiatric symptoms	6 µg
Ascorbic Acid (Vitamin C)	Citrus fruits, potatoes, spinach	Reducing agent in hydroxylation reactions; antioxidant	Scurvy (defective collagen)	60 mg
Biotin	Liver, egg yolk	Coenzyme in carboxylation reactions	Rare	300 µg
Pantothenic Acid	Eggs, liver, yeast	Part of CoA, transferring acyl groups	Unknown	10 mg
Fat Soluble				
Vitamin A	Liver, dairy, kidney, green vegetables	Regulates RNA synthesis; need for visual cycle, reproduction (spermatogenesis), growth, differentiation of epithelial cells	Xerophtalmia (dryness of conjunctiva, cornea →blindness); infertility; growth abnormality	5,000 IU*
Vitamin D	Fish, liver, egg yolk, fortified milk	Regulates gene expression; regulates calcium/phosphorus	Rickets/Osteomalacia (bone demineralization in children/adults)	400 IU
Vitamin E	Vegetable oils, liver, eggs	Antioxidant	Mostly in premature infants; RBC membrane fragility	30 IU
Vitamin K	Greens, egg yolk, liver	Coenzyme in post-translational modification of clotting factors	Rare (hypoprothrombinemia); supplemented in newborns	80 µg

*IU = International units

Source: Brown HE, Roffman JL. Vitamin Supplementation in the Treatment of Schizophrenia. CNS Drugs (2014).

These facts made us decide to renew the current state of knowledge about the role of v itamin C in neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple *sclerosis* and *amyotrophic sclerosis* , as well as psychiatric disorders including depression, anxiety disorders and schizophrenia. Typical toxicity does not occur because vitamin C dissolves in water and is regularly excreted by the body. The advantages of ascorbic acid excreted in urine give false positive test results for glucose.High levels of vitamin C interfere with copper absorption. Vitamin C must be avoided by those who suffer from kidney stones, because it can be converted to oxalate. But some studies show that vitamin C only undergoes transformation in urine after urine is released from the body.

2 .2.2 . Relationship between Vitamin C and Schizofrenia

A review of the Hoffer study shows that, among others, v itamin C deficiency can worsen the symptoms of schizophrenia and that large doses of this vitamin can improve the main metabolic

© 2013- 2019 IJRMHS & K.A.J. All rights reserved

abnormalities that affect some people to develop this disease. According to this study that the pathological process responsible for schizophrenia can increase the utilization of ascorbic acid. Sarandol et al. Also noted lower levels of v itamin serum C compared to the control group, but this was not considered a statistically significant difference. [6]

In addition, antipsychotic treatment for 6 weeks does not change the concentration of this vitamin. Other factors, such as nutrition, physical activity, etc., may be the reason for discrepancies between the results of their research and other studies. Similarly, Young et al observed only slightly decreased levels of v itamin C group compared k ontrol schizophrenia, but which attract a very significant increase in the level of vitamin C in the control group of women compared with controls, and also groups of male schizophrenia observed. The authors suggest that this information may be relevant especially in a recent report that the risk of schizophrenia is higher in men than in women . The supply of vitamin C reduced by diet in patients with schizophrenia was recorded by Konarzewska et al.

Magalha es et al. revealed that the application of v itamin C as an antioxidant with low molecular weight relieves the effects of free radicals in the treatment of schizophrenia. According to Bentsen et al. Membrane lipid metabolism and redox regulation can be disrupted in schizophrenia. In this study conducted a study that aimed to examine the clinical effects of adding vitamin E + C to antipsychotics (D receptor antagonists). People with schizophrenia or psychosis-related individuals receive v itamin C (1000 mg / day) along with vitamin E (364 mg / day) for 16 weeks. This study shows the effect of supplementation of antioxidant vitamins as agents reducing some of the side effects of antipsychotic drugs. Confirmed by subsequent studies involving people with schizophrenia treated with haloperidol.

Classical antipsychotics such as haloperidol are recommended to increase oxidative stress and oxidative cell injury in the brain, which may affect travel and the effects of treatment for schizophrenia. In this study, chronic haloperidol treatment was associated with supplementation of a combination of 3-fatty acids and vitamins E and C showed a significant beneficial effect on the treatment of schizophrenia as measured by *Simpson Angus Scale* (SANS) and *Brief Psychiatric Rating Scale* (BPRS). The total BPRS score and subscale score and SANS score increased significantly from the 4th week of treatment. In addition, in patients with schizophrenia after 16 weeks of treatment, serum vitamin C levels were almost twice as high at the start of the study. These results support the hypothesis of the beneficial effects of supplementation on both positive and negative symptoms of schizophrenia and the severity of side effects caused by haloperidol.

Heiser et al. also stated that *reactive oxygen species* (ROS) is involved in the pathophysiology of psychiatric disorders such as schizophrenia. Their research showed that antipsychotics induced ROS formation in all rat blood, which could be reduced by the application of vitamin C. The ROS formation in whole blood using spin electron spectroscopic resonance is the reason for their study of clozapine, olanzapine and haloperidol at different doses (18, 90 and 180µg / mL). To show the capacity of vitamin C (1 mM) for 30 minutes. Olanzapine causes a significant greater formation of ROS vs. control under all treatment conditions, while the case of haloperidol and clozapine is only a higher concentration result in a significant increase in ROS formation. Vitamin C reduces the production of ROS from all drugs tested, but for olanzapin, the weakening effect does not reach a significant level.

Ascorbic acid (vitamin C) is an antioxidant vitamin and plays an important role in protecting free radical damage in the body. Found in brain tissue and the dominant area of dopamine in higher concentrations than other organs. Ginkgo biloba, ginkgo biloba leaf extract also has antioxidant properties and has been found to improve brain circulation at the microvascular level, possibly increasing improvement in schizophrenia. Long-term treatment with antipsychotics is associated with a variety of motor disorders, including tardive dyskinesia (TD). Both dopamine-receptor super sensitivity and oxidative stress-induced neurotoxicity in the nigrostriatal system are suggested to be involved in their pathogenesis.

