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Role of platelet parameters in thrombocytopenia

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Abstract
Introduction: Modern day analyzers are generating a number of parameters which with time have gained a lot of clinical significance. The platelet indices have been investigated as prospective platelet activation markers. The aim of this study is to predict the relationship between platelet parameters and cause of thrombocytopenia and their role in predicting prognosis in dengue.
Method: It is an observational study conducted at SAKRA World Hospital. The patient's data, platelet count, MPV and PDW were recorded using standard proforma.
Results: The study was conducted on 263 cases of thrombocytopenia that were broadly categorized into three groups- Group A with accelerated platelet destruction, Group B with impaired production and Group C with abnormal pooling. The platelet indices were compared in the three categories. Relationship between the platelet indices were made with severity of thrombocytopenia. Significant relationship was observed between severity of the thrombocytopenia and severity of the disease.
Conclusion: Platelet indices can be used as reliable indicators in differentiating hyperdestructive and hypoproductive thrombocytopenia. They also serve as prognostic markers in indicating the severity of disease in dengue patients. Low MPV (<9fl) and high PDW (>13fl) in dengue patients predicted prognosis to severe thrombocytopenia.

Keywords: Platelet indices, Thrombocytopenia, dengue

Introduction

Thrombocytopenia is not a disease entity by itself, but a finding that may result from a number of disease processes. Thrombocytopenia can be grouped into 3 major categories, based on the causative process, as increased destruction, decreased production and splenic sequestration/abnormal pooling.

Dengue has been the most important emerging tropical viral disease in the world, with thrombocytopenia being the most common of the laboratory findings. The World Health Organization has estimated 50 million cases of dengue cases occur each year, depending on the epidemic activity [1]. In the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries [2]. Antibody detection is an indirect method of diagnosis, and therefore, is prone to false positive and false negative results. However NS1Ag detection is reported to be sensitive as well as highly specific. Apart from the dengue specific parameters, platelet count is the only accessory laboratory test available in the peripheral areas that can support the diagnosis of Dengue. With availability of automated analyzers, new indices related to platelet count are being estimated. Recently, novel platelet indices such as mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT) have been investigated as prospective platelet activation markers [3]. Platelet volume, a marker of platelet function and activity is measured as MPV by hematology analyzers. It is a surrogate marker of bone marrow activity; a high MPV indicates increased megakaryocytic activity. A low MPV indicates marrow suppression and increased risk of bleeding. Correlation of platelet count and MPV with bleeding and severity of the disease can potentially predict outcome. Platelets with increased number and size of pseudopodia differ in size, possibly affecting platelet distribution width (PDW) which increases during platelet activation. Furthermore, platelet activation alters the morphology of these cells, which can be evaluated on the basis of MPV and PDW. Another platelet parameter is PCT, which is a reliable measurement of platelet biomass because it combines the MPV with the absolute platelet count [1].

The study of platelets would have a substantial impact on reducing the morbidity and mortality associated with dengue.

Aim

1. To study the relationship between platelet parameters and cause of thrombocytopenia
2. To study the role of platelet parameters in predicting prognosis in dengue

Materials and methods

An observational study to be conducted in August and September 2017 in the Department of Laboratory Medicine, SAKRA World Hospital, Bengaluru, during an outbreak of dengue infection. The platelet parameters were measured by the Beckman Coulter LH780, a fully automated hematology analyzer on venous samples collected in EDTA from patients presenting with thrombocytopenia.

Inclusion criteria

All cases of thrombocytopenia (platelet count <1 lakh/cmm), measured by the automated analyzer and confirmed on smear, irrespective of the underlying cause

Exclusion criteria

Infants and children (<12years), to rule out age related difference in platelet parameters

Cases without sufficient clinico-hematological workup

Cases with discrepancy in counts by different methods

Serologically confirmed dengue cases were followed up and their platelet count results were classified into 3 groups – severe (20,000), moderate (21-50,000) and mild (50,000-1lakh) thrombocytopenia. The platelet parameters with the severity of the disease was studied, assuming significant correlation between severity of disease and severity of thrombocytopenia.

Clinical features were not taken into account and data analysis was based exclusively on laboratory parameters. Platelet count and platelet indices at initial presentation and subsequent platelet count during the course of illness were noted. Every case of thrombocytopenia was reassessed by peripheral smear examination. Data was entered in Microsoft Office Excel and analysis done.

Results

The total number of 263 cases were studied. The age range of patients in our study was 12 years to 82 years. Our most of the patients fell in the group 21-30 years accounting for 27.8% cases, closely followed by age group of 31-40 years accounting for 27% cases. A slight male predominance was seen overall as well as in almost all age groups, the male to female ratio being 1.27:1.

