Correlation of Platelet Indices with Severity of Acute Ischemic Stroke in Non-Diabetic and Non-Hypertensive Patients in Hubli, Karnataka

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ABSTRACT

BACKGROUND

Platelet size, measured as mean platelet volume (MPV), is a marker of platelet function and is positively associated with indicators of platelet activity, including aggregation and release of thromboxane A2, platelet factor 4, and thromboglobulin.[1] Larger platelets are metabolically more active, produce more prothrombotic factors, aggregate more easily & act as index of homeostasis and its dysfunction thrombosis.[2] The purpose of this study was to examine the relationship between platelet indices and stroke, as well as its severity and outcome.

METHODS

This was a prospective observational case control study. This study was conducted with 105 non-diabetic, non-hypertensive ischemic stroke patients who had no history of previous thrombotic events and who had not previously taken any antiplatelet medications. These patients were examined within 24 hours of onset of symptoms and severity of stroke was calculated by Canadian neurological scale (CNS). The results were compared with 105 age and sex match controls.

RESULTS

Mean age of patients was 61.72 ± 12 and of controls was 62.85 ± 10.68. Based on the CNS score, participants were allocated into two groups; the first group were those who had a comprehension deficit (1st group, 43 patients) and the second group were those without a comprehension deficit (2nd group, 62 patients). Mean values for platelet distribution width (PDW) & MPV in 1st group was 18.329 and 12.55 respectively and in 2nd group was 16.98 and 11.48 respectively. The mean value of PDW and MPV for stroke patients was 17.53 ± 0.76 and 11.92 ± 0.58 and was significantly higher than mean value of PDW & MPV respectively in controls, which were 15.47 ± 0.26 and 10.43 ± 0.23. PDW & MPV was found to be significantly associated with severity of motor deficit.

CONCLUSIONS

Larger studies may be required to determine its utility in day-to-day clinical practice. However, platelet indices can be used for predicting the severity of deficit in patients of acute ischemic stroke.

KEYWORDS

Platelet Indices, Stroke

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BACKGROUND

Ischemic and haemorrhagic stroke are considered to be devastating disorders. The second leading cause of death worldwide, stroke caused 6.2 million deaths in 2011. By encouraging reduction of risk factors, medical professionals play an important role in the avoidance of stroke. Ischemic stroke accounts for > 80 % of total stroke events. If recognized early, these risk factors can be the target for primary prevention strategies, preventing significant morbidity and mortality caused by stroke. A stroke, or cerebrovascular accident, is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause.[3] The incidence of cerebrovascular diseases increases with age, and as the elderly population grows, the number of strokes is projected to increase.[4]

Platelets are small, discoid and non-nucleated structures derived from fragmentation of megakaryocytes. When it comes to the pathogenesis of atherosclerosis, platelets play a very important role. Activated platelets go through release of the contents of their granules, which include nucleotides, adhesive proteins, growth factors, and procoagulants that act by promoting platelet aggregation and blood clot formation and influence the environment of the forming clot.[3] There is a wide variation in platelet size and density. Larger platelets contain more dense granules and produce more thromboxane A2. Therefore, platelets which are larger in size are more metabolically active and have greater prothrombotic potential.[5,6] Mean platelet volume is a frequently used biomarker of platelet function and activation.[7]

Increased MPV has been linked with greater in vitro aggregation in response to ADP and collagen.[8] Elevated MPV levels are associated with higher risk of myocardial infarction in patients with coronary artery disease. It was also related to increased death or recurrent vascular events after myocardial infarction.[9] Also, higher MPV is observed in patients with diabetes mellitus, hypertension, hypercholesterolemia, smoking and obesity.[2] Platelet distribution width represents variation in platelet size. Larger PDW also indicates prothrombotic status.

The purpose of this study was to examine the relationship between platelet indices and stroke, as well as its severity and outcome.