Pineal melatonin is a powerful antioxidant and weakens dopaminergic activity in the release of striatum and dopamine from the hypothalamus. Thus, treatment with antioxidant agents may have beneficial effects for both treatment of psychotic symptoms and prevention of BP. We found 2 Randomized Control trials (RCTs) on vitamin C: found to improve general function and reduce side effects (reduce serum malondialdehyde (MDA), lipid

© 2013- 2019 IJRMHS & K.A.J. All rights reserved

peroxidation when added olanzapine (10 mg), quetiapin (200 mg) or ziprasidon (40 mg) after 8 weeks. One study without antipsychotics found no effect on cognition or motor function after 10 days. Both studies reported no side effects from administration of vitamin C.

Oxyradical pathology can be corrected through at least two mechanisms - inactivation of oxyradicals by intake of antioxidants (eg vitamins E and C, ubiquinones, and [b-carotene], and replacement of phospholipid membrane EPUFAs by supplementing a diet with Esterified Fatty Acid (EFA). preliminary available, what can be concluded about the use of antioxidants in the treatment of schizophrenia? Regarding the question - if antioxidants are shown, what anti-oxidants should be used, on whom and when? The following figure summarizes the balance between the generation of oxyradical and antioxidant defenses, anti-contribution -diet oxidants and EFA supplements to protect and repair membrane EPUFAs, and possibly biochemical defects (dashed lines) in schizophrenia.

Phospholipid and polyunsaturated fatty acids (PUFAs), which are known as important structural elements of the membrane of C entrain N cells (CNS), have also been described as very susceptible to increased production of free radicals and decreased antioxidant defenses. In addition, a significant association between negative symptoms that occurred in the first psychotic episode, oxidative stress, decreased PUFA content, and increased levels of lipid peroxidation have been reported.

In a prospective, double-blind placebo-controlled study, of forty outpatients in India, Dakhale et al. studied vitamin C supplements (500 mg / day) for eight weeks in patients with schizophrenia using second generation antipsychotics. This study found that in the vitamin C group, there was a decrease in serum levels of malondiahldehyde (MDA), an increase in ascorbic acid levels in plasma, and a decrease in BPRS scores. Of note, similar results were also found in the placebo group. When both groups were compared, the vitamin C group experienced a significantly greater decrease in MDA and BPRS scores and a significant increase in ascorbic acid levels. It is not clear whether there are some interactions between second generation antipsychotic drugs and vitamin C, or if vitamin C works through other mechanisms. These studies show that vitamin C supplements improve clinical symptoms and reduce free radical damage in patients.

More and more research shows that ascorbic acid can modulate the effects of dopamine (DA) in the mammalian brain. Ascorbic acid inhibits binding of both DA agonists and antagonists. One of the earliest observations about the interaction of ascorbic acid with the dopaminergic system is ascorbic acid which can completely inhibit DA-stimulating cyclase adenylate activity in mice. Recently, one study showed dopaminergic antagonistic properties of ascorbic acid. Ascorbic acid increases the catalytic effect produced by dopaminergic antagonists and various Nitric Oxide Sinthase (NOS) inhibitors. Also, ascorbic acid blocking induced amphetamine changes behavior in mice with unilateral nigrostriatal lesions produced by 6-hydroxydopamine. This finding was coupled with dopaminergic agonist and antagonist inhibition in radioligand-binding studies which suggested an action of ascorbic acid such as antidopaminergic. Amphetamines and other DA agonists increase the levels of extracellular neostriatal ascorbate, and this effect is reversed by DA antagonists.

In contrast, one observation was that ascorbic acid did not inhibit basal cyclase adenylate cyclase activity or DA in striatal homogenates from several strains of mice. Nitric oxide (NO) is a free radical gas that acts as an atypical neurotransmitter. Inhibition of NO formation interferes with rat exploration behavior in open fields and results in catalepsy. Some evidence shows the involvement of NO in the expression of stereotypical behavior of methamphetamine. However, the results are contradictory and contradictory. Although the interaction between ascorbate and DA or NO, the nervous system underlying the ascorbate release in neostriac remains unclear.

2.3. Risperidon

Synthetic risperidone has been the focus of the drug company's production since 1984 because risperidon is a strong antagonist in D 2 and 5-HT 2 receptors. Then several studies have shown the safety and efficacy of risperidone so that risperidone has been approved as an antipsychotic drug in the United States in 1994. Risperidone is a second generation antipsychotic drug approved in treatment after clozapine. Where clozapine is given to patients who respond poorly to treatment with antipsychotics,

© 2013- 2019 IJRMHS & K.A.J. All rights reserved

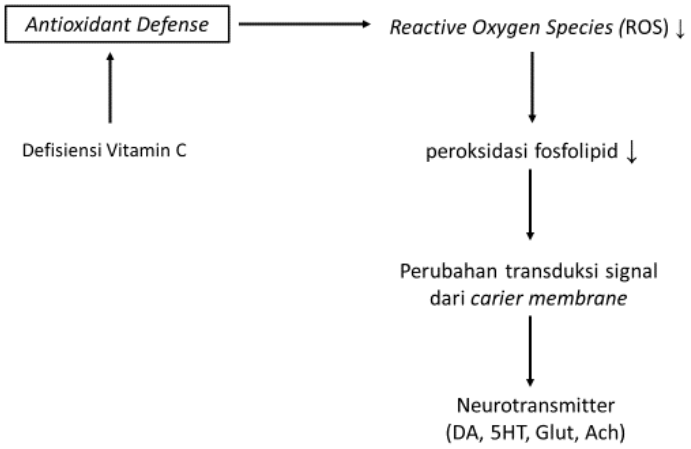
risperidone is a first-line antipsychotic widely administered in patients with psychotic disorders. Risperidone is a derivative of benzisoxazole. Risperidone has a bioavailability of 70%, and studies show that all oral forms of risperidone are bioquivalent. Risperidone is metabolized in the liver to 9-hydroxy risperidone (paliperidone), which generally has the same pharmacological profile as the main compound. After consumption, the peak plasma level of the main compound occurs within 1 hour and within 3 hours becomes 9-OH-risperidone. Steady state is expected to be reached by 5 days. Food does not affect its value or is absorbed widely in the intestine.

Specifically, risperidone has a unique balance of serotonin and dopamine antagonists, namely that its affinity for serotonin 5-HT2A receptors is significantly greater than its affinity for D2 receptors. Risperidone has been shown to have an effect on positive symptoms and negative symptoms of schizophrenia. Risperidone has been used in many studies to assess patient safety, effectiveness, tolerance and satisfaction and get positive results. Risperidone is widely used both for the treatment of acute phase and maintenance. In the treatment of negative symptoms risperidon has better results compared to first generation antipsychotics. Risperidon has a higher risk of hyperprolactinemia compared to first generation antipsychotics, but has lower metabolic side effects compared to other second generation antipsychotic drugs.

