



Correlation of Duration of Antipsychotic Therapy with Hemoglobin Levels in People with Schizophrenia

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Abstract

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Background : Schizophrenia is a serious mental disorder with various unknown causes accompanied by a collection of positive symptoms, negative symptoms, disorganization in thinking, speaking or movement and cognitive dysfunction. The therapeutic modality used to treat these symptoms is antipsychotic therapy. Over a certain period of time, the use of antipsychotics can cause hematological syndrome which affects the process of red blood cell formation and hemoglobin levels. Low hemoglobin levels can worsen neuronal function in the brain, thereby aggravating symptoms in schizophrenia. The aim of this study was to analyzing the relationship between duration of antipsychotic therapy <2 years and ≥2 years with hemoglobin levels in schizophrenia patients.

Methods : This research is an analytical observational study with a cross-sectional approach in which research subjects were obtained using a consecutive sampling method from medical records of patients with schizophrenia (ODS) at RSJD Dr. Amino Gondohutomo Semarang (n=68) divided into 2 groups consisting of patients with a duration of therapy <2 years and a duration of therapy ≥2 years. The relationship between duration of antipsychotic therapy and hemoglobin levels was analyzed using unpaired t-test.

Results : The mean hemoglobin value for people with schizophrenia in the group with a duration of therapy <2 years is 14.09, while that in the group with a duration of therapy ≥2 years is 14.06 with a p value = 0.928.

Conclusion : There was no relationship between hemoglobin levels in people with schizophrenia and duration of therapy both <2 years and ≥2 years.

Keywords : Antipsychotic, Hemoglobin, Hematology, Schizophrenia.

INTRODUCTION

Schizophrenia is a serious mental disorder with various unknown causes, accompanied by a collection of positive symptoms, negative symptoms, disorganization in thinking and cognitive dysfunction. WHO states that around 0.7% people with schizophrenia (ODS) are adults with an age range of 15–35 years, and according to the 2018 National Basic Health Research Report (RISKESDAS) the average prevalence (per mile) of households that have members with schizophrenia mental disorders in Indonesia is 0.67%. Meanwhile, there are 8.7% of the population suffering from schizophrenia in Central Java.^{1,2} The therapy used as the main modality to treat schizophrenia symptoms is antipsychotic therapy categorized into 2 groups; class I (typical) antipsychotics, which have higher effectiveness in treating positive symptoms of schizophrenia and class II (atypical) antipsychotics, which are effective in treating both positive and negative symptoms.³ Antipsychotic therapy is medications for long term use or with repeated administration however, long-term use of antipsychotic therapy may cause intoxication of the blood and neurons. Studies suggest the emergence of hematological syndromes provoked by antipsychotics include blood dyscrasias, pancytopenia and bicytopenia. Dyscrasia refers to abnormalities in the values of red blood cells, white blood cells and platelets which then cause manifestations such as anemia, leukopenia and thrombocytopenia.^{4,5} One of the manifestations - anemia can be assessed by looking at the hemoglobin level as a component of red blood cells transporting oxygen in the blood to all organs, tissues and cells, including neuron cells in the brain. Disruption of the process of forming red blood cells in the bone marrow can result in a decrease in blood hemoglobin levels which in turn provoke worsening of neuronal function in the brain. In schizophrenia, this condition can last for a long time, thus making the symptoms worse.^{6,7}

Hematological syndrome due to antipsychotic therapy is a rare event, but important because it can be fatal or result in mortality (1–2/100,000 cases with a mortality of 8–17%).⁸ Therefore, this study was conducted to find out how long antipsychotic therapy is related to Hemoglobin levels in schizophrenic patients.

METHODS

This research is an analytical observational study with a cross-sectional design assessing the duration of antipsychotic therapy on hemoglobin levels seen at one time. Subjects were recruited using a consecutive sampling method from medical records of people with schizophrenia hospitalized in the period of January to December 2019 at RSJD Dr. Amino Gondohutomo Semarang. The total number of research subjects was

68 medical records that met the inclusion criteria. The research subjects were divided into 2 groups, namely 34 subjects with a duration of therapy <2 years and 34 subjects with a duration of therapy ≥2 years. The inclusion criteria were patients aged 21 to 50 years with a diagnosis of schizophrenia based on medical records and receiving standard schizophrenia management therapy. The exclusion criteria were patients receiving benzodiazepam therapy and patients with comorbid physical illnesses.

