International Journal of Medical and Health Sciences

Journal Home Page: http://www.ijmhs.net ISSN:2277-4505

Original article

Assessing the Risk of Venous Thromboembolism in Psychiatric Patients on Antipsychotic Medication Using Platelet Indices

Timothy Amos Ekwere[1*], FMCPath, Jombo Henry Effiong[2]

[1]Senior Lecturer, Department of Haematology, University of Uyo, Akwa-Ibom State, Nigeria
[2]Senior Lecturer Department of Psychiatry University of Uyo, Akwa-Ibom State, Nigeria

ABSTRACT

Background: Psychiatric patents have a predisposition towards developing venous thromboembolism (VTE). This risk is largely related to the medications used in treating the disorders. The objective of the study was to assess the risk of venous thromboembolism in Psychiatric Patients on antipsychotic drugs using platelet indices. **Methodology**: This was a case-control study involving 92 participants comprising of 51-psychatric patients on antipsychotics and 41 non psychiatric persons (blood donors) as controls. Blood (2.5mls) was collected from both subjects and controls into separate EDTA anticoagulant tubes. A full blood count was performed on each sample using Haematology Auto analyser. Platelet count, mean platelet volume (MPV) and platelet distribution width (PDW) were extracted from the result of each participant. Clinical data of each subjects including age, sex, weight, height, duration of antipsychotic drug use, class of antipsychotic drugs were obtained from their respective case-files. **Results**: The mean platelet count of 194.5±59.80 $X10^9$/L for the subjects was significantly lower than 338.8±159.07 $X10^9$/L for the controls. On the other hand, the MPV value of the subjects (9.4±0.85) was significantly higher than the MPV of 8.7±1.05 for the controls. (p=0.01 in both cases). Furthermore, there was a statistically significant association between the mean MPV of the subjects and the duration of antipsychotic use. (p=0.01). **Conclusion**: A significantly high MPV (a biomarker of platelet activation) may portends VTE risk. Hence, MPV may be used as a surrogate biomarker in assessing VTE risk in psychiatric patients.

KEYWORDS: MPV, PDW, Antipsychotics, Psychiatric-patient, venous thromboembolism, Platelets.

INTRODUCTION

Venous thromboembolism which manifest clinically as deep venous thrombosis (DVT) and/or pulmonary embolism (PE) is an important and preventable cause of morbidity and mortality [1,2]. It poses a public health challenge globally affecting approximately 1 in 1000 – 2000 adults annually [2]. However, the reported incidence may be much higher going by the reports from recent studies. Stein et.al, and Tzoran et.al,[3] reported an incidence of 32% and 35% respectively of silent PE among patients with acute DVT.

The pathogenesis of VTE have been linked to one or more combinations of the Virchow's triad; reduced blood flow or stasis, damage to the vessel wall and changes in the blood composition [4]. The contribution of the first (stasis) and third (changes in blood composition) components of the triad is more pronounced in the pathogenesis of VTE. However in recent time, the contribution of other factors such as abnormally high levels of some coagulation factors and defects in some naturally occurring coagulants also contribute to the pathogenesis of this condition [4].

There are known risk factors of VTE, these include but not limited to the following; age greater than 40 years, obesity, prolonged medical or post-surgical immobilization, pregnancy, malignancies, inherited coagulation abnormalities and medications such as oral contraceptives and hormone replacement therapy (HRT) [5,6]. Several studies have reported association between VTE and psychiatric disorders and drugs used in the treatment of these disorders [7,8]. The risk appears largely related to the medications used for treating this disorder [7,8]. One of such studies reported a five-fold increase mortality rate from pulmonary embolism among psychiatry patients on clozapine [9].

Similarly, a large nested case-control study reported a seven fold increase in VTE risk among psychiatry patients on first generation antipsychotic medication compared to non-users [10]. Several case series and case reports have reported similar findings [11,12]

The underlying mechanism of this adverse reaction of antipsychotics are largely unknown, however the following suggestions relating to obesity, Increase platelet aggregation, increased levels of antiphospholipid antibodies, hyperhomocysteinaemia and hyperprolacteinaemia have been proposed. Thus, the need to identify at risk patients especially those with co-morbidities that favours VTE in psychiatric patients on antipsychotics becomes imperative.

