Mean Platelet Volume in Depression and Anxiety Disorder- a Hospital Based Case-control Study

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ABSTRACT

Introduction: Depression and anxiety disorder are the common mental disorders. Serotonin (5-hydroxytryptamine [5-HT]) is a well-established neurotransmitter in the central nervous system (CNS). It has a role in the anxiety, depression, appetite, motor, cognitive and autonomic functions, platelet aggregation and regulation of vascular tone. As the CNS is difficult to access, peripheral platelet models are widely used as the indicators of central 5-HT metabolism; moreover, they are known to reflect central serotonergic function. Mean platelet volume (MPV) is contemplated as the marker of platelet function. It is a measure of platelet size and a good indicator of platelet activity. In this backdrop the current study was carried out to evaluate the MPV in depression and anxiety disorders.
Methods: Consecutive 90 depressive disorder patients, 76 anxiety disorder patients, diagnosed according to DSM 5 criteria and 49 healthy control subjects were selected for the study. Hamilton

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rating scale for anxiety (HAM-A), Hamilton rating scale for depression (HAM-D), MPV and platelet count were measured in all subjects.
Results: It was revealed that MPV was more in patients with depression (9.73±1.23) and anxiety disorder (9.84±1.32) compared to the controls (8.773±0.44) and this difference was statistically significant (F=14.95, p<0.001). There was no statistical difference in the MPV values between the patients with depression and anxietydisorder. Negative correlation between MPV and platelet count was recorded.
Conclusion: This study suggests that increased MPV is associated with depression and anxiety disorders. Future research should be planned to investigate the effect of depression and anxiety disorders on MPV.

Keywords: mean platelet volume; depression; anxiety disorder; platelet function

1. INTRODUCTION

Depression and anxiety disorder are the common mental illness. Globally, it is estimated that 4.4% of the global population suffer from depressive disorder, and 3.6% from anxiety disorder [1]. Serotonin (5-hydroxytryptamine [5-HT]) is an important neurotransmitter in the central nervous system (CNS) [2] and is considered to be influential in mediating mood and anxiety symptoms. Abnormalities in serotonin pathways are thought to play a pathophysiological role in depressive and anxiety disorder [3]. It also has a pivotal role in the vascular system for regulation of vascular tone and platelet aggregation [4].

Researchers have recorded that a hyper serotonergic state resulting from impaired serotonin transporter (5-HTT) function, can cause fear response and depressive symptoms by stimulating the amygdala [5]. Investigators have suggested that platelet activity is increased by emotional stress and hypothesized that the actions of stressors on platelets may be a primary trigger in coronary events such as myocardial infarction [6].

The uptake, storage and metabolism of serotonin are similar in platelets and neurons [7] and the same gene encodes for the serotonin transporter in both cell types [8]. As more than 99% of the serotonin in the body is found in the dense granules of platelets [3] and the CNS is difficult to access, peripheral platelet models are widely used as indicators of central 5-HT metabolism; moreover, they are known to reflect central serotonergic function [2,5].

Mean platelet volume (MPV) is a measure of platelet size and is a good indicator of platelet activity. Peripheral platelet models are usually used as pointers to reflect the serotonin changes in the brain as CNS is hard to approach. Increased MPV is considered to be closely linked with cardiovascular diseases (CVDs), like acute myocardial infarction (MI), ischemic heart diseases, congestive heart failure and a close affiliation exists between CVDs anxiety and depressive disorders [9,10].

A limited number of studies were done to evaluate the platelet parameters in depression, schizophrenia, bipolar disorder and anxiety disorder which are inconclusive. Their findings were also limited because most of the studies were retrospective, poor inclusion and exclusion criteria, and lack of use of standardized scales. [10-16]. To overcome these limitations, the present study primarily aimed to compare the MPV values in patients with anxiety disorder, depressive disorder and healthy controls.

2. METHODOLOGY

This was a hospital-based, descriptive, cross-sectional case-control study, conducted in the Outpatient Department of Psychiatry, The Oxford Medical College, Hospital and Research Centre (T.O.M.C.H&R.C), Bangalore, India in 2016 for 3 months. Consecutive 76 patients with anxiety disorder and 90 patients with depressive disorder in the age group of 18-65 years were included in the study. Age and gender-matched 49 subjects were taken as controls, who were hospital employees or relatives of the patients and did not have any psychiatric disease. Subjects who had seizure disorders, mental retardation, other psychiatric disorders, hypertension, hypercholesterolemia, acute or chronic physical illnesses, pregnancy, or a history of any drug use during the last month, and history of smoking and alcohol use were excluded from the study. Written informed consents were taken from all the subjects. They were administered a semi-structured proforma to collect sociodemographic details, height and body weight. Hamilton rating

scale for anxiety (HAM-A) and Hamilton rating scale for depression (HAM-D) were assessed by the psychiatrist in the OPD. Complete blood count, MPV and lipid profile were measured and recorded for each subject. The study was approved by the Institutional Ethics Committee of "The Oxford Medical College, Hospital and Research Centre".

