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Original Research Article

A study on mean platelet volume in ischemic cerebrovascular stroke

Vitan Patel, Mahendra Parmar*, Kinjal Shah, Rishikesh Joshi

Department of Medicine, Medical College, Baroda, Gujarat, India

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***Correspondence:**
Dr. Mahendra Parmar,
E-mail: mcparmar1961@gmail.com

ABSTRACT

Background: Ischemic Cerebrovascular stroke is one of the largest cause of death and disability. It is usually caused by thrombosis or thromboembolic phenomena. Large platelets are more reactive, produce more prothrombotic factors and aggregate more easily, and can be a major risk factor/indicator for stroke. While the Mean Platelet Volume (MPV) has been studied in detail in cases of IHD, very few studies have been done in stroke, and none in India – prompting this study. We aim to determine whether an association exists between MPV and incidence/severity of stroke.
Methods: The study was carried out among fifty patients with an acute ischemic stroke. Clinical severity was assessed using Modified Rankin's scale. MPV was measured using an automated analyzer. Fifty controls were recruited and analysed.
Results: MPV has got a statistically significant correlation with Ischemic stroke with a p value of < 0.0001. Average MPV in cases was 9.78+1.25 fl vs. controls who average 8.30+1.14 fl. We did not find a statistically significant correlation between clinical severity of stroke and MPV (P = 0.550).
Conclusions: This study has shown an elevation of MPV in acute phase of Ischemic stroke. Within this relationship and adjusting for other significant variables in multivariate regression analysis, it can be stated that an increase in MPV is independently associated with stroke. Further research is required into the role of platelet volume in stroke pathology, outcome, and, most importantly, in individuals at risk for stroke.

Keywords: Ischemic stroke, Mean platelet volume, Platelets, Stroke outcome

INTRODUCTION

Cerebrovascular diseases are the second leading cause of death (just behind Ischaemic heart disease), also the second leading cause of dementia, and the leading cause of disability. By sex, they are the third leading cause of death in men, (after Ischaemic heart disease and Lung cancer), whereas in women they are the primary cause.[1] Ischemic stroke (IS) accounts for about 85% of cases, primary intracerebral haemorrhage (ICH) for 10% and subarachnoid haemorrhage (SAH) for the remaining 5%.[2] Most cerebrovascular diseases manifest by the abrupt onset of a focal neurologic deficit, as if the patient was "struck by the hand of God."[3] Stroke is associated with increased long term mortality, residual physical, cognitive, and behavioural impairments, recurrence, and increased risk of other types of vascular events.[4] Several factors are known to increase the liability to stroke, and it has been here that large-scale public health measures have had a substantial influence. The most important of these are hypertension, heart disease, atrial fibrillation, diabetes mellitus, cigarette smoking, and hyperlipidemia.[5] Platelet size is also found to be elevated in individuals with hypertension and diabetes mellitus, both conditions that predispose to the development of vascular disease.[6,7]

Since this is such a huge public health problem, other risk factors and possible preventive measures need to be identified. It is in this context that this study has its significance.

Platelets play a crucial role in the pathogenesis of atherosclerotic complications, contributing to thrombus formation.[8] Platelets are anucleate cells and are heterogeneous regarding their size, density and haemostatic potential. Platelet size (mean platelet volume, MPV) is a marker and possibly determinant of platelet function, large platelets being potentially more reactive. For example, large platelets contain more dense granules, undergo greater in vitro aggregation in response to agonists such as ADP and collagen, and release more serotonin and b-thromboglobulin (b-TG). In normal individuals, the platelet count is inversely proportional to MPV; platelet mass (the product of MPV and platelet count) is a near constant. Although platelets are incapable of de novo protein synthesis they are very active metabolically and respond rapidly to vascular injury or trauma by undergoing a series of reactions (adhesion, release of granule contents, shape change and aggregation), which ultimately result in the formation of a platelet-fibrin plug. Thus, there is evidence that platelet function is accentuated in acute ischemic stroke.[9]

Though there have been quite a few studies which have demonstrated an association between myocardial infarction and platelet size, very few studies have looked at the association between platelet size and ischemic stroke. Among them, there has been discrepancy regarding the sample size, methodology used and the final result; hence an attempt has been made to study the association if any between mean platelet volume and stroke in an Indian population, using a precise methodology in an unselected group of stroke patients and compared them with data from age- and sex-matched control subjects.

Present study objectives are to determine whether an association exists between Mean Platelet Volume (MPV) and ischemic stroke and to determine whether an association exists between Mean Platelet Volume and severity of ischemic CV stroke.

