THE INCREASED RISK OF RANDOM BLOOD GLUCOSE, BODY MASS INDEX AND ABDOMINAL CIRCUMFERENCE IN THE SCHIZOPHRENIC PATIENTS USING CLOZAPINE AND QUETIAPINE

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Abstract

The use of atypical antipsychotics often causes an increase in blood glucose levels, body mass index (BMI) and abdominal circumference. This study aims to identify the increased risk of random blood glucose, BMI and abdominal circumference in the schizophrenic patients using clozapine and quetiapine. This cohort study involved 35 schizophrenic patients (19 patients used clozapine and 16 patients used quetiapine). The measurement of random blood glucose BMI and abdominal circumference was done in the zero month, the first month and the second month. The average of random blood glucose, BMI and abdominal circumference were analyzed using Wilcoxon and Chi-square. In the use of clozapine, there is a significant increase in the average of random blood glucose between the first month and the second month (p=0.1) with the difference of 6.37 mg/dl, there is an increase average in BMI between the first month and the second month (p=0.03) with the difference of 0.18 kg/m² and an average increase in abdominal circumference between the zero month and the first month (p=0.04) with the difference of 1.47 cm, between the first month and the second month (p=0.02) with the difference of 1.94 cm. In the use of quetiapine, a significant increase in abdominal circumference between the first month and the second month (p=0.02) with the difference 1.38 cm. The use of clozapine has more risk in increasing random blood glucose (OR 2.00: CI 95% 0.41-9.76), BMI (OR 2.78: CI 95% 0.69-11.10) and abdominal circumference (OR 3.61: CI 95% 0.89-14.64) compared to the use of quetiapine. The use of clozapine has more risk in increasing blood glucose, BMI and abdominal circumference compared to the use of quetiapine.

Keywords: *Clozapine, Quetiapine, Schizophrenic, Blood Glucose, BMI*

1. INTRODUCTION

Schizophrenia is a severe mental disorder that affects 21 million people in the world (Schmidt et al., 2019). Atypical antipsychotics such as clozapine and quetiapine are frequently used for schizophrenic patients because they are effective and have low extrapyramidal side effects (Barbosa et al., 2018; Citrome et al., 2019; Oruch et al., 2020). Atypical antipsychotics has a function as serotonin antagonist (5-HT2, 5-HT1A, 5-HT2A) and it can increase the release of dopamine (C Sullivan et al., 2015; Yatham et al., 2005). Serotonin have a role in glucose homeostatic. Serotonin antagonists especially 5-HT1A causes a decrease in β-pancreatic cells responsiveness which reduce insulin secretion (Kenakin, 2003).

The epidemiological studies show that the use of atypical antipsychotics can increase the risk of Diabetes Mellitus (DM) when it is compared to patients who do not use antipsychotics (Buse et al., 2003; Schwenkreis & Assion, 2004). According to the researches by systematic reviews, meta-analyzes and clinical trial, the result shows that the different use of atypical antipsychotics causes different metabolic side effects (Fedorowicz & Fombonne, 2005; Jafari et al., 2012; Shirzadi & Ghaemi, 2006).

The use of atypical antipsychotics in a long time often causes abnormal carbohydrate metabolism (Gurevich et al., 2012), such as increase in body weight (Akhtar et al., 2004). The evaluation of 5-year clozapine use was conducted in USA, it shows that the body weight of 82 respondents increase significantly every month with a linear coefficient of 0.5 kg/month (Henderson et al., 2000). The previous research reports that the use of clozapine can increase blood glucose levels Click or tap here to enter text. and affect new onset Diabetes Mellitus (DM) (Liebzeit et al., 2001). The use of quetiapine can also increase blood glucose levels (Oruch et al., 2020) and BMI (Gadzik, 2006). In addition, the use of clozapine in greater compared to the use of quetiapine.

The high occurrence of the increase in blood glucose levels and BMI due to the use of atypical antipsychotics leads this study to evaluate the increased risk of random blood glucose, BMI and abdominal circumference in the use of clozapine and quetiapine.