METHODS

This was a prospective observational case control study. It consisted of 105 patients of acute ischemic stroke who presented to Karnataka Institute of Medical Sciences, Hubli, Karnataka from December 2018 to December 2019.

Inclusion Criteria

The study was a diagnosis of acute ischemic stroke on the basis of history, physical examination and further confirmed by computed tomography (CT) performed within 24 hours of arrival to the hospital, and a patient who consented to be a part of the study.

Exclusion Criteria

1. Age < 18 years
2. Histories of transient ischemic attacks (TIA), stroke, autoimmune disorders and peripheral vascular disease.
3. Haemorrhagic stroke
4. Diabetes mellitus
5. Hypertension
6. Liver and kidney failure
7. Cardiac dysfunction.
8. Recent episode of infection
9. Patient on anti-platelet medications, medications for dyslipidaemia, immunosuppressants.

The control group comprised of 105 healthy age and sex matched subject from the same hospital. None of the controls had any past history of stroke/TIA or other risk factors. All patients were subjected to detailed physical and neurological examination at the time of presentation. Severity of stroke was calculated for all cases using the Canadian neurological scale. All patients considered for the study were divided into two groups based on the presence or absence of comprehension deficit. The first group were the patients with comprehension deficit, and the second group were patients without comprehension deficit. This division was based on the CNS. Within 24 hours of admission, samples for platelet indices measurement were collected in an ethylene diamine acetic acid (EDTA) tube, and these samples were analysed using an automated haematological analyser. All the data collected were tabulated in the Microsoft Office Excel Worksheet.

Statistical tests and evaluation were done using Microsoft Excel. Pearson correlation coefficient test was used as the statistical test of significance.

RESULTS

Out of 105 study subjects, 70 were male and 35 were female. Mean age of patients was 61.72 ± 12 and of controls was 62.85 ± 10.68. Based on Canadian neurological scale, 43 patients had comprehension deficit and were classified under the first group with a mean CNS score of 2.60. 62 patients had no comprehension deficit, with a mean CNS score of 7.48, and these patients were classified under the second group. The mean value of PDW and MPV for overall stroke patients was 17.53 ± 0.76 and 11.92 ± 0.58. The mean values of PDW and MPV in controls were 15.47 ± 0.26 and 10.43 ± 0.23 respectively.

	Cases	Controls
Mean age	61.72 ± 12	62.85 ± 10.68
Male	70	63
Female	35	42
With comprehension deficit	43	-
Without comprehension deficit	62	-

Table 1. Demographic Data of Cases and Controls

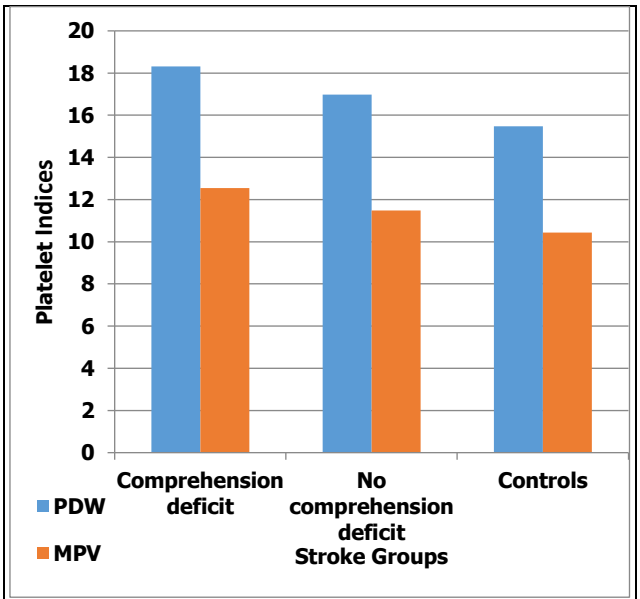

Figure 1. Mean Values of PDW and MPV in Different Stroke Groups and Controls. Pearson Correlation Coefficient Test was Used

Correlation coefficient between the values of motor deficit scores and platelet indices of stroke patients were calculated. The severity of motor deficits, which was based on the CNS, significantly correlated with the values of PDW ($r = -0.82$, $P < 0.01$) and MPV ($r = -0.80$, $P < 0.01$).

