ORIGINAL ARTICLE

Atypical antipsychotic use is an independent predictor for the increased mean platelet volume in patients with schizophrenia: A preliminary study

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Background: Cardiovascular diseases, cardiovascular risk factors, and mortality due to these situations are more frequently encountered in schizophrenic patients when compared with the general population. The mean platelet volume (MPV) is a surrogate biomarker of the platelet activity and an useful prognostic test in cardiometabolic diseases. The aim of this study was to investigate what influenced MPV levels in patients with schizophrenia. **Materials and Methods:** We evaluated hospital records of 60 hospitalized schizophrenia patients. Thirty age- and sex-matched healthy control subjects were also included as a control group. **Results:** MPV levels were significantly higher in patients who were on atypical antipsychotic drugs than in patients who were not using any drug (9.2 ± 0.8 vs. 8.6 ± 0.8 fL, $P = 0.016$) and also higher than control group (9.2 ± 0.8 vs. 8.1 ± 0.9 fL, $P < 0.001$). Furthermore, patients who were not using antipsychotics had higher MPV than control group (8.6 ± 0.8 vs. 8.1 ± 0.9 fL, $P = 0.036$). Atypical antipsychotic use [Odds ratio (OR) =6.152, 95% confidence interval (CI,) $P = 0.003$)] and platelet distribution width (OR = 0.989, 95% CI, $P = 0.032$) were associated with high MPV levels in univariate analysis. In multivariate logistic regression model, only atypical antipsychotics use (OR = 6.152, 95% CI, $P = 0.003$) was found to be independent predictor of high MPV levels after adjustment of other potential confounders (age, gender, presence of hypertension, diabetes mellitus, hyperlipidemia, and smoking). **Conclusion:** MPV seems to be influenced not only by schizophrenia itself but also by atypical antipsychotic drugs. It might be concluded that schizophrenic patients are under increased risk for cardiometabolic diseases and risk factors and this risk is higher in patients on atypical antipsychotic treatment.

Key words: Atypical antipsychotics, cardiovascular disease, mean platelet volume, schizophrenia

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INTRODUCTION

Cardiovascular diseases are more frequently encountered in schizophrenic patients when compared with the general population.[1,2] Cardiovascular risk factors such as diabetes, obesity, and smoking are more common among schizophrenic patients when compared with healthy controls, so the risk for cardiovascular diseases is higher in schizophrenic patients.[3] Also, the mortality rate due to cardiovascular diseases is higher among schizophrenic patients when compared with the general population, and is frequently observed at younger ages. Furthermore, this mortality rate increases by time.[4] One of the explanations for the increased cardiovascular events in schizophrenic patients is increased platelet activity.[5]

It has been shown that platelet size, measured as mean platelet volume (MPV), correlates with their reactivity.[6] There is an increasing interest on MPV as an independent risk factor of atherosclerotic disease. Several studies have documented its association with acute myocardial infarction[7] and its prognosis,[8] with coronary atherosclerosis,[9] the presence and the short-term prognosis of stroke, and the long-term risk of stroke.[10] MPV measurement has now become a routine procedure in many laboratories, and its value is increasingly reported among the standard parameters of the whole blood count. High MPV levels have been reported in patients with hypertension,[11] hypercholesterolemia,[12] and a history of smoking.[13]

The primary objective of the present study was to investigate the relationship among the cardiovascular risk factors and the MPV levels in patients with schizophrenia using atypical antipsychotic drugs or not, along with comparison to healthy controls with regard to accompanying risk factors for cardiovascular disease.

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MATERIALS AND METHODS

Study population

This is a retrospective chart review study of Patients who were diagnosed with schizophrenia by a trained psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[14] criteria of the American Psychiatric Association and hospitalized at the psychiatry clinic. Patients hospitalized between January 2008 and January 2010 were overviewed based on the hospital records. The patients who had alcohol and substance use disorders and who were diagnosed with co-morbid psychiatric disease were excluded from the study. Moreover, schizophrenic patients who were administered anti-depressant drugs, benzodiazepines, or mood stabilizers within the last month, patients who had known coronary artery disease and severe hepatic or renal failure, myelodysplastic syndrome, and patients who were taking anti-platelet and anti-coagulant drugs were also excluded from the study. The age- and sex-matched control group consisted of subjects who were similar to the population in terms of cardiovascular risk factors and had neither psychiatric nor cardiovascular diseases. So, 60 patients with schizophrenia and 30 controls were included in the present study. The patients with schizophrenia were also evaluated as two groups according to the presence or absence of antipsychotic drug use. Study was approved by local ethical committee. Informed consent was taken from all of the participants.