Table 1: Age and sex distribution of cases

SL No	Age group (in years)	Male	Female	Total No.	%
1	12 – 20	22	18	40	15.2
2	21 - 30	40	33	73	27.8
3	31 - 40	47	24	71	27
4	41 - 50	20	16	36	13.7
5	51 - 60	6	7	13	4.9
6	61 - 70	10	18	28	10.6
7	71 - 80	1	0	1	0.4
8	81 - 90	1	0	1	0.4
	Total	147	116	263	

The cases were grouped according to the predominant mechanism of thrombocytopenia as Group A – accelerated destruction, Group B – Impaired production and Group C – splenic pooling.

Table 2: Comparison of platelet indices in Group A, B and C

Platelet indices	Group A	Group B	Group C
MPV (fL)	9.8	8.8	9.9
PDW	17.3	16.2	17.3

Comparison of MPV and PDW of Groups A, B and C with normal shows that MPV is higher in Group A & C with a mean of 9.8 and 9.9 respectively, and similarly PDW is higher in the above two groups with a mean of 17.3. Whereas MPV and PDW in Group B is similar to the normal with a mean of 8.8 and 16.2 respectively.

The cases were classified based on the cause of thrombocytopenia and the platelet parameters were studied.

Table 3: Platelet count and indices in various clinical conditions

	No. of cases	Mean platelet count/cmm	Mean MPV (fL)	Mean PDW	Mean PCT
Bacterial infection	3	57333	10.7	16.7	0.092
Viral infections	243	48772	9.4	17.1	0.070
Malaria	4	39750	9.4	17.7	0.052
Sepsis	3	24000	9.6	17.7	0.039
Malignancy	7	39428	8.8	16.2	0.065
Liver disease	3	41333	9.9	17.3	0.039

We see that mean platelet count was lowest with sepsis. Mean MPV of 10.7fL was highest for bacterial infection, while PDW of 17.7 was highest for both malaria and sepsis. Both MPV and PDW have been found to be lowest in malignancy with 8.8fL and 16.2 respectively.

0f the total 263 cases, 234 were serologically confirmed to have dengue infection.

In order to study the prognostic significance of platelet parameters in dengue patients, all serologically confirmed dengue cases were further grouped as mild (50,000-1lakh), moderate (21,000-50,000) and severe (<20,000) based on the degree of thrombocytopenia. Initial MPV and PDW at the time of presentation for each class of patients were tabulated and mean calculated.

Table 4: Relationship of platelet indices with severity of thrombocytopenia in Dengue

Thrombocytopenia	No. of cases	Mean MPV (fL)	Mean PDW
Mild	105	9.4	15.6
Moderate	65	9.1	16.5
Severe	64	8.4	17

We had most no. of cases (105) with mild thrombocytopenia, and 65 and 64 cases each with moderate and severe thrombocytopenia respectively. Mean MPV was

found to be least and mean PDW highest with severe thrombocytopenia cases while a higher mean MPV and lower mean PDW was noted in moderate and mild groups.
Further, the no. of cases with low MPV (</=9fL) and high MPV(>9fL) at initial presentation in each group were tabulated.

Table 5: Relationship of MPV with severity of thrombocytopenia in Dengue

Thrombocytopenia	Low MPV (</=9 fL)	High MPV (>9fL)	Total
Mild	39 (37%)	66 (63%)	105
Moderate	34 (52%)	31 (48%)	65
Severe	35 (55%)	29 (45%)	64
Total	108	126	234

Similarly cases with low PDW (<16) and high PDW (>16) at initial presentation were tabulated.

Table 6: Relationship of PDW with severity of thrombocytopenia in Dengue

Thrombocytopenia	Low PDW (</=16.8)	High PDW (>16.8)	Total
Mild	47 (73%)	17 (27%)	105
Moderate	34 (52%)	31 (48%)	65
Severe	27 (35%)	78 (75%)	64
Total	108	126	234

Discussion

Thrombocytopenia can be due to increased peripheral destruction, impaired production or splenic pooling. Clinical methods alone do not always permit a confident assessment of mechanism of thrombocytopenia. Diagnosing the cause of thrombocytopenia requires bone marrow examination, platelet-associated IgG and reticulated platelets. These methods are invasive, costly and not available routinely. With advancement of automated analyzers, new platelet parameters are available which are generally considered not interpretable and rarely used by laboratories and physicians. A few studies hint that these platelet parameters are differently altered in various causes of thrombocytopenia and have sufficient sensitivity and specificity in diagnosing cause of thrombocytopenia. There is however a paucity of literature on significance of these platelet indices in thrombocytopenia.