Platelet indices which includes; Mean platelet volume (MPV) and platelet distribution width (PDW) have been shown to be a good biomarkers of platelet function and activation [13].These indices increases during platelet activation because of the morphological changes platelets undergo during this process [13]. PDW measure the variation in the size of platelets while MPV is a measure of the average size of platelets. Large platelets contain denser granules and are metabolically and enzymatically more active with high thrombotic potentials than smaller ones [14].This may serves as useful markers for early diagnosis of thromboembolic diseases.

The traditional markers of platelet activations on the other hand are contents of the platelets granules that are released when platelet are activated and includes β-thromboglobulin, or soluble P-Selectin. However these biomarkers are not readily determined in many laboratories because the assay protocol are quite laborious and expensive to perform. In contrast, platelet indices are routinely measured in most laboratories as a component of the complete blood count.

Therefore, the aim of this study was to determine if any, the VTE risk in psychiatric patients on antipsychotic drugs using platelet indices a simple and easily measured index of platelet activation.

MATERIALS AND METHODS

Study centre

This study was conducted in the Departments of Mental Health and Haematology University of Uyo. The hospital is a 500 bedded tertiary referral centre in Uyo, a capital city in the oil rich south–southern region of Nigeria.

Study design

This was a case- control study. Subjects on antipsychotic medications for a period not less than six months were selected. The subjects were either on the conventional or atypical antipsychotic agents or both. A total of 51 psychiatric patients on antipsychotic medication and 41-healthy controls consisting of individuals who presented at the donor clinic of our hospital for blood donation. Recruitment of subjects and controls lasted for five months between February and June 2015.

Specimen collection/ Analytical procedure

Free flowing venous blood (2.5mls) was collected from each subject including the controls using a pre-coated ethylene-diamine-tetra acetic acid vacutainer blood collection tubes. This was used to determine Full blood count (FBC) using the Sysmex KX 31 Haematology auto-analyser. The FBC analysis was performed within 2 hours of sample collection. From the FBC result, platelet indices including Platelet count, MPV and PDW were extracted for both subjects and controls. Information on the clinical and socio-demographic characteristics of the subjects including age, sex, weight, height, level of education, employment status, duration of illness, duration of anti-psychotics and the class of antipsychotic agent used were obtained from the case-files of each patient and recorded in the study profoma.

Inclusion and Exclusion Criteria

A subject was enrolled in the study if the following eligibility criteria were met: a diagnosis of mental disorder requiring treatment with antipsychotic medication, duration of antipsychotic medication use of at least 6 months, adults above the age of 18years and giving informed consent to participate in the study. The main exclusion criteria were refusal to participate in the study in addition to not meeting any of the above criteria. The control subjects were those who met the blood donor eligibility criteria of our institution and who gave an informed consent to be part of the study.

Data Analysis.

The data were analysed using the Statistical Package for Social (SPSS 20.0). The data was presented in simple tables. Descriptive and inferential statistics using Chi-Square, t-test, anova and correlation were used as appropriate. The level of significance was set at $p< 0.05$

Ethical Consideration

Ethical approval was obtained from the Institutional Health Research Ethical Committee (IHREC) of the University of Uyo Teaching Hospital.

RESULTS

Ninety two participants, comprising 51-test subjects and 41-controls were included in the study. The mean age of the test subjects was 37.61 ± 11.8 years (range 20-60 years). About half of them were females (51%). The majority of the participants (64.7%) were never married and about 51% of them had formal education to at least secondary school level and 45.1% of them were unemployed. The mean duration of illness was 8.33±8.1 years and the mean duration of use of antipsychotic drugs was 2.9±1.35 years. **(**Table 1)

