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Original Article

Effect of Atypical Antipsychotic on Blood Pressure in Inpatients with Schizophrenia of Prof. Dr. Soerojo Mental Health Hospital Magelang

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ABSTRACT

Context: Schizophrenia ranks the top of all mental disorders with poor prognosis. Central Java Province is in the top five of schizophrenia incidents in Indonesia. Antipsychotic is the main therapy for schizophrenia, which is divided into 2, atypical and typical. The atypical antipsychotic is more preferable because of the minimal effect of the extrapyramidal syndrome but affects the blood pressure. **Aims:** To analyze the blood pressure of schizophrenia inpatients during the pre and post-use of atypical antipsychotics in RSJ Prof. Dr. Soerojo Magelang. **Settings and Design:** This study was an observational study with cohort retrospective methods. **Methods and Material:** The research was approved and reviewed by the committee of ethics and law of Prof. Dr. Soerojo Mental Hospital. The inclusion criteria are those diagnosed with schizophrenia based on Diagnostic and Statistical Manual of Mental Disorders-IV (DSM IV), aged about 17-55 years old, receiving antipsychotic atypical therapy for at least 3 months.The exclusion criteria are inpatients who also receive antidepressants and antihypertension, have a history of cardiovascular disease and hypertension, and incomplete medical records. **Statistical analysis used:** Wilcoxon, Mann-Whitney, and Kruskal-Wallis test. **Results:** The result of this study most of them were treated using combination risperidone and clozapine (82.1%). In this study, 43 inpatients experienced a decrease in systolic blood pressure, 57 in systolic blood pressure, 6 with no change in systolic blood pressure, 47 a decrease in diastolic blood pressure, 50 an increase in diastolic blood pressure, and 9 with no change in diastolic blood pressure. **Conclusions:** There was no significant difference in the blood pressure before and after the treatment.

KEYWORDS: *Atypical antipsychotic, blood pressure, schizophrenia*

INTRODUCTION

Schizophrenia has become a threatening mental health problem in the developed countries. It ranks the first in psychotic type of diseases.[1] It is also among the 10 major causes of disabilities in patients.[2] A person with schizophrenia has shorter life span compared to healthy people, which was also caused by other factors such as suicidal feeling.[3]

Schizophrenia is a chronic and severe mental disorder affecting more than 21 million people worldwide. It is associated with considerable disability and may affect educational and occupational performance.[4]

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Besides, the prevalence in America and Canada reached 1%–15%.[5,6] In Indonesia, the prevalence increased from 1.7% in 2003 to 7% in 2013. Among all the provinces, Central Java was placed within the five highest prevalent provinces, reaching 9%.[7]

Atypical antipsychotic drug is the first-line medication for schizophrenia and other types of psychotic illness.

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This medication works against serotonin and dopamine receptors. It is preferable for its ability to decrease the incidence of extrapyramidal side effects. However, other types of this medication, such as clozapine, olanzapine, risperidone, and quetiapine, produce metabolic side effects. One of the examples is the increase in blood pressure.[8,9] Conversely, other research suggested that the use of antipsychotics can also cause hypotension in which clozapine may lead to high orthostatic hypotension.[10,11] The treatment may trigger disobedience, metabolic disorders, cardiovascular disorders, mortality, morbidity, and increasing recurrence.[12]

A study about the cardiometabolic risk of patients with first episode of schizophrenia (FES) mentioned that the percentages of prehypertension and hypertension were 39.9% and 10%, respectively.[9] Hypotension in patients with schizophrenia treated using antipsychotics in RS Grhasia Yogyakarta was 13 patients in 2008 and 7 in 2009.[10]

Prof. Dr. Soerojo Mental Health Hospital Magelang is the central hospital recommended for mental disorders. This hospital is located in Central Java, among the top five provinces with schizophrenic prevalence. Atypical antipsychotic has been commonly used in this hospital. Therefore, it is necessary to describe the blood pressure of the inpatients of schizophrenia treated with an atypical antipsychotic in RSJ Prof. Dr. Soerojo Mental Health Hospital Magelang, Indonesia.[7,13]

Materials and Methods

The research was approved and reviewed by the committee of ethics and law of Prof. Dr. Soerojo Mental Health Hospital Magelang, Indonesia. It was declared as fulfilling the ethical requirements based on the regulation number KEH/001/2019.

Research design

The study belonged to analytical observational research with a cohort retrospective approach. It used the medical records of patients with schizophrenia.