2. RESEARCH METHOD

2.1. Research Design and Sample

This observational cohort study involved all of the schizophrenic patients using single clozapine and quetiapine in the Outpatient Installation of Magelang Mental Hospital of Indonesia in April-May 2018. There were 35 respondents in this study. The study protocol was approved by the Ethics Committee of Mental Hospital of Prof. Dr. Soerojo, Indonesia. All the respondents gave the approval by signing the informed consent.

2.2. Blood Glucose Measurement

Blood glucose measured in this study was random blood glucose (3 hours after eating). According to American Diabetes Association (ADA, 2017) and International Diabetes Federation, random blood glucose is a blood glucose test conducted any time, a diagnosis of diabetes is made if the value is ≥ 200 mg/dl. The sample used capillary blood taken form the patient's finger. The measurement was conducted by the trained nurse using Auto check blood glucose device (MDSS GmbH Schiffgrabe 41 30175 Hannover Germany, 2017). The blood glucose measurement was conducted in the zero month, the first month and the second month.

2.3. BMI

Body Mass Index (BMI) is defined as the weight in kilograms (kg) divided by the square of the height in meters (m²) *(48)*. The weighing is done three hours after eating. The following classification of BMI based on WHO are:
   a) < 18.5 : thin
   b) $18.5 – 24.9$: ideal
   c) $25 – 29.9$: over weight
   d) $30 – 34.9$: obesity I

e) 35 – 40   : obesity II

2.4. Abdominal Circumference

The measurement of abdominal circumference was conducted by a trained nurse. The following are procedures of measurement methodology based on European Health Risk Monitoring (2002):

1. The nurse uses a tape measure that has been checked every month (if the tape stretches, it is replaced)
2. The position of the subject stands upright with a distance between 2 feet around 12-15 cm.
3. The measurement of abdominal circumference by opening stomach cover, circling a tape measure horizontally around the middle part of the abdomen parallel to the umbilical, (one finger should be inserted under the tape measure looped around the stomach)
4. The measurement result is taken in a normal and consistent breathing position on each subject.

2.5. Statistical Analysis

The patient profile data was presented in average ± SD and percentage. The Wilcoxone test was used for paired bivariate analysis (increased random blood glucose, BMI and abdominal circumference). The Mann-Whitney Test was used for unpaired bivariate analysis (comparison of increased random blood glucose, BMI and abdominal circumference using clozapine and quetiapine). The Chi-Square test was used to analyze the comparison of increased risk of blood glucose, BMI and abdominal circumference between the use of clozapine and quetiapine.

3.   RESULT AND DISCUSSION

3.1. Subject Characteristics

This study involved 35 subjects consisting of 18 male subjects and 17 female subjects. The average age is 40.74±13.58, ten subjects are smokers and four subjects with family history of DM. The average of BMI is 23.49±4.22 kg/m², the average duration of medicine consumption is 9.26±8.75 months, the average of clozapine dose is 83.11 mg and the average of quetiapine dose is 164.35 mg. The data of the patient characteristic in detail is presented in Table 1.

Table 1 Characteristic of schizophrenic patients who get clozapine and quetiapine

No	Patient's Characteristics		Clozapine (n=19)	Quetuapine (n=16)	Total (%)
1	Age (years)	20-29	7	4	31,42
		30-39	4	3	20
		40-49	0	8	22,86
		50-65	8	1	25,71
		X±SD = 40,74±13,58			
2	Gender	Male	10	8	51,43
		Female	9	8	48,573
3	DM family history		2	2	11,43

4	Duration of drug use (month)	1-6	9	9	51,44
		7-12	5	4	25,72
		13-24	5	0	14,27
		25-36	0	3	8,57
		X±SD = 9,26±8,758,57			
5	Dosage (mg)	12,5	2	0	5,71
		25	9	0	25,71
		50	3	0	8,57
		100	4	0	11,43
		200	1	6	20
		300	0	6	17,14
		400	0	4	11,43
		X±SD = 164,34±134,28			

3.2. The Increase in Random Blood Sugar

In the use of clozapine, there is a significant increase in random blood glucose levels between the zero month and the first month p=0.03, between the first month and the second month p=0.01. In the use of quetiapine, there is no significant increase in random blood glucose between the zero month, the first month and the second month (p>0.05) (Table 2). There is no significant difference on the average of random blood glucose in the use of clozapine and quetiapine (p>0.05). The use of clozapine has more risk in increasing random blood glucose compared to the use of quetiapine (RR 2.00; CI 95% 0.41-9.76).