2.1 Measurements

2.1.1 Hamilton rating scale for Anxiety (HAM-A)

HAM-A is one of the instruments frequently used to evaluate anxiety. It is a screening tool for anxiety symptoms with 14 items. Each item is rated on a 0 to 4 scale with a final item which rates behavior at interview. Score above 14 is considered as the proof of clinical anxiety. A score less than14 is considered as no anxiety, 14-17 as mild anxiety, 18-24 as moderate anxiety and 25-30 as severe anxiety. [17]

2.1.2 Hamilton depression rating scale (HAM-D)

HAM –D is an observer-rated screening tool. It has 21 items and only 17 items are scored. Four additional items are used for diagnostic purpose. Ratings are made by the clinical interview along with any additional available information such as nursing or family member report. A score ≤7 is considered as normal, 8–13 as mild depression, 14 – 18 as moderate depression, 19–22 as severe depression and ≥23 as very severe depression.[18]

2.1.3 Complete blood count and Biochemical analysis

An amount of 5 ml blood was obtained from the medial cubital vein by venepuncture avoiding hemolysis. Blood samples were drawn from each subject after a fasting period of 12 hours. The first 2 ml venous blood was collected in sterile BD Vacutainer tube with 5.4 mg of K2 Ethylene diaminetetraacetic acid (EDTA) from BD Franklin Lakes NJ USA. Complete blood counts, including MPV, were determined using Sysmex XP -100: A1489 haematology analyser (Sysmex, India). In order to measure MPV reliably and to minimize the potential influence of anticoagulant [EDTA], blood samples were analysed within 60 minutes after venepuncture. MPV and platelet count were measured for all subjects. The reference range for MPV was between 6.9–10.8 fL. Remaining 3ml of blood samples was collected in gel vacutainer. Samples were centrifuged after 30 minutes at 3000 rpm for 10 minutes. All the analysis were carried on serum samples. Serum cholesterol was measured by CHOD- PAP Method, [19, 20] Triglycerides by GPO-PAP method, HDL by Phosphotungstic Acid method and LDL-C, VLDL-C were calculated by using Friedwald's Equations.[21] All the blood samples were analysed at the same laboratory.

2.2 Statistical Analysis

The data was analysed using SPSS for Windows version 16.0 software (SPSS.INC Chicago, IL, USA). Data were tested for normal distribution using Kolmogorov-Smirnov test. Results were analysed using the descriptive and inferential statistical methods. Chi-square test was done for categorical data and student's t test, ANOVA was used for continuous data. Pearsons correlation was used to know the association of MPV, platelet count and anxiety scores and depressive scores.

3. RESULTS

No significant difference was found between the cases and the controls regarding the socio-demographic details and body mass index(Table 1). HAM A and HAM D mean scores were higher in cases than controls and this difference was statistically significant (Table 2). There was no statistically significant difference in the lipid profiles and haemoglobin levels between the groups (Table 2). MPV was significantly ($p<0.001$) more in depressive disorder (9.73±1.23) and anxiety disorder (9.84±1.3) than in the controls (8.77±0.44). Significantly higher platelet count was observed in depression and anxiety groups than in the control group (Table 2). When the MPV and platelet count between depressive disorder and anxiety disorder was compared, no statistically significant difference was found (Table 3).

Among the 90 cases of depression 49 (54.4%) cases exhibited Major Depressive disorder (MDD), 24 (26.5%) cases showed Dysthymic disorder and 17 (19.1%) reports of Recurrent Depressive disorder(RDD) were recorded. Among the 76 cases of Anxiety disorder, 44 (57.8%) cases had Generalized anxiety disorder (GAD), 20 (26.3%) cases showed Panic disorder (PD) and 12(15.9%) cases had Social Anxiety disorder (SAD).