2. 4 . *Positive and Negative Syndrome Scale*

Positive and Negative Scale Syndrome was developed in the late 1980s which aimed to assess clinical symptoms of schizophrenia. This scale was adapted from the scale of previous psychopathology, including the Brief Psychiatric Rating Scale (BPRS). Negative Positive Syndrome Scale contains 30 items in 3 subscales, 7 items include positive symptoms (for example, delusions and hallucinations), 7 items include negative symptoms (for example, social withdrawal, flat affect, lack of motivation), and 16 items include psychopathology general (for example, anxiety and depression). Positive And Negative Scale Syndrome is conceived as an operational instrument that shows a balanced picture of positive and negative symptoms, as well as moods and symptoms of anxiety. Assessment can be completed in 30 to 40 minutes. Reliability is good and the validity is very good.

2.5 . Theoritical Framework



Picture 3 . Framework

3.RESEARCH METHOD

3 .1. Research design

This study was a non-randomized experimental pre-post test design study intervention group that added treatment with vitamin C and the control group, by comparing the two groups.

1. Group I: a group of patients who received risperidone treatment with the addition of vitaminC.
2. Group II: a group of patients who only received risperidone treatment.

May 2019. Vol. 32. No.1 ISSN 2307-2083
International Journal of Research in Medical and Health Sciences
© 2013- 2019 IJRMHS & K.A.J. All rights reserved
http://www.ijsk.org/ijrmhs.html

3.2. Place and time

1. Research site: Hospital outpatient installation. Prof. Dr. M.Ildrem North Sumatra Province.
2. Research Time: July 9, 2018 - January 10, 2019

3.3. Population and research sample

Target population: Men with schizophrenia

Affordable population: Men with schizophrenia who are admitted to Prof. Mental Hospital Dr. M. Ildrem Province of North Sumatra period 09 July 2018 - 10 January 2019.

Study sample: Men with schizophrenia who were admitted to Prof. Mental Hospital Dr. M. Ildrem Province of North Sumatra period 09 July 2018- 10 January 201 9 that meets the inclusion criteria.

How to take the subject: with non probability sampling type consecutive sampling.3.4. Kriteria Inclusion and Exclusion

Inclusion criteria:

1. Men with schizophrenia diagnosed based on PPDGJ III.
2. Ber aged 15-35 years.
3. A number of attacks 3-5 times.
4. Body mass index within normal limits (18.50-24.99 kg / m 2)
5. Cooperative and willing to participate in research.
6. Residing in Medan.
7. Phase stabilization in outpatients
8. Duration of 1 - 10 years

Exclusion criteria:

1. Having general medical disorders and / or other comorbidities
2. History of substance use (except caffeine and nicotine)
3. History of vitamin C supplement use for ± 1 week before.

3.5. Estimated Large Samples

This study is the first research conducted in Indonesia, especially in North Sumatra, which examines the differences in the negative symptoms of men with schizophrenia that have risperidon with the addition of vitamin C, and which only get risperidon. Therefore, to know the sample size, a preliminary study was conducted on July 09, 2018- October 08, 2018 by recruiting 11 subjects who had risperidon with the addition of vitamin C and 11 subjects only got risperidon and conducted the research procedure with the following result:

Table 3. 1. PANSS Total Score in Groups that Get Risperidone with the Addition of Vitamin C at the Beginning Before Therapy and at the End of Week VIII

	average ± sb
Score PANSS week 0	69,09 ± 2,948
Score PANSS end of week VIII	48,36 ± 2,580
ReductionScore PANSS	20,73 ± 2,611

Table 3.2. PANSS Total Scores for Groups Only Receiving Risperidone at the Beginning Before Therapy and at the End of Week VIII

	average ± sb
Score PANSS week 0	67,00 ± 2,898
Score PANSS end of week VIII	51,09 ± 3,145
Reduction Score PANSS	15,91 ± 4,592

3.5.1 Large Sample Estimated to Know the Total Difference PANSS Score between Men with Rispididone Schizophrenia with the Addition of Vitamin C and Only Get Risperidon at Weekend VIII

Previously the combined standard intersections were calculated using the formula:

$$Sg^2 = \frac{S_1^2 (n_1 - 1) + S_2^2 (n_2 - 1)}{n_1 + n_2 - 2}$$

Information:

Sg = Combined standard intersection

$(Sg)^2$ = Combined variant

S_1 = Standard intersection of group 1 in the preliminary study

= The standard deviation of the PANSS total score of the group receiving risperidone with the addition

May 2019. Vol. 32. No.1 ISSN 2307-2083
International Journal of Research in Medical and Health Sciences
© 2013- 2019 IJRMHS & K.A.J. All rights reserved
http://www.ijsk.org/ijrmhs.html

of week-end vitamin C VIII in the preliminary study = 2.580

n_1 = The sample size is group 1 in the preliminary study

= Large group who received risperidone treatment with the addition of vitamin C in the preliminary study = 11

S_2 = Standard group 2 intersection in the preliminary study

= Standard PANSS total score group that only received end-week VIII risperidone treatment in the preliminary study = 3,145

n_2 = Sample size of group 2 in the preliminary study

= Large group that only received risperidon treatment in the preliminary study = 11

From the formula, the following results are obtained:

$$(Sg)^2 = \frac{S_1^2 (n_1 - 1) + S_2^2 (n_2 - 1)}{n_1 + n_2 - 2}$$

$$(Sg)^2 = \frac{2,580^2 (11 - 1) + 3,145^2 (11 - 1)}{11+ 11 - 2}$$

$$(Sg)^2 = \frac{6,656(10) + 9,891 (10)}{20}$$

$$(Sg)^2 = \frac{66,56 + 98,91}{20}$$

$$(Sg)^2 = \frac{165,47}{20} = 8,274$$

$$(Sg) = \sqrt{8,274} = 2,876$$

Quantity of sample we gained:

$$n_1 = n_2 = 2 \frac{(Z\alpha + Z\beta) S}{X1-X2}^2$$

Information:

n_1 = The sample size was the group that received risperidone treatment with the addition of vitamin C

n_2 = The sample size of the group that only received treatment with risperidon

Zα = Error type I (α) is set at 5%, so Zα = 1.96 (two-way hypothesis)