Data collection

The data of the consecutive patients who were hospitalized in the Department of Psychiatry of Sivas Cumhuriyet University, Faculty of Medicine between January 2008 and January 2010 were collected from the hospital records. Else, the present status of the patients was assessed by telephone call. The data regarding age, gender, duration of disease, use of psychiatric medications, presence of hypertension, diabetes mellitus, and hyperlipidemia, and smoking status were obtained from detailed history taken during admission to the psychiatry clinic.

Complete blood counts were determined by the samples which were drawn into vacutainer tubes containing 0.04 ml of the 7.5% K3 salt of ethylenediaminetetraacetic acid (EDTA) within 10-15 min and then analyzed by a Beckman-Coulter Gen-S Hemotology Analyzer.

Statistical analysis

Continuous variables were expressed as mean ± SD or median (min-max) in the presence of abnormal distribution, and categorical variables as percentages. Comparisons between groups of patients were made by use of a χ^2 test for categorical variables, an independent samples *t* test for normally distributed continuous variables, and a Mann-Whitney U test when the distribution was skewed. Multiple logistic regression analysis was used to evaluate independent parameters affecting high MPV levels. Statistical procedures were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL). A $P < 0.05$ was considered significant.

RESULTS

Mean platelet volume levels were significantly higher in patients who were on atypical antipsychotic drugs than in patients who were not using any drug (9.2 ± 0.8 vs. 8.6 ± 0.8 fL, $P = 0.016$) and also higher than control group (9.2 ± 0.8 vs. 8.1 ± 0.9 fL, $P < 0.001$). Furthermore, patients who were not using antipsychotics had higher MPV than control group (8.6 ± 0.8 vs. 8.1 ± 0.9 fL, $P = 0.036$) [Figure 1].

MPV levels were classified into two groups as those with relatively lower to normal (<8.5 fL) and those with higher (≥8.5 fL) according to analysis obtained from ROC curves (best sensitivity) and previous trials which indicated the level of MPV for outcomes.[15-17] Significant difference with respect to atypical antipsychotic drug usage was observed among the two groups classified according to MPV levels (6 [30%] vs. 29 [73%], $P = 0.002$, Table 1).

Results of the univariate and multivariate analysis for determining high MPV levels are listed in Table 2. Atypical antipsychotic drug usage and platelet counts were found to have prognostic significance in univariate analysis. In multivariate logistic regression model with forward stepwise method, only atypical antipsychotic drug usage (OR: 6.152, *P*: 0.003, 95.0% CI: 1.887-20.053) was found to be an independent factor in determining high MPV levels in schizophrenic patients after adjustment for variables and were found to be statistically significant in univariate analysis and other potential confounders (age, gender, presence of hypertension, diabetes mellitus, hyperlipidemia, and smoking).

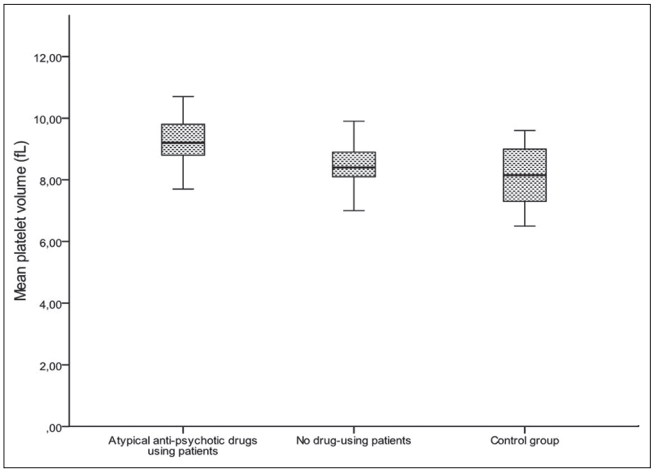

Figure 1: Comparison of mean platelet volume levels between three groups

Table 1: Properties of the schizophrenia patients based on their mean platelet volume levels