Data analysis using the SPSS version 26.0 program included descriptive analysis and relationship testing. Normality test was conducted hemoglobin level and subject age data. Research was carried out using the Shapiro Wilk test. Data on length of therapy with age were explained using the unpaired t-test because the data obtained were normally distributed. Data on length of therapy with BMI, address, gender, diagnosis, therapy history, education level and marital status were analyzed using the Chi-square test. Data on length of antipsychotic therapy and hemoglobin levels were analyzed using unpaired t-test. All results were considered statistically significant if the p value was <0.05 with a 95% confidence interval.

Research protocol had been approved by the issuance of Ethical Clearance No. 188/EC/KEPK/FK-UNDIP/VIII/2020 from the Health Research Ethics Committee (KEPK) of Medical Faculty of Diponegoro University and Ethics Test Certificate Number 420/9774 by the Health Research Ethics Team of RSJD Dr. Amino Gondohutomo, Central Java.

RESULTS

Demographic Characteristics

The demographic characteristics of the 68 research subjects include age, body mass index (BMI), address, gender, education level and marital status (Table 1).

Table 1 shows 68 research subjects have a mean age of 32.82 ± 7.11 years, with a mean BMI value of 21.69 ± 2.36 . The distribution of research subjects based on nutritional status consist of 5 underweight (7.35), 42 normoweight (61.76), 19 overweight (27.94) and 2 obese (0.29). The research subjects consist of 45 male (66.17) and 23 female (33.82). Most of research subjects come from outside Semarang (52 subjects or 76.47%), are single (44 subjects or 64.70%) and graduated from junior high school (29 subjects or 42.64%).

Table 2 shows the distribution of research subjects based on diagnosis and type of antipsychotic used. The majority of schizophrenia diagnoses involve people with paranoid schizophrenia (32 subjects or 47.05%), unspecified schizophrenia (22 subjects or 32.35%), catatonic schizophrenia (11 subjects or 14.70%) and heberphrenic schizophrenia (4 subjects or 5.88%). In terms of antipsychotic use, 38 subjects (55.88) used

TABLE 1
Demographic Characteristics of Research Subjects

Variable	Mean ± SD n (%)	Mean ± SD n (%)		p*
		<2 Year	≥2 Year	
Age (year)	32.82 ± 7.11	33.24 ± 7.41	32.41 ± 6.89	0,637 ^a
IMT (kg/m ²)	21.69 ± 2.36	21.42 ± 2.14	21.95 ± 2.56	0,951 ^b
Underweight	5 (7.35)	3 (0.44)	2 (0.29)	
Normoweight	42 (61.76)	20 (29.41)	22 (32.35)	
Overweight	19 (27.94)	10 (14.70)	9 (13.23)	
Obesity	2 (0.29)	1 (0.14)	1 (0.14)	
Address				
Semarang	16 (23.52)	5 (7.35)	11 (16.17)	0,086 ^b
Outside Semarang	52 (76.47)	29 (42.64)	23 (33.82)	
Gender				
Male	45 (66.17)	20 (29.41)	25 (36.76)	0,200 ^b
Female	23 (33.82)	14 (20.58)	9 (13.23)	
Education level				
Elementary School	13 (19.11)	6 (8.82)	7 (10.29)	0,946 ^b
Junior High School	29 (42.64)	15 (22.05)	14 (20.58)	
Senior High School & College	26 (38.23)	13 (19.11)	13 (19.11)	
Marital Status				
Married	15 (22.05)	8 (11.76)	7 (10.29)	0,915 ^b
Divorced	9 (13.23)	4 (5.88)	5 (7.35)	
Single	44 (64.70)	22 (32.35)	22 (32.35)	

Note: *significant ($p < 0,05$); ^aunpaired t-test; ^bChi Square

atypical antipsychotics consisting of 23 subjects with risperidone therapy (33.82%), 11 subjects with clozapine therapy (16.17%) and 4 subjects with combination therapy with risperidone and clozapine (5.88%), combined antipsychotics in 29 subjects (42.64%) and typical antipsychotics in the form of haloperidol in 1 subject (1.47%).