Research period and location

The research was conducted in Prof. Dr. Soerojo Mental Health Hospital Magelang, Indonesia, from January 2019 to April 2019.

Population and sample

The population included inpatients with schizophrenia fulfilling the inclusion and exclusion criteria. The inclusion criteria covered those with the DSM IV category, aged between 17 and 55 years, and those that received antipsychotic therapy for a minimum of 3 months. Meanwhile, the exclusion criteria included those undergoing antidepressant and antihypertension treatment, having cardiovascular disease and hypertension, as well as those with incomplete medical records. Schizophrenia classification based on DSM IV observed from clinical presentation is divided into 5 subtypes, including paranoid schizophrenia, disorganized / hebefrenik, catatonic, undifferentiated, and residuals.

From those fulfilling the inclusion and exclusion criteria determined, 106 patients were selected, using consecutive sampling, to participate in the study from January 2019 to April 2019.

Research procedures

The collected data from the medical records are in the form of patients' identity (gender, age, types of schizophrenia, educational background, occupation, and smoking habit). The data of medical treatment, either psychotic or other types, or blood pressure were also taken from the records. The data were collected using the data collection sheet. The pre-blood pressure was obtained before the patients were treated using atypical antipsychotic and the post-blood pressure after 3 months of the medication, during which they received one type consecutively without any change. Blood pressure was measured while in a sitting position after a 10-min rest by a nurse or psychiatric residents and recorded in the medical record.

Data analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) program, version 22 (IBM, Armonk, New York, United States). Descriptive analysis was used to analyze the characteristics of patients, their use of antipsychotics, as well as the pre- and post-blood pressure. Those are presented in frequency and percentage tables. Wilcoxon test was used to determine the difference in diastolic and systolic blood pressure before administration of atypical antipsychotics with diastolic and systolic blood pressure after administration of antipsychotics. The results of the Wilcoxon test analysis obtained a significance value (p). $p < 0.05$ showed that significant differences are present.

Results

Characteristics of the research subject

The inpatients with schizophrenia in Prof. Dr. Soerojo Mental Health Hospital Magelang, Indonesia, from January 2019 to April 2019, based on gender, age, types

of schizophrenia, educational background, occupation, and smoking habit are presented in Table 1.

Distribution of atypical antipsychotic treatment

The use of atypical antipsychotic treatment in patients with schizophrenia in Prof. Dr. Soerojo Mental Health Hospital Magelang, is present in Table 2. In this study, it was also observed that the most used treatment was the combination type (88.7%), whereas the single type was 11.3% [Table 3].

Characteristics of patients' blood pressure

The blood pressure of the patients with schizophrenia before and after the treatment showed that the data were not normally distributed, thus it needs to find the median score [Table 4]. It can be observed that the systolic blood pressure improved after the treatment, but the diastolic did not increase nor decrease. Nevertheless, the analysis result of the Wilcoxon test showed no significant difference before and after the atypical antipsychotic treatment ($p > 0.05$). The systolic blood pressure increased after the treatment in 57 patients, but decreased in 43 others. Meanwhile, it did not change in six patients. The diastolic blood pressure increased in 50 patients, decreased in 47, and remained stable in 9 patients [Table 5].

Table 1: Characteristics of the research subject

Demographic characteristics	N = 106	
	Number of inpatients	Percentage (100%)
Gender		
Male	83	78.3
Female	23	21.7
Age		
Late adolescence (17–25 years)	10	9.4
Early adulthood (26–35 years)	42	39.6
Late adulthood (36–45 years)	48	45.3
Early elderly (46–55 years)	6	5.7
Types of schizophrenia		
F 20.0 (paranoid schizophrenia)	47	44.3
F 20.2 (catatonic schizophrenia)	11	10.4
F 20.3 (undefined schizophrenia)	43	40.6
F 20.4 (Post-schizophrenic depression)	2	1.9
F 20.5 (residual schizophrenia)	3	2.8
Educational background		
Elementary school	32	30.2
Middle school	32	30.2
High school	28	26.4
Undergraduate	4	3.8
Uneducated	10	9.4
Occupation		
Working	30	28.3
Jobless	80	71.7
Smoking habit		
Smoking	72	67.9
Nonsmoking	34	32.1

Correlation between gender, age, antipsychotic treatment, smoking habit, and systolic diastolic blood pressure

On the basis of the results of data analysis, a relationship was found between age and antipsychotic therapy with postdiastolic and postsystolic blood pressure ($p < 0.05$). In addition, there was also a relationship between sex and prediastolic blood pressure ($p < 0.05$) [Tables 6 and 7].