Table 1. Socio-demographic details

Variables		Depression N= 90	Anxiety N=76	Controls N=49	Statistical analysis
Age		37.02±9.869	35.07±9.22	34.69±6.84	F=1.433 p=.241
Gender	Male	18	20	12	x^2=0.975
	Female	72	56	37	p=0.614
Marital status	Married	72	64	38	x^2=3.25
	Unmarried	18	8	11	p=0.916
Education	Illiterate	38	36	22	x^2=0.443
	Literate	52	40	27	p=0.80
Socioeconomic status	Upper	2	01	01	x^2=0.32
	Middle	41	35	21	p=0.988
	Lower	47	40	27	
BMI		24.6±4.86	23.15±4.96	22.04±4.14	F=2.239 p=0.11

Table 2. HAM A ,HAM D and Biochemical variables in cases and controls

Variables	Depressive disorder N= 90	Anxiety disorder N=76	Controls N=49	Statistical analysis
HAM A	15.22±5.312	21.5±4.07	9.93±3.53	F=100.84 p<0.001*
HAM-D	18.64±4.25	16.57±5.98	11.6±2.53	F=35.702 p<0.001*
MPV fL	9.73±1.23	9.84±1.32	8.773±0.44	F=14.95 p<0.001*
Platelet count $10^{3/}$µl	311.6±59.89	312.8±59.49	276.3±23.68	F=8.435 p<0.001*
Haemoglobin g/dl	12.09±0.9	11.9±0.5	11.78±1.78	F=1.4701 p=0.2322
Lipid profile				
Total cholesterol	187.15±25.16	184.1±28.33	190.2±23.17	F=0,8427 p=0.4320
Triglycerides	167.84±75.6	168.78±75.8	167.99±74.9	F=0.035 p=0.996
HDL cholesterol	46.25±2.54	45.78±3.4	44.93±3.9	F=2.6988 p=0.0696
LDL cholesterol	103.54±31.62	104.54±30.44	103.17±32.68	F=0.0339 p=0.966
VLDL cholesterol	33.85±15.62	32.95±16.16	33.72±15.99	F=0.0720 p=0.9306

**significant*

Table 3. Platelet count and MPV in Depressive disorder and Anxiety disorder

Parameters	Depressive disorder N=90	Anxiety disorder N=76	Statistical analysis Df=164
MPV fL	9.73±1.23	9.84±1.32	t=0.5551 p=0.5996
Platelet count 103/µl	311.6±59.89	312.8±59.49	t=0.1290 p=0.8979

There was negative correlation between MPV and platelet count (r value was - 0.067). A positive correlation between HAM-A scores and MPV (r value was +0.245) and between HAM-D scores and MPV (r value was +0.312) was found.

4. DISCUSSION

MPV has been defined as a decisive factor in platelet function. It has been shown that platelet size, measured as MPV, correlates with platelets' reactivity [22]. Serotonin neurotransmission is considered to be important in mediating positive affect and mood. Abnormalities in serotonin pathways are thought to play a pathophysiological role in case of major depression and anxiety. This takes on importance when considering platelet function because most of the serotonin in the body is found in the dense granules of platelets. [3] The storage and metabolism of serotonin are similar in platelets and CNS. [8]. Depression and anxiety disorders are one of the important factors in the aetiology of mortality in CVDs.[23] It has been suggested that platelet activity is influenced by emotional stress and coronary events such as MI, which may get provoked by these stressors.[6]

In the present study, increased MPV levels in patients with depressive disorder and anxiety disorder was found as compared to the controls. There are few studies that have investigated MPV in psychiatric populations. Ataoglu et al., reported that MPV was found to be elevated in 15 patients with MDD and after 8 weeks of treatment with escitalopram. It was observed that MPV levels were statistically significantly lower than baseline in 15 patients.[11] In a population-based study Canan et al. reported that, 289 patients with major depression were found to have increased MPV levels in comparison with control subjects[12]. Kokacya et al., and Asoglu et al., also showed increased MPV levels in patients with PD.[13,14] Almis and Aksoy found increased MPV levels in GAD patients as compared to the healthy controls.[15] In contrary to the findings in the present study, Gul et al., and Ransingh et al. found lower MPV levels in PD patients as compared to the control group. They speculated that abnormal 5-HT metabolism, such as specific alterations of the 5-HT receptor functional state in platelets of PD patients, could lead to decreased MPV. [10, 16] But they could not explain the exact mechanism of or reason for the decreased MPV in PD patients. Stressful life events, anxiety, depression or disruptive behavior disorder are the reasons for increased catecholamine levels, sympathetic activity, and cortisol secretion. [24, 25] Vizioli et al., have shown that increased sympathetic activity can also cause higher MPV values.[26]
On the basis of these reports, some investigators have postulated that the sympathoadrenal activation may stimulate platelets via 2-adrenoreceptor activation, which in turn induces shape change and thereby increases MPV.[27] Anxiety and depressive disorders are also associated with the increased inflammatory cytokine levels, endothelial dysfunction, and platelet reactivation. In the central nervous system, plasma platelets play a role in serotonin synthesis, secretion, and reuptake. Serotonin not only has a pivotal role in the pathophysiology of depression and anxiety disorder, but also participates in hemostasis by affecting platelet aggregation. [7] It has been reported that patients with anxiety and depressive disorders have increased platelet reactivation related to serotonin. [28, 29]