Zβ = Type II (β) errors are set at 10%, so Zβ = 1,28

S = Combined standard intersection = 2,876

$X_1 - X_2$ = Mean differences between the two groups were considered significant = 51,09-48,36 = 2,7 3

$$n_1 = n_2 = 2 \frac{(Z\alpha + Z\beta) S}{X1-X2}^2$$

$$= 2 \frac{(1,96+ 1,28) 2,876}{2,73}^2$$

$$= 2 \frac{(3,24) 2,876}{2,73}^2$$

$$= 2 \frac{9,318}{2,73}^2$$

$$= 2 (3,413)^2$$

$$= 2 (11,649)$$

$$= 23,29$$

3.5.2. The estimated size of the S ampere will be to find out the total Score PANSS difference in the L at the time with Skizophrenia which gets Risperidone with the addition of V itamin C, at the beginning before given intervention and at the end of week VIII:

$$n_1 = n_2 = \frac{(Z\alpha + Z\beta) S}{X1-X2}^2$$

INFORMATION :

Zα = Error type I (α) is set at 5%, so Zα = 1.96 (two-way hypothesis)

Zβ = Error type II (β) is set at 10%, soZβ = 1,28

$X_1 - X_2$ = the minimum difference in average is considered meaningful = 69,09- 48,36 = 20,73

S = standard deviation from the difference in value between groups

= the standard intersection in the paired group was the standard intersection of the difference from the group receiving risperidone treatment with the addition of vitamin C at baseline and at the end of week VIII in the preliminary study = 2,611

$$n_1 = n_2 = \frac{(Z\alpha + Z\beta) S}{X1-X2}^2$$

$$= \frac{(1,96+ 1,28) 2,611}{20,73}^2$$

$$= (0,408)^2$$

$$= 0,166 \rightarrow 1$$

3.5.3. The magnitude of the D is estimated to know the total S PANSS difference in L male with Skizofrenia which only gets R isperidone at the start of the intervention before the end of week VIII:

$$n_1 = n_2 = \frac{(Z\alpha + Z\beta) S}{X1-X2}^2$$

INFORMATION :

© 2013- 2019 IJRMHS & K.A.J. All rights reserved

Zα = Error type I (α) is set at 5%, so Zα = 1,96 (two way hypothesis)
Zβ = Error type II (β) is set at 10%, so Zβ = 1,28
$X_1 - X_2$ = the minimum difference in average is considered meaningful = 67,00-51,09 = 15,91
S = standard deviation from the difference in value between groups
= standard deviation in the paired group is the standard intersection of the difference from the group receiving risperidone at baseline and at the end of week VIII in the preliminary study =4,592

$$n_1 = n_2 = \frac{(Z\alpha + Z\beta)\, S}{X1-X2}^{\,2}$$

$$= \frac{(1,96+ 1,28)\, 4,592}{15,91}^{\,2}$$

$$= (0,493)^2$$

$$= 0,243 \rightarrow 1$$

It can be concluded that the sample size for each group, namely the group who received risperidone by adding vitamin C as many as 24 subjects and those who only received risperidone as many as 24 subjects.

3.6. Approval after explanation / Inform ed Cons

All research subjects were asked to fill in a written agreement to participate in the study after first being given a detailed and clear explanation.

3.7. Research Ethics

This research has been approved by the Research Ethics Committee at the Faculty of Medicine, University of North Sumatra.

3.8. Ways of working

This research was conducted after obtaining approval from the Research Ethics Committee of the Faculty of Medicine, University of North Sumatra.

Data retrieval was preceded by structured interviews using Mini International Classification of Diseases (ICD-10) and enforcement of diagnoses using diagnostic guidelines based on PPDGJ I-III, then continued by screening using inclusion and exclusion criteria.

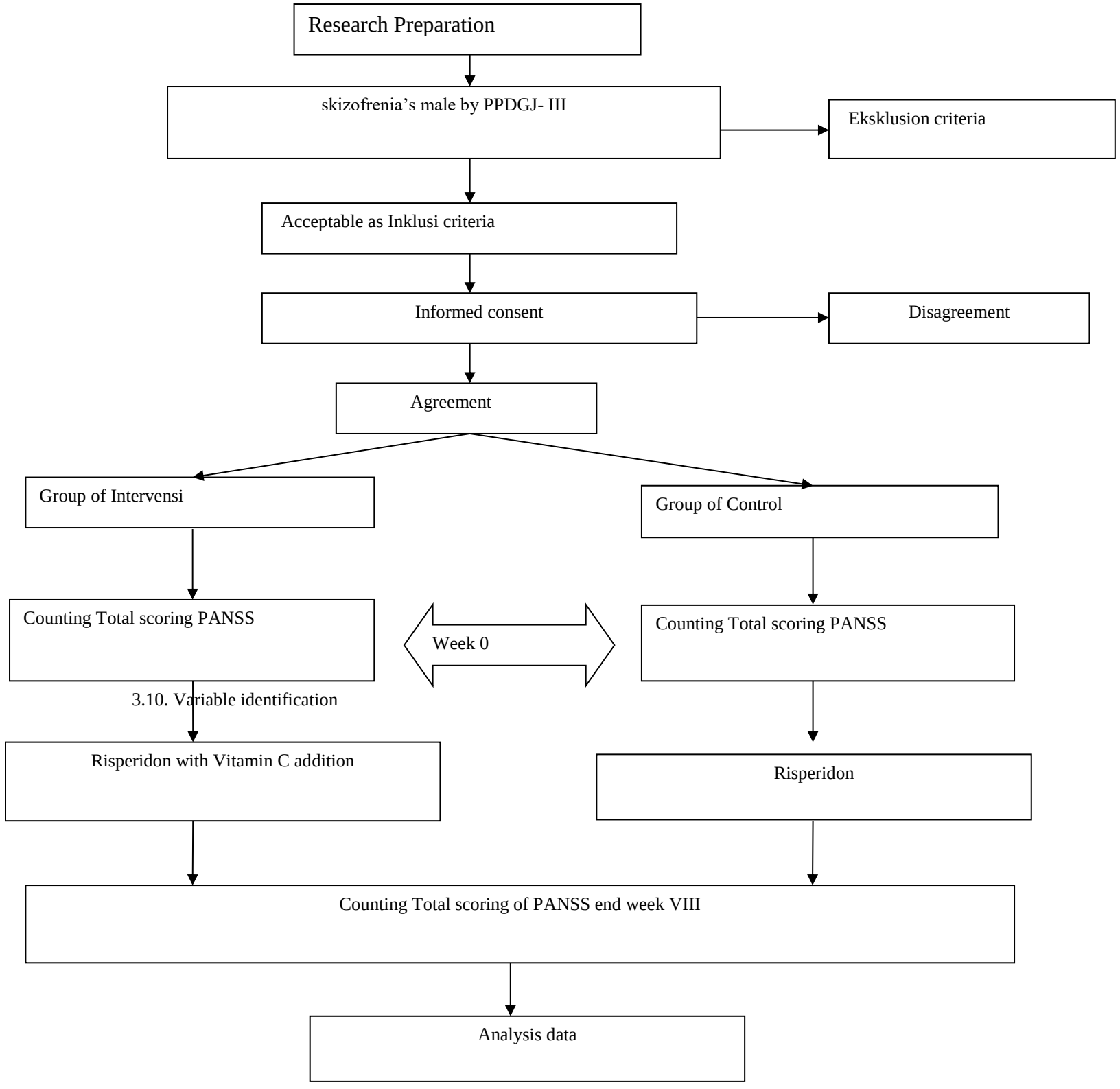
All men with schizophrenia who meet the inclusion and exclusion criteria are given detailed and clear explanations from the author and if the patient is willing, the patient is asked to sign an agreement to be the subject of this study.This research is an open clinical trial that is both researchers and subjects know the treatment given. However, for the allocation of subjects, simple random sampling will be chosen to be included in groups I or II.- Group I was the intervention group, namely the group receiving risperidon with fixed dose 4 mg / day / oral divided into 2 doses with the addition of vitamin C at a dose of 500mg / day / oral on the morning after meals, which was given for 8 weeks. Group II was the control group, ie the group that only received risperidone treatment with fixed dose 4 mg / day / oral was divided into 2 doses for 8 weeks.