	MPV<8.5 fL (*n*=20)	MPV ≥8.5 fL (*n*=40)	*P*
Baseline characteristics			
Age, years[a]	40±10	42±11	0.537
Male gender[b] (%)	7 (35)	23 (58)	0.098
Hypertension[b] (%)	2 (10)	7 (18)	0.704
Diabetes mellitus[b] (%)	1 (5)	6 (15)	0.407
Hyperlipidemia[b] (%)	5 (25)	13 (33)	0.546
Smoking[b] (%)	10 (50)	14 (35)	0.266
Atypical anti-psychotic drug usage[b] (%)	6 (30)	29 (73)	0.002
Duration of disease (years)[a]	13.3±9.0	13.3±9.6	1.000
Types of schizophrenia[b] (paranoid/disorganized/rezudual/ undifferentiated)	9/5/1/5	20/11/3/6	0.813
Labaratory findings			
Mean platelet volume (fL)[a]	8.1±0.3	9.4±0.6	<0.001
Blood glucose (mg/dL)[c]	94.5 (61-288)	96.5 (71-333)	0.962
Creatinine (mg/dL)[a]	0.8±0.1	0.9±0.2	0.103
Alanine aminotransferase (IU/L)	19 (6-43)	21 (11-123)	0.212
Aspartate aminotransferase (IU/L)[c]	21 (11-75)	22.5 (12-115)	0.375
Hemoglobin (g/dL)[a]	14.5±1.7	14.1±1.7	0.361
Platelet distribution width (%)[a]	16.1±0.4	16.3±0.5	0.089
Mean corpuscular volume (fL)[a]	86±5	88±5	0.227
Red cell distribution width (%)	13.7±1.0	13.6±0.9	0.679
Platelet counts ($\times 10^3/\mu L$)[a]	276±74	239±48	0.053

MPV=Mean platelet volume; [a]Independent samples *t* test; [b]Chi-square test; [c]Mann-Whitney U test; Values are presented as number (%); mean±SD or median (min-max)

Table 2: Univariate and multivariate analyses of high mean platelet volume level (MPV ≥8.5 fL)

	Univariate			Multivariate		
	P	OR	(95% CI)	*P*	OR	(95% CI)
Statistically significant variables						
Atypical anti-psychotic drug usage	0.003	6.152	1.887-20.053	0.003	6.152	1.887-20.053
Platelet counts ($\times 10^3/\mu L$)	0.032	0.989	0.979-0.999			
Potential confounders						
Platelet distribution width (%)	0.095	2.641	0.846-8.243			
Age (years)	0.530	1.017	0.964-1.074			
Male gender (%)	0.105	2.513	0.826-7.642			
Hypertension (%)	0.449	1.909	0.358-10.173			
Diabetes mellitus (%)	0.279	0.353	0.375-29.964			
Hyperlipidemia (%)	0.551	1.444	0.431-4.840			
Smoking (%)	0.266	0.538	0.181-1.603			
Statistically non-significant variables						
Duration of disease (years)	1.000	1.000	0.944-1.059			
Types of schizophrenia (%)	0.477	0.883	0.627-1.244			
Blood glucose (mg/dl)	0.747	1.002	0.990-1.013			
Creatinine (mg/dL)	0.107	21.078	0.516-861.257			
Alanine aminotransferase (IU/L)	0.161	1.031	0.988-1.077			
Aspartate aminotransferase (IU/L)	0.343	1.019	0.980-1.061			
Hemoglobin (g/dL)	0.356	0.857	0.617-1.190			
Mean corpuscular volume (fL)	0.227	1.070	0.959-1.194			
Red cell distribution width (%)	0.674	0.888	0.512-1.541			

Statistically significant variables (atypical anti-psychotic drug usage and platelet counts) and potential confounders (platelet distribution width, age, gender, hypertension, diabetes mellitus, hyperlipidemia, and smoking) were entered into the multivariate logistic regression model, OR=Odds ratio; CI=Confidence interval; MPV=Mean platelet volume

DISCUSSION

In the present study, MPV levels were significantly higher among patients with schizophrenia when compared with the healthy controls. In the schizophrenia group, it was also shown that atypical antipsychotic drug usage was an independent predictor for increased MPV levels.

Several factors such as genetic vulnerability,[18] illness-related outcomes,[19] unhealthy lifestyle choices,[20] and antipsychotic

treatment,[21-23] are accused of increasing cardiometabolic risk factors in schizophrenia. Change in platelet activity has also been reported to contribute to increased cardiovascular disease and metabolic syndrome in patients with schizophrenia.[5] The platelets are considered to be a peripheral marker in major psychiatric diseases including schizophrenia.[24] In the *in vitro* study by Dietrich-Muszalska and Olas,[25] aggregation of blood platelets induced by ADP was found to be higher in schizophrenia patients than in healthy individuals. The findings of our study support the previous literature showing that patients with schizophrenia exhibit increased platelet activation. We believe we are the first to use MPV as an indicator of platelet activity in patients with schizophrenia.