In conclusion, patients with higher motor deficit, indicated by a lower score on the CNS had higher mean platelet volumes and platelet distribution widths, when compared to those who had better scores and lesser motor deficits.

DISCUSSION

Cerebrovascular diseases consist of some of the most widespread and devastating disorders: ischemic stroke and haemorrhagic stroke. The second leading cause of death worldwide, stroke caused 6.2 million deaths in 2011. All the physicians have a major role to play in the avoidance of stroke by encouraging risk factor reduction. Ischemic stroke accounts for > 80 % of total stroke events. Early on recognition of persons at risk could be of use in primary prevention strategies. A stroke, or cerebrovascular accident, is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause.[10]

Cerebral ischaemia is a major cause of disability and death globally and has a profoundly negative impact on the individuals it affects, those that care for them and society as a whole. For India, community surveys have shown a rough prevalence rate for 'hemiplegia' in the range of 200 per 100,000 persons, which makes up for nearly 1.5 % of all urban hospital admissions, and 4.5 % of all medical and around 20 % of neurological cases.[4,11]

The incidence of stroke increases considerably as age advances, and increasing age is the most potent risk factor for stroke. The incidence of stroke increases by two times each decade past 55 years of age. Half of all strokes occur in those older than 75 years. Women have higher stroke case-fatality rates as compared with men. Men aged 45 – 75 years develop ischaemic strokes at higher rate than women; after which, stroke rates are higher in women.[12]

Brain infarcts secondary to arterial occlusion are divided based on their macroscopic appearance into white (bland) and red (haemorrhagic) infarcts. By gross anatomy, the white infarcts are composed of few or no petechiae while the latter are characterized by grossly visible blood. This latter term is equivalent to haemorrhagic transformation, which refers to leaking of red blood cells into a dying and ischemic brain tissue, and should not be confused with parenchymal hematoma, which represents a homogenous collection of blood usually resulting from a ruptured blood vessel.[13]

The role played by thrombophilia in the causation of stroke is often underrecognized and warrants more meticulous investigation in selected patients.[14] The Canadian neurological scale was designed to monitor mentation and motor functions in stroke patients.[15] For medical and nursing personnel, this standardized neurological assessment is reliable.[16] The scale amalgamates the following components: comprehension, level of consciousness, speech and motor function of arms, legs and face. Lower CNS scores indicate greater stroke severity. Generally, CNS score ≥ 8 is mild, score 5 - 7 is moderate and 1 - 4 is severe.[2,15,16]

The role of platelets in the pathophysiology of stroke has always been known. Hence, the rationale of using antiplatelets as a staple treatment in patients of ischemic stroke. In individuals with acute ischemic stroke, it is recommended to administer aspirin within 24 to 48 hours of stroke onset. Giving aspirin can be delayed by 24 to 48 hours, in case the patient has been treated with IV alteplase, but it should be considered vis-à-vis the following: for those with associated conditions that might independently benefit by the use of aspirin, or there will be a great risk to the patient by withholding it. 2 large clinical trials, providing doses of aspirin between 160 – 300 mg established the safety and benefit of aspirin in patients with acute ischemic stroke.