Characteristics of research subjects in the two research groups show no significant differences in all variables involving age ($p=0.637$), BMI ($p=0.951$), address ($p=0.086$), gender ($p=0.200$), education level ($p=0.946$), marital status ($p=0.915$), diagnosis ($p=0.430$) and type of antipsychotic ($p=0.206$).

Analysis of the Relationship between Duration of Antipsychotic Therapy and Hemoglobin Levels

The following table shows the relationship analysis

between duration of antipsychotic therapy and hemoglobin levels, in which 68 research subjects are grouped based on length of therapy involving <2 years (34) and ≥2 years (34).

Most subjects have normal hemoglobin levels involving 30 subjects in the <2 years group (44.11%) and 23 subjects in the ≥2 year group (33.82%), while subjects experiencing decreased hemoglobin levels are in the <2 year group as many as 4 subjects (5.88%) and 11 subjects in the ≥2 year group (16.17) with p value= 0.041 which is statistically significant.

T-test analysis of the duration of antipsychotic therapy with hemoglobin levels shows no significant relationship in either the group with <2 year therapy or the group with ≥2 year therapy ($p > 0.05$).

TABLE 2
Research subject distribution

Variable	Mean ± SD n (%)	Mean ± SD n (%)		p*
		<2 Year	≥2 Year	
Diagnose				
Paranoid Schizophrenia	32 (47.05)	13 (19.11)	19 (27.94)	0.430 ^b
Heberphrenic Schizophrenia	4 (5.88)	22 (2.94)	2 (2.94)	
Catatonic Schizophrenia	10 (14.70)	5 (7.35)	5 (7.35)	
Schizophrenia Unspecified	22 (32.35)	14 (20.58)	8 (11.76)	
Types Antipsychotic				
Typical Antipsychotic – HLP	1 (1.47)	1 (1.47)	0 (0)	0.206 ^b
Atipikal Antipsychotic	38 (55.88)	22 (32.35)	16 (23.52)	
Risperidon	23 (33.82)	15 (22.05)	8 (11.76)	
Klozapin	11 (16.17)	6 (8.82)	5 (7.35)	
Risperidon – Klozapin	4 (5.88)	1 (1.47)	3 (4.41)	
Combination	29 (42.64)	11 (16.17)	18 (26.47)	

Note: *significant (p<0.05); ^bChi Square

TABLE 3
Description of hemoglobin levels in each group

Variable	<2 Year n (%)	≥2 Year n (%)	p*
Decreased	4 (5.88)	11 (16.17)	0.041 ^b
Normal	30 (44.11)	23 (33.82)	

Note: *significant (p<0.05); ^bChi Square

TABLE 4
Relationship between duration of antipsychotic therapy and hemoglobin levels

Variable	<2 Year	≥2 Year	p*
	Mean ± SD Median (Min–Max)	Mean ± SD Median (Min–Max)	
Hemoglobin (gr/dl)	14.09 ± 1.49 14.20 (10.8–16.5)	14.06 ± 1.16 13.95 (11.4–16.2)	0.928 ^a

Note: *significant (p<0.05); ^aunpaired t-test

DISCUSSION

The mean age of the research subjects showed the incidence of schizophrenia in productive age (32.82 ±

7.11). This can be explained by various stressors arising in productive age range, such as family problems, financial problems, educational or work problems as well as the burden of responsibility affecting an individual's

emotional development.⁹

Nutritional status of research subjects are categorized into 4 groups based on BMI involving underweight (BMI <18.5), normoweight (BMI 18.5–22.9), overweight (23–24.9) and obesity (BMI >25).¹⁰ More than half of the subjects had good nutritional status and are categorized as normoweight, which explains that there is no significant relationship between the length of antipsychotic therapy and nutritional status in people with schizophrenia. Nutritional status is influenced by several factors such as nutritional intake or eating patterns, daily activities, socio-economic status, environmental conditions and fat percentage.^{11,12}