Discussion

Characteristics of the research subjects

Patients with schizophrenia in Prof. Dr. Soerojo Mental Health Hospital Magelang are dominated by male patients (78.3%). This study is in line with another study conducted in a hospital from 2007 to 2009.[10] Theoretically, schizophrenia between male and female patients is in balance. However,

Table 2: Use of atypical antipsychotic to patients with schizophrenia in RSJ Prof. Dr. Soerojo Magelang

Antipsychotic	N = 106
Risperidone	10 (9.4%)
Clozapine	2 (1.9%)
Risperidone + clozapine	87 (82.1%)
Risperidone +quetiapine	3 (2.8%)
Clozapine + olanzapine	2 (1.9%)
Clozapine + aripiprazole	1 (0.9%)
Clozapine + quetiapine	1 (0.9%)

Table 3: Use of atypical antipsychotic based on the amount of medication in RSJ Prof. Dr. Soerojo Magelang

Treatment	N = 106
Single	12 (11.3%)
Combination	94 (88.7%)

Table 4: Blood pressure before (pre-) and after (post-) atypical antipsychotic therapy to patients with schizophrenia in RSJ Prof. Dr. Soerojo Magelang

Blood pressure	Median (minimum–maximum)	*p* value*
Pre-systolic blood pressure (mm Hg)	120.5 (90–176)	0.418
Post-systolic blood pressure post (mm Hg)	125.0 (95–178)	
Pre-diastolic blood pressure (mm Hg)	80.0 (55–103)	0.592
Post-diastolic blood pressure (mm Hg)	80.0 (54–115)	

*Wilcoxon test: *p* value < 0.05 = significant

Table 5: Number of patients with schizophrenia whose blood pressure decreased and increased after atypical antipsychotic therapy in RSJ Prof. Dr. Soerojo Magelang

Systolic blood pressure	Frequency	Diastolic blood pressure	Frequency
BP pre > BP post	43	BP pre > BP post	47
BP pre < BP post	57	BP pre < BP post	50
BP pre = BP post	6	BP pre = BP post	9

BP = blood pressure

Table 6: Correlation between gender, age, antipsychotic treatment, smoking habit, and systolic blood pressure on patients with schizophrenia in RSJ Prof. Dr. Soerojo Magelang

Demographic characteristics	Frequency	SBP pre (mm Hg) median (minimum–maximum)	*p* value	SBP post (mm Hg) median (minimum–maximum)	*p* value
Gender					
Male	83	121 (100–176)	0.206	128 (95–178)	0.175
Female	23	120 (90–158)		111 (100–154)	
Age					
Late adolescence (17–25 years)	10	120.50 (100–140)	0.159	126.50 (103–136)	0.023
Early adulthood (26–35 years)	42	120 (96–153)		120 (95–166)	
Late adulthood (36–45 years)	48	124.50 (90–176)		130 (98–178)	
Early elderly (46–55 years)	6	115 (100–125)		119 (100–140)	
Atypical antipsychotic treatment					
Single	12	120 (100–156)	0.300	110 (96–161)	0.036
Combination	94	121 (90–176)		128 (95–178)	
Smoking habit					
Smoking	72	121 (100–156)	0.620	128 (95–178)	0.560
Nonsmoking	34	120 (90–176)		120.5 (100–154)	

SBP = systolic blood pressure

previous study showed that male patients dominated the number of patients with schizophrenia (75%) in RSJ Prof. HB Saanin, Padang (72%). Male patients were 2.37 times higher in having the disease ($p = 0.011$).[14] Meanwhile, those in the late adulthood (36–45 years) were in danger of it, followed by those in early adulthood (26–35 years) (45.3% and 39.6%, respectively). Similar results were also observed in X Hospital, Bantul, Yogyakarta, Indonesia. Schizophrenic disorders were present mostly in those in the productive age. Among the influencing factors is stress, which is caused by greater responsibilities.[15] Other research generating similar results in RSJ Prof. HB Saanin, Padang, West Sumatra, Indonesia, stated that patients aged between 25 and 35 years were 1.8 times prone to the disease compared to those aged between 17 and 24 years.[14]