In people presenting with minor stroke, treatment for 21 days with dual antiplatelet therapy (aspirin and clopidogrel) that began within 24 hours can be advantageous for early secondary stroke prevention for a period of up to 90 days from symptom onset.[17]

Platelets are released from the megakaryocyte, under the influence of flow in the capillary sinuses. The normal blood platelet count is 150,000 to 450,000/microL. The major regulator of platelet production is the hormone thrombopoietin (TPO), which is synthesized in the liver. Synthesis is increased with inflammation and specifically by interleukin 6. TPO binds to its receptor on platelets and megakaryocytes, by which it is removed from the circulation. Platelets circulate with an average lifespan of 7 - 10 days. Platelets are physiologically very active, but are anucleate, and thus have a limited capacity to synthesize new proteins.[3]

Platelets, once activated undergo release of contents of their granules. These platelet granules contain procoagulants, nucleotides, growth factors and adhesive proteins that help to promote platelet aggregation and further blood clot formation as well as to influence the

atmosphere of the forming clot. Platelet activation and aggregation occurs subsequent to platelet adhesion. Platelet adhesion is mediated mainly by Von Willebrand factor (VWF). VWF is a large protein present both in plasma and extracellular matrix of the vessel wall. It provides sufficient strength to endure high levels of shear stress which would ordinarily detach with the flow of blood. Platelet adhesion is also enabled by direct binding to subendothelial collagen by the aid of specific platelet membrane collagen receptors. This process is improved and augmented by mediators released from activated platelets like adenosine diphosphate and serotonin, humoral mediators in plasma like epinephrine and thrombin, and vessel wall extracellular matrix contents that come into contact with adherent platelets like collagen and Von Willebrand factor. Activated platelets go through release reaction. During this release reaction, they secrete contents that additionally promote aggregation and help to inhibit the endothelial cell factors, which are naturally anticoagulant. During platelet aggregation, more and more platelets are recruited from the circulation to the site of vascular injury, leading to the formation of an occlusive platelet thrombus. The platelet plug is anchored and further stabilized by the developing fibrin mesh. GPIIb / IIIa, which is normally an inactive receptor, is converted to the active form by platelet activation, thus enabling binding to fibrinogen and Von Willebrand factor.[3]

Platelet indices (PI) i.e. mean platelet volume and platelet distribution width and many others, are a group of derived platelet parameters obtained as a part of the automatic complete blood count. Emerging evidence suggests that PIs may have diagnostic and prognostic value in certain diseases.[18]

Platelet count in the blood can be rapidly measured using an automated haematologic analyser. They allow extensive clinical investigations focusing on the diagnostic and prognostic values in a variety of settings without bringing extra costs. Among these platelet indices, platelet crit (PCT), mean platelet volume and platelet distribution width (PDW) are a group of platelet parameters determined together in automatic complete blood count profile (CBC) profiles. They are related to platelet's morphology and proliferation kinetics.[18]

With regards to MPV, the thrombocyte volume measurement which is calculated by the analyser can be directly determined by performing an analysis of the platelet distribution curve. The platelet distribution curve is calculated from a logarithmic transformation of the platelet volume distribution curve, which, in impedance technology systems, will yield a geometric mean for this parameter. Rather than the platelet itself, the MPV is determined in the megakaryocyte, which is the progenitor cell. The platelet volume is found to be linked to cytokines that regulate megakaryocyte ploidy and platelet number and results in the production of larger platelets. When platelet production is decreased, young platelets become bigger and more active, and MPV levels increase. Increased MPV indicates increased platelet diameter, which can be used as a marker of production rate and platelet activation. During activation, platelets shape changes from biconcave discs to spherical, and a pronounced pseudopod formation occurs that leads to MPV increase during platelet activation.[18]

The most frequently studied platelet parameter is mean platelet volume . The MPV denotes the mean size of platelets in blood. The normal values of MPV in healthy subjects ranges between 7.2 and 11.7 fL. In event of platelet hyper destruction, young platelets enlarge in size and increase in activity, which leads to an MPV of more than 13 fL. Reduced production of platelets is reflected in an MPV less than 8 fL. MPV changes can be heavily influenced by the method of laboratory analysis, and not just by an abnormality in platelet count. MPV is modified by many factors such as, physical activity, smoking, age and alcohol consumption. Now considered to be a potential biomarker of platelet prognosis, many studies have associated higher values of MPV to worse clinical outcomes. Lower MPV level can be related to low-grade inflammation, such as rheumatoid arthritis.[19]