Platelet function has a significant role in the development of atherothrombotic events that result in cardiovascular outcomes. MPV is an useful test that is easily obtained during routine clinical practice.[15] Platelets are heterogeneous cells in terms of size and density. MPV measurement is the most frequently used test to measure the size of platelets and it acts as a potential marker of platelet reactivity. An increase in MPV is associated with other parameters that indicate the platelet activity (e.g., platelet aggregation, increased thromboxane synthesis and b-thromboglobulin release, and increased expression of adhesion molecules).[15] MPV is an inexpensive and easy-to-interpret and -measure test carried out via automated cell counters, thus the measurement of MPV is ideal for routine clinical use.

MPV has been reported to be a determinant of platelet function. It has been previously reported that larger platelets have a greater mass, denser granules,[26] and are more active enzymatically and metabolically[27] than smaller platelets. They have a greater thrombotic potential caused by higher levels of intracellular thromboxane A2 and also express more procoagulant surface proteins such as *P* Selectin and Gp IIb/IIIa.[28] Additionally, larger platelets aggregate more rapidly than smaller platelets.[27] Increases in platelet volume are often associated with decreases in platelet count perhaps as a result of small platelets being consumed to maintain a constant platelet functional mass.[29] Concordant with this finding in our study, we found platelet count to be negatively and significantly related with MPV.

Increased MPV was shown to be associated with current (1 month) diagnosis of major depression in a large community-based population ($n = 2286$), even after excluding the subjects with risk factors capable of influencing platelet activity.[30] Also, in a clinical setting, MPV was found to be elevated in patients with major depression (11 women, 4 men) when compared with healthy individuals. Moreover, normalization of MPV levels was observed after 8 weeks treatment of escitalopram.[31] In the present study, we found that patients with schizophrenia exhibited elevated levels of MPV in comparison with healthy individuals as well.

Antipsychotic drugs are widely used in the treatment of psychotic disorders. Atypical antipsychotics are known to induce weight gain as well as cardiovascular and metabolic abnormalities, thereby increasing the patient's risk of obesity, the metabolic syndrome, type 2 diabetes mellitus and associated cardiovascular morbidity.[32] Increased risk of thrombotic events in schizophrenic patients treated with antipsychotic drugs have also been reported.[33-35] The antipsychotic treatment may cause the modification of platelet reactivity *in vivo* and *in vitro*.[36,37] The antiplatelet effects of antipsychotics have been established.[33,38]

The mechanisms explaining the relation between antipsychotics and blood platelet responses are not clear. Antipsychotics can alter platelet membrane lipid, receptors on the surface, intracellular messengers, or signal transduction. They may have some effects on platelet membrane structure and dynamics via lipid peroxidation caused by free radicals.[38,39] In the present study, we have found that atypical antipsychotics may affect blood platelet structure, namely, increase its volume. This finding may contribute to the explanation of the association of atypical antipsychotics with platelet activity.

LIMITATIONS

The relatively small size of the population resulting in the lower number of variables for the log regression model was one of the limitations for our study. Typical and atypical antipsychotics are shown to exhibit different cardiovascular and metabolic side effects.[21,40] Unfortunately, in our study, the patients who were on medication consisted of patients using solely atypical antipsychotics. Therefore, we could not compare the effects of typical and atypical antipsychotics on MPV. Additionally, the severity of psychotic symptoms was not measured with an instrument such as Positive and Negative Syndrome Scale. Thus, the correlation of psychotic symptom severity with MPV levels could not be performed. Also, there was no control over the time lag between collection of sample and analysis, as it is a retrospective study. Nevertheless, this paper was aimed to provide initial data on the association of MPV levels with increased cardiac mortality and risk factors in patients with schizophrenia, especially in the ones on the atypical antipsychotic drugs and promoted large-scale studies in a controlled, prospective design.

CONCLUSION

To our awareness, the present study was the first to evaluate the MPV levels as well as its association with other cardiovascular

risk factors in patients with schizophrenia, whether they were on atypical antipsychotics or not, and compared with the healthy controls. The data presented here demonstrate that MPV, which is associated with platelet activity, is higher in patients with schizophrenia than in healthy volunteers. The results of this study also indicate that atypical antipsychotics, which are commonplace in the treatment of schizophrenia, might cause an increase in the size of platelets in patients with schizophrenia. According to these results, it can be concluded that schizophrenic patients using atypical antipsychotic drugs should be monitored more closely and carefully regarding cardiovascular risk factors and MPV levels.

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