The present study was carried out to study the platelet parameters in various clinical conditions causing thrombocytopenia. A total of 264 cases, presenting with thrombocytopenia, platelet count of <1lakh/µL were studied. Age and sex distribution was tabulated [Table 1]. More than half of these patients were between the age group 21-40 years accounting to 54.8%, with a slight male predominance, as seen in other studies [4, 5].

As in few other studies, the cases were grouped based on the predominant mechanism of thrombocytopenia, into Group A, B and C [Table 2]. Group A comprises of increased platelet destruction as in bacterial and viral infections, sepsis and malaria. Group B consisted of impaired production as a result of bone marrow suppression as in solid malignancies and chemotherapy/radiotherapy-induced suppression, while Group C consisted splenic pooling of platelets as in chronic liver disease. Both MPV and PDW was found to be higher for Group A and C. A study by Nelson *et al*. [6] noticed similar findings and explains that patients having thrombocytopenia secondary to increased destruction have larger platelets, reflecting active bone marrow compensation with release of young platelets. Studies by Pritam *et al*, Kaito *et al*, Ntaios *et al* also give similar findings [7-9].

Mean platelet count, MPV and PDW were analysed for different causes of thrombocytopenia [Table 3]. In our study MPV was found to be highest with 10.7fL for bacterial infections while study by Sridhar *et al* noted highest MPV for malaria and sepsis with 10.9 and 10.7 respectively. PDW was highest for malaria and sepsis with 17.7, similar to Sridhar at al study with PDW of 17.6 and 17.03 for malaria and sepsis respectively.

The mechanism of thrombocytopenia in dengue infection is complex and remains unclear, possible mechanisms could be antibody-mediated platelet destruction, peripheral consumption of platelets and direct bone marrow suppression by the virus. The release of high levels of platelet-activating factor may induce platelet consumption and augment adhesiveness of vascular endothelial cells resulting in thrombocytopenia. MPV, a marker of platelet function and activity, can be used as independent predictor of bleeding.

With reference to studies by Jayashree *et al*. [10] and Navya *et al*. [3], which say there is a significant association between platelet counts and severity of the disease, all serologically confirmed dengue cases were grouped as mild, moderate, severe based on degree of thrombocytopenia [Table 4]. Majority of these patients presented with mild thrombocytopenia with a mean MPV of 9.4fL and mean PDW of 15.6. We see that patients who progressed to severe thrombocytopenia had a relatively lower MPV and higher PDW at presentation, with a mean of 8.4fL and 17 respectively. Whereas patients who had a relatively higher MPV and lower PDW, mean of 9.4fL and 15.6 respectively, recovered with mild thrombocytopenia. These findings were in accordance with study by Navya *et al*. [3] which classified the dengue cases as Dengue fever (DF), Dengue Hemorrhagic fever (DHF) and Dengue Shock Syndrome (DSS). The study showed majority of cases of DHF presenting with low MPV(<9fL) and high PDW [13] at presentation, compared to cases of DF. It is important to note that study by Jayashree *et al*. [10] states that there is a significant association between platelet count and severity of the disease.

From table 5 & 6 we see that among the patients presenting with mild thrombocytopenia, 63% had higher MPV(>9fL) and 73% had lower PDW(>16.8) at the time of presentation, compared to patients with severe thrombocytopenia. This correlated with the study by Navya *et al*. [3].

Research points

Other lesser studied platelet parameters, plateletcrit (PCT) and platelet large cell ratio (p-LCR) are also being studied for determining the prognosis in thrombocytopenia [1, 11]. Newer studies, by Kurata *et al*, have assessed reticulated platelets which are newly released from the marrow by using RNA binding dyes and flow cytometric analysis. These immature platelets were found to be successful as a discriminating guide to determine the etiology of thrombocytopenia [12].

Conclusion

The platelet number alone does not give a complete picture

of platelet maturity and function, therefore, the platelet indices have been the subject of intensive study in recent years, but they have not been firmly established.

Platelet indices provide useful information regarding the mechanism of thrombocytopenia. MPV and PDW are a very useful and reliable indicators to differentiate hyperdestructive thrombocytopenia from hypoproductive and abnormal pooling thrombocytopenia.

Platelet indices also play a significant role in predicting prognosis in dengue patients. Patients with lower MPV and higher PDW at presentation progressed to severe thrombocytopenia when compared to patients with normal to high MPV and low PDW who recovered following mild to moderate thrombocytopenia. Thus correlation of platelet count and platelet indices with bleeding and severity of the disease can potentially predict outcome and also determine if the patient needs platelet transfusions.

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