PDW indicates variability of volume in the size of platelets. i.e., it is increased in platelet anisocytosis. Measured at the level of 20 % relative height in a platelet size distribution curve, PDW is a distribution curve of platelets. The reported value of this index markedly differs, with reference values ranging from 8.3 to 56.6 %. PDW measures any variables with platelet size as well as the changes that occur with platelet activation, revealing the broad heterogeneity in platelet morphology. Normally, changes between the MPV and PDW are directly proportional, however when it comes to the relationship between platelet count and volumes, the literature has been conflicting, as they are affected by different mechanisms. Being a marker of platelet anisocytosis, PDW describes the size distribution of platelets produced by their progenitor cells, and this value increases on platelet activation. This parameter varies from 10 to 18 % normally, as analysed by various studies. Many studies have also observed that a change in PDW is non-specific and can occur in individuals suffering from many diseases. It allows for this parameter to be considered as a potential biomarker. PDW seems to be proportionally related to MPV in healthy individuals, however, under non-physiological conditions, such as, threatened preterm labour, they show significant dissonance – a rise in PDW and decrease in MPV.[19]

There is a modest amount of evidence found by research groups that there is a relationship between changes in PDW and MPV, and activation of the coagulation cascade, as well as with thrombotic disease, trauma, severe infection, and systemic inflammatory reaction syndrome. These platelet indices have been shown to have diagnostic value in inflammatory diseases like atherosclerosis, inflammatory bowel disease, ankylosing spondylitis and rheumatoid arthritis.[18]

Platelet indices are markers of functionality of platelets. They are very well-known risk factors in cerebrovascular and cardiovascular diseases.

Our study revealed that platelet indices such as MPV and PDW are significantly raised in acute ischemic stroke patients compared to controls. Also increased values of MPV and PDW are significantly associated with greater functional impairment as indicated by motor deficits. All these implicate

the role of platelet activation as an important underlying principle in the pathogenesis of stroke.

MPV and PDW are simple indices which are inexpensive and readily available. When platelets are activated, there is a change in their shape from discoid to spherical and there is formation of pseudopodia. The changes, along with release of cytokines lead to increased values of PDW and MPV. These indices are easily measured by automated analysers. These analysers are based on impedance technology and measure these parameters by deformation of the electric field.[20]

Many studies worldwide have been conducted in attempts to correlate these findings with acute thrombotic events. A study conducted by Balcik et al. showed that there is an acute rise in TPO and MPV in patients 24 hours following acute stroke.[21] A study with 112 patients of acute ischemic stroke was conducted by Chen et al. had similar findings. They further compared the size of the infarct with the values of MPV, and showed there was no correlation between the two.[22] A similar study was conducted by Sarkar et al. with 70 patients, who were not diabetic or hypertensive, and it showed a significant increase in both MPV and PDW in patients with acute ischemic stroke, and further that degree of motor deficit correlates with the values of both MPV and PDW.[2]

The reason why both diabetics and hypertensives were excluded from this study is because both these classes of patients have been demonstrated to be associated with endothelial dysfunction, which can cause platelet activation independent of stroke. Hence, the value of platelet indices could be studied with which are independent of diabetes and hypertension.