METHODS

This was an Analytical cross-sectional study carried out from April 1st, 2016 to November 31st, 2016 at SSG hospital, Vadodara-a tertiary care referral centre. The study was carried out among fifty patients diagnosed with an acute ischemic stroke and presenting to the medical wards in the hospital within forty-eight hours of onset of symptoms and satisfying the inclusion and exclusion criteria. Fifty age and sex matched controls were also recruited. The study was approved by scientific review committee and institutional ethical committee of Baroda Medical College. Informed and written consent was obtained from patient or a responsible attendant before including the patient in the study. Data was collected for a 1-year period, starting from from approval date of the study to November 2016.

Clinically, a Stroke was defined as Focal neurological deficit lasting more than 24hrs with no evidence of a non -vascular cause.[10]

Inclusion criteria

- Gender: Males/Females
- Age Range: 18 years and above.

Exclusion criteria

- Thrombocytopenia.
- Known cases of hereditary disorders of large platelets.
- Medications that can affect the platelet count: hydroxyurea, antiplatelet agents, antineoplastic Agents, and inhibitors of the platelet integrin αIIbβ3.
- Haemorrhagic stroke on CT scan.
- Patients unable to communicate because of severe stroke, aphasia or dementia without a valid surrogate respondent. (A valid surrogate respondent is considered a spouse or first degree relative that is living in the same home or is self- identified as aware of the participant‘s previous medical history and current therapies).
- Patients presenting 48hrs after the onset of neurological symptoms.
- Peripheral smear showing platelet aggregates.

Controls were primarily hospital based. Each control was matched for sex and age (+/- 5years) matching was done by Group matching. We included relatives or unrelated visitor of any patient or Patients attending the hospital or outpatient clinic for other illness, who were willing to participate in our study. We excluded individuals with a previous history of stroke, thrombocytopenia or peripheral smear showing platelet aggregates.

All the patients were subjected to a detailed clinical history and examination. They all underwent complete clinical evaluation and proper history of any drugs taken. We measured MPV in the above target groups who had a complete blood count done using an automatic blood counter. Venous blood samples were collected in di-potassium EDTA and tested within 1 hour of collection to minimize variations due to sample aging. Various parameters of two groups were compared by using prevalence ratio, multivariate logistic regression and student’s t test wherever applicable. Microsoft excel software were used for data analysis.

RESULTS

In our study, 136 patients of strokes admitted to the medical and neurology wards were screened to get 50

cases, 86 were excluded (Figure 1). Delay in presenting to the hospital i.e. 48hrs from the onset of symptoms comprised of 42% of the total exclusion. Hemorrhagic stroke, delay in recruiting, absence of an informed consent and platelet aggregates in peripheral smear were other causes of exclusion. Age and sex group matching was done in Case and control groups to reduce bias (Figure 2 and 3).

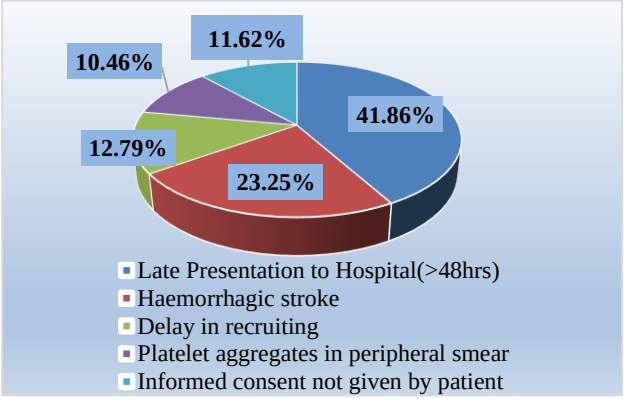

Figure 1: Stroke log and reasons for exclusion.

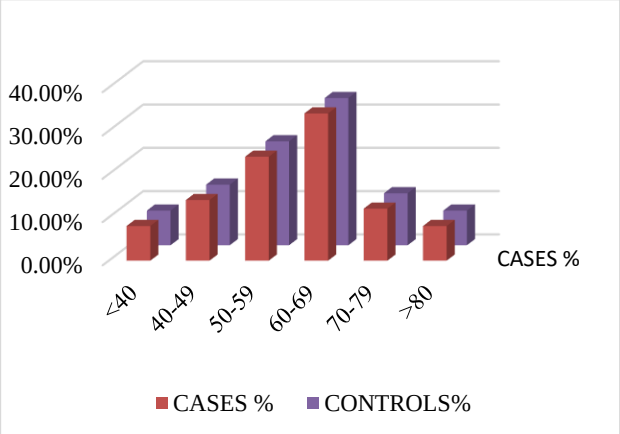

Figure 2: Age distribution.