Before the intervention is carried out each group will be assessed the total PANSS score as baseline data for ± 30-45 minutes.In measuring the total PANSS score, a suitability test between interraters and authors was conducted using a comparative numerical suitability test (Bland Altman) because the variable used was a variable with a numerical scale.

- If in the course of the research the treatment side effects arise in the form of symptoms of tardive dyskinesia, the patient will be excluded.
- At the end of week VIII the measurement of the total PANSS score will be carried out again.
- This research is an on treatment analysis so that every drop out occurs, the subject will be replaced with a new one. Drop out criteria are subjects who are not adherent to treatment, resign, or appear to have tardive dyskines side effect
- After all the data collected will be processed and analyzed data and presented in table form.

May 2019. Vol. 32. No.1 ISSN 2307-2083
International Journal of Research in Medical and Health Sciences
© 2013- 2019 IJRMHS & K.A.J. All rights reserved
http://www.ijsk.org/ijrmhs.html

3.9. Research Framework



May 2019. Vol. 32. No.1 ISSN 2307-2083
International Journal of Research in Medical and Health Sciences
© 2013- 2019 IJRMHS & K.A.J. All rights reserved
http://www.ijsk.org/ijrmhs.html

After the data is collected, data processing is carried out with the following stages: (I) Editing, is a step to examine the completeness of the data obtained through interviews, (2) Coding, is an attempt to classify existing answers according to their type, (3) Tabulation, is the activity of entering data from research results into tables based on the variables under study, (4) Analysis of data, research data were analyzed using SPSS statistical test. Normality test for the data of each group was conducted using the Saphiro-Wilk test because the number of subjects in each group was smaller than 51. Hypothesis testing is carried out as follows:

1. To find out the difference in total PANSS scores in men with schizophrenia who get risperidone by adding vitamin C, at the beginning before being given vitamin C and at the end of week VIII using a paired t-test if it meets the test requirements, if it does not fulfill it will be done data transformation, if it still does not meet the test requirements, the Wilcoxon test will be carried out.

4.RESEARCH RESULT

This research was conducted at the Psichiatric Hospital Prof. Dr. M. Ildrem Government of North Sumatra Province. The study subjects were taken by nonprobability sampling, consecutive sampling. The group who received risperidone therapy with the addition of vitamin C were 24 subjects and those who only received risperidone were 24 subjects. All research subjects completed this study to the end, therefore in this study there were no subjects who dropped out.

Tabel 4.1 Characteristic Demografic

	Group Risperidon+VitC n (%)	Group Risperidon n (%)	P
Ages { Average (sb)}	27,7 1(3,7 4)	28,13(5,0 7)	0,747 *
Level education			
- Junior high school	6 (40 ,0 %)	9 (60 ,0 %)	0,533 * *
- High school	13 (54,2%)	11 (45, 8%)	
- College	5 (55,6%)	4 (44,4%)	
Occupations			
- work	4 (26,7%)	11 (73,3%)	0,062 * *
- don't work	20 (60,6%)	13 (39,4%)	
Marital Status			
- Marriage	8 (53,3%)	7 (46,7%)	1,000 * *
- Not marriage	16 (48,5%)	17 (51,5%)	
Hospitality { Median (Min-Max) }	5,00 (2 ,00 – 10 ,00)	6,50 (2,00 – 10,00)	0 ,617 ***
Body Mass Index {Median(Min-Max)}	22,54 (20,76-25,28)	22,81 (20,76-24,15)	0,967 ** *
Aveg { Rerata (sb)}	21,3 0 (2,18)	21,79 (2,59)	0,952 *
Total attack {Median(Min-Max)}	3 , 00 (3 ,00 -5 ,00)	3 , 00 (3 ,00 -5 ,00)	0,890 ** *
Total Score PANSS week 0 {Rerata (sb)}	73,88 (4,59)	73,25 (4,12)	0,622 *

* *T test-Independent* ; ** *Chi-Square test Continuity Correction* ; *** *Mann Whitney-Utest*

Table 4.1 shows the demographic characteristics of each group, where the mean age of the risperidon group with the addition of vitamin C is 27.7 1 (3.74) years and the only risperidon group is 28.13 (5.07) years.The highest level of prevalence in both groups was high school in which the group had risperidon with 13 (54.2%) vitamin C supplementation, and only 1 (4 5.8%) of riseridon group.

The highest occupational status in both groups was not working, in the group that had risperidon with the addition of vitamin C as much as 20 people (60.6%), and in the group only got risperidon as much as 13 people (39.4%).The highest marital status in both groups was unmarried, in the group with 16% (48.5%) vitamin C supplementation, with only 17 (51.5%) risperidons.