Table 1 Socio-demographic and Clinical characteristics of the participants

Variables	**No (%)**
Age in years (mean ±SD)	37.61±10.7
Age	

≤40 years	36(70.6)
>40 years	15(24.4)
Sex	
Male	25(49.0)
Female	26(51.0)
Marital status	
Single	33(64.7)
Married	18(35.3)
Educational level	
Primary	2(3.9)
Secondary	26(51.0)
Tertiary	23(45.1)
Employment status	
Employed	27(52.1)
Unemployed	23(45.1)
Duration of illness	
≤10 years	39(78.0)
>10 years	11(22.0)
Mean duration of Antipsychotic use (years)	2.90 ±1.35
Class of antipsychotic medication	
Conventional	15(29.4)
Atypical	12(23.5)
Combination	24(47.1)
Body Mass Index (BMI)	
High	25(49.0)
low	26(51.0)

*BMI was dichotomised at the sample median score.

The mean platelet counts of subjects (194.5±59.8) was significantly lower than that of the controls (338.8±159.07) p=0.01, while the subject had a significantly higher MPV (9.4±0.85) than the controls (8.7±1.05) p= 0.01. However, there was no statistically significant differences in the PDW between the subjects and the controls (p= 0.13). (Table 2)

Table 2. Platelet Indices among Subjects and Controls

Variables	Subjects	Controls	Test statistics	p-value
Platelet Indices				
PLT	194.5±59.80	338.8±159.07	t= -5.65	**0.01**
MPV	9.4±0.85	8.7±1.05	t=-3.34	**0.01**
PDW	16.16±0.42	15.72±1.77	t=-1.55	0.13

*****PLT: Platelet, MPV: Mean Platelet Volume, PDW: Platelet Distribution Width

The association between the outcome measures (PLT, MPV, PDW) and various independent variables of the study subjects. Socio-demographic variables of age and gender had varied impact on the outcome variables. The PLT values showed significant correlation with age of study participants and PDW values were significantly different on gender parameter. (Table 3)

PLT and the PDW did not show any significant correlation with the class of antipsychotics used for treatment, duration of its use and the BMI values. MPV values however, was significantly correlated with the duration of antipsychotic use (p value 0.01)

Table 3: Association between Independent variables and Platelets Indices (Outcome variables)

Independent variables	Outcome variables (Platelets indices)		
	PLT value, statistics	**MPV value, statistics**	**PDW value, statistics**
Age	Pearson's r=0.38 P value= **0.007**	Pearson's r=0.11 P value = 0.46	Pearson's r= -0.10 P value= 0.47
Sex			
Male	1.76±0-52 t=0.54	9.31±0.83 t=0.10	16.25±0.41 t=2.40
Female	1.86±0.50**P=0.59**	9.29±0.85**P=0.92**	1.5.99±0.36**P=0.02**
Antipsychotic Class			
Atypical	198.00±51.7	9.47±0.74	1.90±0.52
Conventional	181.17±65.22	8.99±0.79	1.61±0.51

mixed	201.63±59.5 ANOVA (F=0.50) **P= 0.81**	9.35±0,84 ANOVA= (F=1.19) **P=0.34**	1.86±0,54 ANOVA(F=1.16) **P=0.32**
Duration of antipsychotic use	Pearson's r = -0.35 **P=value =0.4**	Pearson's r = -0.35 **P value= 0.01**	Pearson's r = 0.02 **P value=0.8**
BMI	Pearson's r = -0.001 **P value= 0.9**	Pearson's r = 0.03 **P value= 0.9**	Pearson's r = -0.003 **P value= 0.9**

*PLT: Platelet, MPV: Mean Platelet Volume, PDW: Platelet Distribution Width, BMI: Body Mass Index

DISCUSSION

Haematological abnormalities occur occasionally during treatment with antipsychotic drugs especially the atypical antipsychotic drugs. However, in most cases these abnormalities are often mild and clinically insignificant [15]. Thrombocytopaenia following antipsychotic used is quite rare [16]. A prospective study on the incidence of thrombocytopaenia among hospitalized psychiatric patients receiving different classes of antipsychotic agents did not show any statistical difference with respect to the incidence of thrombocytopaenia between the subjects and the controls. The mean platelet counts of subjects in this study, though significantly lower than that of the controls ($p<0.01$), does not qualify as thrombocytopaenia. Studies among healthy Africans have reported lower platelet count usually within the range of 100-300 x 10^9 /L compared to the Caucasians [17]. The disparity in the mean platelet count between the subjects and controls may well be attributed to the effect of the antipsychotics which perhaps may have induced some form of bone marrow suppression in the former group.