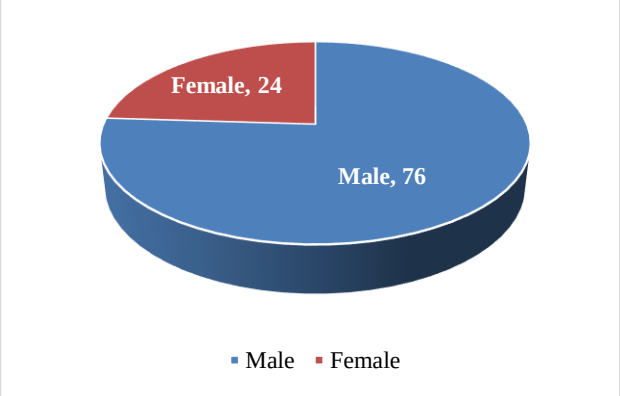

Figure 3: Gender distribution.

There was a trend for lower platelet count in cases, but this was not significant (p value = 0.841) Thus the platelet counts in the cases averaged 2.60±0.61 when compared to the controls in whom the average was 2.63±0.52 (Table 1). In our study, MPV has got a statistically significant correlation with Ischemic stroke with a P value of P< 0.0001 with an average MPV in cases being 9.78+1.25 compared to controls who average 8.30+1.14 (Table 2). We compared various risk factors for stroke (Hypertension, Diabetes smoking, age, gender, cholesterol, HDL) with MPV to look for any positive correlation. However, proper subgroup analysis was not possible due to small numbers. The association of MPV with severity of stroke was determined by comparing the modified Rankin's score with corresponding mean values of MPV in each group (Figure 4). MPV showed a p value of 0.555 which was statistically insignificant.

Table 1: Comparison of blood parameters in cases and controls.

Blood parameters	Cases Mean ±SD	Controls Mean ±SD	Significance
Haemoglobin (g/dl)	12.93±2.33	13.37±1.40	T=1.147; p = 0.2541
Platelet count (%)	2.60±0.61	2.63±0.52	T=0.201; p=0.841

Table 2: Comparison of MPV in cases and controls.

MPV (FL)	Cases Mean ±SD	Controls Mean ±SD	Significance
MPV (EDTA)	9.78±1.25	8.30+1.14	T= (6.171); p=< 0.0001

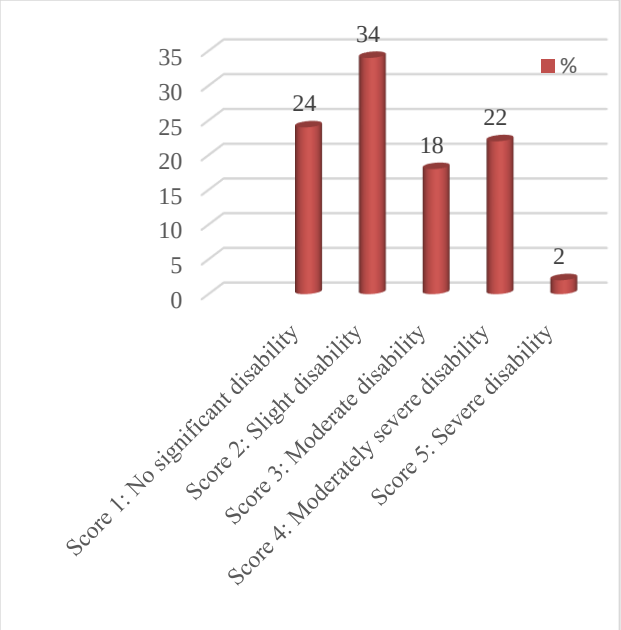

Figure 4: Stroke-clinical severity score.

In our study, MCA territory was involved in 50% of the patients. This was followed by involvement of the vertebrobasilar artery (posterior circulation) and vertebrobasilar artery combined with MCA each

constitutes 14 % of the cases. Involvement of ICA and MCA together comprised of 8% of the cases. Involvement of ICA also comprised of 8% of cases. Pure ACA territory involvement was seen with 6% of cases (Table 3). The infarct territory and MPV were compared to look for any correlation, on applying ANOVA test of variance among the mean MPV of different groups of territory of arteries, it was seen that difference was significant among all groups of vascular territories (p=0.0466). We demonstrated by multiple logistic regression analysis that MPV with a p value of 0.009 and an adjusted OR (Odds ratio) of 8.10, MVP is one of the most important risk factors associated with stroke only second to hypertension which had a p value of <0.001and adjusted OR of 10.10 (Table 4).

Table 3: Infarct teritory and association with MPV.