© 2013- 2019 IJRMHS & K.A.J. All rights reserved

Long-term median illness in the group that got risperidon with the addition of vitamin C is 5.62 with a minimum value of 2.00 and a maximum value of 10.00. In groups with only risperidon is 6.13 with minimum value of 2.00 and maximum value of 10.00.The median body mass index (IMT) in the group that got risperidon with the addition of vitamin C was 22.54 with a minimum value of 20.76 and a maximum value of 25.28. The only risperidone group was 22.81 with a minimum value of 20.76 and a maximum of 24.15.The average age of the patient in the group who had risperidon with the addition of vitamin C was 2 1.83 (2.18) years, and in the group having only risperidon was 2 1.79 (2.59) years.

The median number of attacks in the group that got risperidon with the addition of vitamin C was 3, 00 with a minimum value of 3, 00 and a maximum of 5, 00. The only risperidon group is 3, 00 with a minimum value of 3, 00 and a maximum value of 5, 00.The mean of total score of PANSS week 0 in group that got risperidon with addition of vitamin C is 73,88 with standard deviation 4,59. In groups that only got risperidon was 73.25 with standard deviation 4,12.There were no significant differences between the two groups with sociodemographic characteristics, with a value of p> 0.05.

Table 4.1.Normality Test Table Decreased PANSS Total Scores of Paired Groups Receiving Risperidone + Vit C Therapy

	Therapy	n	*Shapiro-Wilk* *p*
Decreasing Total Score PANSS	Risperidon +Vit C	24	0,555

Uji *Shapiro-Wilk p* >0,05

From the results of the normality test above, the data obtained are normally distributed, then a paired t-test is carried out.

Table 4.2 PANSS Total Score Differences in Men with Schizophrenia Who Get Risperidone Therapy with the Addition of Vitamin C at Week 0 and on Week VIII

	Average (s . b)	Reduction (s . b)	IK95%	P Value
Risperidon +Vit C week 0 (n= 24)	73,86 (4,59)	39,50 (3,73)	37,93 – 41.07	<0,001
Risperidon + Vit C week VIII (n=24)	34,38 (1,64)			

Uji t – pairs p<0,05

In the paired group who received risperidone therapy with the addition of vitamin C, a paired t-test was conducted where at week 0 the average PANSS total score was 73.86 and standard deviation 4.59 and in week VIII the average total PANSS score was 34.38 and standard deviation 1.64 with p <0.001. This means, there are significant differences in PANSS total scores between before receiving therapy and after getting therapy in 8 weeks of observation.

Normality Test Table Decreasing Total S Cor PANSS Pairing Group Only Getting Risperidone Therapy

	Therapy	n	*Shapiro-Wilk* *p*
Decrease Total Score PANSS	Risperidon	24	0,256

Shapiro-Wilk test p >0,05

© 2013- 2019 IJRMHS & K.A.J. All rights reserved

In the above normality test the data is normally distributed p = 0.256 (p> 0.05), then the t-test is then carried out in pairs.

Table 4.3 PANSS Total Score Differences in Men with Schizophrenia who Only Get Risperidone Therapy p Week 0 and Week VIII

	Average(sb)	Reductions (sb)	IK95%	P Value
Risperidon week 0 (n= 24)	73,25 (4,12)	37,17 (3,53)	38,21 – 40.95	<0,001
Risperidon week VIII (n=24)	36,08(2,41)			

T test- pairs *p<0,05*

In the paired group who only received risperidone therapy the PANSS total score difference before and after therapy was 37.17 with a standard deviation of 3.53. Statistically there were significant differences in PANSS total scores between before receiving therapy and after getting therapy in 8 weeks of observation with p <0.001.

Table of Normality Test of Total PanSS Total Scores of Non-Paired Groups that Get Risperidone Therapy with Addition of Vitamin C and Only Therapy for Risperidone

	Therapy	n	*Shapiro-Wilk P*
Total Score PANSS	Risperido n +Vit C	24	0,0 31
	Risperidon	24	0,0 03

Uji *Shapiro-Wilk p* >0,05

From the results of the normality test above, the data obtained is not normally distributed, then the data transformation will be done as a step so that the data is normally distributed.

Data Transformation Normality Test Table

	Therapy	n	*Shapiro-Wilk p*
Log Total Score PANSS	Risperidon +Vit C	24	0,0 07
	Risperidon	24	0,0 20

Shapiro-Wilk test *p* >0,05

From the results of the normality test on data transformation, it was found that the data remained not normally distributed, so the Mann Whitney U test was performed.

Table 4. 4 PANSS Total Score Differences in Men with Schizophrenia who Get Risperidone Therapy with Addition of Vitamin C and Only Therapy Get Risperidone is Weekend VIII From the results of the normality test on data transformation, it was found that the data remained not normally distributed, so the Mann Whitney U test was performed.

Table 4. 4 PANSS Total Score Differences in Men with Schizophrenia who Get Risperidone Therapy with Addition of Vitamin C and Only Therapy Get Risperidone is Weekend VIII

	Median (Min-Max)	P Value
Risperidon + Vit C (n= 24)	35,00 (33,68 – 35, 07)	0.033
Risperidon (n=24)	35,00 (35,06 – 3 7, 10)	

Test *Mann Whitney U p<0,005*

In the unpaired group, after data transformation, the data remained non-normalized, so Mann Whitney U test was performed, where the therapeutic group with risperidone with the addition

© 2013- 2019 IJRMHS & K.A.J. All rights reserved

of median vitamin C was 35, 00 (33.68-35.07) and in the ok group that only received peridon ris a value was 35.00 (35.06-37.10). Statistically, there was a significant difference in the total PANSS scores between therapeutic groups that had risperidon with the addition of vitamin C and group who received only risperidon therapy at week 8 with p = 0.033 (p <0.05).

5.DISCUSSION

The results of this study showed a significant difference in the total PANSS scores in males with schizophrenia that had risperidone with the addition of vitamin C and only had risperidon, which was assessed based on the total PANSS scores, in which this instrument has shown validity and good reability to assess the symptoms in schizophenia. The dosage of risperidone used was fixed dose 4mg / day / oral in divided doses ie 2 mg in the morning and 2 mg in the evening, while the vitamin C dosage was 500 m g / day / oral in the morning after 8 weeks of eating.