Based on marital status, it was found that more than half of the research subjects are single. Schizophrenia that appears in early adulthood can affect social abilities disrupting patient's ability to build relationships such as marriage.^{9,13} Similarly, previous study conducted by Mawar DY *et al* (2017) at the Sambang Lihum Mental Hospital, South Kalimantan shows more than half of the research subjects with schizophrenia are at the age range of 17 to 40 years old and single.

Based on subjects characteristics, the majority of patients are male suggesting that there is a different response between men and women to antipsychotic therapy. Previous studies show slower disease progression in women than men. There is a neuroprotective function of the hormone estrogen in women.¹⁴ There are different pharmacokinetics in women such as slower absorption and higher body fat increasing antipsychotics accumulation in adipose tissue which in turn increasing the half-life of medications. Slower CYP1A2 activity and drug elimination in women prolong drug accumulation in the body. Thus, women show better response to antipsychotic therapy than men do.^{5,16}

In this study, class II antipsychotics, such as risperidone and clozapine, are the main therapeutic modality for schizophrenia. The most common side effect of clozapine is agranulocytosis, so patients with clozapine therapy are advised to carry out differential count laboratory checks every week during the first 6 months of therapy. Higher effectiveness in treating positive and negative symptoms as well as a lower incidence of extrapyramidal side effects than class I antipsychotics due to a more selective mechanism of action in inhibiting dopamine receptors in the cortical and limbic areas rather than the nigrostriatal pathway could be the reason why generation II antipsychotics are preferred as therapy.^{12,17}

This study analyzed the relationship between the duration of antipsychotic therapy and the hemoglobin levels of people with schizophrenia which are categorized found a difference in the mean value of hemoglobin levels in the group with duration of therapy both <2 years and ≥2 years, but there is no statistically significant relationship in both groups. The results of this study are in accordance with previous research which

reported that no significant relationship was found with hemoglobin levels while in a different study it was also found that there is no significant relationship between red blood cell parameters and duration of antipsychotic therapy and BMI.^{11,18} Anemia which can be assessed by a decrease in hemoglobin levels <12 gr/dL or red cells <4.5×10⁶/uL is the rarest antipsychotic therapies-related abnormality in people with mental disorders such as schizophrenia.^{19,4} However, previous study conducted by Jimmy L *et al* (2015) showed a high incidence of anemia in the first 2 years of therapy, although it was later stated that there were various factors playing role in the incidence of anemia such as the preferred antipsychotic medication, physical condition, poor lifestyle and nutritional intake.^{20,21}

The normal range of hemoglobin levels in both groups could be caused by improved toxicity. Improvement can occur when antipsychotic therapy is stopped or replaced. However, it was found that the number of research subjects experiencing a decrease in hemoglobin levels is greater in the ≥2 year group. This is related to the chronic conditions experienced, the drugs consumed and lifestyle.^{4,21} This is different from other research which states that the lower mean value of hemoglobin levels in the <2 year group could occur due to the toxicity process at the beginning of therapy. Based on previous studies, clinical symptoms appeared around 4 to 5 weeks after the commencement of therapy.¹¹

Study Limitation

The hemoglobin level data was obtained from medical records where the blood tests were not carried out at the same time and analysis of several factors possibly influencing hemoglobin were not carried out, such as gender grouping in female samples, so the age group must be taken into account when carrying out blood tests, patient's diet and lifestyle. Differences in antipsychotic therapy received by each subject can also bias the results. Suggestions for further research are to control data variations, especially subject demographic data.

CONCLUSION

There is no significant relationship between duration of antipsychotic therapy <2 years and ≥2 years and hemoglobin levels in people with schizophrenia.

It is necessary to control variations in subject demographic data and pay attention to other factors that can influence blood hemoglobin levels such as the time of blood sampling, diet and lifestyle.

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