Territory	Number (n=50)	MPV (EDTA)
ACA	3	11.9000±1.8520
MCA	25	9.6381±1.0938
VBA+MCA	7	9.4857±1.6718
VBA	7	10.3000±1.0801
MCA+ICA	4	9.5±0.7439
ICA	4	9.3±0.5292

Table 4: Multivariate logistic regression analysis to predict stroke.

Variables	Logit co-efficient	P value	Adj. OR
Age in years	-0.03	0.099+	0.97
Female	-0.02	0.977	0.98
H/O hypertension	2.31	<0.001**	10.10
H/O DM	-0.12	0.833	0.89
Smoking	0.08	0.951	1.08
Alcohol	-0.10	0.944	0.91
MPV citrate	2.09	0.009**	8.10
MPV EDTA	-1.02	0.156	0.36

DISCUSSION

We excluded patients with delayed presentation or inclusion in study because platelet parameters would have changed by then. The mean age in our study was much lower (58.10±13.67) compared to western studies, which lines up well with studies that show South Asian people are predisposed to having strokes 15years early.[11] The male preponderance was clear in our studies, which matches with most studies. However, we must take a note that the impact of gender on stroke carries with it other co-factors.[12]

MPV assessment using EDTA and Citrate has been done only in one study i.e. Butterworth et al and the values were 8.04±1.04 (7.69±0.83) for EDTA and 7.35±1.05 (7.09±0.74) for citrate.[13] The values were comparable even though these studies have been done in different populations. All the other studies have used EDTA as the anticoagulant and there is no uniformity in the collection method, time of analysis, transport of the specimen or the storage. O 'Malley study has performed the test after 24hrs of storage in room temperature.[14] Most of the other studies have performed the test after 2hrs. In this study the samples were analysed after 2hrs. Of storage in room temperature. The only study with a lower MPV in cases compared to controls is Tohji et al.[15] This study did not specify the time after venipuncture at which samples were analysed or temperature at which it was stored. The pattern of strokes case having a trend of lower platelet count has been seen in all the other case control studies.[13-15] We were pleased to find that we could not find citations at the time of the study of any western study that analysed various stroke territories and their association with MPV, and that it was positive across the board. However, for us, the most important find was that MPV was the most significant risk factor associated in our study after Hypertension.

There is indirect evidence that the changes in MPV and platelet count are likely to have preceded the vascular event and are unlikely to be due to platelet consumption at the infarct site. Because the average life span of the platelet is about 8days, the elevated MPV seen within the first 48hours after stroke probably represents platelets released before infarction. Furthermore, it is unlikely that platelet consumption due to localized thrombosis would affect peripheral venous estimations of platelet variables. The observation that there was no difference in MPV between large cortical strokes and smaller lacunar infarctions also lends support to this view.

We suggest that large platelets may promote the thrombotic event in a susceptible individual and that the increase in MPV may have contributed to the development of the stroke rather than simply being a consequence of the acute event itself. In conclusion, this study has shown an elevation of MPV and reduction of platelet count in acute stroke. Within this relationship and adjusting for other significant variables in multivariate regression analysis, an increase in MPV is independently associated with stroke. The observations here suggest a role for larger platelets in the genesis of cerebral thrombosis and are likely to represent changes occurring at thrombopoiesis. Further research is required into the role of platelet volume in stroke pathology, outcome, and, most importantly, in individuals at risk for stroke.

Despite our best efforts, there are a few limitations to this study that need to be mentioned. There were only 50 patients and controls in the study. Sample size was calculated and found adequate for such a study. But the sample size was smaller than some of the western studies. There was no follow up done of the cases due to the time constraint. Seriously ill patients directly admitted to the intensive care unit have not been included in the study due to difficulty in getting consent. This could have led to

selection bias. This would have reflected on the correlation with MPV and stroke severity.

CONCLUSION

This study has shown an elevation of MPV in acute phase of ischemic stroke. Within this relationship and adjusting for other significant variables in multivariate regression analysis, it can be stated that an increase in MPV is independently associated with stroke. The observations here suggest a role for larger platelets in the genesis of cerebral thrombosis and are likely to represent changes occurring at thrombopoiesis. Further research is required into the role of platelet volume in stroke pathology, outcome, and, most importantly, in individuals at risk for stroke. However, this study did not find a statistically significant correlation between clinical severity of stroke and mean platelet volume. In this study strokes were sub typed based on the vascular territory on MRI. There is significant statistical correlation was obtained when MPV was compared to the various subtypes of stroke. Thus, Thrombomegaly as a factor is restricted not just to patients with cortical ischemic stroke but also with lacunar syndromes.

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