The following mechanisms have been suggested by Nemeroff and Musselman leading to platelet abnormalities in major depression: altered platelet function by increased plasma concentrations of 5-HT and epinephrine, affected platelet function by increased intraplatelet calcium mobilization, upregulation of 5-HT2A receptors or a-adrenoreceptors, downregulation of 5-HT transporter number, altered second messenger signal transduction, or altered intraplatelet concentrations of monoamines and catecholamines.[30]

Patients with major depression have been shown to exhibit alterations of multiple platelet parameters, including reduction of serotonin transporter [3H]-imipramine binding sites in platelets,[31] as well as increase in 5-HT2 receptor binding sites on the platelet surface compared with controls.[32] Platelet monoamine oxidase activity has been shown to be elevated in depressed patients.[33] Additionally, there are several reports indicating decreased platelet activity after treatment of depression especially with selective serotonin re-uptake inhibitors.[18,19]

In the present study, there was no difference in the MPV values of depression and anxiety disorder and this can be explained as both the disorders share common pathological mechanisms and both are treated by similar drugs(SSRI).[13]

In the current study there was a negative correlation between MPV and platelet count. It has been previously reported that larger platelets have a greater mass, denser granules and are more enzymatically and metabolically active than the smaller platelets. [34] 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.[35] Additionally, larger platelets aggregate more rapidly than the smaller platelets. Increase in platelet volume are often associated with the decrease in platelet count perhaps as a result of small platelets being consumed to maintain a constant platelet functional mass.[36]

There was positive correlation between the HAM-A score and MPV and also between HAM-D and MPV. Depression and anxiety disorders have been suggested to be the main risk factors in the etiology of mortality in CVD. [37] At pathophysiological levels, it has been hypothesized that biological mechanisms may be affected by stress-related conditions, resulting in worsening of cardiovascular functions. Platelet activity increases with the emotional stress, and coronary events such as myocardial infarction are induced. The MPV has been thought as a determinant marker of the platelet function. Furthermore, increased MPV levels may indicate either increased platelet activation or an increased number of large and hyperaggregated platelets. [38, 39] Results of the present study showed that this increase may reflect the abnormality of platelets rather than increase in their counts.

To the best of our knowledge this is the first study in India to examine the relationship of MPV, depressive disorder and anxiety disorder. The previous reports did not use scales to measure the severity of the depressive and anxiety symptoms and could not correlate the severity of the disorder and the MPV and had quoted these as the limitations of the study. The present analysis did not include individuals with conditions such as hypertension, coronary artery disease, diabetes mellitus, malignancy, dyslipidemia, stroke, drug use, smoking and alcohol abuse which are known to affect platelet activity. Earlier studies have investigated either depressive disorder or anxiety disorder, whereas, this study compared both the disorders with controls.

Despite the strengths of the study, there were certain limitations. As it is a hospital-based case-control study with small sample size, it cannot be generalised to community. This study was a single centre study and not a multicentre study.

5. CONCLUSION

It was revealed from the study that increased MPV is associated with depressive disorder and anxiety disorder. There was no significant difference in the MPV of anxiety disorder and depressive disorder, which was due to the common pathological mechanisms. There was a positive correlation between MPV and severity of depressive and anxiety symptoms. Further research for the estimation of MPV as a tool for neuropsychiatry and psychopharmacology to examine how certain mental diseases and medications influence the central nervous system is required. Studies to investigate the effect of MPV, anxiety disorder and depressive disorder on CVDs and the effect of treatment on MPV need to be carried out.

CONSENT AND ETHICAL APPROVAL

Written informed consents were taken from the cases and controls. The study was approved by the Institutional Ethics Committee of “The Oxford Medical College, Hospital and Research Centre”.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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