In this study, the result of comparative test between the variables of sociodemographic characteristic of the research subject, it is concluded that there is no significant difference for the mean age, level of education, job status, marriage status, duration of illness, body mass index, PANSS score week 0 in both groups.

From table 4. 4 shows that in the unpaired group, after the data transformation, the data remained non-normalized, so that the Mann Whitney U test was performed, where the therapeutic group that had risperidon with the addition of median vitamin C was 35, 00 (33.68 -35.07) and in the group that only received treatment was estimated at 35.00 (35.06-37.10). Statistically, there was a significant difference in the total PANSS scores between therapeutic groups that had risperidon with the addition of vitamin C and group who received only rsiperidon therapy at week 8 with p = 0.033 (p <0.05).

This study showed that in the therapy group that received risperidone with the addition of vitamin C it was found that there was a significantly lower PANSS total score compared to the therapy group that only received risperidone therapy in week VIII. During the search for journal literature, researchers did not find the same literature with this study so a preliminary study was conducted. But there is some literature that examines the relationship between vitamin C supplementation and improvement of clinical symptoms in schizophrenia.

In a study conducted by Dakkhale GN et al in 2005 on 40 people with schizophrenia who were randomly divided into two groups, each group consisted of 20 people with schizophrenia who received vitamin C and 20 people with schizophrenia who received placebo, reported that significant statistics improved the BPRS score in the group receiving vitamin C (500 mg / oral / day) compared to the placebo group for 8 weeks. The reduction in BPRS scores was first seen and significant starting at week 4, namely in the vitamin C group (33.23 ± 5.25) while in the placebo group (31.76 ± 5.82) and continuing throughout the treatment until the end of the week VIII, which is in the vitamin C group (19.30 ± 5.46) while in the placebo group (28.96 ± 6.16) with a value of p <0.01.

In this study it was concluded that treatment of atypical schizophrenia with atypical antipsychotics can be combined with vitamin C supplementation because it can change ascorbic acid levels, reduce oxidative stress, and improve BPRS scores. 1.21 The mechanism of vitamin C can cause this change is actually unknown. Ascorbic acid inhibits binding to dopamine receptor agonists. If the concentration of ascorbic acid is high, it will reduce the work of dopamine and at the same time potentiate the effect of the drug acting as an antagonist. Thus, dopamine regulation induced by ascorbic acid receptors may have functional consequences. Ascorbic acid can also inhibit the phospholipid membrane peroxidation and act as a free radical hunter. Ascorbic acid is a water-soluble keto aseton, which has an important role in suppressing superoxide radicals by blocking chlorolamine autooxidation which inhibits the formation of potentially toxic products such as 6-hydroxy dopamine (6-OHDA), semiquinone, hydrogen peroxide, and hydroxyl radicals, which can cause damage nerves in the brain and cause symptoms of defects, this is probably one reason for the decrease in BPRS scores after vitamin C supplementation.

Ascorbic acid can modulate the effects of dopamine (DA) in the mammalian brain. Ascorbic acid inhibits binding of both DA agonists and antagonists. The interaction of ascorbic acid with the dopaminergic system is ascorbic acid by inhibiting DA-stimulating cyclase adenylate activity in mice. Ascorbic acid increases the catalytic effect produced by dopaminergic antagonists and various Nitric

© 2013- 2019 IJRMHS & K.A.J. All rights reserved

Oxide Sinthase (NOS) inhibitors. Ascorbic acid blocks induced amphetamine changes behavior in mice with unilateral nigrostriatal lesions produced by 6-hydroxydopamine. This finding is coupled with the inhibition of dopaminergic agonists and antagonists in radio ligand-binding studies, which are considered the action of ascorbic acid such as ant dopaminergic. Amphetamines and other DA agonists increase the levels of extracellular neostriatal ascorbate, and DA antagonists reverse this effect. In contrast, one observation was that ascorbic acid did not inhibit basal adenylate cyclase activity or DA in striatal homogenates from several strains of mice. Nitric oxide (NO) is a free radical gas that acts as an atypical neurotransmitter. Inhibition of NO formation interferes with rat exploration behavior in open fields and results in catalepsy.

In a study conducted by Ghodake SR et al in 2012, which evaluated the effects of a combination of antioxidant supplementation of vitamin E (400 IU / day) and vitamin C (250 mg / day) given for 12 weeks in people with schizophrenia who received haloperidol antipsychotic therapy reported that statistically there was a significant improvement in PANSS scores in the group given antioxidant supplements E and C compared to those with only antipsychotic treatment.

There is increasing evidence that oxidative stress contributes to the pathophysiology of schizophrenia, which is indicated by an increase in plasma lipid peroxidation products and cerebro spinal fluid and an increase in enzymatic and non-enzymatic oxidants in schizophrenia. The brain has a large lipid content and the myelin sheath has high oxidative metabolism, therefore the brain is the target of free radicals that are more susceptible to damage, so antioxidant supplementation orally can be given as a secondary therapy to prevent oxidative damage and nerve tissue so that it can improve clinical symptoms and the application of antioxidants in clinical trials is useful for preventing or reducing disease progression. In a case-control study conducted by Arvindakshan et al, in 28 people with schizophrenia who received vitamin E supplementation (400 IU / day) and vitamin C (500mg / day) and omega 3 for 4 months it was reported that symptom improvement after supplementation was reduced significant in psychopathology was based on a reduction in the total BPRS, PANSS scores and an increase in Henrich's Quality of Life (QOL).

The limitation of this study is to only evaluate the total PANSS score at week 0 and end of week VIII, not seeing when the PANSS score starts to change. The study also did not examine vitamin C levels in people with schizophrenia both before and after therapy.

6.CONCLUSIONS AND RECOMMENDATIONS

Of the subjects followed in this study divided into two groups where 24 subjects received risperidone with the addition of vitamin C and 24 people only received risperidone, the following conclusions were obtained:

1. The sociodemographic characteristics of the study subjects in each group based on age, education level, marital status, occupational status, duration of illness, body mass index, onset, number of attacks, and total PANSS score of week 0 were not found to be significantly different between the two group, with a value of $p > 0.05$.

2. In the group that received risperidone with the addition of vitaminsC performed paired t test where at week 0 the average PANSS total score was 73.86 and standard deviation 4.59 and in week VIII the average PANSS total score was 34.38 and standard deviation was 1.64 with $p < 0.001$. This means, there are significant differences in PANSS total scores between before receiving therapy and after getting therapy in 8 weeks of observation.