Excessive platelet activation have been reported in patients with psychiatric disorders either related directly with the disease itself or with the antipsychotic medication used in the treatment of the disease [18]. The mean MPV of subjects in this study was significantly higher than that of the control group ($p<0.01$).Our finding was similar to the study by Semiz M, et.al, [18] who also reported a significantly higher MPV in patients who were on atypical antipsychotics than in patients who were not on drugs and equally much higher than that of the control group. Furthermore, the study also showed that atypical antipsychotic drug usage was an independent predictor for increased MPV [18].

In a population based nested case control study conducted in United Kingdom, the authors found an association between the use of antipsychotics and risk of VTE; increased risk was found to be more pronounced among new users and those on atypical antipsychotics [12]. Although underlying mechanism of this adverse reaction remains largely unclear, various hypothesis have been proposed; including platelet activation/aggregation, sedation by antipsychotic which could enhance venous stasis, obesity, increased antiphospholipid antibodies, enhanced hyperhomocysteinaemia and hyperprolactinamia [7].

Enhanced platelet activation have been reported in various psychiatry disorders including schizophrenia. The authors found that aggregation of blood platelets induced by adenosine diphosphate (ADP) was higher in schizophrenic patients than the controls [19]. In a similar study using blood samples from healthy volunteers, atypical antipsychotic agents (clozapine) was found to cause an increase in platelet adhesion and aggregation [20]. Therefore, increased platelet activation which correlates with MPV plays a significant role in the development of venous thrombotic events.

Platelet distribution width has also been shown to be valuable in predicting the development of venous thromboembolic events being a marker of platelet activation. However in the current study, there was no significant difference in the mean PDW of both the subjects and the healthy controls. PDW is an index of variability in platelet size and is increased when there is platelet anisocytosis. Report from previous studies showed that antipsychotic agents especially the atypical subclass affect primarily platelet structure by increasing its volume as opposed to causing platelet sizes anisocytosis [18]. This perhaps may explain why there was no significant difference between PDW in subjects and the healthy controls.

Studies have shown that the thromboembolic effect of antipsychotics may be evident within three months of initiating therapy [8]. Data from analysed clinical studies including meta –analyses of VTE risk factors in patients on antipsychotics showed that the main risk factors for VTE are duration of treatment and patients related factors such as age, gender, body mass and physical activity [8]. Association between MPV and duration of antipsychotic treatment was demonstrated in this study. Subjects in this study were on antipsychotic medications for at least six months. Thus implying that the longer the duration of treatment, the greater the increase in MPV of the subjects. However, our finding contrast with that of Kleijer BC et.al, [21] who found no association between the risk of VTE and duration, dose and type of antipsychotic drug usage.

Furthermore, association between antipsychotic drug usage and obesity have been reported by some authors. A longitudinal retrospective study among adult population reported an association between antipsychotic use and obesity regardless of the drug class [22]. However, this study did not show any association between the platelet indices and the body mass of subjects. Perhaps the near equal representation of subjects with normal and high body mass index may have accounted for this observation.