The most common types of schizophrenia observed in the patients of the recent study were paranoid and undefined (44.3% and 40.6%, respectively). In paranoid type, the patients have one or more doubts or auditory hallucinations as well as less dominant negative symptoms. Meanwhile, the symptoms of undefined schizophrenia, as the name suggests, cannot be identified.[16,17]

In terms of education, most of the patients graduated from elementary school and middle school, with the same proportion (30.2%). Among 2654 research subjects older than 17 years in Iran, those from the lower level of education had 2.48 times higher potentials of having schizophrenia.[18]

The patients in Prof. Dr. Soerojo Mental Health Hospital Magelang smoked (67.9%). Indeed, smoking is one of the risk factors of cardiovascular diseases for those with psychotic disorders.[19]

Distribution of atypical antipsychotic treatment

The combination of risperidone and clozapine is commonly used (82.1%), followed by risperidone (9.4%) [Table 2]. Other researches showed the use of risperidone was higher than the combination of it and clozapine (27% and 17%, respectively).[15] In another study conducted in January 2016 to March 2016, at the Prof. Soerojo Mental Health Hospital Magelang, the presentation of atypical polypharmacy of clozapine and risperidone was 20.62% of the overall use of atypical antipsychotics.[13]

Not only atypical antipsychotics block dopamine receptors in the mesolimbic system, but they also block serotonin receptors in the mesocortical system, thus decreasing the negative symptoms. Clozapine is used

to treat patients who are resistant to antipsychotic therapy.[11]

In this study, it was also observed that the most used treatment was the combination (88.7%), whereas the single was 11.3% [Table 3]. It was preferred because it produces varied and greater receptor targets. It improves the therapeutic effect by increasing D2 dopaminergic receptor antagonist. Besides, it is also expected to reduce the side effects as the result of the dose of each treatment.[20] In addition, the antipsychotic combination is given to the patients with chronic disorder, when they are resistant to a single treatment. The combination is to decrease the symptoms.[11]

Characteristics of patients' blood pressure

The effects of metabolic syndrome on the use of atypical antipsychotics occur on average after initiation therapy for 6–16 weeks. One effect of metabolic syndrome is an increase in blood pressure.[21-24] In addition, other studies concerning the evaluation of metabolic disorders in schizophrenic patients (METEOR) were observed after 3 months of antipsychotic use where one of the monitoring parameters was blood pressure. Therefore, in this study the effect on blood pressure was observed after 3 months of antipsychotic use.[25]

The occurrence of hypotension after the treatment was caused by the blockage of receptor α1 that plays a role in smooth muscle contractility in various tissues, including cardiac muscle contractility.[26] The blockade of receptor α1 in cardiac muscle causes the blood pressure to decrease (hypotension). The obstruction to adrenoreceptor α1 also decreased the baroreceptor's sensitivity in detecting the decrease of blood pressure. It leads to the failure of homeostasis system that causes orthostatic hypotension.[27]

The use of atypical antipsychotics also might increase blood pressure. The dopamine receptor takes part in regulating the blood pressure, and the change of system may cause hypertension. D1, D3, and D4 receptors interact with the renin–angiotensin–aldosterone system, whereas D2 and D5 with the sympathetic nervous presynaptic post-ganglia. When it is activated, the receptor inhibits the production of norepinephrine at the sympathetic nerve ending, leading to increase in the blood pressure.[28]

The retrospective study conducted in Malaysia that involved 174 participants of FES of General Hospital Kuala Lumpur, Malaysia, reported metabolic syndrome in 67 patients (36.2%), of which 36 patients (23.2%) had hypertension. The rest, 41 patients (28.1%), had diabetes.[29] Meta-analysis research showed that compared to placebo, most antipsychotic medication was related to weight gain. In turn, it increased the possibility of developing various physical diseases such as diabetes, cardiovascular diseases, and cancer.[30] The multicenter study conducted in 12 European countries in 2270 patients with schizophrenia receiving antipsychotic therapy showed 34.8% of patients experiencing hypertension and 11.7% experiencing hypotension.[25]

Hypotension can cause complications from several conditions such as syncope, transient ischemic attack, stroke, myocardial infarction, and mortality. Prospective observation of blood pressure is necessary because patients with psychotic disorders do not show subjective symptoms such as dizziness. Non-pharmacology therapy and education to the relevant patients by moving slowly from sitting or lying position to standing is the first significant step in preventing orthostatic hypotension. Symptomatic and asymptomatic therapies are useful as well. Pharmacology therapy is recommended when the symptoms still occur after the non-pharmacology therapy is given and the patient still receives antipsychotic treatment.[27]