CONCLUSIONS

In conclusion, this study suggests that increased levels of PDW and MPV are associated not only with the diagnosis of acute ischemic stroke, but also correlate with the degree of motor disability.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
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REFERENCES

[1] Bath P, Algert C, Chapman N, et al. Association of mean platelet volume with risk of stroke among 3134 individuals with history of cerebrovascular disease. Stroke 2004;35(3):622-626.
[2] Sarkar RN, Das CK, Bhattacharjee U, et al. Platelet indices as a marker of severity in non-diabetic non-hypertensive acute ischemic stroke patients. The J of the Association of Physicians of India 2018;66(7):40-42.
[3] Jameson LJ, Fauci AS, Kasper DL, et al. Harrison's Principles of Internal Medicine. Vol. 1 & 2. 20th edn. McGraw-Hill Education 2018.
[4] Munjal YP. API Textbook of Medicine. Vol. 1 & 2. 9th edn. Jaypee Brothers Medical Publishers 2012.
[5] Projahn D, Koenen RR. Platelets: key players in vascular inflammation. J Leukoc Biol 2012;92(6):1167-1175.
[6] Lievens D, von Hundelshausen P. Platelets in atherosclerosis. Thromb Haemost 2011;106(5):827-838.
[7] Bath PM, Butterworth RJ. Platelet size: measurement, physiology and vascular disease. Blood Coagul Fibrinolysis 1996;7(2):157-161.
[8] Smith NM, Pathansali R, Bath PM. Platelets and stroke. Vasc Med Lond Engl 1999;4(3):165-172.
[9] Endler G, Klimesch A, Sunder-Plassman H, et al. Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease. Br J Haematol 2002;117(2):399-404.
[10] Smith WS, Johnston CS, Hemphill CJ 3rd. Cerebrovascular Diseases. Chap - 419. In: Harrison's Principles of Internal Medicine. 20th edn. McGraw-Hill Publication 2019: p. 3790.
[11] Flynn RWV, MacWalter RSM, Doney ASF. The cost of cerebral ischaemia. Neuropharmacology 2008;55(3):250-256.
[12] Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation 2020;141(9):e139-e596.
[13] Jovin T, Demchuk A, Gupta R. Pathophysiology of acute ischemic stroke. Contin Lifelong Learn Neurol 2008;14:28-45.
[14] Biller J, Ruland S, Schneck MJ. Ischemic cerebrovascular disease. Chap – 65. In: Daroff RB, Jankovic J, Mazziotta JC, et al. eds. Bradley's Neurology in Clinical Practice. 7th edn. Philadelphia, PA: Elsevier 2016.
[15] Côté R, Hachinski VC, Shurvell BL, et al. The Canadian Neurological Scale: a preliminary study in acute stroke. Stroke 1986;17(4):731-737.
[16] The Canadian Neurological Scale, Neurology. (Accessed Feb. 05, 2021). https://n.neurology.org/content/39/5/638.short
[17] Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2018;49(3):e46-e99.
[18] Budak YU, Polat M, Huysal K. The use of platelet indices, plateletcrit, mean platelet volume and platelet distribution width in emergency non-traumatic abdominal surgery: a systematic review. Biochem Medica 2016;26(2):178-193.
[19] Pogorzelska K, Krętowska A, Krawczuk-Rybak M, et al. Characteristics of platelet indices and their prognostic significance in selected medical condition – a systematic review. Adv Med Sci 2020;65(2):310-315.
[20] Vagdatli E, Gounari E, Lazaridou E, et al. Platelet distribution width: a simple, practical and specific

marker of activation of coagulation. Hippokratia 2010;14(1):28-32.

[21] "Thrombopoietin and Mean Platelet Volume in Patients With Ischemic Stroke - Özlem Sahin Balcik, Sule Bilen, Ersin Kasim Ulusoy, Derya Akdeniz, Sema Uysal, Mustafa Ikizek, Fikri Ak, Ali Kosar, 2013." https://journals.sagepub.com/doi/full/10.1177/1076029611434528 (accessed Jan. 29, 2021).

[22] C. Y et al., "The Role of Circulating Platelets Microparticles and Platelet Parameters in Acute Ischemic Stroke Patients.," J. Stroke Cerebrovasc. Dis. Off. J. Natl. Stroke Assoc., vol. 24, no. 10, pp. 2313–2320, Jul. 2015, doi: 10.1016/j.jstrokecerebrovasdis.2015.06.018.