In the group, that only received risperidone therapy the PANSS total score difference before and after therapy was 37.17 with a standard deviation of 3.53. Statistically there were significant differences in PANSS total scores between before receiving therapy and after getting therapy in 8 weeks of observation with $p < 0.001$.

In the unpaired group, after the data transformation, the data remained not normally distributed, so the Mann Whitney U test was performed, where in the treatment group that received risperidone with the addition of median vitamin C was 35, 00 (33.68-35.07) and in the group receiving only risperidone the value was 35.00 (35.06-37.10). Statistically, there were significant differences in PANSS total scores between the therapy groups who received risperidone and the addition of vitamin C and the group that only received risperidone therapy at week 8 with $p = 0.033$ ($p < 0.05$).

© 2013- 2019 IJRMHS & K.A.J. All rights reserved

Provision of vitamin C supplements as adjunctive therapy in people with schizophrenia can be considered considering the results of the study indicate a significant difference.

For the next author, this study is expected to be a reference material or the like with more subjects and longer observation times.

REFFERENCES

1. Dakhale GN, Khanzode SD, Khanzode SS. Supplementation of vitamin C with atypica l antipsychotics reduces oxidative stress and improves the outcome of sch izophrenia. Psychopharmacology , 200 5:182: 49 4- 98.
2. Firth J, Stubbs B, Sarris J, Rosenbaum S, Teasdale S, Berk M et al, The effect of vitamin and mineral supplementation on symptoms of schizophrenia: a systematic review and meta-analysis.Psychological Medicine , 2017 : 1-13.
3. Ghodake SR, Suryakar AN, Padalkar RK, Shaikh K. The Effect of combined vitamin E and C supplementation on the oxidative stress parameters in patients with schizophrenia. BioChemistry An Indian Journal 2012: 6(5): 155- 61.
4. Bode Am. Metabolism of Vitamin C in Health and Disease . Advance in Pharmachology 1997. Volume 38.
5. Gunes M, Altindag A, Bulut M, Demir S, Ibiloglu AO, Kaya MC et al. Oxidative metabolism may be associated with negative symptoms in schizophrenia. Psychiatry and Clinical Psychopharmacology(2017).vol 27. No .1, 54-
6. Kocot J, Kocot DL, Kielczykowska M, Musik I, Kurzepa J. Does Vitamin C Influence Neurodegenerative Diseases and Psychiatric Disorders? *Nutrients* 2017, 9, 659: 1-29.
7. Brown HE, Roffman JL. Vitamin Supplementation in the Treatment of Schizophrenia. *CNS Drugs* 2014 .
8. Ramachandran P, Thirunavakarasu P. Vitamins in Schizophre nia: a literature review. *AP J Psychological Medicine* 2012: 13(2): 74-9.
9. Sadock BJ, Sadock VA, Ruiz P. Schizophrenia spectrum and other psychotic disorders. In Kaplan & Sadock's Synopsis of Psychiatry Behavioral Sciences / Clinical Psychiatry. Eleventh Edition: Philadelphia: Wolters Kluer, 2015.
10. Health Department of the Republic of Indonesia. Guidelines for Classification and Diagnosis of Mental Disorders in Indonesia III (PPDGJI-III). Jakarta, 1993
11. Mahadik SP, Mukherjee S. Free radical pathology and antioxidant defense in schizophrenia: a rev iew. Schizophrenia Research 19,1996: 1-17.
12. Iqbal K, Khan A, and Khattak MMA. Biological Significance of Ascorbic Acid (Vitamin C) in Human Health - A Review. Pakistan Journal of Nutrition .2004: 3 (1): 5-13.Hoenders HJR, Bartels-Velthuis AA, Vollbehr NK, Bruggemn R, Knegtering H, de Jong JTVM. Natural medicines in schizophrenia: a systemic review. University Medical Center Groningen : 2014 .
13. Schiavone S, Trabace L. The use of antioxidant compounds in the treatment of first psychotic episode: Highlights from preclinical studies. *CNS Neurosci Ther* .2018:24: 465-472.
14. Deshpande C, Dhir A, Kulkarni SK. Antagonis Activity of Ascorbic Acid (Vitamin C)on Dopaminergic Modulation: Apomorphine-Induced Stereotypic Behaviorin Mice . *Pharmacology* 2006: 77:38-45
15. Marder SR, Davis MC. Second-Generation Antipsychotic. In: Sadock BJ, Sadock VA, Ruiz P. *Kaplan& Sadock's Comprehensive Textbook of Psychiatry* , Vol I, 10 th ed. Philadelphia: Lippinc ontt William & Wilkinsi, 2017. p .8125-32
16. Mehbedbasic AB. Risperidone in the treatment of schizophrenia. *Med Arh* . 2011;65 (6): 345-47

© 2013- 2019 IJRMHS & K.A.J. All rights reserved

17. Gottlieb JD, Fan X, Goff DC. Rating of scales in schizophrenia. In: Baer L, Blais MA, editor. Handbook of clinical rating scale and assessment in psychiatry and mental health. New York: Human Press, 2010. h. 209-11)

18. Dahlan MS. Numerical comparative hypothesis test in pairs. In Statistics for medicine and health, descriptive, bivariate, and multivariate equipped with SPSS applications. Edition 6. Jakarta a: Epidemiology of Indonesia; 2015: h. 91-135

19. Dahlan MS. Unpaired numerical comparative hypothesis test. In Statistics for medicine and health, descriptive, bivariate, and multivariate equipped with SPSS applications. Edition 6. Jakarta: Indonesian Epidemiology; 2015. h. 137-62

20. Leza JC, Bueno BG, Bioque M, Arango C, Parellada M, Do K., et al., Inflammation in schizophrenia: A question of balance. Neuroscience and Biobehavioral Reviews. 55. 2015: 612-26.

21. D'Souza B, D'Souza V. Oxidative Injury And Antioxidant Vitamin E And C In Schizophrenia. Indian journal of Clinical Biochemistry. 2003: 18 (1): 87-90.

22. Arvindakshan M, Ghate M, Ranjekar PK, Evans Dr., Mahadik SP., Supplementation with a combination of omega-3 fatty acids and antioxidants (vitamin E and C) improves the outcome of schizophrenia. Schizophrenia Research 62 2003: 95-204.