Correlation between gender, age, antipsychotic treatment, smoking habit, and systolic diastolic blood pressure

Mann–Whitney and Kruskal–Wallis tests were conducted to determine whether there was a relationship between gender, age, antipsychotic therapy, and smoking habits with diastolic and systolic blood pressure (pre and post). Both of these tests were chosen because the data were not normally distributed. The Mann–Whitney test was performed on gender variables, antipsychotic therapy, and smoking habits, whereas the Kruskal–Wallis test was performed on the age variables because the variables consisted of more than two groups.

On the basis of the results of data analysis, a relationship was observed between age and antipsychotic therapy with postdiastolic and postsystolic blood pressure ($p < 0.05$). In addition, there was also a relationship between sex with prediastolic blood pressure ($p < 0.05$) [Tables 6 and 7].

In a study conducted on patients diagnosed with FES aged 15–40 years who received antipsychotic therapy for less than 6 months, a total of 39.9% experienced prehypertension and 10% had hypertension, of which only 3.6% received antihypertensive drugs. The results of the study also stated that male

Table 7: Correlation between gender, age, antipsychotic treatment, smoking habit, and diastolic blood pressure on patients with schizophrenia in RSJ Prof. Dr. Soerojo Magelang

Demographic characteristics	Frequency	DBP pre (mm Hg) median (minimum–maximum)	*p* value	DBP post (mm Hg) median (minimum–maximum)	*p* value
Gender					
Male	83	80 (60–103)	0.005	80 (60–115)	0.598
Female	23	70 (55–98)		80 (54–100)	
Age					
Late adolescence (17–25 years)	10	80 (60–98)	0.996	74 (64–90)	0.010
Early adulthood (26–35 years)	42	80 (56–102)		76 (54–99)	
Late adulthood (36–45 years)	48	80 (55–103)		81 (65–115)	
Early elderly (46–55 years)	6	75 (70–89)		78.50 (60–90)	
Atypical antipsychotic treatment					
Single	12	75 (56–96)	0.262	69.50 (54–115)	0.001
Combination	94	80 (55–103)		80 (60–102)	
Smoking habit					
Smoking	72	80 (60–103)	0.050	80 (60–115)	0.418
Nonsmoking	34	73.50 (55–102)		80 (54–100)	

DBP = diastolic blood pressure

patients had significantly higher systolic ($p < 0.001$) and diastolic ($p = 0.01$) blood pressure and more frequent prehypertension ($p < 0.001$) than female patients, who received more antihypertensive drugs ($p = 0.047$).[9]

The agents that most commonly cause hypotension, include clozapine, quetiapine, and risperidone. Olanzapine does not block alpha-adrenergic receptors and has not been linked to orthostatic hypotension, although dizziness has been reported in some patients. Risperidone can occasionally cause orthostatic dizziness, hypotension including orthostatic hypotension, and reflex tachycardia. The least hypotensive effects are reported with ziprasidone.[31]

Atypical antipsychotic drugs can cause cardiovascular side effects such as arrhythmias and deviations in blood pressure. In rare cases, they can also cause congestive heart failure, myocarditis, and sudden death. Patients with schizophrenia have a higher risk of cardiovascular death than healthy individuals. Increasing awareness of the potential for these complications can enable pharmacists and doctors to better manage and monitor high-risk patients. Regular patient monitoring through blood sampling and blood pressure checks, heart rate, and electrocardiogram can help identify clinical problems and prevent further complications. Finally, the education of patients and family members, pharmacists, in particular, can play a key role, which is known to be positive for morbidity and mortality in these patients.[31]

This study was limited in terms of the number of patients involved. It was also related to the limited time and incomplete medical records. The researchers did not measure blood pressure directly. Instead, the data were obtained from the medical records. Other variables such as physical activities and food intake also influenced the patients' blood pressure. Besides, not all atypical antipsychotics are used to compare the risk value of the change in blood pressure. The suggestion for the next study is to evaluate the risk of atypical antipsychotic side effects both to changes in blood pressure or other side effects with a prospective cohort method and a greater number of samples by controlling several confounding factors.

Conclusion

It can be concluded that no significant difference was observed in the blood pressure before and after the treatment.

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Conflicts of interest

There are no conflicts of interest.

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