CONCLUSION

A significantly high MPV (a biomarker of platelet activation) as well as a demonstrable association between MPV and duration of antipsychotic drug usage portends an increased VTE risk among the subjects. Therefore, it is important for clinicians to be aware of this untoward effect

of antipsychotics and perhaps assess or monitor these patients closely using MPV levels

REFERENCES

1. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, et.al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. ThrombHaemost 2007; 98: 756-764.
2. Cushman M. Epidemiology and risk factors for venous thrombosis. SeminHaematol 2007; 44(2): 62-69.
3. Stein P, Matta F, Musani M, Diaczok B. Silent pulmonary embolism in patients with deep venous thrombosis: A systematic review. The American journal of medicine. 2010; 123 (5):426–31.
4. Esmon CT. Basic mechanisms and pathogenesis of venous thrombosis. Blood Rev. 2009; 23(5): 225-229
5. Previtali E, Bucciarelli P, Passamonti SM, Martinelli I. Risk factors for venous and arterial thrombosis. Blood Transfus 2011; 9(2): 120-138
6. Goldhaber S. Risk factors for venous thromboembolism. Journal of the American College of Cardiology. 2010; 56(1): 1-7
7. Hägg S, Spigset O. Antipsychotic-induced venous thromboembolism: A review of the evidence. CNS drugs 2002; 16 (11): 765-776
8. Bałkowiec-Iskra E, Cessak G, Kryńska Ł, Łoza B, Wojnar M. Venous thromboembolism as an adverse effect of antipsychotic treatment. Psychiatriapolska 2014; 48(5): 997-1014.
9. Paciullo C. Evaluating the association between clozapine and venous thromboembolism. American journal of health-system pharmacy (AJHP) 2008; 65(19): 1825-1829
10. Zornberg GL, Jick H. Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. Lancet 2000;356:1219-23
11. Skokou M, Gourzis P, Corporation HP. Pulmonary Embolism related to Amisulpride treatment: A case report. Case Reports in Psychiatry. 2013; Article ID 718950: 3
12. Parker C, Coupland C, Hippisley-Cox J. Antipsychotic drugs and risk of venous thromboembolism: nested case-control study. BMJ 2010; 341: c4245.
13. Vagdatli E, Gounari E, Lazaridou E, Katsibourlia E, Tsikopoulou F, Labrianou I. Platelet distribution width: A simple, practical and specific marker of activation of coagulation. Hippokratia 2010; 14 (1): 22-32.
14. Sevuk U, Altindag R, Bahadir MV, Ay N, Demirtas E, Ayaz F. Value of Platelet indices in identifying complete resolution of Thrombus in deep Venous thrombosis patients. Indian J Hematol Blood Transfus 2015; 31(1):71-76
15. Hall R, Smith A, Edwards J. Haematological safety of antipsychotic drugs. Expert opinion on drug safety 2003; 2(4): 395-399
16. Mihaljevi-Peles A, Jakovljevic M, Mrsic M, Sagud M. Thrombocytopenia associated with clozapine and fluphenazine Nordic Journal of Psychiatry 2001; 55(6):449- 50.
17. Essien EM, Usanga EA, Ayeni O. The normal platelet count and platelet factor-3 availability in some Nigerian population groups. Scand J Haemat 1973; 10: 378-383.
18. Semiz M, Yücel H, Kavakçı Ö, Yıldırım O, Zorlu A, Yılmaz MB, Küçükdurmaz Z, Canan F. Atypical antipsychotic use is an independent predictor for the increased mean platelet volume in patients with schizophrenia: A preliminary study. J Res Med Sci 2013; 18(7) 561-566
19. Dietrich-Muszalska A, Olas B. The changes of aggregability of blood platelets in schizophrenia. World J Biol psychiatry 2009; 10(2): 171-176
20. Axelsson S, Hägg S, Eriksson AC, et al. In vitro effects of antipsychotics on human platelet adhesion and aggregation and plasma coagulation. ClinExpPharmacolPhysiol 2007; 34:775-780
21. Kleijer B, Heerdink E, Egberts T, Jansen P, Marum van. Antipsychotic drug use and the risk of venous thromboembolism in elderly patients. Journal of clinical psychopharmacology 2010 ; 30(5): 526-530
22. Sicras-Mainar A, Navarro-Artieda R, Rejas-Gutiérrez J, Blanca-Tamayo M. Relationship between obesity and antipsychotic drug use in the adult population: A longitudinal, retrospective. Neuropsychatr Dis Treat 2008; 4 (1): 219-226.

---

*Corresponding author:Timothy Amos. Ekwere
E-Mail: timothyekwere@yahoo.com