Table 2 The increase in random blood glucose of schizophrenic patients who get clozapine and quetiapine

Group	GDS (mg/dl)							
	Month-0	Month-1	Deviation	p	Month-1	Month-2	Deviation	p
Clozapine (n=19)	111,42±19,71	106,16±22,37	-5,26	0,28	106,16±22,37	112,47±19,39	6,37	0,01*
Quetiapine (n=16)	128,38±72,38	118,75±54,37	-9,63	0,16	118,75±54,37	115,88±51,31	-2,87	0,84

The increase in blood glucose is happened because of the effect of serotonin antagonism especially (5-HT1A). Antagonism (5-HT1A) causes a decrease in the responsiveness of β-pancreatic cells which causes reduced insulin secretion (Richards et al., 2010). Atypical antipsychotics also block muscarinic which causes reduced pancreatic insulin secretion. It is caused by the activity of acetylcholine that helps pancreatic insulin secretion mediated by type 3-muscarinic receptor activities (de Azua et al., 2011). If there is a decrease in the pancreatic insulin secretion, it will cause insulin retention (Richards et al., 2010).

3.3. The Increase in BMI

In the use of clozapine, there is significant increase in BMI between the first month and the second month with p=0.03. Meanwhile, in the use of quetiapine, there is no increase in BMI (p>0.05) (Table 3). The average of BMI using clozapine and quetiapine has no significant difference (p>0.05) (Table 3). The use of clozapine has more risk in increasing BMI compared to the use of quetiapine (RR 2.78: CI 95% 0.69-11.10).

Table 3 The increase in BMI of schizophrenic patients who get clozapine and quetiapine

Group	IMT kg/m^2)							
	Month-0	Month-1	Deviation	p	Month-1	Month-2	Deviation	p
Clozapine (n=19)	21,89	22,19	0,30	0,29	22,19	22,37	0,18	0,03*
Quetiapine (n=16)	25,38	25,25	-0,13	0,34	25,24	25,31	0,07	0,07

Wilcoxon : *significance p<0,05

The increase in BMI in the use of clozapine is in line with the review involving 97 patients who received clozapine with a duration of 3-12 weeks, the result shows that there is an increase in BMI, 0.9-9.5 kg. The similar result was also reported by (Henderson et al., 2000b) involving 82 subjects and the result shows a significant increase in IBM on each month with a linear coefficient of 0.5kg/month. The increase in IBM is happened from the 12th month to the 60th month after using clozapine, with a linear coefficient of 0.2 kg/month. 5 report that 61 subjects who used clozapine and quetiapine (13.1%) were obese (BMI>30kg/m²).

It shows that use of clozapine can increase the risk of obesity of 63%. The increase in BMI is happened because the atypical antipsychotics are antagonistic (H1) and have a high affinity for histaminergic system. VMHN and PVN have an important role in obesity. (H1) has a function as suppressor of food supply in VMHN and PVN and mediates the effect of leptin. If H1 is inhibited, it will cause an increase in appetite. The increase in IBM is also caused by HT2C receptors blockade.

3.4. The Increase in Abdominal Circumference

In the use of clozapine, there is significant increase in abdominal circumference between the zero month and the first month with p=0.04, between the first month and the second month with p=0.02. Meanwhile, in the use of quetiapine, the significant increase in abdominal circumference happens between the first month and the second month with p=0.02 (Table 4). The average of abdominal circumference in the use of clozapine and quetiapine has no significant difference (p>0.05). The use of clozapine has more risk in increasing abdominal circumference compared to the use of quetiapine (RR 3.61; CI 95% 0.89-14.64)

Table 4 The increase in abdominal circumference of schizophrenic patients who get clozapine and quetiapine

Group	GDS (mg/dl)							
	Month-0	Month-1	Deviation	p	Month-1	Month-2	Deviation	p
Clozapine (n=19)	81,74±11,43	83,21±11,43	1,47	0,06[1]	83,21±11,43	83,68±11,92	1,9	0,02[1]*
Quetiapine (n=16)	84,06±7,23	85±7,96	0,94	0,67[2]	85±7,96	85,44±7,98	0,44	0,02[2]*

Paired t-test : *significance p<0,05
Wilcoxon : *significance p<0,05

The increase in abdominal circumference in the use of clozapine and quetiapine is in line with the research by Chen et al. (2018) involving 87 patients (33.2%) who experienced metabolic syndrome with the larger average of abdominal circumference of 93.6±8.1 cm compared to patients with non-metabolic syndrome, 82.2±8.5 cm. the similar result is also reported by P.-Y. Chen et al. (2018) in which the average of abdominal circumference of the clozapine group is higher, 87.29±11.41 compared to the control group 79.31±14.28 cm.

The use of clozapine has more risk in increasing random blood glucose, BMI and abdominal circumference compared to the use of quetiapine. This result is in line with the previous research by (Shen et al., 2018) who reports that the patient's blood glucose level who used clozapine is higher than the one who uses quetiapine, 4.9±0.66 mmol/L *vs* 4.71±0.71 mmol/L. Moisan, Turgeon, Desjardins, & Grégoire (2013) report that the use of quetiapine has lower risk of DM (OR 0.88; CI 95% 0.80–0.96) compared to the use of clozapine OR 0.87; CI 95% 0.47-1.61). (Fraguas et al., 2011) report that the increase average in weight of the patients who used clozapine is 0.9–9.5kg, while the quetiapine is 2.3–6.1kg. Olsson (2015) reports that abdominal circumference of the clozapine group is higher than that of the control group.

This is due to the fact that clozapine binds muscarinic and histamine receptors are stronger than other antipsychotics. The muscarinic has a function to mediate pancreatic insulin secretion acetylcholine, if the muscarinic is bound, it will cause insulin retention. (H1) has a function as a suppressor of food supply in VMHN and PVN and mediates the effect of leptin. If H1 is inhibited it will cause an increase in appetite.

The result of this cohort study shows an increase in blood glucose, BMI and abdominal circumference in the use of clozapine, whereas in the use of quetiapine, there is only an increase in abdominal circumference. The result of this study is in line with the previous study (Gadzik, 2006) that the use of clozapine can increase BMI and the risk of diabetes mellitus. The similar result was also reported by Wirsing (2013) in a study involving 39 patients using clozapine with the average duration of 43.3 months, the result shows an increase in blood glucose of 4% (p=0.05). Lappin et al. (2018) in their research involving a larger sample, 452 patients with the age average 43.7±11.2, the result shows that 248 patients had increased blood glucose levels. Wysokiński (2014) in his research involving 24 patients who used clozapine and 24 patients in control group, reports that the blood glucose level of the patients who used clozapine are higher than the control group (103.5±31.6 vs 87±811.7 mg/dl, p=0.04). Further, Grover et al. (2016) report that an increase in blood glucose is happened after using clozapine for three months, 80.92±9.95 mg/dl becomes 88.08±11.6 mg/dl.

4. CONCLUSION

The result of this study proves that the use of clozapine can increase random blood glucose, BMI and abdominal circumference. In addition, the use of quetiapine can increase abdominal circumference. While the use of clozapine has a higher risk in increasing random blood glucose if compared to the use of quetiapine (OR 2.00; CI 95% 0.41-9.76). The use of clozapine has higher risk in increasing BMI if compared to the use of quetiapine (OR 2.78; CI 95% 0.69-11.10). The use of clozapine has higher risk in increasing abdominal circumference if compared to the use of quetiapine (OR 3.61; CI 95% 0.89-14.64).

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